Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, September 29, 2016 1:00 - 5:00 PM
HP Conference Room
4070 27th Ct. SE
Salem, OR 97302

MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

I. CALL TO ORDER

1:00 PM	A. Roll Call & Introductions	R. Citron (OSU)
	B. Conflict of Interest Declaration	R. Citron (OSU)
	C. Approval of Agenda and Minutes	B. Origer (Chair)
	D. Department Update	D. Weston (OHA)

II. DUR OLD BUSINESS

1:10 PM	A. Botulinum Toxins 1. Prior Authorization Criteria Revision 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	A. Gibler (OSU)
	B. Vitamin D Supplements 1. Preferred Drug List Recommendation 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	R. Citron (OSU)

III. PREFERRED DRUG LIST NEW BUSINESS

1:20 PM	A. Newer Diabetes Agents Drug Class Update 1. DERP Summary Review/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	K. Sentena (OSU)
1:40 PM	B. Asthma/COPD Drug Class Update 1. DERP Summary Review/Prior Authorization Criteria	K. Sentena (OSU)

	2. Public Comment 3. Discussion of Clinical Recommendations to OHA	
2:00 PM	C. Biologics Drug Class Update 1. DERP Summary Review/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	A. Gibler (OSU)
2:20 PM	D. Substance Use Disorders Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	A. Gibler (OSU)
2:45 PM	E. Class Literature Scans 1. Growth Hormones 2. Parenteral Antipsychotics 3. Public Comment 4. Discussion of Clinical Recommendations to OHA	D. Moretz (OSU) A. Gibler (OSU)
3:00 PM	BREAK	
3:10 PM	F. Hepatitis C Class Update 1. Class Update/Prior Authorization Criteria 2. Public Comment 3. Discussion of Clinical Recommendations to OHA	M. Herink (OSU)
3:45 PM	IV. EXECUTIVE SESSION	
4:45 PM	V. RECONVENE for PUBLIC RECOMMENDATIONS	
5:00 PM	VI. ADJOURN	

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Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Residency Faculty	Albany	December 2017
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2017
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2017
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2017
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 2016
Stacy Ramirez, Pharm.D.	Pharmacist	Community Pharmacist	Corvallis	December 2016
Cathy Zehrung, R.Ph.	Pharmacist	Pharmacy Manager	Silverton	December 2018
Phil Levine, Ph.D.	Public	Retired	Lake Oswego	December 2018
Rich Clark, M.D., M.P.H.	Physician	Anesthesiologist	Salem	December 2018
Walter Hardin, D.O., M.B.A.	Physician	Medical Director	Hillsboro	December 2018
Kelley Burnett, D.O.	Physician	Pediatric Medical Director	Grants Pass	December 2019

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, July 28, 2016 1:00-5:00 PM
Hewlett-Packard Building
Salem, OR 97302

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to utilization control recommendations to the OHA. Timing, sequence and inclusion of agenda items presented to the Committee may change at the discretion of the OHA, P&T Committee and staff. The DUR/P&T Committee functions as the Rules Advisory Committee to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9).

Members Present: Bill Origer, MD; Tracy Klein, PhD, FNP; Rich Clark, MD, MPH; James Slater, PharmD; Walter Hardin, D.O., MBA; Phillip Levine, PhD; Caryn Mickelson, PharmD

Members Present by Phone: Kelley Burnett, D.O.

Staff Present: Andrew Gibler, PharmD; Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD, BCPS; Dee Weston; Dave Engen, PharmD, CGP; Sarah Servid, PharmD; Kim Wentz, MD; Deanna Moretz, PharmD, BCPS; Kim Wentz, MD;

Staff Present by Phone: Kathy Sentena, PharmD;

Audience: Mark Borromeo (Teva)*; Barry Benson (Merck); Jim Graves (BMS); Rick Frees (Vertex); Ellison Suthoff (Vertex); Jamie Tobitt (Vertex); Dwight Cobb (Quintiles); David Barhoum (Genentech); Renee Hasler (Genentech); Jacob White (UCB)*; Greg Boutman (Sunovion)*; Mae Kwong (Janssen)*; Peter Zoob (Vertex); Venus Holder (Lilly); Chris Conner (BMS)*; Steve Isaki (Sunovion); Bobbi Jo Drumm (BMS); Kim Laubmeier (Sunovion)*; Lisa Boyle (WVP); John Schillo (Lundbech); Pierre Thoumsin (Pfizer); Samantha Sweeney (Otsuka); Jen Lee (AllCare); Betty Tran (Jazz); Jon Bloomfield (Jazz); Sylvia Churchill (Amgen); Christine Oh (Teva); Jennifer Beighle (Janssen); Nik Seifter (GSK)*;

(*) Provided verbal testimony

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:15 pm. Introductions were made by Committee members and staff.

B. Mr. Citron reported there were no new conflicts of interest to declare and welcomed Doctor Kelley Burnett to the Committee.

C. Approval of agenda and May minutes presented by Dr. Origer. (pages 4 - 9)

Dr. Clark said the minutes did not reflect the concern he voiced regarding the "Antidiabetic Treatments and Cardiovascular Implications" newsletter as it appeared to him to indicate that the empagliflozin was clinically superior. Dr. Clark requested the Committee review the newsletter article and provide specific feedback to staff.

Dr. Moretz corrected the minutes to reflect that Elizabeth Le was a PGY2 resident, not a PharmD candidate.

ACTION: Motion to approve as amended, 2nd, All in Favor.

D. Department updates for OHA presented by Ms. Weston.

II. DUR ACTIVITIES

A. Quarterly Utilization Reports (pages 10 - 14)
Presented by Mr. Citron.

B. ProDUR Report (pages 15 – 17)
Presented by Mr. Holsapple.

C. RetroDUR Report (pages 18 - 22)
Presented by Dr. Williams.

D. Oregon State Drug Reviews (pages 23 – 24)
Presented by Dr. Sentena.

1. Autism Spectrum Disorder Still Not Linked to the MMR Vaccine: A Review of the Studies since the 1998 Wakefield Study

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III. DUR OLD BUSINESS

A. Ivacaftro/Lumacaftor (Orkambi™) Concerns (page 25)

1. The Committee discussed the lack of COI disclosure from the CF Foundation, or that of the OHSU specialists being clearly brought to their attention.
2. Updated COI disclosure form was reviewed.
3. The Committee discussed whether the new knowledge of apparent COI would have changed their previous recommendations.

ACTION: The Committee recommended amending the COI disclosure form to include organizations and also requested that experts engaged to review and provide expert opinion on documents being prepared for P&T also be required to complete COI disclosure. The Committee agreed that the current PA criteria should remain in effect and that the anticipated review in November of Orkambi's expanded FDA indication would suffice. **Motion to approve, 2nd. All in favor. Approved.**

IV. DUR NEW BUSINESS

A. ADHD Drug Policy Evaluation (pages 26-48)
Dr. Herink presented the policy evaluation and following recommendations:

1. Update safety edit to require adults with a history of alcohol abuse or SUD within past 12 months, a mental health specialist consult.
2. Approve lisdexamfetamine for binge eating disorder only for adults with an absence of co-morbid mental health illness and amend PA criteria to require CBT.
3. Require PA for adults 18 years and older
4. Streamline PA processing for stable ADHD regimens for children
5. Perform RetroDUR with change order forms to promote preferred products
6. Evaluate comparative costs in executive session.

ACTION: The Committee did not recommend adopting the update to the safety edit to require a mental health specialist consult for adults with a history of alcohol abuse or SUD within past 12 months, or to require PA for all claims for every adult 18 years and older. The Committee did recommend the OHA adopt the other recommendations. **Motion to approve, 2nd. All in favor. Approved.**

IV. PREFERRED DRUG LIST NEW BUSINESS

A. Smoking Cessation Drug Class Update (pages (49 – 73)
Dr. Herink presented the class update and following recommendations:

1. No changes to the PDL based on the clinical evidence
2. Allow initial treatment with varenicline for 24 weeks
3. Evaluate whether current PA policy is meeting goal
4. Evaluate comparative costs in executive session

ACTION: The Committee did not support allowing continued treatment with varenicline for 24 weeks without PA, but did recommend the OHA adopt the other recommendations. **Motion to approve, 2nd. All in favor. Approved.**

B. Drug Class Literature Scans

1. Antidepressants (pages 74 – 87)
Dr. Moretz presented the scan and following recommendations:

   a. No further research is needed at this time
   b. Evaluate comparative costs in executive session

ACTION: Motion to approve, 2nd. All in favor. Approved.

2. Erythropoiesis Stimulating Agents (pages 88 – 94)
Dr. Moretz presented the scan and following recommendations:

   a. No further research is needed at this time
   b. Maintain current PA criteria
   c. Evaluate comparative costs in executive session

ACTION: Motion to approve, 2nd. All in favor. Approved.

3. Antivirals for Herpes Simplex Virus (pages 95 – 102)

Dr. Sentena presented the scan and following recommendations:

a. No further research is needed at this time
b. Adopt proposed changes to PA criteria
c. Evaluate comparative costs in executive session

ACTION: Motion to approve, 2nd. All in favor. Approved.

4. Drugs for BPH (pages 103 – 111)
   Dr. Sentena presented the scan and following recommendations:

   a. No further research is needed at this time
   b. Evaluate comparative costs in executive session

ACTION: Motion to approve, 2nd. All in favor. Approved.

5. Anti-Parkinson's Agents (pages 112 – 123)
   Dr. Engen presented the scan and following recommendations:

   a. No further research is needed at this time
   b. Evaluate comparative costs in executive session

ACTION: Motion to approve, 2nd. All in favor. Approved.

6. Bone Resorbption Inhibitors (pages 124 – 135)
   Dr. Gibler presented the scan and following recommendations:

   a. No further research is needed at this time
   b. Evaluate comparative costs in executive session

ACTION: Motion to approve, 2nd. All in favor. Approved.

C. Antiepileptic Drug Class Update (pages 136 – 163)
   Dr. Moretz presented the class update and following recommendations:

   1. No further research is needed at this time
   2. Maintain brivaracetam as a non-preferred on the PMPDP
   3. Evaluate comparative costs in executive session

Public Comment:
Jacob White from UCB Pharma gave public comment
Kim Laubmeier and Greg Broutman from Sunovion Pharmaceuticals Inc. gave public comment

ACTION: Motion to approve, 2nd. All in favor. Approved.

D. Direct-acting Oral Anticoagulants Class Update (pages 164 – 176)
   Dr. Sentena presented the class update and following recommendations:

   1. No changes to the PMPDP based on the DERP report
   2. Continue open access to all DOACs without PA

Public Comment:
Christopher Conner with Bristol-Myers Squibb gave public comment
Mae Kwong with Janssen gave public comment

ACTION: Motion to approve, 2nd. Majority in favor with one opposed. Approved.

E. Lesinurad New Drug Evaluation (pages 177 – 186)
Dr. Engen presented the NDE and following recommendations:

1. Due to limited evidence and unknown long-term safety risks maintain lesinurad as non-preferred on the PMPDP

ACTION: Motion to approve, 2nd. All in favor. Approved.

F. Monoclonal Antibodies for Asthma Class Review (pages 187 – 210)
Drs. Herink and Gibler presented the class review and following recommendations:

1. Maintain mepolizumab and reslizumab as a non-preferred on the PMPDP
2. Adopt proposed PA criteria as amended to require age ≥12 years for Nucala

Public Comment:
Nik Seifter, PharmD with GSK gave public comment.
Mark Borromeo with Teva gave public comment

ACTION: Motion to approve, 2nd. Majority in favor with two opposed. Approved.

V. EXECUTIVE SESSION

VI. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. ADHD Drug Policy Evaluation (pages 26 - 48)
***ACTION:** recommend making Daytrana non-preferred on the PMPDP
Motion, 2nd, All in Favor. Approved.

B. Smoking Cessation Drug Class Update (pages (49 – 73)
***ACTION:** Recommend no changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

C. Drug Class Literature Scans
1. Antidepressants (pages 74 – 87)
2. Erythropoiesis Stimulating Agents (pages 88 – 94)
3. Antivirals for Herpes Simplex Virus (pages 95 – 102)
4. Drugs for BPH (pages 103 – 111)
5. Anti-Parkinson's Agents (pages 112 – 123)
6. Bone Resorbption Inhibitors (pages 124 – 135)

***ACTION:** Recommend no changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

D. Antiepileptic Drug Class Update (pages 136 – 163)
***ACTION:** Recommend no changes to the PMPDP.

Motion, 2nd, All in Favor. Approved.

VII. ADJOURN

Botulinum Toxins

Goal(s):

- Approve botulinum toxins for funded OHP conditions supported by evidence of benefit (eg, dystonia or spasticity associated with certain neurological diseases).
- Require positive response to therapy for use in chronic migraine headaches or overactive bladder.

Length of Authorization:

- From 90 days to 12 months

Requires PA:

- Use of botulinum toxins without associated dystonia or neurological disease diagnosis in last 12 months.

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache or detrusor over-activity (eg, overactive bladder)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	

Approval Criteria		
3. Does patient have diagnosis of neurological-induced dystonia or spasticity in which a botulinum toxin is a first-line treatment option? Examples: • Genetic torsion dystonia (G241); • Acquired torsion dystonia (G803; G2402; G248); • Blepharospasm (G245); • Spasmodic torticollis (G243); • Other fragments of torsion dystonia (G249); • Paralysis associated with CVD (I69931-I69969); • Multiple sclerosis (G35); • Neuromyelitis optica (G360); • Spastic hemiplegia, other specified hemiplegia (G8100-G8194); • Cerebral palsy (G800-G809); • Quadriplegia and quadraparesis (-G8250-G8254); • Paraplegia (G8220); • Diplegia of upper limbs (G830); • Monoplegia of lower limb (G8310-G8314); • Monoplegia of upper limb (G8320-G8324); • Unspecified monoplegia (G8330); • Other specified paralytic syndrome (G8381-G8389); • Muscular dystrophies (G710-G712); or • Strabismus in other neuromuscular disorders (H5089).	**Yes:** Approve for up to 12 months	**No:** Go to #4
4. Does patient have a diagnosis of chronic migraine with ≥15 headache days per month, of which ≥8 days are with migraine?	**Yes:** Go to #5	**No:** Go to #7
5. Is the botulinum toxin administered by, or in consultation with, a neurologist or headache specialist?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Has the patient had an inadequate response, or has contraindications, to ≥1 drugs from each of the following 3 drug classes? • Beta-blockers: (propranolol; metoprolol; atenolol; nadolol; or timolol) • Tricyclic antidepressants: (nortriptyline or amitriptyline) • Anticonvulsants: (divalproex sodium/valproic acid; carbamazepine; topiramate; or gabapentin) • Calcium channel blockers (diltiazem; verapamil; or nimodipine)	**Yes:** • Baseline headaches/month: _____. Approve no more than 2 treatments given ≥3 months apart. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of preferred alternatives at www.orpdl.org/drugs/
7. Does patient have a diagnosis idiopathic or neurogenic detrusor over-activity (eg, overactive bladder syndrome) (ICD10-CM N32.81)?	**Yes:** Go to #8	**No:** Pass to RPh. Go to #9
8. Has the patient had an inadequate response to, or is intolerant of, ≥2 incontinence anti-muscarinic drugs (eg, fesoterodine, oxybutynin, solifenacin, darifenacin, tolterodine, or trospium)?	**Yes:** • Baseline urine frequency/day: _____. • Baseline urine incontinence episodes/day: _____. Approve for up to 90 days. Additional treatment requires documented positive response to therapy from baseline (see Renewal Criteria).	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria

9. RPh only: Medical literature with evidence for use in funded conditions must be submitted and determined to be appropriate for use before approval is granted.

Deny for the following conditions; not funded by the OHP
Neurologic conditions with none or minimally effective treatment or treatment not necessary (G244; G2589; G2581; G2589; G259); Facial nerve disorders (G510-G519); Spastic dysphonia (J387); Anal fissure (K602); Disorders of sweat glands (eg, focal hyperhidrosis) (L301; L740-L759; R61); Other disorders of cervical region (M436; M4802; M530; M531; M5382; M5402; M5412; M542; M6788); Acute and chronic disorders of the spine without neurologic impairment (M546; M545; M4327; M4328; M532X7; M532X8; M533; M438X9; M539; M5408; M545; M5430; M5414-M5417; M5489; M549); Disorders of soft tissue (M5410; M609; M790-M792; M797); Headaches (G44209; G44009; G44019; G44029; G44039; G44049; G44059; G44099; G44209; G44219; G44221; G44229; G44309; G44319; G44329; G4441; G4451-G4453; G4459; G4481-G4489; G441; R51); Gastroparesis (K3184)
Deny for medical appropriateness for the following conditions; evidence of benefit is insufficient
Dysphagia (R130; R1310-R1319); Other extrapyramidal disease and abnormal movement disorders (G10; G230-GG238; G2401; G244; G250-G26); Other disorders of binocular eye movements (eg, esotropia, exotropia, mechanical strabismus, etc.) (H4900-H518); Tics (F950-F952; F959); Laryngeal spasm (J385); Spinal stenosis in cervical region or brachial neuritis or radiculitis NOS (M4802; M5412-M5413); Spasm of muscle in absence of neurological diagnoses (M6240-M62838); Contracture of tendon (sheath) in absence of neurological diagnoses (M6240; M62838); Amyotrophic sclerosis (G1221); Clinically significant spinal deformity or disorders of spine with neurological impairment (M4800; M4804; M4806; M4808; M5414-M5417); Hyperplasia of prostate (N400-N403; N4283)

Renewal Criteria

1. Is this a request for renewal of a previously approved prior authorization for management of migraine headache?	**Yes:** Go to #2	**No:** Go to #3

Renewal Criteria		
2. Is there documentation of a reduction of ≥6~~>7~~ headache days per month compared to baseline headache frequency?	**Yes:** Approve for up to 12 months Baseline:____ headaches/month Current:____ headaches/month	**No:** Pass to RPh. Deny; medical appropriateness
3. Is this a request for renewal of a previously approved prior authorization for management of idiopathic or neurogenic detrusor over-activity?	**Yes:** Go to #4	**No:** Go to Approval Criteria
4. Is there a reduction of urinary frequency of ≥8 episodes per day or urinary incontinence of ≥2 episodes per day compared to baseline frequency?	**Yes:** Approve for up to 12 months • Baseline:____ urine frequency/day • Current:____ urine frequency/day -or- • Baseline:____ urine incontinence episodes/day • Current:____ urine incontinence episodes/day	**No:** Pass to RPh. Deny; medical appropriateness

P&T / DUR Review: *9/16 (AG); 11/15 (AG); 9/14; 7/14*
Implementation : *1/1/16*

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Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
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Newer Diabetes Medications and Combinations (GLP-1 receptor agonists, DPP-4 inhibitors, SGLT-2 inhibitors) Drug Effectiveness Review Project Summary Report

Date of Review: September 2016 **Date of Last Review:** September 2015

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:
1. What is the comparative efficacy and effectiveness of newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) for adults with type 2 diabetes mellitus (T2DM)?
2. What is the comparative tolerability and frequency of adverse events for newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) for adults with T2DM?
3. Are there subgroups of patients based on demographics (e.g., age, racial groups, gender), comorbidities (e.g., drug-disease interactions, obesity), or other medications (drug-drug interactions) for which newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) differ in efficacy/effectiveness or tolerability and frequency of adverse events?

Conclusions:
- There was insufficient evidence to make conclusions on health outcomes (macrovascular disease, microvascular disease and all-cause mortality) for *between* class comparisons of the newer diabetes medications listed in Table 1.[1]
- *Within* class comparisons of low strength evidence were available for dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) receptor agonists. Comparison of sitagliptin and saxagliptin found similar hemoglobin A1c (A1c) lowering (-1.07% and -1.34% at 24 weeks, respectively). Pooled analysis of 3 studies found exenatide XR to lower A1c to a greater extent than exenatide (weighted mean difference [WMD] -0.46%; 95% CI, -0.69 to -0.23). Other GLP-1 receptor agonists comparisons varied in A1c lowering by -0.20% to -0.33%. Risk of adverse events were similar for *within* class comparisons of DPP-4 inhibitors and for *within* class comparisons of GLP-1 receptor agonists.[1]
- In comparisons *between* DPP-4 inhibitors and GLP-1 receptor agonists, greater A1c lowering and weight loss were seen with GLP-1 receptor agonists based on low strength evidence. However, GLP-1 receptor agonists were more commonly associated with higher withdrawal rates due to adverse events (i.e., gastrointestinal effects) compared to DPP-4 inhibitors.[1]
- Moderate strength evidence found canagliflozin (a sodium-glucose cotransporter 2 (SGLT2) inhibitor) to lower A1c by -0.24% more than sitagliptin (a DPP-4 inhibitor) in one study. Two studies found the number of patients who obtained a goal A1c of less than 7% was greater with SGLT2 inhibitors compared to DPP-4 inhibitors but one study did not find any difference between the classes (low to moderate strength evidence). Rates of overall adverse events were similar *between* classes except there were higher rates of genital mycotic infections with SGLT2 inhibitors when compared to DPP-4 inhibitors.[1] Urinary tract infections and risk of hypoglycemia were similar between groups.[1]

- Metformin was found to decrease A1c more than DPP-4 inhibitors with a mean treatment difference of -0.3% to -0.6% based on moderate evidence. Small differences in weight changes favored metformin over DPP-4 inhibitors. Withdrawals due to adverse events were similar between metformin and DPP-4 inhibitors with less hypoglycemia seen in patients treated with metformin.[1]
- In one study, the GLP-1 receptor agonist dulaglutide was found to decrease A1c more than metformin with similar changes in weight and more hypoglycemia in the dulaglutide group (low strength evidence).[1]
- Low strength evidence found comparisons of SGLT2 inhibitors to have similar A1c lowering as metformin and metformin XR with more weight changes in the SGLT2 groups (mean difference -1.18 kg to -3.9 kg). Risk of adverse events and withdrawals due to adverse events were similar between groups.[1]
- Fixed-dose combinations of DPP-4 inhibitors and metformin were found to decrease A1c by a difference of -0.44% to -1.10% compared to their monotherapy components. Changes in weight were imprecise depending on the DPP-4 inhibitor studied.[1]
- Low strength of evidence found SGLT2 inhibitors plus metformin to be more effective at lowering A1c compared to their monotherapy components. Comparisons of SGLT2 inhibitor and DPP-4 combinations also demonstrated more A1c lowering compared to their monotherapy components; however, comparisons to DPP-4 monotherapy were not clinically significant (MD -0.14%; 95% CI, -0.33 to -0.06). Weight loss was similar with dual therapy and SGLT2 inhibitor monotherapy based on moderate strength of evidence.[1]
- Limited evidence was available for subgroup comparisons therefore no conclusions could be drawn.[1]

Recommendations:
- Evidence from the Drug Effectiveness Review Project (DERP) report supports our current PDL. Review comparative drug costs in the executive session.
- Recommend to continue current prior authorization (PA) criteria with minor modification to the GLP-1 receptor agonist criteria (Appendix 2).

Previous Conclusions:
- There is insufficient new comparative evidence for efficacy/effectiveness on differences of microvascular outcomes (retinopathy, nephropathy and neuropathy) between different treatments for T2DM. Evidence-based recommendations in new clinical practice guidelines and a systematic review of diabetes agents from the Agency for Healthcare Research and Quality (AHRQ) support the current status of non-insulin antidiabetic therapies on the preferred drug list (PDL).[2]
- High quality evidence suggest patients on metformin, pioglitazone, metformin plus a DPP-4 inhibitor, or metformin plus a SGLT-2 inhibitor have similar rates of all-cause mortality based on one systematic review.[2]
- In patients with a history of cardiovascular (CV) disease, there is moderate strength of evidence that empagliflozin (pooled data from 10 mg and 25 mg doses) can decrease risk for CV death, non-fatal myocardial infarction (MI), or non-fatal stroke versus placebo (10.5% vs. 12.1%), with a number needed to treat (NNT) of 63 over 3.1 years (hazard ratio [HR] 0.86; 95.02% CI, 0.74 to 0.99) in patients with high cardiovascular risk. Reduction in risk is primarily driven by a 2.2% reduction in CV death (3.7% vs. 5.9%) and not non-fatal MI or non-fatal stroke.[2]
- There is high quality evidence that monotherapy with either metformin, a thiazolidinedione (TZD) or a sulfonylurea (SU) results in similar lowering of A1c based on one systematic review.[2]
- There is moderate quality evidence that DPP-4 inhibitors lower A1c less than metformin and glimepiride.[2]
- Moderate quality evidence suggests that DPP-4 inhibitors do not reduce major CV outcomes compared to placebo. Evidence finds these agents to be non-inferior to placebo when a composite of CV outcomes are evaluated.[2]
- Moderate quality evidence showed a statistically significant increase in heart failure (HF) outcomes with DPP-4 inhibitors compared to placebo or active treatment.[2]

- High quality evidence suggests hypoglycemia rates are higher with SU than comparative T2DM therapy. Evidence suggests glyburide is associated with at least one episode of hypoglycemia compared to secretagogues [relative risk (RR) 1.52, 95% CI 1.21 to 1.92] and compared to other SUs (RR 1.83, 95% CI 1.35 to 2.49).[2]
- There is low quality evidence to recommend metformin use in patients with mild to moderate kidney disease. Evidence suggests metformin is safe in patients with mild to moderate chronic kidney disease (eGFR >30-60 mL/min per 1.73m^2) without increased risk of lactic acidosis. The frequency of lactic acidosis in the setting of metformin therapy is very low and numerically similar to what appears to be the background rate in the population with T2DM.[2]
- In December of 2014, Saxenda (liraglutide for injection) was approved for chronic weight management in addition to a reduced-calorie diet and physical activity. Treatments for weight loss are not funded by the OHP.[2]

Previous Recommendations:
- Make Byetta (exenatide) a preferred agent but subject to current PA for GLP-1 receptor agonists.
- Make Glyxambi (empagliflozin/linagliptin) non-preferred drug subject to current PA for SGLT-2 inhibitors.
- Remove clinical PA for pramlintide due to low overall utilization and current FDA-mandated Risk Evaluation Mitigation Strategy (REMS) already in place to promote safe use through education.
- Modify SGLT-2 inhibitor clinical PA criteria to require monitoring renal function every 6 months.
- Continue clinical PA criteria for all DPP-4 inhibitors and all GLP-1 receptor agonists.

Methods:
The July 2016 Drug Class Review on newer diabetes medications and combinations by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.[1]

The final original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:
In July 2016, DERP released a drug class update on newer diabetes medications in adults with T2DM. The report included 52 studies.[1] The review classified the amylin agonists, DDP-4 inhibitors, GLP-1 receptor agonists, and SGLT2 inhibitors as newer diabetes medications (Table 1).[1] Fixed-dose formulations and fixed-dosed regimens, administered as separate agents at the same time (defined as dual therapies), were also included. Patient characteristics were predominately middle-aged white women and men who were obese with a history of T2DM of less than 10 years and a baseline A1c of less than 9%.[1] No evidence, or insufficient evidence, was found for health outcomes (microvascular disease, macrovascular disease and all-cause mortality) comparisons *between* classes.[1]

Table 1. Newer Diabetes Medications Included in the DERP Review.[1]

Generic Name	Trade Name	Formulation
DPP-4 Inhibitors		
Sitagliptin	Januvia®	Oral
Saxagliptin	Onglyza®	Oral
Linagliptin	Tradjenta®	Oral
Alogliptin	Nesina®	Oral
GLP-1 Receptor Agonists		
Albiglutide	Tanzeum™	Injection
Dulaglutide	Trulicity®	Injection
Exenatide	Byetta®	Injection
Exenatide XR	Bydureon®	Injection
Liraglutide	Victoza®, Saxenda®	Injection
Sodium-glucose co-transporter-2 inhibitor (SGLT2)		
Canagliflozin	Invokana®	Oral
Dapagliflozin	Farxiga®	Oral
Empagliflozin	Jardiance®	Oral
Fixed Dose Combination Products (FDCPs)		
Alogliptin + Pioglitazone	Oseni	Oral
Metformin + Sitagliptin	Janumet®	Oral
Metformin + Sitagliptin XR	Janumet XR®	Oral
Metformin ER + Saxagliptin	Kombiglyze XR®	Oral
Metformin + Alogliptin	Kazano®	Oral
Metformin + Linagliptin	Jentadueto®	Oral
Metformin + Canagliflozin	Invokamet®	Oral
Metformin + Empagliflozin	Synjardy®	Oral
Metformin ER + Dapagliflozin	Xigduo XR®	Oral
Empagliflozin + Linagliptin	Glyxambi®	Oral

Within Class Comparisons:

GLP-1 Receptor Agonists

- Exenatide XR was found to be more effective at lowering A1c compared to exenatide (weighted mean difference [WMD] -0.46%; 95% CI, -0.69 to -0.23%) based on moderate evidence from 3 studies.[1]
- Single study comparisons are listed below in Table 2.

Table 2. Within Class Comparisons of GLP-1 Receptor Agonists.[1]

Comparators	Trial Duration	Outcome	Results	Strength of Evidence
Liraglutide 1.8 mg once daily vs. exenatide 10 mcg twice daily	26 weeks	A1c lowering	MD -0.33%; 95% CI, -0.47 to -0.18; P<0.0001	Low
Exenatide 5-10 mcg twice daily vs. Dulaglutide 0.75 mg or 1.5 mg once weekly	26 weeks	A1c <7%	Exenatide: 52% Dulaglutide 0.75 mg: 66% (P < 0.001) Dulaglutide 1.5 mg: 78% (P < 0.001)	Low
Albiglutide 30-50 mg once weekly vs. Liraglutide 0.6 to 1.8 mg once daily	32 weeks	A1c lowering A1c <7%	Albiglutide: -0.79% Liraglutide: -0.99% RR 1.23; 95% CI, 1.06 to 1.42	Low Low
Abbreviations: A1c – hemoglobin A1c; MD – mean difference				

- Liraglutide was associated with more weight loss than dulaglutide and albiglutide. Exenatide and dulaglutide 1.5 mg had similar weight loss with a difference of -0.24 kg. Dulaglutide 0.75 mg was associated with more weight loss compared to exenatide (mean difference [MD] 1.27 kg; P<0.001).[1]
- No difference in adverse events or withdrawals were found in within class comparisons of GLP-1 receptor agonists.[1]
- Evidence was imprecise for the incidence of gastrointestinal (GI) effects with dulaglutide and exenatide. One trial showed less GI effects with dulaglutide 0.75 mg compared with exenatide; however, higher strengths of dulaglutide were not found to have any differences in incidence of GI adverse events compared to exenatide.[1]

DPP-4 Inhibitors

- Sitagliptin and saxagliptin were associated with similar A1c lowering (-0.62% and -0.52% over 18 weeks and -1.07% and -1.34% over 24 weeks, respectively).[1]
- Low strength evidence did not find differences in adverse events or withdrawals between the different DPP-4 inhibitors in studies lasting 18 to 24 weeks. Hypoglycemia rates were higher with saxagliptin compared to sitagliptin (3.2% vs. 2.8%, respectively).[1]

Between Class Comparisons

DPP-4 Inhibitors vs. GLP-1 Receptor Agonists

- Low strength evidence for comparisons between DDP-4 inhibitors and GLP-1 receptor agonists comes from 8 trials. Specific comparisons are presented in Table 3. Overall, more A1c lowering was seen with GLP-1 receptor agonists compared to DPP-4 inhibitors.[1]

Table 3. Between Class Comparisons between DPP-4 Inhibitors vs. GLP-1 Receptor Agonists.[1]

Comparators	Trial Duration	Outcome	Results	Strength of Evidence
Exenatide XR vs. sitagliptin 100 mg*	26 weeks	A1c lowering	WMD -0.48; 95% CI -0.69 to -0.26	Low
Exenatide 10 mcg vs. sitagliptin 100 mg	24 weeks	A1c lowering	No difference	Insufficient
Liraglutide 1.2-1.8 mg vs. sitagliptin 100 mg	26 weeks	A1c lowering	Liraglutide 1.2 mg: -1.24% Liraglutide 1.8 mg: -1.5% Sitagliptin: -0.6% L1.2 vs. S: - 0.34% (95% CI, -0.51 to -0.16; p<0.0001) L1.8 vs. S: - 0.60% (95% CI, -0.77t o -0.43; p<0.001)	Low
Liraglutide 1.2 mg vs. sitagliptin 100 mg	24 weeks	A1c lowering	Liraglutide: -1.4% Sitagliptin: -1.3%	Low
Albiglutide 30 mg vs. sitagliptin 100 mg	104 weeks	A1c lowering	Albiglutide: -0.63% Sitagliptin: 0.28% P<0.001	Low
Liraglutide 1.2 mg vs. saxagliptin 5 mg	24 weeks	A1c lowering	Liraglutide: -1.5% Saxagliptin: -1.23%	Low
Dulaglutide 0.75 mg vs. sitagliptin 100 mg Dulaglutide 1.5 mg vs. sitagliptin 100 mg	104 weeks	A1c <7%	Dulaglutide 0.75: 45% Dulaglutide 1.5: 54% Sitagliptin: 31% D 0.75 vs. S: RR 1.44 (95% CI, 1.17 to 1.77) D 1.5 vs. S: RR 1.75 (95% CI, 1.44 to 2.12)	Low
*Pooled data Abbreviations: A1c – hemoglobin A1c; WMD – weighted mean difference				

- There was consistently more weight loss with GLP-1 receptor agonists compared to DPP-4 inhibitors.[1]
- Exenatide XR was associated with more withdrawals due to adverse events than sitagliptin 100 mg and more GI effects based on low strength evidence.[1]
- Liraglutide 0.9 mg, 1.2 mg and 1.8 mg were associated with an increased incidence of any adverse event versus comparators (moderate strength evidence). More withdrawals due to adverse events and GI events were found with linagliptin compared to sitagliptin 100 mg (59% vs. 48%, respectively).[1]
- Low strength evidence found albiglutide 30 mg and sitagliptin 100 mg to have similar rates of adverse events and withdrawals. However, albiglutide was associated with more nausea (12% vs. 7%) and diarrhea (15% vs. 9%).[1]
- Sitagliptin and dulaglutide were found to have similar rates of hypoglycemia and withdrawals due to adverse events. However, low strength of evidence found dulaglutide to have an increased incidence of GI adverse events (35% vs. 17%).[1]

DPP-4 Inhibitors vs. SGLT2 Inhibitors

- A systematic review found canagliflozin 300 mg to be more effective at A1c lowering than sitagliptin 100 mg (MD -0.24%; 95% CI, -0.40 to -0.09) based on moderate strength of evidence.[1]
- A pooled analysis of 2 studies that compared canagliflozin 100 mg to sitagliptin 100 mg found low strength of evidence that canagliflozin was associated with a higher incidence of patients who obtained a goal A1c of less than 7% (RR 1.20; 95% CI, 1.07 to 1.33).[1]
- Comparison of empagliflozin and sitagliptin did not find any difference in A1c lowering; however, more weight loss was found in the empagliflozin group (pooled data from 2 studies) based on moderate strength of evidence.[1]
- Moderate strength of evidence from pooled data of 2 studies that empagliflozin 25 mg improves the chance of obtaining an A1c less than 7% compared to linagliptin 5 mg (OR 3.3; 95% CI, 1.9 to 4.6). Results were similar for empagliflozin 10 mg compared to linagliptin 5 mg.[1]
- Dapagliflozin 10 mg was found to be similar in efficacy to saxagliptin 5 mg in one small study based on low strength evidence.[1]
- Adverse events and withdrawals due to adverse events were similar between canagliflozin 300 mg and sitagliptin 100 mg, between empagliflozin 25 mg and sitagliptin 100 mg, and between dapagliflozin and sitagliptin 100 mg.[1]
- Moderate strength evidence found canagliflozin to be associated with increased risk for genital mycotic infections (RR 4.20; 95% CI, 2.51 to 7.03). Hypoglycemia rates were similar based on low strength of evidence.[1]
- Genital mycotic infections were 4-times more common with empagliflozin compared to sitagliptin (3.5% vs. 0.7%). Dapagliflozin was also found to have increased genital mycotic infections compared to saxagliptin (6% vs. 0.6%; RR 9.83, 95% CI, 1.27 to76).[1]

Newer Diabetes Medications Compared with Metformin

DPP-4 Inhibitors vs. Metformin

- 12 studies compared DDP-4 inhibitors to metformin. Metformin was found to be more effective in A1c lowering compared to DPP-4 inhibitors (Table 4).[1]

Table 4. Between Class Comparisons between DPP-4 Inhibitors and Metformin[1]

Comparators	Trial Duration	Outcome	Result1	Strength of Evidence
Metformin 2000 mg* vs. linagliptin 5 mg	24 weeks	A1c lowering	MD -0.60%; 95% CI, -0.32 to -0.88%	Moderate
Metformin 2000 mg* vs. alogliptin 12.5 mg	26 weeks	A1c lowering	MD -0.55%; 95% CI, -0.29 to -0.81%	Moderate
Metformin 2000 mg vs. sitagliptin 100 mg^	24-52 weeks	A1c lowering	WMD -0.30%; 95% CI -0.52 to -0.09%	Moderate
* Metformin given as 1000 mg twice daily ^ Pooled analysis Abbreviations: A1c – hemoglobin A1c; MD – mean difference; WMD – weighted mean difference				

- Metformin 1000 mg (twice daily) was associated with greater weight loss compared to linagliptin 5 mg (MD -0.70 kg; 95% CI, -0.11 to -1.29%) but differences are unlikely to be clinically significant. Greater weight loss was also found with metformin in a comparison to alogliptin and sitagliptin.[1]

- Meta-analysis of 2 trials found no difference in A1c between increasing the dose of metformin (in patients on submaximal doses) compared to adding saxagliptin 5 mg (WMD -0.31, 95% CI, -0.74 to 0.13) based on low strength of evidence.[1]
- Up-titration of metformin was associated with greater weight loss compared to the addition of saxagliptin 5 mg with a between group difference of -0.9 kg.[1]
- Metformin compared to linagliptin, alogliptin, and saxagliptin all had similar risk of withdrawals due to adverse events.[1]
- Hypoglycemia rates were higher with linagliptin and saxagliptin compared with metformin.[1]

GLP-1 Receptor Agonists vs. Metformin

- Low strength of evidence from one trial found dulaglutide 1.5 mg resulted in more patients obtaining an A1c less than 7% compared to metformin (RR 1.16; 95% CI, 1.01 to 1.34) with no difference in weight change between the groups.[1]
- Hypoglycemia was more common with exenatide compared to metformin (12% vs. 3.2%, respectively; $p<0.05$). Similar rates of withdrawals due to adverse events were seen with exenatide XR and metformin.[1]
- Low strength of evidence found dulaglutide and metformin have similar risk of overall adverse events and withdrawals due to adverse events.[1]

SGLT2 Inhibitors vs. Metformin

- Comparisons between dapagliflozin and metformin found more A1c lowering with dapagliflozin (WMD -0.12%, 95% CI, -0.16 to -0.08%). A second trial found similar results when comparing dapagliflozin to metformin XR (WMD -0.11%, 95% CI, -0.11 to -0.0%5). Changes in A1c are too small to be clinically significant.[1]
- A meta-analysis of 2 studies found dapagliflozin 5 mg resulted in greater weight loss compared to metformin XR 1,500-2,000 mg/day (WMD -1.18 kg; 95% CI, -1.86 to -0.26).[1] Dapagliflozin 10 mg, as compared to metformin 1,500-2,000 mg, was also associated with more weight (WMD -1.3 kg; 95% CI, -1.8 to -0.7 kg).[1]
- Empagliflozin and canagliflozin comparisons to metformin found similar A1c reduction and number of patients who obtained an A1c of less than 7% based on low strength of evidence. More weight loss was experienced in the empagliflozin group compared to metformin in trials of 52 weeks duration. Canagliflozin was also associated with more weight loss compared to metformin (-3.9 kg vs. -2.1 kg, respectively).[1]
- Metformin XR, dapagliflozin 5 mg, and dapagliflozin 10 mg had overall similar incidence of adverse events or withdrawals due to adverse events based on low strength of evidence. Low strength evidence of metformin compared to empagliflozin 25 mg also found similar risks of overall adverse events or withdrawals due to adverse events.[1]

Fixed-dose Combination Products or Dual Therapy

- Greater A1c lowering was found when dual therapy (individual medications taken together) or fixed-dose combinations were initiated in patients not controlled on metformin monotherapy compared to component monotherapy.[1]

Table 5. Fixed-dose Combinations or Dual Therapy Product Comparisons for DPP-4 Inhibitors[1]

Comparators	Trial Duration	Outcome	Results	Strength of Evidence
Alogliptin 12.5 mg/pioglitazone 30 mg* vs. pioglitazone 30 mg Alogliptin 25 mg/pioglitazone 30 mg* vs. pioglitazone 30 mg Alogliptin 25 mg/pioglitazone 30* mg vs. alogliptin 25 mg	26 weeks	A1c lowering	Alo 12.5/Pio: -1.56% vs. Pio: -1.15% (P<0.05) Alo 25/Pio: -1.71% vs. Pio: -1.15% (P<0.05) Alo 25/Pio: - 1.71% vs. Alo: -0.96% (P<0.05)	Low
Alogliptin 12.5 mg/metformin 500 mg twice daily† vs. alogliptin 25 mg daily Alogliptin 12.5 mg/metformin 500 mg twice daily† vs. metformin 500 mg twice daily Alogliptin 12.5 mg/metformin 1000 mg twice daily† vs. alogliptin 12.5 mg daily Alogliptin 12.5 mg/metformin 1000 mg twice daily† vs. metformin 1000 mg daily	26 weeks	A1c lowering	Alo/Met: -1.22% vs. Alo: -0.52% (P<0.001) Alo/Met: -1.22% vs. Met: -0.65% (P<0.001) Alo/Met: -1.55% vs. Alo: -0.56% (P<0.001) Alo/Met:-1.55% vs. Met: -1.11% (P<0.001)	Moderate
Linagliptin 2.5 mg/metformin 500 mg twice daily* vs. linagliptin 5 mg once daily Linagliptin 2.5 mg /metformin 500 mg twice daily* vs. metformin 500 mg twice daily Linagliptin 2.5 mg/metformin 1000 mg twice daily* vs. linagliptin 5 mg daily Linagliptin 2.5 mg/metformin 1000 mg twice daily* vs. metformin 1000 mg twice daily	26 weeks	A1c lowering	MD -0.70%; 95% CI, -0.98 to -0.42 MD -0.60%; 95% CI, -0.88 to -0.32 MD -1.10%; 95% CI, -1.38 to -0.82 MD -0.50%; 95% CI, -0.78 to -0.22	Moderate Moderate Moderate Moderate
Linagliptin 5 mg/metformin 1500 to 2000 mg once daily* vs. linagliptin 5 mg daily	24 weeks	A1c lowering	MD -0.8%; 95% CI, -1.1 to -0.5%	Moderate
Sitagliptin 100 mg/metformin 1000 mg versus metformin^*†	24-104 weeks	A1c lowering	WMD -0.60%; 95% CI, -0.75 to -0.45	Moderate

^ Pooled data
* Dual therapy
† Fixed-dose combination
Abbreviations: A1c – hemoglobin A1c; MD – mean difference; WMD – weighted mean difference

- Moderate evidence found alogliptin 12.5 mg/metformin 1000 mg resulted in greater weight reductions than alogliptin 12.5 mg twice daily.[1]
- Low strength of evidence found imprecise results for linagliptin plus metformin versus comparators for weight changes. One study found no differences while a second study found evidence for greater weight loss in the combination group.[1]
- Weight changes were similar between sitagliptin/metformin compared to component monotherapy.[1]
- Low strength of evidence found withdrawal rates due to adverse events ranged from 1.8% to 9.6% with fixed-dose alogliptin/metformin and dual therapy of metformin and alogliptin. Metformin at the highest doses were found to be associated with higher rates of hypoglycemia.[1]
- Withdrawal rates due to adverse events and adverse events were similar between fixed-dose linagliptin and metformin and dual therapy with linagliptin and metformin.[1]
- Sitagliptin and metformin dual therapy and fixed-dose treatment were associated with similar rates of adverse events and low incidence of hypoglycemia.[1]

SGLT2 Inhibitor Combinations

Table 6. Dual Combination Product Comparisons for SGLT2 Inhibitors.[1]

Comparators	Trial Duration	Outcome	Results	Strength of Evidence
Canagliflozin 100 mg/metformin vs. metformin Canagliflozin 300 mg/metformin vs. metformin Canagliflozin 100 mg/metformin vs. canagliflozin 100 mg Canagliflozin 300 mg/metformin vs. canagliflozin 300 mg	26 weeks	A1c lowering	MD -0.46%; 95% CI, -0.66 to -0.27 MD -0.48%; 95% CI, -0.67 to -0.28 MD -0.40%; 95% CI, -0.59 to -0.21 MD -0.36%; 95% CI, -0.56 to -0.17	Low
Empagliflozin 25 mg/linagliptin 5 mg vs. linagliptin 5 mg Empagliflozin 25 mg plus/linagliptin 5 mg vs. empagliflozin 5 mg	24 weeks	A1c lowering	MD -0.41%; 95% CI, -0.61 to -0.22 MD -0.14%; 95% CI, -0.33 to -0.06	Moderate

- In canagliflozin/metformin comparisons, combination therapy resulted in more weight loss compared to metformin monotherapy, with differences that ranged from -1.2 kg to -2.0 kg based on low strength evidence.[1]
- Empagliflozin 25 mg plus linagliptin 5 mg resulted in more weight loss compared to linagliptin alone (MD -1.2 kg; 95% CI, -2.2 to -0.2 kg). However, combination therapy compared to empagliflozin alone resulted in similar weight loss. Results were similar for empagliflozin 10 mg and linagliptin 5 mg compared to their monotherapy components.[1]
- Empagliflozin and linagliptin fixed-dose therapy compared to their monotherapy components did not find any differences in rates of adverse events, withdrawals due to adverse events or hypoglycemia risk based on low strength of evidence.[1]

Subgroup Analysis

- Gender had no influence on risk of genital mycotic infections in studies that compared SGLT2 inhibitors and DPP-4 inhibitors.[1]
- Use of albiglutide and sitagliptin in patients with renal impairment found A1c lowering was greater with albiglutide compared to sitagliptin (-0.83% vs. -0.52%, respectively) with no difference in risk of adverse reactions, withdrawals due to adverse events or hypoglycemia (after controlling for sulfonylurea use).[1]

New Safety Alerts

In August 2015, the FDA issued a warning that DPP-4 inhibitors (saxagliptin, sitagliptin, linagliptin, and alogliptin) may cause severe and disabling joint pain.[3] The warning prompted labeling changes for the DPP-4 inhibitor prescribing information. Symptoms appeared 1 day to years after initiation of a DPP-4 inhibitor. Upon discontinuation of the DPP-4 inhibitor, symptom resolution occurred in a month or less. Recurrence of joint pain was noted in some patients resuming therapy with the same or another DPP-4 inhibitor.

A FDA safety warning was issued in May 2016 for the increased risk of leg and foot amputations with canagliflozin.[4] The warning is a result of increased amputations associated with canagliflozin use during an ongoing clinical trial in which initial results suggest the risk of amputations over a 1-year period were 7/1,000 for canagliflozin 100 mg; 5/1,000 for canagliflozin 300 mg; and 3/1,000 patients treated with placebo. The FDA is continuing to investigate this association.

In June of 2016, the FDA issued warnings of acute kidney injury (AKI) for 2 SGLT2 inhibitors, canagliflozin and dapagliflozin.[5] One hundred and one cases of AKI, some cases requiring hospitalization and dialysis, have been identified. Acute kidney injury occurred within 1 month of starting the drug in approximately half of the cases. Patients with conditions that may predispose them to increased risk of AKI should be evaluated before starting canagliflozin or dapagliflozin. Co-morbidities include decreased blood volume; chronic kidney disease; heart failure; and use of some common medications (i.e., diuretics, ACE inhibitors, ARBs and NSAIDs). Renal function tests are recommended before initiating therapy and should be rechecked periodically throughout therapy.

New Formulations or Indications

Jentadueto XR (linagliptin and metformin)

This fixed-dose combination of linagliptin and metformin was originally approved in 2012 and then approved as an extended-release formulation in 2016.[6] The combination can be given once a day in doses of up to 5 mg linagliptin and 2000 mg metformin. Four double-blind, randomized, placebo-controlled studies of the once daily formulation (given as separate medications) were used for FDA approval. In a 24-week study of treatment-naïve patients with high baseline A1c (mean 9.9%), metformin 1500-2000 mg daily and linagliptin 5 mg daily decreased A1c -2.9% from baseline compared to linagliptin and placebo with a -2% decrease (MD -0.8%; 95% CI, -1.23% to -0.45%; $p<0.0001$). A second 24-week study added linagliptin 5 mg or placebo to patients with uncontrolled A1c levels on metformin at a dose of at least 1500 mg per day. Linagliptin and metformin were found to decrease A1c more than placebo and metformin (MD -0.6%; 95% CI, -0.8% to -0.5%). The number of patients who achieved an A1c goal of less than 7% was also higher in the linagliptin and metformin group compared to the placebo and metformin group (26% and 9%, respectively). No differences in weight loss were observed between the groups. In a 104-week non-inferiority study, linagliptin 5 mg or glimepiride 1-4 mg per day was added to patients with uncontrolled glycaemia despite metformin therapy.[6] The linagliptin/metformin combination was less effective in lowering A1c compared to glimepiride/metformin with a mean difference in A1c at week 52 and week 104 of 0.2% (95% CI, 0.1% to 0.3%). The fourth study was a 24-week comparison of linagliptin 5 mg, metformin and a sulfonylurea compared to placebo, metformin and a sulfonylurea. Change in A1c favored the linagliptin group compared to the placebo combination (MD -0.6%; 95% CI, -0.7% to -0.5%). Twenty-nine percent of patients in the linagliptin group obtained an A1c less than 7% compared to 8% in the placebo combination group. Body weight changes were not significantly different between groups. Nasopharyngitis and diarrhea were more commonly experienced (≥5%) in the linagliptin/metformin group compared to placebo.[6]

Randomized Controlled Trials

No additional randomized controlled trials provided evidence to prompt changes to current policy.

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6. Jentadueto XR. Ridgefield CT, Boehringer Ingelheim Pharmaceuticals, Inc. May 2016.

Appendix 1: Current Status on Preferred Drug List

GLP-1 RECEPTOR AGONISTS

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-CUT	PEN INJCTR	BYETTA	EXENATIDE	Y
SUB-CUT	PEN INJCTR	VICTOZA 3-PAK	LIRAGLUTIDE	N
SUB-CUT	VIAL	BYDUREON	EXENATIDE MICROSPHERES	N
SUB-CUT	PEN INJCTR	BYDUREON PEN	EXENATIDE MICROSPHERES	N
SUB-CUT	PEN INJCTR	TANZEUM	ALBIGLUTIDE	N
SUB-CUT	PEN INJCTR	TRULICITY	DULAGLUTIDE	N

DPP-4 INHIBITORS

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	JANUMET	SITAGLIPTIN PHOS/METFORMIN HCL	Y
ORAL	TABLET	JANUVIA	SITAGLIPTIN PHOSPHATE	Y
ORAL	TABLET	GLYXAMBI	EMPAGLIFLOZIN/LINAGLIPTIN	N
ORAL	TABLET	JENTADUETO	LINAGLIPTIN/METFORMIN HCL	N
ORAL	TABLET	KAZANO	ALOGLIPTIN BENZ/METFORMIN HCL	N
ORAL	TABLET	NESINA	ALOGLIPTIN BENZOATE	N
ORAL	TABLET	ONGLYZA	SAXAGLIPTIN HCL	N
ORAL	TABLET	OSENI	ALOGLIPTIN BENZ/PIOGLITAZONE	N
ORAL	TABLET	TRADJENTA	LINAGLIPTIN	N
ORAL	TBMP 24HR	JANUMET XR	SITAGLIPTIN PHOS/METFORMIN HCL	N
ORAL	TBMP 24HR	KOMBIGLYZE XR	SAXAGLIPTIN HCL/METFORMIN HCL	N

SGLT-2 INHIBITORS

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TAB BP 24H	XIGDUO XR	DAPAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	FARXIGA	DAPAGLIFLOZIN PROPANEDIOL	N
ORAL	TABLET	GLYXAMBI	EMPAGLIFLOZIN/LINAGLIPTIN	N
ORAL	TABLET	INVOKAMET	CANAGLIFLOZIN/METFORMIN HCL	N
ORAL	TABLET	INVOKANA	CANAGLIFLOZIN	N
ORAL	TABLET	JARDIANCE	EMPAGLIFLOZIN	N
ORAL	TABLET	SYNJARDY	EMPAGLIFLOZIN/METFORMIN HCL	N

Glucagon-like Peptide-1 (GLP-1) Receptor Agonists

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All GLP-1 receptor agonists

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #4

Approval Criteria		
4. Has the patient tried and failed metformin and sulfonylurea therapy or have contraindications to these treatments? (document contraindication, if any)	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness. Recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

Initiating Metformin

1.	Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
2.	After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
3.	If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
4.	The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T/DUR Review: *9/16 (KS); 9/15; 1/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *10/15; 2/15; 1/14*

Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 12 months

Requires PA:
- All DPP-4 inhibitors

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Author: Sentena Date: September 2016

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code	
2. Does the patient have a diagnosis of Type 2 diabetes mellitus?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Has the patient tried and failed metformin and a sulfonylurea, or have contraindications to these treatments? (document contraindication, if any)	**Yes:** Go to #4	**No:** Pass to RPh; deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.
4. Will the prescriber consider a change to a preferred product? <u>Message</u>: • Preferred products do not require a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Approve for up to 12 months

Initiating Metformin

5. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
6. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
7. If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
8. The maximum effective dose can be up to 1,000 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T/DUR Review: *9/16 (KS); 9/15; 9/14; 9/13; 4/12; 3/11*
Implementation: *10/15; 1/15; 9/14; 1/14; 2/13*

Sodium-Glucose Cotransporter-2 Inhibitors (SGLT-2 Inhibitors)

Goal(s):
- Promote cost-effective and safe step-therapy for management of type 2 diabetes mellitus (T2DM).

Length of Authorization:
- Up to 6 months

Requires PA:
- All SGLT-2 inhibitors

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	**Yes:** Go the **Renewal Criteria**	**No:** Go to #2
2. What diagnosis is being treated?	Record ICD10 code	
3. Does the patient have a diagnosis of T2DM?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient tried and failed metformin and a sulfonylurea, have contraindications to these treatments or is requesting a SGLT-2 inhibitor to be used with metformin and a sulfonylurea? (document contraindication, if any)	**Yes:** Go to #5	**No:** Pass to RPh. Deny and recommend trial of metformin or sulfonylurea. See below for metformin titration schedule.

Approval Criteria		
5. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <60 mL/min/ 1.73 m^2?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #6
6. Has the patient tried and failed (unable to maintain goal A1c) all of the following drugs, or have contraindications to all of these drugs? 1. Insulin 2. Thiazolidinedione 3. DPP-4 inhibitor 4. GLP-1 receptor agonist 5. Amylin analog	**Yes:** Approve for up to 6 months	**No:** Pass to RPh. Deny and require a trial of insulin, thiazolidinedione, DPP-4 inhibitor, GLP-1 agonist, and amylin analog.

Renewal Criteria		
1. Is the request for the following treatments (including combination products) with an associated estimated glomerular filtration rate (eGFR): • Canagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Empagliflozin and eGFR <45 mL/min/ 1.73 m^2, or • Dapagliflozin and eGFR <60 mL/min/ 1.73 m^2?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Approve for up to 6 months

Initiating Metformin

9. Begin with low-dose metformin (500 mg) taken once or twice per day with meals (breakfast and/or dinner) or 850 mg once per day.
10. After 5-7 days, if gastrointestinal side effects have not occurred, advance dose to 850 mg, or two 500 mg tablets, twice per day (medication to be taken before breakfast and/or dinner).
11. If gastrointestinal side effects appear with increasing doses, decrease to previous lower dose and try to advance the dose at a later time.
12. The maximum effective dose can be up to 1,000 mg twice per day but is often 850 mg twice per day. Modestly greater effectiveness has been observed with doses up to about 2,500 mg/day. Gastrointestinal side effects may limit the dose that can be used.

Nathan, et al. Medical management of hyperglycemia in Type 2 Diabetes: a consensus algorithm for the initiation and adjustment of therapy. *Diabetes Care*. 2008; 31;1-11.

P&T Review: *9/16 (KS); 3/16; 9/15; 1/15; 9/14; 9/13*
Implementation: *2/3/15; 1/1/14*

Drug Class Review

Newer Diabetes Medications and Combinations

Final Update 2 Report
Executive Summary

July 2016

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Shelley Selph, MD, MPH
Ian Blazina, MPH
Ines Guttmann-Bauman, MD
Brittany Holzhammer, MPH

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

INTRODUCTION

Diabetes mellitus (diabetes) is a chronic disease associated with significant morbidity and healthcare costs. The prevalence of diabetes among adults has increased substantially over the past 2 decades. Among people diagnosed with diabetes, 90% to 95% have type 2 diabetes, while 5% to 10% have type 1 diabetes. Type 1 diabetes is characterized by autoimmune destruction of beta cells of the pancreas resulting in absolute insulin deficiency. Type 2 diabetes encompasses a heterogeneous group of disorders characterized by slow progressive loss of beta cell function and mass, leading to variable degrees of insulin resistance, impaired insulin secretion, and increased hepatic glucose production. Higher glucagon levels relative to insulin also play a significant role in the pathogenesis and management of type 2 diabetes.

The 2016 American Diabetes Association treatment guidelines recommend an HbA1c goal of <7% for most nonpregnant adults in order to prevent adverse microvascular and macrovascular outcomes. The guidelines acknowledge that less stringent (HbA1c <8%) or more stringent (HbA1c <6.5%) goals may be appropriate for certain populations. Insulin is the standard treatment for type 1 diabetes. Pharmacologic options for type 2 diabetes include sulfonylureas, biguanides, thiazolidinediones, meglitinides, alpha-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) analogs, sodium-glucose cotransporter 2 (SGLT2) inhibitors, combination products, and insulin.

Within recent years, several new antihyperglycemic agents have been approved (Table A). These agents offer mechanisms of glycemic control beyond that of "traditional" oral agents and insulin by targeting alternate gluco-regulatory receptors and hormones such as amylin, GLP-1, glucose-dependent insulinotropic peptide (GIP), DPP-4, and sodium-glucose cotransporter 2 (SGLT2). For the purposes of this report, we consider the following to be "newer diabetes medications": amylin agonists, DPP-4 inhibitors, GLP-1 analogs, and SGLT2 inhibitors.

For this report, we've included 10 fixed-dose combination products (FDCPs) approved for the treatment of type 2 diabetes. In addition, we've included studies of the individual components of those FDCPs when used together but in separate pills—we refer to this as "dual therapy" throughout the review. We only evaluate dual therapy when there is a US Food and Drug Administration-approved fixed dose combination product.

Table A. Characteristics of included drugs

Class	Generic Name	Trade Name	Delivery
DPP-4 Inhibitors	Sitagliptin	Januvia®	Oral
	Saxagliptin	Onglyza®	Oral
	Linagliptin	Tradjenta®	Oral
	Alogliptin	Nesina®	Oral
GLP-1 Analogs (Incretin mimetics)	Albiglutide	Tanzeum™	Injection
	Dulaglutide	Trulicity®	Injection
	Exenatide	Byetta®	Injection
	Exenatide XR	Bydureon®	Injection
	Liraglutide	Victoza®, Saxenda®	Injection
Sodium-glucose co-transporter-2 inhibitor (SGLT2)	Canagliflozin	Invokana®	Oral
	Dapagliflozin	Farxiga®	Oral
	Empagliflozin	Jardiance®	Oral
Fixed Dose Combination Products (FDCPs)**	Alogliptin + Pioglitazone	Oseni	Oral
	Metformin + Sitagliptin	Janumet®	Oral
	Metformin + Sitagliptin XR	Janumet XR®	Oral
	Metformin ER + Saxagliptin	Kombiglyze XR®	Oral
	Metformin + Alogliptin	Kazano®	Oral

Class	Generic Name	Trade Name	Delivery
	Metformin + Linagliptin	Jentadueto®	Oral
	Metformin + Canagliflozin	Invokamet®	Oral
	Metformin + Empagliflozin	Synjardy®	Oral
	Metformin ER+ Dapagliflozin	Xigduo XR®	Oral
	Empagliflozin + Linagliptin	Glyxambi®	Oral

**The FDCPs or the individual components of those FDCPs used together but in separate pills (AKA dual therapy) are both included in the review

Scope and Key Questions

We compare the efficacy and tolerability of newer diabetes medications and combinations, and also look for subgroups that may differ in these areas. Representatives of organizations participating in the Drug Effectiveness Review Project approved the following key questions to guide this review:

1. What is the comparative efficacy and effectiveness of newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) for adults with type 2 diabetes mellitus?

2. What is the comparative tolerability and frequency of adverse events for newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) for adults with type 2 diabetes mellitus?

3. Are there subgroups of patients based on demographics (e.g. age, racial groups, gender), comorbidities (e.g., drug-disease interactions, obesity), or other medications (drug-drug interactions) for which newer diabetes medications and drug combinations (administered as fixed dose combination products or dual therapy) differ in efficacy/effectiveness or tolerability and frequency of adverse events?

METHODS

Inclusion Criteria

Populations

- Adults with type 2 diabetes
- *Excluded: Children, individuals with Type 1 diabetes, individuals with gestational diabetes, pre-diabetes (impaired fasting glucose or impaired glucose tolerance), metabolic syndrome without diabetes, or polycystic ovary syndrome*

Interventions

"Newer diabetes medications" refer to DPP-4 inhibitors, GLP-1 analogs, and SGLT2 inhibitors (see Table A).

Comparators

- Other newer diabetes medications, fixed dose combination products containing a newer diabetes medication, metformin, or dual therapy with 1 or more newer diabetes medications

- Add-on therapy to any other diabetes medication

Efficacy and Effectiveness Outcomes

- Intermediate outcomes:
    1. Hemoglobin A1c (differences and proportions meeting targets)
    2. Changes in weight
- Health outcomes:
    1. Microvascular disease: chronic kidney disease including renal dialysis, renal transplantation, end-stage renal disease and renal failure with proteinuria; retinopathy including proliferative retinopathy and blindness; peripheral neuropathy
    2. Macrovascular disease: cardiovascular events, cardiovascular morbidity (e.g. myocardial infarction and peripheral arterial disease), cardiovascular mortality, stroke/TIA, coronary heart disease, cardiovascular procedures, extremity amputation
    3. All-cause mortality

Harms/Adverse Events Outcomes

- Overall adverse events
- Withdrawals due to adverse events
- Serious adverse events (e.g., diabetic ketoacidosis, non-ketotic hyperosmolar coma)
- Specific adverse events (e.g., cancers/neoplasms, infections, hypoglycemia, gastrointestinal effects, congestive heart failure, pancreatitis, weight gain, fractures)

Study Designs

- Good-quality systematic reviews
- Head-to-head randomized controlled trials for all outcomes (any size)
- For harms only, head-to-head prospective cohort and case-control studies (N≥100)

Duration

- For all study designs and all key questions ≥12 weeks

We followed standard DERP methods for literature searching, study selection, data abstraction, validity assessment, data synthesis, and grading the strength of the body of evidence. Detailed methods can be found in the full report. To identify relevant citations, we searched electronic databases through February Week 1 2016 using terms for included drugs, indications, and study designs (see Appendix C of the full report for complete search strategies). We also requested dossiers of published and unpublished information from the relevant pharmaceutical companies.

RESULTS

Table B. Summary of evidence by Key Question

Key Question 1.
What is the comparative efficacy and effectiveness of newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?
Key Question 2.
What is the comparative tolerability and frequency of adverse events for newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?

Strength of evidence[a]	Conclusions
Within Class Comparisons: Saxagliptin vs. Sitagliptin	
Low	Two trials (n=801 and 139) found no difference between sitagliptin and saxagliptin for reducing HbA1c or in the proportion of patients achieving an HbA1c <7% over 18 and 24 weeks.
Insufficient	Evidence was insufficient to determine the comparative efficacy of sitagliptin and saxagliptin for reducing weight.
Moderate	Rates of adverse events were similar between groups over 18 or 24 weeks.
Low	Rates of withdrawals due to adverse events were similar between groups over 18 or 24 weeks.
Within Class Comparisons: Exenatide XR vs. Exenatide	
Insufficient	Two trials (n=547) found no difference between exenatide XR and exenatide for improving cardiovascular events. One trial measured “myocardial infarction” and the other “fatal myocardial infarction.” (1 trial for each measurement; unknown consistency; imprecise findings).
Moderate	We pooled data from 3 trials (n=1,225) comparing exenatide XR with exenatide administered twice daily over 24 to 30 weeks. Exenatide XR was more efficacious in reducing mean HbA1c than exenatide twice daily: WMD −0.46% (95% CI −0.69 to −0.23).
Low	Three trials found no difference between exenatide XR and exenatide administered twice daily for weight changes over 24 to 30 weeks; 2 trials found no difference between groups and 1 trial found a small reduction in weight (−0.33 kg; *P*<0.001) favoring exenatide twice daily.
Low	There was no difference between groups for rates of withdrawals because of adverse events (3 trials, n=1,223, RR 0.72, 95% CI 0.35 to 1.50).
Within Class Comparisons: Exenatide vs. Liraglutide	
Low	In 1 trial (n=464), liraglutide 1.8 mg once daily reduced mean HbA1c more than exenatide 10 µg twice daily (between-group difference: −0.33%, 95% CI −0.47 to −0.18).
Insufficient	One trial (n=464) found no difference between exenatide and liraglutide 1.8mg for weight changes. Both drugs were associated with weight loss.
Low	In 1 trial, rates of withdrawal due to adverse events were similar between groups over 26 weeks.
Within Class Comparisons: Exenatide vs. Dulaglutide	
Low	One trial (n=976) compared exenatide with dulaglutide and reported that rates of achieving HbA1c <7% were significantly higher for dulaglutide 1.5 mg (78%) and 0.75 mg (66%) than exenatide (52%) (all *P*<0.001). Similarly, mean change in HbA1c was also significantly greater in patients receiving dulaglutide than those receiving exenatide (*P*<0.001).
Low	One trial (n=976) compared exenatide with dulaglutide, reporting no differences between groups were reported for overall adverse events.
Insufficient	One trial (n=976) compared exenatide with dulaglutide, reporting no differences between groups were reported for withdrawal due to adverse events, or specific adverse events.

Key Question 1.
What is the comparative efficacy and effectiveness of newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?
Key Question 2.
What is the comparative tolerability and frequency of adverse events for newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?

Strength of evidence[a]	Conclusions
Within Class Comparisons: Exenatide vs. Albiglutide	
Insufficient	One trial (n=66) reported no difference between groups in weight loss.
Insufficient	Evidence for HbA1c was insufficient.
Insufficient	One trial (n=66) compared albiglutide with exenatide, reporting no differences between groups were reported for overall adverse events, withdrawal due to adverse events, or specific adverse events.
Within Class Comparisons: Dulaglutide vs. Liraglutide	
Low	One trial (n=599) of dulaglutide compared with liraglutide found no differences in mean reduction in HbA1c or the proportion of patients achieving an HbA1c <7% (RR 1.01, 95% CI 0.90 to 1.12).
Low	Body weight was significantly reduced with liraglutide (treatment difference: 0.71 kg).
Low	No difference in rates of gastrointestinal events (36% vs. 36%; RR 1.00, 95% CI 0.81 to 1.24).
Insufficient	One trial (n=599) compared dulaglutide with liraglutide, reporting no differences between groups were reported for overall adverse events or withdrawal due to adverse events.
Within Class Comparisons: Albiglutide vs. Liraglutide	
Low	One trial (n=841) of albiglutide compared with liraglutide found that mean HbA1c reduction and the proportion of patients achieving HbA1c <7% was significantly greater with liraglutide (RR 1.23, 95% CI 1.06 to 1.42).
Low	Liraglutide was also associated with significantly more weight loss (treatment difference: 1.55 kg, 95% CI 1.05 kg to 2.06 kg).
Low	One trial (n=841) compared albiglutide to liraglutide, reporting no differences between groups were reported for overall adverse events.
Insufficient	One trial (n=841) compared albiglutide to liraglutide, reporting no differences between groups were reported for withdrawal due to adverse events.
Between Class Comparisons: Exenatide XR vs. Sitagliptin	
Low	Two trials (n=753) indicated greater reduction in HbA1c and greater proportions of patients achieving a HbA1c < 7% with exenatide XR compared with sitagliptin 100 mg (62% vs. 39%, RR 1.57, 95% CI 1.34 to 1.83)
Low	Exenatide XR treatment resulted in greater reduction in weight loss compared with sitagliptin (WMD −1.32, 95% CI −1.87 to −0.76)
Low	Increased withdrawals due to adverse events found with exenatide XR vs. sitagliptin (RR 2.61, 95% CI 1.03 to 6.61)
Low	Nausea (RR 2.62, 95% CI 1.66 to 4.15), vomiting (RR 3.67, 95% CI 1.63 to 8.24) and diarrhea (RR 1.91, 95% CI 1.22 to 3.00) increased with exenatide compared with sitagliptin
Between Class Comparisons: Liraglutide vs. Sitagliptin	
Low	One trial (n=665) found increased proportions of patients achieving a HbA1c <7% with liraglutide at both dosages (1.2 mg and 1.8 mg) compared with sitagliptin 100 mg once daily (liraglutide 1.2 mg: OR

Key Question 1.
What is the comparative efficacy and effectiveness of newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?
Key Question 2.
What is the comparative tolerability and frequency of adverse events for newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?

Strength of evidence[a]	Conclusions
	2.75, 95% CI 1.78 to 4.25; liraglutide 1.8 mg OR 4.50, 95% CI 2.90 to 6.97) at 26 weeks. At 52 weeks: OR 2.80 (95% CI 1.74 to 4.48) for liraglutide 1.2 vs. sitagliptin; OR 4.37 (95% CI 2.74 to 6.98) for liraglutide 1.8
Low	One trial (n=665) found liraglutide at both dosages (1.2 mg and 1.8 mg) to be more efficacious than sitagliptin 100 mg once daily in reducing weight at 26 and 52 weeks. Change in weight at 26 weeks: liraglutide 1.2 mg −2.86 kg, liraglutide 1.8 mg −3.38 kg; sitagliptin −0.96 kg; *P*<0.001 for both comparisons. Weight loss at 52 weeks −2.78 kg (liraglutide 1.2 mg), −1.8 (liraglutide 1.8 mg), −1.16 kg (sitagliptin), *P*<0.001; second trial (n=547) found similar results (liraglutide lowered weight by an average of 2.3 kg, 95% CI 1.8 to 2.9 more than treatment with sitagliptin)
Low	Gastrointestinal adverse events were more likely with liraglutide (RR 1.75, 95% CI 1.31 to 2.32)
Between Class Comparisons: Albiglutide vs. Sitagliptin	
Low	HbA1c was lowered more with albiglutide compared with sitagliptin at 104 weeks (0.63% vs. 0.28%, *P*<0.001) but there was no difference in proportion of patients achieving HbA1c <7% based on 1 trial (n=604)
Low	There were no differences between groups in weight loss at 24 weeks or 104 weeks from baseline.
Low	There were no differences between groups in withdrawal due to adverse events, having one or more adverse events, or having hypoglycemic event
Low	Diarrhea and nausea were more common with albiglutide (RR 1.64, 95% CI 1.06 to 2.56; RR 1.68, 95% CI 1.03 to 2.78)
Between Class Comparisons: Dulaglutide vs. Sitagliptin	
Low	Achieving HbA1c <7% was more likely with dulaglutide 0.75 mg and 1.5 mg compared with sitagliptin 100 mg at 26 weeks (n=230; 55% and 61% vs. 38%, *P*<0.001 for both comparisons) and at 104 weeks (n=1,098; RR 1.44, 95% CI 1.17 to 1.77; RR 1.75, 95% CI 1.44 to 2.12) based on one adaptive trial with a second randomization at 26 weeks.
Low	At 26 weeks weight loss was greater for both doses of dulaglutide compared with sitagliptin (*P*<0.001 for both comparisons) but at 104 weeks only dulaglutide 1.5 mg was associated with greater weight loss (*P*<0.05)
Low	There were no differences between dulaglutide and sitagliptin in withdrawal due to adverse events or in hypoglycemic events.
Low	Gastrointestinal events were more likely with dulaglutide at both 26 weeks (RR 1.84, 95% CI 1.38 to 2.46) and at 104 weeks (RR 1.44, 95% CI 1.19 to 1.74)
Between Class Comparisons: Liraglutide vs. Saxagliptin	
Low	There were no differences between treatment with liraglutide and saxagliptin in change in HbA1c levels based on 1 trial (n=121)
Low	Liraglutide resulted in greater weight loss compared with saxagliptin (−6 kg, 95% CI −6.8 to −5.3 vs. −0.9 kg, 95% CI −1.5 to −0.4)
Low	There were no differences between groups in study withdrawals due to adverse events and in hypoglycemic events.

Key Question 1.
What is the comparative efficacy and effectiveness of newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?
Key Question 2.
What is the comparative tolerability and frequency of adverse events for newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?

Strength of evidence[a]	Conclusions
Low	Liraglutide was associated with increased risk of experiencing any adverse event (RR 2.46, 95% CI 1.43 to 4.23) and nausea (RR 8.37, 95% CI 2.02 to 35)
Between Class Comparisons: Canagliflozin vs. Sitagliptin	
Moderate	There was moderate strength evidence based on a good quality systematic review (n=1,575) that canagliflozin 300 mg improved HbA1c values at 52 weeks by 0.24% (95% CI −0.40 to −0.09) versus sitagliptin. More patients also achieved HbA1c values < 7% at 52 weeks (RR 1.20, 95% CI 1.07 to 1.33)
Low	There was low strength evidence that treatment with canagliflozin 100 mg was less effective than sitagliptin at achieving a HbA1c <7% (RR 0.66, 95% CI 0.48 to 0.91) based on 1 trial (n=734)
Moderate	Treatment with canagliflozin was associated with greater weight loss than sitagliptin by 2.84 kg (95% CI 2.48 to 3.21)
Low	There were no differences between canagliflozin 300 mg and sitagliptin in study withdrawal due to adverse events, having one or more adverse events or having hypoglycemic events
Moderate	Genital mycotic infections were 4 times more likely with canagliflozin 300 mg than with sitagliptin (RR 4.20, 95% CI 2.51 to 7.03)
Between Class Comparisons: Empagliflozin vs. Sitagliptin	
Moderate	There were no differences between treatment with empagliflozin 25 mg and sitagliptin in achieving a HbA1c <7% based on 2 trials (n=1,003; RR 1.17, 95% CI 0.96 to 1.43); results were similar when treated with empagliflozin 10 mg (RR 0.88, 95% CI 0.70 to 1.10)
Moderate	Weight loss was greater with empagliflozin 25 mg (2.48 kg to 4.30 kg) and empagliflozin 10 mg (2.26 kg to 3.1 kg) compared with sitagliptin (0.4 kg loss to 0.18 kg gain), *P*<0.05 for all comparisons with sitagliptin
Moderate	There was moderate strength evidence of no difference between empagliflozin and sitagliptin in withdrawal due to adverse events (RR 0.77, 95% CI 0.31 to 1.90), having 1 or more adverse events (RR 1.06, 95% CI 0.95 to 1.19)
Low	There was no difference between empagliflozin and sitagliptin in hypoglycemic events based on 1 trial (n=388)
Moderate	Genital infections were more common with empagliflozin treatment than with sitagliptin (RR 3.99, 95% CI 1.08 to 14)
Between Class Comparisons: Empagliflozin vs. Linagliptin	
Moderate	There was moderate strength evidence based on 2 trials (n=767) that treatment with empagliflozin 25 mg increased the proportion of participants achieving HbA1c <7% at 24 weeks (OR 3.3, 95% CI 1.9 to 4.6) compared with linagliptin; results were similar with empagliflozin 10 mg (OR 3.3, 95% CI 1.9 to 4.7)
Moderate	Weight loss also favored empagliflozin 25 mg (2.0 kg to 3.0 kg) and empagliflozin 10 mg (2.6 kg to 2.7 kg) compared with linagliptin (0.7 kg to 0.8 kg), *P*<0.01 for comparisons with linagliptin
Moderate	There was moderate strength evidence of no difference between empagliflozin and linagliptin in withdrawal due to adverse events (RR 1.99, 95% CI 0.83 to 4.77), risk of having any adverse event (RR 1.03, 95% CI 0.94 to 1.13) or risk of hypoglycemic (RR 1.43, 95% CI 0.47 to 4.36)

Key Question 1.
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Strength of evidence[a]	Conclusions
Moderate	Genital infections were more likely with empagliflozin than with linagliptin (RR 2.50, 95% CI 1.11 to 5.47)
Between Class Comparisons: Dapagliflozin vs. Saxagliptin	
Low	There was no difference between dapagliflozin and saxagliptin at 24 weeks in lowering of HbA1c based on 1 trial (n=355)
Low	Weight loss at 24 weeks was greater with dapagliflozin (2.4 kg, 95% CI 1.9 to 2.9) compared with saxagliptin (0 kg, 95% CI 0.5 kg weight loss to 0.5 kg weight gain)
Low	There were no differences between treatments in study withdrawals due to adverse events or risk of experiencing any adverse event
Low	Genital infections were more common with dapagliflozin than with saxagliptin (RR 9.83, 95% CI 1.27 to 76)
Insufficient	Evidence for hypoglycemic events was insufficient to draw conclusions
Newer Diabetes Medications compared with Metformin: Alogliptin vs. Metformin	
Insufficient	One trial (n=338) found no difference between alogliptin and metformin (at either dose) for improving the following health outcomes: mortality, ischemic stroke, heart failure related events, and myocardial infarction (1 trial; unknown consistency; imprecise findings).
Low	One trial (n=338) found no difference between alogliptin 12.5 mg and metformin 500 mg at 26 weeks (0.09%, 95% CI −0.17 to 0.35).
Moderate	One trial (n=338) found a greater reduction in HbA1c with metformin 1,000 mg than alogliptin 12.5 mg twice daily (between-group difference −0.55, 95% CI −0.29 to −0.81).
Low	One trial (n=338) found a greater reduction in weight with metformin 500 mg than alogliptin 12.5 mg twice daily (−0.79 kg, 95% CI −0.003 to −1.58) and metformin 1000 mg twice daily compared with alogliptin 12.5 mg twice daily (−1.4 kg, 95% CI −2.02 to −0.45).
Low	Metformin 1,000 mg twice daily was associated with higher rates of diarrhea, and nausea than the metformin 500 mg twice daily and alogliptin 25 mg once daily groups.
Newer Diabetes Medications compared with Metformin: Sitagliptin vs. Metformin	
Low	Three trials reported mortality over 24 to 26 weeks; there was no difference between groups.
Moderate	Our meta-analysis (3 trials; n=1,655) found that metformin 2,000 mg per day was more efficacious for reducing HbA1c than sitagliptin 100 mg daily (WMD −0.30%, 95% CI −0.52 to −0.09, I^2=84.7%); all trials found a statistically significant benefit favoring metformin; 1 trial found a smaller magnitude of effect (−0.14%) than the other 2 trials (−0.33% and −0.47%).
Low	Metformin was associated with a greater reduction in weight compared with sitagliptin over 24 to 54 weeks (2 trials). Mean difference between groups ranged from −1.2 kg to −1.7 kg.
Low	Compared with metformin monotherapy, sitagliptin was associated with lower incidence of nausea and diarrhea (n=3, RR for nausea 0.45, 95% CI 0.24 to 0.84; n=3, RR for diarrhea 0.35, 95% CI, 0.24 to 0.51).

Key Question 1.
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Strength of evidence[a]	Conclusions
Newer Diabetes Medications compared with Metformin: Saxagliptin vs. Uptitrated Metformin	
Insufficient	One trial (n=286) found no difference in mortality between the addition of saxagliptin and uptitration of metformin in patients not at goal on submaximal metformin (over 24 weeks); a second trial (n=282) found no difference between saxagliptin and uptitration of metformin for improving cardiovascular events (myocardial infarction and myocardial ischemia).
Low	Our meta-analysis (2 trials; n=1,677) found no difference in HbA1c with the addition of saxagliptin 5 mg compared with uptitration of metformin in patients not at goal on submaximal doses of metformin (WMD −0.31, 95% CI −0.74 to 0.13) (low strength of evidence). Two trials found inconsistent results. One trial found greater reduction in HbA1c with the addition of saxagliptin 5 mg compared with uptitration of metformin (between-group difference: −0.53, 95% CI −0.74 to −0.32). A second trial and another trial found no difference in the change from baseline (between-group difference −0.09%, 95% CI −0.26 to 0.08).
Low	In 1 trial (n=282), the uptitration of metformin was associated with a greater reduction in weight compared with adding saxagliptin 5 mg (between-group difference −0.9 kg, 95% CI −0.24 kg to −1.56 kg).
Low	Compared with metformin, saxagliptin was associated with an increased risk of hypoglycemia (n=2, RR 2.93, 95% CI 1.08 to 7.97), but no differences between groups were found with our meta-analyses for nausea, vomiting, diarrhea, or urinary tract infections.
Newer Diabetes Medications compared with Metformin: Exenatide twice daily vs. Metformin	
Insufficient	One trial (n=59) found greater reduction in HbA1c with exenatide twice daily compared with metformin: −2.6% vs. −1.6%; *P*<0.045 (1 trial; unknown consistency).
Insufficient	One trial found greater reduction in weight with exenatide (−5.8 kg) compared with metformin (−3.81 kg) over 26 weeks, *P*<0.01 (1 trial; unknown consistency).
Newer Diabetes Medications compared with Metformin: Exenatide XR vs. Metformin	
Insufficient	One trial (n=494) found no difference in mortality between exenatide XR and metformin over 24 weeks (1 trial; unknown consistency; imprecise findings).
Low	One trial (n=494) found no difference for reducing HbA1c between exenatide XR and metformin: −1.53% vs.−1.48%, *P*=0.62.
Low	One trial (n=494) found no difference in weight reduction between exenatide XR and metformin; both groups lost an average of 2 kg over 24 weeks.
Newer Diabetes Medications compared with Metformin: Dulaglutide vs. Metformin	
Low	One trial (n=807) of dulaglutide compared with metformin found greater mean reduction in HbA1c and proportion of patients achieving HbA1c <7% with dulaglutide than metformin (RR 1.16, 95% CI 1.01 to 1.34)
Low	Weight change was less with dulaglutide 0.75 mg than metformin, while there was no difference in weight change between dulaglutide 1.5 mg and metformin.
Low	No differences between groups were reported for overall adverse events or withdrawal due to adverse events, and there were no cases of severe hypoglycemia.

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Strength of evidence[a]	Conclusions
Newer Diabetes Medications Compared with Metformin: Dapagliflozin vs. Metformin	
Low	Three trials found no difference in mortality rates between groups receiving metformin XR 1,500 mg-2,000 mg daily and dapagliflozin.
Low	We pooled 2 trials (n=522) in a meta-analysis; there was no difference between dapagliflozin 5 mg compared with metformin XR 1500 mg-2000 mg daily (WMD −0.12, 95% CI −0.16 to −0.08). For dapagliflozin 10 mg compared with metformin XR 1,500 mg-2,000 mg daily there was a statistically significant reduction in HbA1c favoring dapagliflozin but the overall magnitude of effect was small and not within a range considered clinically significant (WMD −0.11%, 95% CI −0.11 to −0.05).
Low	Dapagliflozin (at both dosages) is associated with greater weight reduction than metformin XR 1,500 mg-2,000 mg over 24 weeks. Our meta-analysis (2 trials; n=522) found a greater reduction with dapagliflozin 5 mg compared with metformin XR 1,500 mg-2,000 mg daily (WMD −1.18 kg, 95% CI −1.86 to −0.26); similarly, across 2 trials (n=505) a greater reduction in weight was seen with dapagliflozin 10 mg compared with metformin XR 1,500 mg-2,000mg (WMD −1.3kg, 95% CI −1.8 to −0.7).
Moderate	Our meta-analyses showed a significant difference in favor of dapagliflozin in the rate of diarrhea between dapagliflozin 10 mg and metformin XR (n=2, RR 0.26, 95% CI 0.12 to 0.60).
Low	Meta-analyses showed no significant differences between dapagliflozin 5 mg and metformin XR for any of the outcomes for which we conducted meta-analysis (withdrawals because of adverse events, hypoglycemia, nausea, diarrhea, and urinary tract infection)
Newer Diabetes Medications Compared with Metformin: Empagliflozin vs. Metformin	
Low	Two trials (n=660 and 336) of empagliflozin compared with metformin found no differences in mean reduction in HbA1c or the proportion of patients achieving HbA1c <7%.
Low	Weight was reduced more with empagliflozin over 52 weeks, while no difference in weight reduction was observed in the shorter (12-week) study
Low	No differences in overall adverse events or withdrawal due to adverse events.
Newer Diabetes Medications Compared with Metformin: Canagliflozin vs. Metformin	
Low	One trial (n=1,186) of canagliflozin compared with metformin found no differences in mean HbA1c reduction or in the proportion of patients achieving HbA1c <7%.
Low	Weight reduction was greater with canagliflozin 100 mg (−3.0 kg; treatment difference −0.9 kg, 95% CI −1.6 to −0.2 kg) and 300 mg (−3.9 kg; treatment difference −1.8 kg, 95% CI −2.6 to −1.1 kg) compared to metformin (−2.1 kg).
Low	No differences in overall adverse events or withdrawal due to adverse events.
Fixed–dose combination products or dual-therapy; Oseni® or dual therapy with alogliptin plus pioglitazone	

Key Question 1.
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Strength of evidence[a]	Conclusions
Low	One trial (n=654) found greater mean reduction with dual therapy (–1.56% to –1.71% for dual therapy vs. –0.96% and –1.15% for component monotherapy (p<0.05), and greater proportion achieving HbA1c <7% (53%-63% vs. 24%-34%; RRs ranging from 1.58, 95% CI 1.22 to 2.05 to 2.58, 95% CI 1.92 to 3.46)
Low	Weight gain with higher-dose combination therapy compared to with component monotherapy (3.14 kg vs. –0.29 kg with alogliptin and 2.19 kg with pioglitazone; p<0.05 for both)
Insufficient	No difference between the group with the most events and the group with the least events (RR 1.19, 95% CI 0.99 to 1.42; other data NR)
Insufficient	No difference between the group with the most events and the group with the least events (RR 0.43, 95% CI 0.11 to 1.62; other data NR)
Fixed–dose combination products or dual-therapy; Kazano® or dual therapy with alogliptin plus metformin	
Low	One trial (n=784) compared 2 doses of Kazano® (12.5/500 mg twice daily and 12.5/1,000 mg twice daily) to various doses of its component monotherapies. Both Kazano® 12.5/500 mg twice daily and 12.5/1,000 mg twice daily were more efficacious than component monotherapies in reducing mean HbA1c over 26 weeks. Mean HbA1c change from baseline HbA1c changes from baseline were −1.22% (0.094) and −1.55% (0.090) with 12.5/500 mg and 12.5/1,000 mg twice daily combination therapies, respectively, versus −0.56% (0.093) with alogliptin 12.5 mg twice daily, and −0.65% (0.094) and −1.11% (0.092) with metformin 500 mg and 1,000 mg twice daily monotherapies (*P*<0.001 for all comparisons of combination therapy vs. component monotherapies).
Low	Kazano® 12.5/1,000 mg twice daily resulted in greater weight loss than treatment with alogliptin 12.5 mg twice daily alone (−1.17 kg vs. −0.01 kg *P*=0.003). No difference in weight was found between the remaining comparators: alogliptin 25 mg daily: 0.13 kg, metformin 500 mg twice daily: −0.80 kg, metformin 1,000 mg twice daily: −1.25 kg, Kazano® 12.5/500 mg twice daily: −0.57 kg.
Low	Those receiving metformin 1,000 mg either as monotherapy or in combination with alogliptin had higher rates of hypoglycemia, nausea, and diarrhea compared with those receiving alogliptin 25 mg monotherapy or lower doses of metformin.
Fixed-dose combination products or dual-therapy: Jentadueto® or dual therapy with linagliptin plus metformin	
Moderate	Two trials (n=287 and 316) found greater reduction in HbA1c with linagliptin plus metformin dual therapy than with component monotherapy over 24 weeks (–0.70%, 95% CI –0.98% to –0.42% for 1,000 mg metformin and –1.10%, 95% CI –1.38% to –0.82% for 2,000 mg metformin in one study and −0.8%, 95% CI −1.1% to −0.5% for 1,500-2,000 mg metformin in the other); results were similar compared to metformin monotherapy.
Low	Linagliptin 5 mg plus metformin 1,000-2,000 mg daily was not associated with differences in weight change compared to linagliptin monotherapy in one study (–0.30 kg, 95% CI –0.89 to 0.29), while significantly more weight reduction was observed with combination therapy in the other study (treatment difference −1.31 kg, 95% CI −2.18 kg to −0.44 kg). The group receiving linagliptin 5 mg daily plus metformin 1,000 mg had a small but statistically significant weight gain compared to patients receiving metformin 1,000 mg daily (0.60 kg, 95% CI 0.01 to 1.19). No other groups experienced a significant change in weight.
Low	The rates of withdrawal due to adverse events in two trials of Jentadueto® or dual therapy with

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Strength of evidence[a]	Conclusions
	linagliptin plus metformin ranged from 1.3% to 4.2%, with no differences between groups, and rates of overall adverse events also did not differ between groups.
Fixed-dose combination products or dual-therapy: Janumet® or dual therapy with sitagliptin plus metformin	
Moderate	Two trials assessed an FDCP or dual therapy with sitagliptin plus metformin. One compared dual therapy to monotherapy with metformin (but not a sitagliptin arm). Our meta-analysis (2 trials; n=1,478) found greater reduction in HbA1c with sitagliptin 100 mg plus metformin 2,000 mg over 18 to 24 weeks compared with metformin monotherapy (WMD −0.60%, 95% CI −0.75 to −0.45). Greater reduction in HbA1c with dual therapy with metformin and sitagliptin than with component monotherapy in a 24-week trial with additional 30 and 52 week extensions (range 0.4% to 1.2%).
Low	Two trials found no difference in weight reduction between sitagliptin plus metformin and component monotherapy. In 1 trial, sitagliptin plus metformin was associated with greater weight loss than metformin alone at 18 weeks (between-group difference −1.6 kg, 95% CI −2.1 to −1.1). The second trial found a similar reduction in weight with both dosages of sitagliptin plus metformin (−0.7 kg to −1.7 kg), metformin monotherapy (−1.0 kg to −1.7 kg), and sitagliptin (−0.8 kg) over 26 weeks.
Low	Gastrointestinal events were reported with similar frequency across treatment arms in both trials, with the higher-dose metformin monotherapy patients reporting the highest rates. Our meta-analyses of 2 trials comparing the combination of sitagliptin 50 mg plus metformin 1,000 mg twice daily with monotherapy of metformin 1,000 mg twice daily found a significant difference in favor of combination therapy for diarrhea outcomes (RR 0.74, 95% CI 0.58 to 0.95). Meta-analyses for hypoglycemia (RR 1.75, 95% CI 0.50 to 6.10), nausea (RR 0.83, 95% CI 0.57 to 1.22), and vomiting (RR 1.39, 95% CI 0.62 to 3.13) were not statistically significant.
Fixed-dose combination products or dual-therapy: Invokamet® or dual therapy with canagliflozin plus metformin	
Low	One trial (n=1,186) of canagliflozin plus metformin compared to component monotherapy found that dual therapy was superior in mean reduction in HbA1c (canagliflozin 100 mg plus metformin vs. metformin: treatment difference −0.46%, 95% CI −0.66% to −0.27%; canagliflozin 300 mg plus metformin vs. metformin: treatment difference −0.48%, 95% CI −0.67% to −0.28%; canagliflozin 100 mg plus metformin vs. canagliflozin 100 mg: treatment difference −0.40%, 95% CI −0.59% to −0.21%; canagliflozin 300 mg plus metformin vs. canagliflozin 300 mg: treatment difference −0.36%, 95% CI −0.56% to −0.17%). The proportion of patients achieving an HbA1c <7% was significantly greater in the higher dose of dual therapy compared to metformin (56.8% vs. 43.0%; RR 1.32, 95% CI 1.10 to 1.59) but not for the lower dose of dual therapy (49.6% vs. 43%; RR 1.16, 95% CI 0.95 to 1.41); dual therapy superior to canagliflozin monotherapy at canagliflozin doses of 100 mg (49.6% vs. 38.8%; RR 1.28, 95% CI 1.05 to 1.57) and 300 mg (56.8% vs. 42.8%; RR 1.32, 95% CI 1.11 to 1.60).
Low	Weight change was also significantly reduced with dual therapy compared to monotherapy (canagliflozin 100 mg plus metformin vs. metformin: treatment difference −1.4 kg, 95% CI −2.1 kg to −0.6 kg; canagliflozin 300 mg plus metformin vs. metformin: treatment difference −2.1 kg, 95% CI −2.9 kg to −1.4 kg).
Insufficient	No differences in overall adverse events or withdrawal due to adverse events.
Fixed-dose combination products or dual-therapy: Glyxambi® or dual therapy with empagliflozin plus linagliptin	

Key Question 1. **What is the comparative efficacy and effectiveness of newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?** **Key Question 2.** **What is the comparative tolerability and frequency of adverse events for newer diabetes medications and drug combinations (administered as fixed-dose combination products or dual therapy) for adults with diabetes mellitus?**	
Strength of evidence[a]	**Conclusions**
Moderate	Two trials (n=667 and 686) found dual therapy with empagliflozin plus linagliptin to be superior to component monotherapy in mean reduction in HbA1c, the proportion of patients achieving HbA1c <7%, and mean weight reduction in drug-naïve patients and patients on background metformin therapy.
Low	No differences in overall adverse events or withdrawal due to adverse events.

Abbreviations: CI, confidence interval; HbA1c, hemoglobin A1c; OR, odds ratio; RR, relative risk; WMD, weighted mean difference; XR, extended release

Limitations of this Report

Methodological limitations of the review within the defined scope included the exclusion of trials published in languages other than English. For this streamlined update, our scope was also limited to head-to-head trials of included drugs and comparisons with metformin only. There were also no between class comparisons of a GLP-1 analog with a SGLT2 inhibitor. Most between-class trials used sitagliptin as the active comparator. In addition, there were no trials of alogliptin compared with a GLP-1 analog or a SGLT2 inhibitor or of the combination product empagliflozin with linagliptin. Finally, the data from some randomized controlled trials included in this report have limited utility for assessing real-world adherence to medications. This is largely because they enrolled selected populations, often requiring adherence during a run-in period before randomization.

CONCLUSIONS

As a class, GLP-1 analogs reduce HbA1c and increase weight loss to a greater degree than DPP-4 inhibitors, but at the risk of increased gastrointestinal side effects. As a class, SGLT2 inhibitors also improve HbA1c and weight compared with DPP-4 inhibitors but at greater risk of genital infection. Treatment with metformin alone was associated with better HbA1c values and greater weight loss than several DPP-4 inhibitors but less weight loss than with several SGLT-2 inhibitors. However, while overall weight loss and weight loss differences between drugs and drug classes may be statistically significant, these differences may not clinically meaningful in some cases. Dual therapy or a fixed-dose combination product including metformin resulted in improved HbA1c values than component monotherapy.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Long-acting Asthma and COPD Drugs

Drug Effectiveness Review Project Summary Report

Date of Review: September 2016 **Date of Last Review:** September 2015

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:

1. What is the comparative *within-class* and *across-class* efficacy and effectiveness of long-acting inhaled and long-acting oral medications used to treat outpatients with asthma or chronic obstructive pulmonary disease (COPD)?
2. What is the comparative *within-class* and *across-class* tolerability and frequency of adverse events of long-acting inhaled and long-acting oral medications used to treat outpatients with asthma or chronic obstructive pulmonary disease (COPD)?
3. Are there subgroups of patients [e.g. groups defined by demographics (age, racial groups, gender), asthma or COPD severity, comorbidities, other medications (drug-drug interactions), smoking status, genetics, or pregnancy] for which asthma or COPD controller medications differ in efficacy, effectiveness, or frequency of adverse events?

Conclusions:

- There is low to moderate quality evidence of no *within-class* differences in efficacy or harms for long-acting inhaled (i.e., beta-agonists (LABAs), muscarinic antagonists (LAMAs), or corticosteroids (ICS)) and long-acting oral medications (i.e., leukotriene modifiers [LM]) for patients with asthma or COPD.[1] There was insufficient evidence in subgroup populations with asthma or COPD to establish meaningful conclusions on efficacy or harms.[1]

Asthma

- There was low to high strength of evidence that ICS is associated with less exacerbations than LMs in patients with asthma.[1]
- Low to moderate evidence found ICS to have no difference in risk of exacerbations compared to LABAs.[1]
- ICS were found to be more effective than LABAs at decreasing exacerbations based on one comparison (moderate strength of evidence).[1]
- Risk of exacerbations were found to be similar between LABA and LAMA based on low strength of evidence.[1]
- Risk of adverse events were similar for most comparisons *between* the difference classes when used in patients with asthma.[1]

COPD

- Low to moderate strength of evidence found no difference in exacerbation rates when ICS were compared to LABA in COPD patients. One trial found ICS use to have an increased risk of mortality compared to LABA (low strength of evidence).[1]
- No difference in exacerbation rates were found when LAMA/LABA were compared to ICS/LABA based on low to moderate strength of evidence.[1]
- Moderate strength of evidence found patients treated with LABAs to have more exacerbations than LAMA treated patients.[1]

- ICS/LABA and LABA were found to have similar risk of exacerbations based on low strength of evidence.[1]
- Three comparisons found low strength of evidence that mortality rates were similar between ICS/LABA and LAMA.[1]
- For the outcomes of exacerbations, mortality, daily activities and quality of life there was low strength of evidence that LAMA/LABA was similar to LAMA.[1]
- An increased risk of serious pneumonia was associated with ICS use compared to LABA (OR 1.48; 95% CI 1.13 to 1.94) based on moderate strength of evidence.[1]

Recommendations:
- Evidence from the Drug Effectiveness Review Project (DERP) does not support any changes to the current PDL. Review comparative drug costs in the executive session.
- Continue current clinical prior authorization (PA) criteria (Appendix 2).

Previous Conclusions:
- There is insufficient new comparative evidence for efficacy/effectiveness for the treatment of COPD. Evidence-based recommendations in new clinical practice guidelines from The Global Initiative for Chronic Obstructive Lung Disease (GOLD), The American College of Chest Physicians (ACCP) and Canadian Thoracic Society (CTS), and the Veterans Administration (VA)/Department of Defense (DoD) do not differentiate between drugs within a pharmacological class. Therefore, these guidelines cannot be used to support placement of specific therapies on Practitioner-Managed Prescription Drug Plan (PMPDP).
- There is insufficient new comparative evidence for efficacy/effectiveness for the treatment of asthma. New evidence primarily focuses on the use of omalizumab for severe asthma and continues to support the recommendation to reserve omalizumab to patients with allergic asthma who have failed other treatments.
- There is insufficient new comparative safety data for the treatment of COPD or asthma. New evidence primarily focuses on individual treatments and do not support a change to current placement of therapies for asthma or COPD on the Preferred Drug List (PDL).
- Two new formulations of drug products for COPD previously reviewed by the Pharmacy & Therapeutics Committee were identified. Both products were approved by the FDA based on short-term, 24-week studies that evaluated surrogate outcomes of lung function.
    - Tiotropium/olodaterol (Stiolto™ Respimat®) is indicated for long-term management of COPD. Tiotropium is a preferred inhaled anticholinergic for COPD and olodaterol is a non-preferred long-acting beta-agonist for COPD. Over 5,000 patients from two replicate studies with moderate to very severe COPD were studied for 52 weeks. Patients were randomized to one of 5 treatment arms: tiotropium 2.5 mcg, tiotropium 5 mcg, olodaterol 5 mcg, tiotropium 2.5 mcg/olodaterol 5 mcg and tiotropium 5 mcg/olodaterol 5 mcg. There is moderate level of evidence that tiotropium/olodaterol fixed-dose combination products are superior compared to its monotherapy components for the outcomes of change from baseline in FEV_1 $AUC_{0\text{-}3hr}$ ($p<0.0001$ for all comparisons) and trough FEV_1 ($p<0.05$ for all comparisons) at 24 weeks. There is insufficient evidence of comparative efficacy or safety between tiotropium/olodaterol and other drugs for the management of COPD.
    - Fluticasone furoate (Arnuity™ Ellipta®) is an ICS indicated for the maintenance treatment of asthma in patients 12 years and older. Fluticasone furoate demonstrated superiority over placebo with a mean difference in baseline evening trough FEV_1 of 146 mL (95% CI, 36 to 257 mL; $p=0.009$) at 24 weeks.
- A new indication for asthma in patients 18 years of age or older was identified for fluticasone furoate/vilanterol (Breo® Ellipta®). Approval for asthma by the FDA for the 100/25 mcg and 200/25 mcg dose of fluticasone furoate/vilanterol was based on short-term, 12 to 24-week studies.
    - There is moderate quality evidence that the once-daily fixed dose combination products are more effective than their fluticasone furoate monotherapy counterparts in the ability to improve weighted mean FEV_1 (0-24 hours) from baseline. In addition, fluticasone furoate 100

mcg/vilanterol 25 mcg decreased time to first asthma exacerbation compared to fluticasone furoate 100 mcg alone (HR 0.80; 95% CI, 0.64 to 0.99; p=0.036).

Previous Recommendations:

- Make tiotropium/olodaterol, fluticasone furoate and fluticasone furoate/vilanterol products non-preferred at this time due to limited evidence.
- Create new PDL class for long-acting muscarinic antagonist/long-acting beta-agonist (LAMA/LABA) fixed-dose combination inhaler products.
- Re-organize and modify clinical PA criteria to promote step-therapy that is consistent with Oregon Asthma Guidelines and with medical evidence for COPD:
    - All non-preferred LABA inhalers must go through the LABA PA criteria for appropriate step therapy.
    - All non-preferred inhaled corticosteroids (ICS) must go through the ICS PA criteria for appropriate step therapy.
    - Remove clinical PA for "asthma controllers" and indacaterol. Drugs under these PAs will be incorporated into the ICS or LABA PA criteria.
    - Remove clinical PA for leukotriene inhibitors. Non-preferred leukotriene inhibitors will go through the generic non-preferred PDL PA.
    - Clerical changes to the roflumilast PA criteria.
    - Update LABA/ICS clinical PA and LABA/LAMA clinical PA to reflect best practices for initial COPD management. Bring back PAs to next P&T meeting.

Methods:

The June 2016 Drug Class Review on long-acting asthma and COPD drugs by the DERP at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The final original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:

Literature was searched through October 2015 and 35 new studies were identified for this class update.[1] Asthma patients 12 months of age and older and adult COPD patients were included in the studies. Drugs included in the search are listed in Table 1. There was low- to moderate-strength of evidence that there were no differences in efficacy of drugs *within* the same class. Evidence for available comparisons are presented below, separated by diagnosis of asthma or COPD. There was insufficient evidence on benefits and harms in subgroup populations.

Table 1. Drugs for Asthma and COPD.[1]

Generic Name	Trade Name	Formulation
Long-acting Beta-Agonists (LABA)		
Arformoterol tartrate	Brovana	Inhalation solution (nebulized)
Formoterol fumarate	Foradil Perforomist	Inhalation powder (DPI) Inhalation solution (nebulized)

	Aerolizer and Certihaler	Inhalation powder (DPI)
Indacaterol maleate	Arcapta	Inhalation powder (DPI)
Olodaterol hydrochloride	Striverdi Respimat	Metered soft-mist spray (SMI)
Salmeterol xinafoate	Serevent	Inhalation powder (DPI)
Long-acting Muscarinic Antagonists (LAMA)		
Aclidinium	Tudorza Pressair	Inhalation powder (DPI)
Glycopyrrolate bromide	Seebri Breezhaler	Inhalation powder (DPI)
Tiotropium bromide	Spiriva Spiriva Respimat	Inhalation powder (DPI) Metered soft-mist spray (SMI)
Umeclidinium bromide	Incruse Ellipta	Inhalation powder (DPI)
Inhaled Corticosteroids (ICS)		
Beclomethasone dipropionate	QVAR	Inhalation aerosol (MDI)
Budesonide	Pulmicort Respules Pulmicort Flexhaler	Inhalation suspension (nebulized) Inhalation powder (DPI)
Ciclesonide	Alvesco	Inhalation aerosol (MDI)
Flunisolide hemihydrate	Aerospan	Inhalation aerosol (MDI)
Fluticasone furoate	Arnuity Ellipta	Inhalation powder (MDI)
Fluticasone propionate	Flovent DISKUS	Inhalation powder (MDI)
Mometasone furoate	Asmanex Twisthaler Asmanex HFA	Inhalation powder (DPI) Inhalation aerosol (MDI)
Fixed-dose Combination Products – ICS/LABA		
Formoterol/budesonide	Symbicort	Inhalation aerosol (MDI)
Formoterol/mometasone furoate	Dulera	Inhalation aerosol (MDI)
Slameterol xinafoate/fluticasone propionate	Advair Diskus Advair HFA	Inhalation powder (DPI) Inhalation aerosol (MDI)
Fixed-dose Combination Products – LABA/LAMA		
Indacaterol/glycopyrrolate	Utibron Neohaler	Inhalation powder (DPI)
Olodaterol hydrochloride/tiotropium bromide	Stiolto Respimat	Soft-mist spray (SMI)
Umeclidinium bromide/vilanterol trifenatate	Anoro Ellipta	Inhalation powder (DPI)
Vilanterol/fluticasone furoate	Breo Ellipta	Inhalation powder (DPI)
Leukotriene Modifiers (LM)		
Montelukast sodium	Singulair	Chewable tablets
Zileuton	Zyflo Zyflo CR	Tablet Extended release tablet
Zafirlukast	Accolate	Tablet
Phosphodiesterase-4 inhibitor (PDE-4)		
Roflumilast	Daliresp	Tablet

ASTHMA

Within Class Comparisons:

ICS

- For the outcomes of asthma symptoms, exacerbations, rescue medications, quality of life, or adverse events there were no differences in ICSs at equivalent doses based on 47 trials (low to moderate strength).
- Low quality evidence of outcome differences between the ICSs are presented in Table 2.

Table 2. ICS Efficacy Comparisons in Patients with Asthma.[1]

Comparison	Findings	Strength of Evidence
Budesonide vs. mometasone	Mometasone associated with less rescue medication use compared to budesonide	Low
Beclomethasone vs. budesonide	Beclomethasone was found to have less risk of nocturnal awakenings compared to budesonide.	Low
Fluticasone propionate vs. beclomethasone	Fluticasone demonstrated lower risk of exacerbations compared to beclomethasone (RR 0.71; 95% CI, 0.51 to 0.99)	Low
Fluticasone propionate vs. budesonide	Fluticasone had better functional capacity results compared to budesonide.	Low
Abbreviations: RR – relative risk		

- Growth velocity in children was less affected by fluticasone propionate compared to beclomethasone. Height increases in children were less affected by ciclesonide versus budesonide.

LABA

- Three study comparisons of LABAs found no differences in the outcomes of asthma symptoms, exacerbation prevention, improved quality of life, hospitalizations and emergency room visits in patients not controlled on ICS alone (moderate strength of evidence). The one exception was a higher quality of life associated with olodaterol compared to formoterol.
- There were no differences found in tolerability or adverse events in a comparison of formoterol and salmeterol (with or without concomitant ICS use).

LM

- There was insufficient evidence to compare LMs.

ICS/LABA

- No difference between ICS/LABA formulations was found when 10 randomized controlled trials were compared. Two trials had insufficient evidence to compare efficacy. Comparative agents are detailed below in Table 3.

Table 3. ICS/LABA Efficacy Comparisons in Patients with Asthma.[1]

Comparison	Findings	Strength of Evidence
Beclomethasone/formoterol extrafine vs. fluticasone propionate/salmeterol	Comparative efficacy evidence was insufficient.	Insufficient
Budesonide/formoterol vs. fluticasone propionate/formoterol	Comparative efficacy evidence was insufficient.	Insufficient
Budesonide/formoterol vs. fluticasone propionate/salmeterol (+ medium-dose ICS in both groups)	No difference in exacerbations.	Moderate
Budesonide/formoterol vs. fluticasone propionate/salmeterol (+ high-dose ICS in both groups)	No difference in exacerbations.	Low
Fluticasone propionate/salmeterol vs. fluticasone furoate/vilanterol	No difference in quality of life.	Low

- Within class comparisons of ICS/LABA found no difference in adverse events or insufficient evidence to draw conclusions based on low to moderate strength of evidence. Specific comparisons are described in Table 4.

Table 4. ICS/LABA Harms Comparisons in Patients with Asthma.[1]

Comparison	Findings	Strength of Evidence
Beclomethasone/formoterol extrafine vs. fluticasone propionate/salmeterol	Comparative harms evidence was insufficient.	Insufficient
Budesonide/formoterol vs. fluticasone propionate/formoterol	Comparative harms evidence was insufficient.	Insufficient
Budesonide/formoterol vs. fluticasone propionate/salmeterol	Withdrawals due to adverse events were similar between groups.	Moderate
Mometasone/formoterol vs. fluticasone propionate/salmeterol	No difference in withdrawals due to adverse events or serious adverse events. Ocular toxicity was similar between groups.	Low -moderate Low
Fluticasone/salmeterol vs. fluticasone furoate/vilanterol	No difference in withdrawals due to adverse events or serious adverse events.	Low

<u>Comparisons between Different Classes</u>:

ICS vs. LM

- ICS use was associated with better outcomes compared to LM use with similar occurrence of adverse events. Table 5 below provides details on comparisons of specific ICSs to LMs.

Table 5. ICS vs. LM Efficacy Comparison in Patients with Asthma.[1]

Comparisons	Findings	Strength of Evidence
Fluticasone propionate vs. montelukast	Fluticasone was shown to have less exacerbations (OR 0.70; 95% CI 0.57 to 0.86) and improved quality of life compared to montelukast. Emergency department visits and missed school days were less with fluticasone compared to montelukast.	High Low
Beclomethasone vs. montelukast	Exacerbation rates were lower with beclomethasone compared to montelukast (SMD -0.15; 95% CI -0.30 to 0.00).	Low
Budesonide vs. montelukast	Two trials reported no significant difference in symptoms between groups. One trial found no difference in quality of life between the groups. One trial found budesonide to be associated with less daytime symptoms compared to montelukast.	Low to moderate
Fluticasone propionate vs. zafirlukast	Lower exacerbation rates were seen with fluticasone (SMD -0.21; 95% CI, -0.31 to -0.11)	High
Abbreviations: OR – odds ratio; SMD – standard mean difference		

- No difference in adverse events were shown between ICSs and LMs.

ICS vs. LABA

- Seventeen trials evaluated ICS to LABA comparisons. Four studies included pediatric patients while the majority included adults only. Specific comparisons are detailed below in Table 6.

Table 6. Efficacy Comparison of ICS to LABA in Patients with Asthma.[1]

Comparison	Findings	Strength of Evidence
Beclomethasone vs. salmeterol	No difference was demonstrated.	Moderate
Budesonide vs. formoterol	Trend favored budesonide for fewer symptoms, nocturnal awakenings, and exacerbations compared to formoterol.	Moderate
Fluticasone propionate vs. formoterol	No difference in exacerbations was found.	Low
Fluticasone propionate vs. salmeterol	No difference was found in outcomes.	Not provided
Mometasone vs. formoterol	Mometasone was favored over formoterol for less asthma deteriorations or clinically judged deteriorations.	Moderate

- Analysis of 16 trials found no difference in overall adverse events and withdrawals between ICSs and LABAs. LABA monotherapy is not recommended in patients with asthma.

LM vs. LABA
- There was insufficient evidence for conclusions to be made.

LABA vs. LAMA
- There was low strength of evidence from 3 trials comparing salmeterol to tiotropium that were no differences in exacerbation rate or quality of life.
- No difference was found between tiotropium and salmeterol in withdrawals due to adverse events or serious harms based on low strength of evidence.
- Overall adverse events, withdrawal due to adverse events or specific harms were similar between salmeterol and tiotropium.

ICS vs. PDE-4 Inhibitors
- Beclomethasone was found to be associated with fewer exacerbations compared to roflumilast (RR 3.6; 95% CI, 1.10 vs. 9.11). Wide confidence intervals led to the conclusion that roflumilast is noninferior to beclomethasone based on the results of one fair quality trial.
- There was insufficient evidence for harms comparisons between ICSs and PDE-4s.

ICS/LABA vs. ICS (different drug)
- Fluticasone furoate/vilanterol was found to have similar risk of exacerbation rates as fluticasone propionate based on the evaluation of 3 trials based on low strength of evidence.
- Low strength of evidence found ciclesonide to have more adverse events compared to fluticasone propionate/salmeterol (RR 1.15; 95% Cl, 1.01 to 1.30).
- No difference was found in serious adverse events or withdrawals between fluticasone furoate/vilanterol compared to fluticasone propionate based on low strength of evidence.

ICS/LABA vs. LM
- There is high strength of evidence from 5 randomized controlled trials of asthma patients that fluticasone propionate/salmeterol was associated with fewer exacerbations compared to montelukast (SMD 0.26; 95% CI, 0.16 to 0.35).
- Moderate strength of evidence showed no difference in adverse events or withdrawals due to adverse events between ICS/LABA and LM.

LABA/ICS vs. LM/ICS
- Exacerbations were decreased more with the addition of a LABA to ICS compared to adding a LM to ICS in adolescents and adults based on high-strength of evidence.
- High strength of evidence found no difference in withdrawals due to adverse events in comparisons of LABA/ICS and LM/LABA.
- The addition of LABA to ICS therapy was associated with more serious harms compared to adding LM to ICS (moderate strength of evidence).

LM/LABA vs. ICS/LABA
- There was insufficient evidence to make comparative efficacy conclusions.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Within Class Comparisons:

LAMA

- There was no difference in benefits or harms between the LAMA formulations based on low-strength of evidence (6 studies in patients with moderate to very severe COPD).

ICS/LABA

- No differences were found in studies comparing different ICS/LABA formulations. Specific comparisons are detailed in Table 7 below.

Table 7. ICS/LABA Efficacy Comparisons in Patients with COPD.[1]

Comparisons	Findings	Strength of Evidence
Beclomethasone/formoterol vs. fluticasone propionate/salmeterol	No difference was found in exacerbations, symptoms, 6-minute walk-test, or use of rescue medication. Quality of life evidence was insufficient.	Low Insufficient
Budesonide/formoterol vs. beclomethasone/formoterol	No difference in quality of life, total exacerbations or exacerbations leading to an ER visit, hospitalization or requiring corticosteroid treatment.	Low
Fluticasone 100 mcg/vilanterol 25 mcg vs. fluticasone propionate 500 mcg/salmeterol 100 mcg	No difference in exacerbations, rescue-free days or quality of life.	Moderate
Fluticasone furoate 100 mcg/vilanterol 25 mcg vs. fluticasone propionate 1000 mcg/salmeterol 100 mcg	No difference in rescue free days or quality of life.	Low

- ICS/LABA harms comparisons between different agents found insufficient evidence for comparison, low to high strength of evidence of no difference or imprecise data (Table 8).

Table 8. ICS/LABA Harms Comparisons in Patients with COPD.[1]

Comparisons	Findings	Strength of Evidence
Beclomethasone extra fine/formoterol vs. fluticasone propionate/salmeterol	Comparative harms evidence was insufficient.	Insufficient
Budesonide/formoterol vs. beclomethasone/formoterol	Comparative harms evidence was insufficient.	Insufficient
Fluticasone propionate/salmeterol vs. budesonide/formoterol	Imprecise evidence. Increased risk of pneumonia with fluticasone/salmeterol compared to budesonide/formoterol (RR 1.73;	Insufficient

	95% CI, 1.57 to 1.90) and increased risk of mortality. No difference in pneumonia incidence was found in a second study.	
Fluticasone furoate 100 mcg/vilanterol 25 mcg vs. fluticasone propionate 500 mcg/salmeterol 100 mcg	No difference in overall adverse events. No difference in pneumonia, withdrawals due to adverse events or serious adverse events.	High Moderate
Fluticasone furoate 100 mcg/vilanterol 25 mcg vs. fluticasone propionate 1000 mcg/salmeterol 100 mcg	No difference in overall adverse events or withdrawals due to adverse events.	Low

LABA

- Data from 7 studies was used to compare the efficacy of LABA therapies in patients with COPD. Specific therapy comparisons are detailed in Table 9.

Table 9. LABA Efficacy Comparisons in Patients with COPD.[1]

Comparison	Findings	Strength of Evidence
Arformoterol vs. formoterol	Exacerbation rates and quality of life similar between groups.	Low
Formoterol nebulized vs. formoterol via DPI	Exacerbation rates and quality of life similar between groups.	Low
Indacaterol vs. formoterol	Exacerbation rates and quality of life similar between groups.	Low
Indacaterol vs. salmeterol	Improvement in quality of life was higher for indacaterol compared to salmeterol (OR 1.59; 95% CI, 1.12 to 2.25).	Low
Olodaterol vs. formoterol	Exacerbation rates were similar. Olodaterol was found to increase quality of life scores more than formoterol.	Low Moderate

- An increased incidence of serious adverse events associated with indacaterol compared with salmeterol with no difference in withdrawals.
- A comparison between arformoterol and formoterol and between lower-dose indacaterol and formoterol found low strength of evidence that withdrawals and severe adverse events were similar for each comparison.

LAMA/LABA

- In LAMA/LABA comparisons exacerbations and quality of life outcomes were similar between glycopyrrolate/indacaterol and tiotropium/formoterol (low strength of evidence).
- Overall adverse events or withdrawals due to adverse events were similar between glycopyrrolate/indacaterol and tiotropium/formoterol based on low and moderate strength of evidence.

Comparisons between Different Classes:

ICS vs. LABA

- Majority of evidence shows similar results for efficacy outcomes in patients treated with either ICSs or LABAs. Comparisons of specific therapies are presented below in Table 10.

Table 10. Efficacy Comparisons of ICS to LABA in Patients with COPD.[1]

Comparison	Findings	Strength of Evidence
Budesonide vs. formoterol	No difference in mortality, exacerbations or exacerbations.	Low
Fluticasone propionate vs. salmeterol	Mortality was increased with fluticasone compared to salmeterol (OR 1.23; 95% CI, 1.01 to 1.51). SGRQ scores were significantly better with fluticasone compared with salmeterol (MD -0.77; 95% CI, -1.49 to -0.06). Exacerbation rates and hospitalizations were similar between groups.	Low Low Moderate
Mometasone vs. formoterol	SGRQ scores were similar between groups.	Low
Abbreviations: MD – mean difference; SGRQ – St. George's Respiratory Questionnaire		

- There was an increased incidence of pneumonia with ICS compared to LABA in COPD patients.
- Moderate strength of evidence found no difference in any adverse events between LABAs versus ICS in a meta-analysis of 5 studies (OR 1.12; 95% CI 0.96 to 1.30). The risk of serious pneumonia was higher for ICS compared to LABA (OR 1.48; 95% CI 1.13 to 1.94).
- Comparison of mometasone to formoterol found no difference in withdrawals due to adverse events, risk of experiencing an adverse event and risk of a serious adverse event (low strength of evidence).

LAMA/LABA vs. ICS/LABA

- Comparisons of vilanterol 25 mcg/umeclidinium 62.5 mcg and fluticasone propionate 500 mcg/salmeterol 100 mcg found no differences in exacerbations based on moderate strength of evidence. High quality evidence found no difference in quality of life between the two groups. No difference in rescue medication use was found.
- Low strength of evidence found no difference in exacerbation rates between vilanterol 25 mcg/umeclidinium 62.5 mcg and fluticasone propionate 1000 mcg/salmeterol 100 mcg. There was also moderate strength of evidence that there were differences in quality of life.
- High dose indacaterol 110 mcg/glycopyrrolate 50 mcg was found to have a lower risk of moderate to severe exacerbations than fluticasone propionate 100 mcg/salmeterol 1,000 mcg (RR 0.69, 95% CI, 0.48 to 1.00).
- A study between glycopyrrolate/indacaterol and fluticasone propionate/salmeterol found no difference in overall adverse events, withdrawals due to adverse events, pneumonia and adverse events leading to hospitalization.
- Moderate strength of evidence found no difference in vilanterol 25 mcg/umeclidinium 62.5 mcg and fluticasone propionate 500 mcg/salmeterol 100 mcg in overall adverse events, serious adverse events and withdrawals due to adverse events or pneumonia. There was also no difference in withdrawals due to adverse events or pneumonia or in overall adverse events between vilanterol 25 mcg/umeclidinium 62.5 mcg and fluticasone propionate 1000 mcg/salmeterol 100 mcg DPI daily.

LABA vs. LAMA

- Salmeterol was associated with more exacerbations than tiotropium (36% vs. 32%; OR 1.19; 95% CI, 1.09 to 1.30) based on moderate strength of evidence from one systematic review. Quality life and hospitalization rates were the same in both groups.
- In patients with severe COPD indacaterol was associated with more frequent exacerbations and similar effects on quality of life and mortality as tiotropium.
- Low strength of evidence found quality of life to improve in fewer patients using tiotropium compared to indacaterol with no difference in hospitalizations or exacerbations.
- Moderate strength of evidence found tiotropium to have less risk of nonfatal serious adverse events salmeterol. Tiotropium was also associated with less risk of withdrawal due to adverse events compared to salmeterol based on low strength of evidence.
- Tiotropium versus indacaterol and tiotropium compared to formoterol were found to have similar risk of nonfatal serious harms and withdrawals due to harms.

ICS/LABA vs. LABA

- Low strength of evidence from one trial found ICS/LABAs and LABAs to have a similar risk of exacerbations in patients with moderate to severe COPD.
- Indacaterol was associated with less serious adverse events compared to salmeterol/fluticasone propionate (RR 0.29; 95% CI, 0.11 to 0.74).

ICS/LABA vs. LAMA

- Eight studies met inclusion criteria for ICS/LABA vs. LAMA comparisons in COPD patients. Outcome findings were mixed. Findings of individual studies are presented in table 11.

Table 11. Efficacy Comparison of ICS/LABA vs. LAMA in Patients with COPD.[1]

Comparison	**Findings**	**Strength of Evidence**
Tiotropium vs. fluticasone propionate/salmeterol	Fluticasone/salmeterol was found to have a lower risk of mortality, higher hospitalization risk and improved quality of life compared to tiotropium.	Low
Tiotropium vs. vilanterol/fluticasone furoate	No difference in mortality was found.	Low
Tiotropium vs. fluticasone furoate/vilanterol	No difference in mortality was found.	Low
Tiotropium 18 mcg vs. umeclidinium bromide 62.5 mcg/vilanterol 25 mcg	No difference in mortality or quality of life was found.	Low

- Withdrawals due to adverse events were similar between tiotropium and fluticasone propionate/salmeterol but serious harms were significantly lower with tiotropium based on low strength of evidence.
- There is low strength of evidence that tiotropium is similar to fluticasone furoate/vilanterol in the risk of serious adverse events.
- Withdrawals due to adverse events were similar for tiotropium and umeclidinium bromide/vilanterol in patients with COPD.

LAMA/LABA vs. LAMA

- No difference was found between umeclidinium/vilanterol and tiotropium in mortality, quality of life, daily activities, or exacerbations based on low strength of evidence. Moderate strength of evidence found higher utilization in rescue medication use compared to tiotropium.
- Less rescue medication use was associated with umeclidinium/vilanterol compared to umeclidinium monotherapy based on low strength of evidence.
- A comparison between umeclidinium/vilanterol and tiotropium found low strength of evidence of no difference in overall adverse events, pneumonia, death, serious adverse events or withdrawals due to adverse events.

Subgroups

- Data was insufficient to make subgroup comparisons regarding efficacy and safety for asthma or COPD severity, comorbidities, use of other medications, smoking status, genetics or pregnancy.

New Safety Alerts

No new safety alerts identified.

New Formulations or Indications

Glycopyrrolate and formoterol fumarate (Bevespi Aerosphere™)

Glycopyrrolate/formoterol was studied in 2 phase III confirmatory trials involving 3,699 patients with COPD. Both trials were 24-week, randomized, double-blind, placebo-controlled trials.[2] Included patients had moderate to very severe COPD, at least a 10 pack-year history of smoking, a baseline mean FEV1 <80% of predicted normal values (post-albuterol) and a FEV1/FVC ratio <0.7. At baseline patients were a mean age of 63 years old, 54% were smokers, 91% were white, and 44% were female. Patients were randomized to glycopyrrolate 18 mcg/formoterol 9.6 mcg twice daily, glycopyrrolate 18 mcg twice daily, formoterol 9.6 mcg twice daily or placebo in both studies. The first trial also had an open-label active control arm.[2] The primary endpoint in both studies was change in trough FEV1 at week 24 compared to baseline. Minimally important values from research in COPD patients suggest minimally important FEV_1 changes range from 100-140 ml.[3] A key secondary endpoint was change in St. George's respiratory questionnaire (SGRQ), which measures quality-of-life for patients with obstructive airway disease.[4] A 50 item questionnaire determines the score, which can range from 0 to 100, with higher scores indicating more limitations. A change of 4 points is associated with slightly efficacious treatment, 8 points for moderately efficacious treatment, and 12 points for very efficacious treatment.[4]

Glycopyrrolate/formoterol combination improved FEV1 more than all comparators in both studies. The least squares mean change from baseline between glycopyrrolate/formoterol compared to placebo, glycopyrrolate and formoterol monotherapy were 150 mL (95% CI, 114 to 186 mL), 59 mL (95% CI, 31 to 88 mL) and 64 mL (95% CI, 36 to 92 mL), respectively.[2] The second study had similar findings with least squares (LS) mean changes between glycopyrrolate/formoterol and placebo of 103 mL, 54 mL for glycopyrrolate comparison and 56 mL for formoterol comparison. Changes in FEV1 versus placebo comparisons were clinically significant in the both studies, however, at the lower end in the second study. Changes in SGRQ scores were based on a responder rate which was an improvement in score of 4 points or more. Responder rates were 37% for glycopyrrolate/formoterol, 30% for glycopyrrolate, 35% for formoterol and 28% for placebo in the first trial. In the second trial, responder rates by SGRQ scores favored glycopyrrolate/formoterol compared to glycopyrrolate, formoterol and placebo with odds ratios (OR) of 1.2, 1.3 and 1.3, respectively.[2]

Tiotropium (Spiriva Respimat®)

Tiotropium was previously approved for COPD, but in 2015 it received an indication for use as long-term maintenance therapy for the treatment of asthma in patients 12 years and older. Tiotropium was studied for 12-24 weeks in adult patients who were on ICS therapy with or without other inhalers in 3 trials.[5]

Patients were non-smokers 18-75 years of age (mean age of 46 years) with pre-bronchodilator FEV1 ranging from 2.18-2.30 L. Trial 1 primary endpoint was change from pre-treatment baseline in peak FEV1, 0-3hr at week 12. Trials 2 and 3 had co-primary efficacy endpoints: change from pre-treatment baseline in peak FEV1, 0-3hr and change from pre-treatment baseline in trough FEV1 at week 24. Trials 2 and 3 also included salmeterol 100 mcg as a second comparison arm.[5] Key secondary endpoints were asthma exacerbations, Asthma Control Questionnaire (ACQ), and Asthma Quality of Life Questionnaire (AQLQ). The ACQ is an asthma symptom assessment tool with a range of scores from 0 (totally controlled) to 6 (severely uncontrolled), with a score of change of 0.5 representing a minimally clinical important difference.[6] The Asthma Quality of Life Questionnaire (AQLQ) quantifies both the physical and emotional impact of asthma.[6] The AQLQ scores range from 1 to 7, with higher scores indicating better quality of life. [6] A difference of 0.5 overall and for each item is the minimally clinical important difference for this instrument.[6]

Tiotropium 2.5 mcg was found to be superior to placebo in all 3 trials when used in patients on low to medium strength ICS therapy. In Trial 1, change from baseline FEV1, 0-3 hours, between tiotropium and placebo at 12 weeks was 0.16 L (95% CI, 0.09 to 0.23L) (p-value not provided).[5] Results in the second trial found a change in baseline FEV1, 0-3 hours, of 0.24 L (95% CI, 0.18 to 0.29 L) for tiotropium compared to placebo and 0.21 L (95% CI, 0.16 to 0.27 L) for salmeterol compared to placebo. In change in trough FEV1 from baseline, the difference between tiotropium compared to placebo was 0.19 L (95% CI, 0.13 to 0.24 L) and 0.12 L (95% CI, 0.06 to 0.18 L) for salmeterol compared to placebo.[3] Results in the third trial were similar with a change in baseline FEV1, 0-3 hours, of 0.21 L (95% CI, 0.16 to 0.26 L) for tiotropium compared to placebo and 0.18 L (95% CI, 0.12 to 0.23 L) for salmeterol compared to placebo and for trough FEV1 change from baseline, tiotropium compared to placebo was 0.18 L (95% CI, 0.12 to 0.23 L) and 0.11 L (95% CI, 0.05 to 0.16 L) for salmeterol compared to placebo. Studies of tiotropium 5 mcg yielded less benefit than the 2.5 mcg dose and maximal bronchodilator effect took 4 to 8 weeks.[5] The mean rate of asthma exacerbations were 0.08 for tiotropium compared to 0.24 for placebo in Trial 2 and 0.13 for tiotropium and 0.18 for trial 3 (not assessed in trial 1); however, significance level was not provided. In trial 2 the ACQ-7 responder rate (change in score of ≥ 0.5) was 63% for tiotropium 2.5 mcg and 53% for placebo. The responder rate for AQLQ assessments (change in score of ≥ 0.5) were 58% for tiotropium compared to 50% for placebo.[5]

In studies of adolescents 12-17 years, tiotropium 2.5 mcg once daily was found to be more effective than placebo with a mean difference in peak FEV1, 0-3hr of 0.13 L (95% CI 0.03, 0.23) and 0.11 L (0.002, 0.22) for the 48-week and 12-week trials, respectively).[5]

Randomized Controlled Trials

No additional randomized controlled trials provided evidence to prompt changes to current policy.

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Appendix 1: Current Status on Preferred Drug List

Long-acting Anticholinergics (LAMA)

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	CAP W/DEV	SPIRIVA	TIOTROPIUM BROMIDE	**Y**
INHALATION	AER POW BA	TUDORZA PRESSAIR	ACLIDINIUM BROMIDE	N
INHALATION	BLST W/DEV	INCRUSE ELLIPTA	UMECLIDINIUM BROMIDE	N
INHALATION	CAP W/DEV	SEEBRI NEOHALER	GLYCOPYRROLATE	N
INHALATION	MIST INHAL	SPIRIVA RESPIMAT	TIOTROPIUM BROMIDE	N

Inhaled Corticosteroids (ICS)

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	AER POW BA	PULMICORT FLEXHALER	BUDESONIDE	**Y**
INHALATION	AER W/ADAP	FLOVENT HFA	FLUTICASONE PROPIONATE	**Y**
INHALATION	AER W/ADAP	QVAR	BECLOMETHASONE DIPROPIONATE	**Y**
INHALATION	BLST W/DEV	FLOVENT DISKUS	FLUTICASONE PROPIONATE	**Y**
INHALATION	AER POW BA	ASMANEX	MOMETASONE FUROATE	N
INHALATION	AMPUL-NEB	BUDESONIDE	BUDESONIDE	N
INHALATION	AMPUL-NEB	PULMICORT	BUDESONIDE	N
INHALATION	BLST W/DEV	ARNUITY ELLIPTA	FLUTICASONE FUROATE	N
INHALATION	HFA AER AD	ALVESCO	CICLESONIDE	N
INHALATION	HFA AER AD	ASMANEX HFA	MOMETASONE FUROATE	N

Long-acting Bronchodilators (LABA)

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	BLST W/DEV	SEREVENT DISKUS	SALMETEROL XINAFOATE	**Y**
INHALATION	CAP W/DEV	FORADIL	FORMOTEROL FUMARATE	**Y**
INHALATION	VIAL-NEB	PERFOROMIST	FORMOTEROL FUMARATE	N
INHALATION	VIAL-NEB	BROVANA	ARFORMOTEROL TARTRATE	N
INHALATION	CAP W/DEV	ARCAPTA NEOHALER	INDACATEROL MALEATE	N
INHALATION	MIST INHAL	STRIVERDI RESPIMAT	OLODATEROL HCL	N

LAMA/LABA

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	BLST W/DEV	ANORO ELLIPTA	UMECLIDINIUM BRM/VILANTEROL TR	N
INHALATION	MIST INHAL	STIOLTO RESPIMAT	TIOTROPIUM BR/OLODATEROL HCL	N

ICS/LABA

ROUTE	FORMULATION	BRAND	GENERIC	PDL
INHALATION	BLST W/DEV	ADVAIR DISKUS	FLUTICASONE/SALMETEROL	**Y**
INHALATION	HFA AER AD	ADVAIR HFA	FLUTICASONE/SALMETEROL	**Y**
INHALATION	HFA AER AD	SYMBICORT	BUDESONIDE/FORMOTEROL FUMARATE	**Y**
INHALATION	BLST W/DEV	BREO ELLIPTA	FLUTICASONE/VILANTEROL	N
INHALATION	HFA AER AD	DULERA	MOMETASONE/FORMOTEROL	N

Inhaled Corticosteroids (ICS)

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- Step-therapy required prior to coverage for non-preferred ICS products:
  - Asthma: inhaled short-acting beta-agonist.
  - COPD: short-acting and long-acting bronchodilators (inhaled anticholinergics and beta-agonists). Preferred short-acting and long-acting bronchodilators do NOT require prior authorization. See preferred drug list options at http://www.orpdl.org/drugs/.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred ICS products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3

Approval Criteria		
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD10 J4520-J4522, J45901-45998)?	**Yes:** Go to #7	**No:** Go to #4
4. Does the patient have a diagnosis of COPD (ICD10 J449), chronic bronchitis (ICD10 J410-418, J42, J440-449) and/or emphysema (ICD10 J439)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Does the patient have an active prescription for an inhaled long-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
7. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *9/16 (KS); 9/15 (KS/AG)*
Implementation: *10/9/15*

Long-acting Beta-agonists (LABA)

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- Step-therapy required prior to coverage of non-preferred LABA products:
  - Asthma: inhaled corticosteroid and short-acting beta-agonist.
  - COPD: inhaled short-acting bronchodilator.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class	**No:** Go to #3
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD10 J4520-J4522; J45901-45998)?	**Yes:** Go to #6	**No:** Go to #4

Approval Criteria		
4. Does the patient have a diagnosis of COPD (ICD10 J449), chronic bronchitis (ICD10 J410-418; J42; J440-449) and/or emphysema (ICD10 J439)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
6. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness
7. Does the patient have an active prescription for an inhaled corticosteroid (ICS) or an alternative asthma controller medication?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *9/16 (KS); 9/15 (KS/AG); 5/12; 9/09; 5/09*
Implementation: *10/9/15; 8/12; 1/10*

Long-acting Beta-agonist/Corticosteroid Combination (LABA/ICS)

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- Promote use that is consistent with Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines. See also: http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html
- Step-therapy required prior to coverage:
  - Asthma: short-acting beta-agonist and inhaled corticosteroid or moderate to severe persistent asthma.
  - COPD: short-acting bronchodilator and previous trial of a long-acting bronchodilator (inhaled anticholinergic or beta-agonist) or GOLD C/D COPD. Preferred LABA/ICS products do NOT require prior authorization.

Length of Authorization:

- Up to 12 months

Requires PA:

- Non-preferred LABA/ICS products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the provider consider a change to a preferred product? Message: • Preferred products do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform provider of covered alternatives in class	**No:** Go to #3

Approval Criteria		
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD10 J4520-J4522, J45901-45998)?	**Yes:** Go to #7	**No:** Go to #4
4. Does the patient have a diagnosis of COPD (ICD10 J449), chronic bronchitis (ICD10 J410-418, J42, J440-449) and/or emphysema (ICD10 J439)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is there a documented trial of an inhaled long-acting bronchodilator (anticholinergic or beta-agonist), or alternatively has the patient been assessed with GOLD C/D COPD?	**Yes:** Approve for up to 12 months. Stop coverage of all other LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.
7. Does the patient have an active prescription for an on-demand short-acting beta-agonist (SABA) or an alternative rescue medication for acute asthma exacerbations?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is there a documented trial of an inhaled corticosteroid (ICS) or does the patient have moderate to severe persistent asthma (Step 3 or higher per NIH EPR 3)?	**Yes:** Approve for up to 12 months. Stop coverage of all other ICS and LABA inhalers.	**No:** Pass to RPh. Deny; medical appropriateness

P&T Review: *9/16 (KS); 11/15 (KS); 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *1/1/16; 1/15; 1/14; 9/12; 1/10*

Long-acting Muscarinic Antagonist/Long-acting Beta-agonist Combination (LAMA/LABA)

Goals:

- Promote use that is consistent with Oregon Asthma Guidelines and the NIH EPR 3 Guidelines on Asthma. See also: http://public.health.oregon.gov/DiseasesConditions/ChronicDisease/Asthma/Pages/index.aspx and http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report
- Promote COPD therapy that is consistent with Global Initiative for Chronic Obstructive Lung Disease (GOLD) Guidelines. See also: http://www.goldcopd.org/guidelines-global-strategy-for-diagnosis-management.html
- Step-therapy required prior to coverage:
    - COPD: short-acting bronchodilator and previous trial of a long-acting bronchodilator (inhaled anticholinergic or beta-agonist) or GOLD C/D COPD. Preferred LAMA and LABA products do NOT require prior authorization.

Length of Authorization:

- Up to 12 months

Requires PA:

- All LAMA/LABA products

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 Code	
2. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require PA or a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred LAMA and LABA products in each class	**No:** Go to #3

Approval Criteria		
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD10 J4520-J4522, J45901-45998)?	**Yes:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.	**No:** Go to #4
4. Does the patient have a diagnosis of COPD (ICD10 J449), chronic bronchitis (ICD10 J410-418, J42, J440-449) and/or emphysema (ICD10 J439)?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness. Need a supporting diagnosis. If prescriber believes diagnosis is appropriate, inform prescriber of the appeals process for Medical Director Review.
5. Does the patient have an active prescription for an on-demand short-acting bronchodilator (anticholinergic or beta-agonist)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Has the patient been assessed with GOLD C/D COPD?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers.	**No:** Go to #7
7. Is there a documented trial of a LAMA or LABA, or alternatively a trial of a fixed dose combination short-acting anticholinergic with beta-agonist (SAMA/SABA) (i.e., ipratropium/albuterol)?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA and LABA inhalers or scheduled SAMA/SABA inhalers (PRN SABA or SAMA permitted).	**No:** Pass to RPh. Deny; medical appropriateness.

Drug Class Review

Drugs to Treat Asthma and Chronic Obstructive Pulmonary Disease (COPD)

Final Update 1 Report
Executive Summary

June 2016

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

Marian McDonagh, PharmD
Rebecca Holmes, MD, MS
Ian Blazina, MPH
Brittany Holzhammer, MPH
Melody Thompson, BS

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

INTRODUCTION

Asthma is a chronic lung disease characterized by reversible airway obstruction, inflammation, and increased airway responsiveness. Symptoms include wheezing, difficulty breathing, or coughing. The Expert Panel of the National Asthma Education and Prevention Program (NAEPP) has identified intermittent asthma and persistent asthma as the 2 main severity categories. Persistent asthma is further subdivided into mild, moderate, or severe; however, exacerbations can be severe in any category. Severity is determined by symptoms, short-acting beta-2 agonist use, interference with daily activity, and pulmonary function test performance. In the United States, approximately 22.7 million individuals suffer from asthma and 3,630 deaths were attributed to this condition in 2013.

Chronic obstructive pulmonary disease (COPD) is a chronic, progressive lung disease characterized by persistent airflow limitation, typically in individuals over the age of 40. Smoking is the most common risk factor. COPD typically becomes more severe over time. Chronic inflammation may destroy lung tissue, causing emphysema, and/or lead to small airway damage and obstruction. As in asthma, exacerbations may occur. The severity of airflow obstruction in patients with COPD is classified as mild, moderate, severe, and very severe according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria, based on the level of symptoms, future risk of exacerbations, the severity of airflow obstruction, and the identification of comorbidities. COPD affects over 24 million people in the United States.

This review is an update of the May 2014 Original Report on drugs to treat asthma and chronic obstructive pulmonary disease, which incorporated 2 previous reports on asthma (completed in 2011) and inhaled corticosteroids (completed in 2006).

Scope

We compared the efficacy, effectiveness, and harms of controller medications used in the treatment of persistent asthma and COPD both within and between the major classes of controller drugs. Comparative effects of rescue medications are not included. Representatives of organizations participating in the Drug Effectiveness Review Project approved the following key questions to guide this review:

Key Questions

1. What is the comparative *within-class* and *across-class* efficacy and effectiveness of long-acting inhaled and long-acting oral medications used to treat outpatients with asthma or chronic obstructive pulmonary disease (COPD)?

2. What is the comparative *within-class* and *across-class* tolerability and frequency of adverse events of long-acting inhaled and long-acting oral medications used to treat outpatients with asthma or chronic obstructive pulmonary disease (COPD)?

3. Are there subgroups of patients [e.g. groups defined by demographics (age, racial groups, gender), asthma or COPD severity, comorbidities, other medications (drug-drug interactions), smoking status, genetics, or pregnancy] for which asthma or COPD

controller medications differ in efficacy, effectiveness, or frequency of adverse events?

METHODS

Inclusion Criteria

Populations

- Adult or pediatric (12 months to 18 years) patients with persistent or chronic asthma.
- Adult patients with COPD (≥18 years).

Included Drugs

Table A. Included interventions

Drug type	Active ingredient(s)	Abbreviation	Trade name	Dosage Form
Long-acting beta-2 agonists	Arformoterol tartrate	ARF	Brovana	Solution; Inhalation (nebulized)
	Formoterol fumarate (formerly eformoterol)	FOR	Foradil Perforomist, Aerolizer and Certihaler	Powder; Inhalation (DPI) Solution; Inhalation (nebulized) Powder; Inhalation (DPI)
	Indacaterol maleate	IND	Arcapta	Powder; Inhalation (DPI)
	Olodaterol hydrochloride	OLO	Striverdi Respimat	Soft-mist Spray, Metered (SMI)
	Salmeterol xinafoate	SAL	Serevent	Powder; Inhalation (DPI)
Long-acting muscarinic antagonists[a]	Aclidinium	ACL	Tudorza Pressair	Powder; Inhalation (DPI)
	Glycopyrrolate bromide[b]	GLY	Seebri Breezhaler	Powder; Inhalation (DPI)
	Tiotropium bromide	TIO	Spiriva Spiriva Respimat	Powder; Inhalation (DPI) Soft-mist Spray, Metered (SMI)
	Umeclidinium bromide	UME	Incruse Ellipta	Powder; Inhalation (DPI)
Inhaled corticosteroids	Beclomethasone dipropionate	BEC	QVAR	Aerosol, Metered; Inhalation (MDI)
	Budesonide	BUD	Pulmicort Respules Pulmicort Flexhaler	Suspension; Inhalation (nebulized) Powder, Inhalation (DPI)
	Ciclesonide	CIC	Alvesco	Aerosol, Metered; Inhalation (MDI)
	Flunisolide hemihydrate	FLUN	Aerospan	Aerosol, Metered; Inhalation (MDI)
	Fluticasone furoate	FF	Arnuity Ellipta	Powder; Inhalation (DPI)
	Fluticasone propionate	FP	Flovent DISKUS Flovent HFA	Powder; Inhalation (DPI) Aerosol, Metered; Inhalation (MDI)
	Mometasone furoate	MOM	Asmanex Twisthaler Asmanex HFA	Powder; Inhalation (DPI) Aerosol, Metered; Inhalation (MDI)
Fixed-dose combination products	***ICS/LABA***			
	Formoterol/budesonide	FOR	Symbicort	Aerosol, Metered; Inhalation (MDI)
	Formoterol/mometasone furoate	FOR/MOM	Dulera	Aerosol, Metered; Inhalation (MDI)
	Salmeterol xinafoate/fluticasone propionate	SAL/FP	Advair Diskus Advair HFA	Powder; Inhalation (DPI) Aerosol, Metered; Inhalation (MDI)
	Vilanterol/fluticasone furoate	VIL/FF	Breo Ellipta	Powder; Inhalation (DPI)
	LABA/LAMA			
	Indacaterol/glycopyrrolate	IND/GLY	Utibron Neohaler	Powder; Inhalation (DPI)
	Olodaterol hydrochloride/tiotropium bromide	OLO/TIO	Stiolto Respimat	Soft-mist Spray, Metered (SMI)

Drug type	Active ingredient(s)	Abbreviation	Trade name	Dosage Form
	Umeclidinium bromide/vilanterol trifenatate	UME/VIL	Anoro Ellipta	Powder; Inhalation (DPI)
Leukotriene modifiers	Montelukast sodium	MON	Singulair	Tablet, Chewable tablet, Granules
	Zileuton	SIL	Zyflo Zyflo CR	Tablet Tablet, Extended Release
	Zafirlukast	ZAR	Accolate	Tablet
Phosphodiesterase-4 inhibitor	Roflumilast	ROF	Daliresp	Tablet

Abbreviations: DPI, dry powder inhaler; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonists; LAMA, long-acting muscarinic antagonists MDI, metered dose inhaler; SMI, soft mist inhaler.
[a] The LAMA category includes anticholinergic drugs as well as those specific for muscarinic receptors.
[b] Note, the active ingredient is glycopyrronium. 15.6 mg of glycopyrrolate bromide = 12.5 mg glycopyrrolate.
Excluded: short-acting drugs, combination products containing a short-acting drug, oral corticosteroids.
Shading indicates drugs newly approved since the last report.

Comparisons

- Head-to-head.
- One drug, 2 devices.
- *Excluded: add-on therapy (e.g. comparing fixed-dose combination A/B to either included drug [A or B but not both]), FDCP vs. components at same dose (A/B vs. A+B).*

Efficacy and Effectiveness Outcomes

- Asthma and COPD control (e.g., exacerbations, days/nights frequency of symptoms, frequency of rescue medication use, courses of oral steroids).
- Quality of life assessed using validated scales.
- Ability to participate in work, school, sports, or physical activity, improved sleep.
- Emergency department/urgent medical care visits.
- Hospitalization (all-cause, unless otherwise specified).
- Decreasing mortality.

Adverse Event Outcomes

- Overall adverse events reported, withdrawals due to adverse events.
- Specific adverse events (e.g., growth suppression, bone mineral density, osteoporosis/fractures, ocular toxicity, suppression of the HPA axis, pneumonia, anaphylaxis, death).

Study Designs

- Efficacy/Effectiveness:
    - Randomized controlled clinical trials of at least 12 weeks duration and N≥100
        - Head-to-head trials only *(placebo-controlled trials excluded)*
    - Recent comparative good-quality systematic reviews
        - Search dates May 2014 or later.
- Adverse Events:
    - Randomized controlled clinical trials of at least 12 weeks duration and N≥100
        - Head-to-head trials only
    - Recent comparative good-quality systematic reviews
        - Search dates May 2014 or later
    - Observational studies of at least 6 months duration and N≥1000.

We followed standard DERP methods for literature searching, study selection, data abstraction, validity assessment, data synthesis, and grading the strength of the body of evidence. Detailed methods can be found in the full report. To identify relevant citations, we searched electronic databases through November Week 1 2015 using terms for included drugs, indications, and study designs (see Appendix C of the full report for complete search strategies).

We conducted meta-analyses on outcomes which a sufficient number of studies reported and for studies which were homogeneous enough that combining their results could be justified. We conducted meta-analyses only for the same subset of outcomes for which we graded the strength of the evidence: exacerbations, quality of life, mortality, number of people with serious adverse events, and withdrawals due to adverse events. The I^2 statistic (the proportion of variation in study estimates due to heterogeneity) was calculated to assess heterogeneity between the effects from the studies. When meta-analyses could not be performed, the data are summarized qualitatively.

RESULTS

Table B. Summary of evidence: Comparative benefits and harms of controller medications for the treatment of persistent asthma or COPD

Strength of evidence	Conclusions
Intra-class comparisons (within class)	
Monotherapy	
Inhaled corticosteroids (ICSs) compared with ICSs:	
Low to Moderate (≥12 years) 37 RCTs/3 SRs	**Asthma** • For most comparisons ICSs do not differ in asthma symptoms, exacerbations, rescue medication, or quality of life at equipotent doses. Relatively few studies reported exacerbations, healthcare utilization, or quality of life outcomes. Long-term data beyond 12 weeks is lacking for most of the comparisons. Differences are limited to: o BUD vs. MOM: No difference for symptoms, MOM better than BUD for rescue medication use. (Low-strength evidence) o BEC vs. BUD: Nocturnal awakening: BEC better than BUD. (Low-strength evidence) o FP vs. BEC: lower risk of exacerbation (Low-strength evidence) Nocturnal awakening: No difference (Moderate-strength evidence) o FP vs. BUD: FP better than BUD on functional capacity. (Low-strength evidence) • The overall incidence of adverse events, withdrawals due to adverse events, and specific adverse events (other than oral candidiasis) are similar for equipotent doses of ICSs. o Meta-analysis of equipotent doses of CIC vs. FP found lower risk of oral candidiasis-thrush with CIC (**OR 0.33, 95% CI 0.17, 0.64).**
Moderate (<12 years) 5 RCTs/3 SRs	• In children, the body of evidence supports the above conclusion, but data was only available for 5 comparisons: BEC vs. BUD, BEC vs. FP, BUD vs. CIC, BUD vs. FP, and CIC vs. FP. • 3 fair head-to-head trials provide evidence that short-term (20 weeks to 1 year) growth velocity is reduced less with FP than with BEC or BUD. A 4th head-to-head trial found that CIC-treated subjects had a greater mean body height increase than budesonide-treated subjects over 12 weeks. Evidence on final adult height is not available.
	COPD: No eligible studies of ICS vs. ICS in patients with COPD.
Leukotriene modifiers (LMs) compared with LMs: Insufficient evidence, asthma only	
Long-acting beta-2 agonists (LABAs) compared with LABAs: Contraindicated for monotherapy in Asthma	

Table B. Summary of evidence: Comparative benefits and harms of controller medications for the treatment of persistent asthma or COPD

Strength of evidence	Conclusions
Low to Moderate	**COPD** • ARF and FOR had similar exacerbation rates, improvements in quality of life, and rates of serious adverse events and withdrawals due to adverse events. • Nebulized FOR is similar to FOR via DPI in exacerbations and quality of life. • FOR and IND have similar exacerbations and quality of life. In comparisons of standard dose FOR with high-dose IND, there was not a statistically significant difference in withdrawals due to adverse events, though patients taking an even higher dose of IND were less likely to withdraw due to harms than those taking FOR (**RR 0.58, 95% CI 0.36 to 0.94**). • Important improvement in quality of life was more likely with IND than SAL (**OR 1.59, 95% CI 1.12 to 2.25**). • Greater improvement in quality of life with OLO than FOR (**RR 1.28, 95% CI 1.10 to 1.48** for 5 mcg OLO, **RR 1.26, 95% CI 1.09 to 1.46** for 10 mcg).
Long-acting muscarinic antagonists (LAMAs) compared with LAMAs:	
Low	**COPD** • 3 trials of high-dose GLY vs. standard-dose TIO and 2 of UME and TIO found no differences in rates of exacerbations, use of rescue medication, or quality of life. • Compared with TIO, no differences in overall adverse events, withdrawal due to adverse events, pneumonia, or death with high-dose GLY or UME.
Combination therapy compared with combination therapy	
ICS+LABA compared with ICS+LABA	
Moderate (≥12 years)	**Asthma** **BUD/FOR compared with FP/SAL:** • Large trials up to 6 months in duration find no significant difference in efficacy or quality of life. Meta-analyses show no difference between BUD/FOR and FP/SAL in exacerbations requiring oral steroids, exacerbations requiring ED visit or hospital admission. • Data from 4 large head-to-head trials (5,818 subjects) provide no evidence of a difference in overall adverse events, serious adverse events or withdrawal due to adverse events between BUD/FOR and FP/SAL in adults and adolescents.
Moderate (standard doses) **Low (High doses)** (≥12 years) **Low** (≥12 years)	**FP/SAL compared with MOM/FOR** • Moderate-strength evidence from 2 trials (12 and 52 weeks) indicated no difference in asthma deteriorations and no difference in withdrawal due to adverse events or risk of serious adverse events at medium ICS doses. • For combinations including higher ICS doses, there is low-strength evidence from a single study that there were no statistically significant differences in exacerbations, withdrawal due to adverse events or incidence of serious adverse events between MOM/FOR and FP/SAL. • Ocular toxicity did not differ between treatments at either dose (low-strength evidence) **FP/SAL compared with FF/VIL** • Low-strength evidence suggests no difference in quality of life between the treatments. • Low-strength evidence from a single study of fixed- dose combination inhalers of FP/VIL compared with FP/SAL suggests no difference in rates of withdrawal due to adverse events or serious adverse events between drugs.

Table B. Summary of evidence: Comparative benefits and harms of controller medications for the treatment of persistent asthma or COPD

Strength of evidence	Conclusions
Low (Moderate for QOL *BUD/FOR vs. BEC/FOR*) (6 RCTs)	**COPD** ***BEC/FOR compared with FP/SAL*** • Low-strength evidence of no difference in exacerbations, symptoms, 6-minute walk-test, use of rescue medication. Evidence on quality of life was insufficient. ***BUD/FOR compared with BEC/FOR*** • No differences in quality of life (moderate-strength evidence) or total exacerbations, exacerbations requiring an emergency department visit or hospitalization, or exacerbations requiring corticosteroid treatment (low-strength evidence). • A single good-quality trial did not suggest differences in adverse events, withdrawals due to adverse events, pneumonia or mortality. ***F)/VIL compared with FP/SAL*** • **FF/VIL 100 mcg/25 mcg daily vs. FP/SAL *500 mcg/100 mcg daily.*** Moderate-strength evidence from 3 good-quality 12-week trials finds no difference in exacerbations (pooled 3.7% vs. 2.9%; RR 1.25, 95% CI 0.76 to 2.06), rescue medication use (pooled difference 0.06 per day, 95% CI −0.19 to 0.07) or rescue-free days (54 vs. 49 per 12 weeks). • **FF/VIL 100 mcg/25 mcg daily vs. FP/SAL 1,000 mcg/100 mcg daily.** Low-strength evidence from a single good-quality 12-week trial suggests no difference in rescue-free days or quality of life. **BUD/FOR compared with FP/SAL:** • Evidence (2 good-quality observational studies) on the risk of pneumonia is conflicting. • After a mean 3.5 years follow-up, greater risk with FP/SAL than with BUD/FOR (RR 1.73, 95% CI 1.57 to 1.90), event rates per 100 patient-years 11% and 6.4%). Mortality due to pneumonia was also increased (HR 1.8% CI 1.22 to 2.53; crude incidence 3.6% vs. 1.9%). A 2nd study with 12 months of follow-up finds no difference between the drugs in pneumonia (OR 0.92, 95%, CI 0.81 to 1.04; event rates 17.3% vs. 19.0%) for BUD/FPR vs. FP/SAL.
Inter-class Comparisons (between classes)	
Monotherapy	
ICSs compared with leukotriene modifiers:	
High	**Asthma** • Efficacy studies up to 56 weeks provide consistent evidence favoring ICSs over LMs for both children and adults. ICSs had significantly lower risk of exacerbations than LMs (**OR 0.70; 95% CI 0.57 to 0.86** for FP vs. MON). Meta-analysis found statistically significant differences in favor of ICSs over LMs for quality of life. • No evidence of a difference in risk of withdrawal due to adverse effects (RR 1.24, 95% CI 0.95 to 1.63, 25 trials) comparing LMs with ICSs in adults and children.
Low	An analysis of a subset of 154 children age 6 to 14 in 1 trial found that those treated with FP had significantly fewer ED visits (0.10 vs. 0.35, P=0.002) and missed school days (1.4 vs. 2.1, P<0.001) than those treated with MON.
ICSs compared with LABAs:	
Low to Moderate	**COPD** • No difference in mortality (OR 1.17, 95% CI 0.97 to 1.42; 1 SR of 7 RCTs), exacerbations (OR 0.96, 95% CI 0.89 to 1.02, 1 SR of 4 RCTs), or in hospitalizations due to exacerbations (Risk Ratio 1.07, 95% CI 0.91 to 1.26, 1 study; moderate-strength evidence). • No difference in risk of having any adverse event (OR 1.12, 95% CI 0.96 to 1.30). Serious pneumonia AEs were more frequent with ICS than LABA based on a good-quality SR of 5 studies (**OR 1.48, 95% CI 1.13 to 1.94**)
ICS compared with PDE-4 inhibitors:	

Table B. Summary of evidence: Comparative benefits and harms of controller medications for the treatment of persistent asthma or COPD

Strength of evidence	Conclusions
Low	**Asthma** • More patients taking ROF experienced exacerbations (**RR 3.16, 95% CI 1.10 to 9.11**) and withdrew due to adverse events (**RR 8.75, 95% CI 1.45 to 53.3**) than those taking BEC.
LABAs compared with LAMAs	
	Asthma: monotherapy with LABAs contraindicated
Moderate	**COPD** **SAL compared with TIO** • A systematic review found higher risk of exacerbations with SAL than TIO (**36% vs. 32%; pooled OR 1.19, 95% CI 1.09 to 1.30**) and no differences in hospitalizations or quality of life between SAL and TIO.
Low	• 3 trials found moderate-strength evidence of increased rates of withdrawal due to adverse events for SAL compared with TIO (**OR 1.23, 95% CI 1.05 to 1.45**).
Low	**IND compared with TIO** • Evidence from 3 trials suggested that IND is associated with more frequent exacerbations (**RR 1.11, 95% CI 1.03 to 1.19**), with similar effects on mortality (1.4% vs. 1.5%) and quality of life (SGRQ improvement ≥4 points: OR 1.03, 95% CI 0.88 to 1.21) in patients with severe COPD. • In patients with moderate-to-severe COPD, quality of life improved in fewer patients receiving TIO than IND (**42% vs. 50%; RD −0.08, 95% CI −0.13 to −0.03**), with no differences in hospitalizations or exacerbations • These trials provided low-strength evidence of no differences in serious adverse events or withdrawal due to adverse events.
Combination therapy compared with monotherapy	
ICS/LABA compared with LABA:	
Low	**COPD** • One good-quality trial suggested that exacerbation rates did not differ between patients switching to IND and those continuing treatment with SAL and FP. • There were significantly lower rates of serious adverse events for patients switching to IND than for those continuing treatment with SAL and FP (RR 0.29, 95% CI 0.11 to 0.74).
ICS/LABA compared with ICS (different drug)	
Low **(5 RCTs)**	**Asthma** ***FP/VAL compared with FP*** • 3 good-quality trials find no statistically significant difference in severe exacerbation rates. 2 trials do not find important differences between drugs in quality of life scores using the AQLQ • Meta-analyses of these trials also find no statistically significant difference in withdrawals due to adverse events; or serious adverse events. ***FP/SAL compared with CIC*** • Evidence from a fair-quality study finds that quality of life (AQLQ) was significantly improved with CIC vs. FOR/SAL **(mean change 0.36 vs. 0.27, P<0.0001**); The risk exacerbations was significantly greater in the CIC group than the FP/SAL group (0.30 vs. 0.18; **RR 1.67, 95% CI 1.18 to 2.36**). • Adverse events more common with CIC than FP/SAL **(RR 1.15, 95% CI 1.01, 1.30).**
ICS/LABA compared with LAMA	

Table B. Summary of evidence: Comparative benefits and harms of controller medications for the treatment of persistent asthma or COPD

Strength of evidence	Conclusions
Low	***COPD*** **FP/SAL compared with TIO** • Compared with TIO, FP/SAL was associated with lower risk of mortality, better quality of life, but higher risk of hospitalization. There was no difference in exacerbations. • Compared with FP/SAL, TIO is associated with a significantly lower proportion of patients with serious harms, but no difference in withdrawals due to adverse events. **FF/VIL compared with TIO** • No difference in mortality or serious adverse events.
ICS/LABA compared with LMs	
High (Moderate for age ≤ 12 years) **Low**	**Asthma** • Meta-analysis of 5 RCTs finds FP/SAL to be more efficacious than MON for preventing exacerbations. • 3 trials find greater efficacy for ICS/LABA in children ages 6 to 14 or a mixed age group with 15% of subjects <12 years of age. • No difference in overall adverse events and withdrawals due to adverse events.
LABA/LAMA compared with LAMA	
Low to Moderate	**COPD** ***UME/VIL compared with UME*** • 1 trial found less frequent rescue medication use in patients receiving UME/VIL than UME alone (difference in mean puffs per day: **−0.6, 95% CI −1.2 to 0.0** for the 62.5/25 µg dose). ***UME/VIL compared with TIO*** • 3 unpublished trials found no differences in deaths, quality of life, daily activities, or exacerbations (low-strength evidence) but moderate-strength evidence that reductions in use of rescue medication were greater for UME/VIL vs. TIO **(−3.2 vs. −2.1 in 1 study and −2.0 vs. −1.4** in another). • There were no differences in serious adverse events, withdrawal due to adverse events, overall adverse events, death, or pneumonia
Combination therapy compared with combination therapy	
LABA/LAMA compared with ICS/LABA	
Moderate and High (2 RCTs)	**COPD** ***UME /VIL compared with FP/SAL (standard doses)*** • Based on 2 good-quality 12-week trials, there is moderate-strength evidence of no difference in exacerbation rates (3% each group), and high-strength evidence of no difference in quality of life between UME/VIL and FP/SAL on the EQ5D or SGRQ • There was no difference in overall adverse events, serious adverse events, and withdrawals due to adverse events or pneumonia
Low to Moderate (1 RCT)	***UME/VIL compared with FP/SAL (higher dose ICS)*** • Based on a good quality 12-week trial, there is no difference in exacerbation rates or rescue medication use, and moderate-strength evidence of no difference in quality of life based on the EQ5D or SGRQ. • No difference in overall adverse events, withdrawals due to adverse events or pneumonia.
ICS/LABA compared with LM/ICS	
Moderate to High	**Asthma** • For the drug classes overall, fewer patients taking ICS/LABA had exacerbations than those taking LM/ICS (**RR 0.83, 95% CI 0.71 to 0.97**), but important differences in quality of life were not found (high-strength evidence). • No difference in withdrawals due to adverse events between ICS/LABA and LM/ICS (high-strength evidence) but more patients taking LABAs/ICSs had *serious* adverse events than patients taking LM/ICSs (**RR 1.35, 95% CI 1.00 to 1.82**; moderate-strength evidence)

Table B. Summary of evidence: Comparative benefits and harms of controller medications for the treatment of persistent asthma or COPD

Strength of evidence	Conclusions
LM/LABA compared with ICS/LABA	
Low ≥12 years	**Asthma** **LM/LABA had significantly shorter time to treatment failure than ICS/LABA (P=0.0008; 29 vs. 8 subjects failed) in a 12 week trial.**

Table C. Summary of evidence for controller medications for the treatment of persistent asthma or COPD: Key Question 3

Key Question 3. Are there subgroups of these patients based on demographics (age, racial groups, gender), asthma severity, comorbidities (drug-disease interactions, including obesity), other medications (drug-drug interactions), smoking status, genetics, or pregnancy for which asthma controller medications differ in efficacy, effectiveness, or frequency of adverse events?	
Strength of evidence	**Conclusions**
Insufficient	Evidence on differences based on age, (younger or older), racial groups, gender, pregnancy status, and genetic markers was limited to small subgroup analyses of single trials, or small observational studies. Evidence is summarized in full report.

Limitations of this Report

As with other types of research, the limitations of this systematic review are important to recognize. These can be divided into 2 groups, those relating to applicability of the results (addressed below) and those relating to methodology within the scope of this review.

Methodological limitations of the review within the defined scope included the exclusion of studies published in languages other than English and lack of a specific search for unpublished studies. In addition, the data from most RCTs included in this report have limited utility for assessing real-world adherence to medications. This is largely because they enrolled selected populations, often requiring a high degree of adherence to be included in the trial, and were short-term studies. For example, many of the trials had a run-in period during which adherence was assessed and then only included subjects that met a threshold for good adherence (e.g., adherence to 80% of recommended doses). Unfortunately, for many drugs, there are few or no effectiveness studies and many efficacy studies.

CONCLUSIONS

In intra-class comparisons, few differences were found between drugs, with low- to moderate-strength evidence. In adults or children with asthma, ICSs at equipotent doses do not differ in asthma symptoms, exacerbations, rescue medication, quality of life or adverse events. While **growth velocity is less affected with fluticasone propionate (FP) than beclomethasone dipropionate (BEC), and height increase was less affected with ciclesonide (CIC) than budesonide (BUD) in children,** evidence on final adult height is not available. Similarly, in patients with asthma differences were not found between long-acting beta-2 agonists (LABAs) in benefits or harms, except that **olodaterol hydrochloride (OLO) resulted in better quality of**

life than formoterol fumarate (FOR). Evidence on long-acting muscarinic antagonists (LAMAs) in patients with COPD indicates no differences in benefit or harm outcomes. Evidence on leukotriene modifiers (LMs) in patients with asthma was insufficient to draw conclusions. Comparisons of ICSs/LABAs with each other in patients with asthma or chronic obstructive pulmonary disorder (COPD) showed no differences in benefits, and most comparisons found no differences in adverse event outcomes. However, **FP/salmeterol (SAL) was associated with increased risk of pneumonia and pneumonia-related death compared with BUD/FOR.**

Inter-class comparisons found statistically significant differences between classes in multiple instances, with mostly low- and moderate-strength evidence. In patients with COPD, there was no difference in benefits between ICSs and LABAs but **pneumonia was more frequent with ICSs than LABAs**. In patients with asthma, **ICSs result in better outcomes than LMs**, with no difference in adverse event outcomes. In patients with asthma there were no differences between LABAs and LAMAs in outcomes, but in patients with COPD evidence was mixed. There were **more exacerbations and withdrawals due to adverse events with SAL (LABA) than tiotropium (TIO) (LAMA)** but not for indacaterol (IND) (LABA) compared with TIO (LAMA). There were no differences in hospitalizations or quality of life. Limited evidence suggested that in patients with asthma, more patients taking roflumilast (PDE-4 inhibitor) experienced exacerbations and withdrawals due to adverse events than those taking beclomethasone. In patients with asthma, ICS/LABA was not different to a different ICS, but in patients with COPD switching to IND may result in fewer serious adverse events than staying on FP/SAL. In patients with asthma, **ICS/LABA (FP/SAL) resulted in fewer exacerbations than LM (montelukast [MON])**, but no difference adverse events. In patients with COPD there was no difference in outcomes between ICS/LABAs and LABAs and there was mixed evidence between ICS/LABAs and LAMAs. In patients with asthma, **ICS/LABAs had fewer exacerbations and more serious adverse events, but there was no difference in quality of life or other adverse event outcomes compared with ICS/LMs**. **LABA/LM had shorter time to treatment failure than ICS/LABA in patients with asthma**. In patients with COPD, LABA/LAMA compared with ICS/LABA differed based on the specific drugs compared. In patients with COPD, LABA/LAMA compared with ICS/LABA, there were no differences between umeclidinium bromide (UME)/vilanterol (VIL) and FP/SAL. Evidence on variation in effectiveness or harms in subgroups of populations with asthma or COPD was insufficient to draw conclusions.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Drug Effectiveness Review Project Summary Report – Biologics (Targeted Immune Modulators)

Date of Review: September 2016

Date of Last Review: September 2014
Literature Search: Up to January 2016

Current Status of PDL Class:
See **Appendix 1**.

Research Questions:
1. How do biologic immunosuppressants compare in their efficacy and long-term effectiveness for alleviating symptoms and stabilizing the disease in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis?
2. What are the comparative incidence and severity of harms associated with the use of these drugs?
3. Do the biologic immunosuppressants differ in effectiveness or harms in the following subgroups:
    - Different genders or different racial, age, or socioeconomic groups?
    - Patients with comorbidities?
    - Patients taking other commonly prescribed drugs?
    - Patients with early aggressive compared with persistent rheumatoid arthritis?

Conclusions:
EFFICACY COMPARISONS:
- Low quality evidence suggests that all biologic immunosuppressant treatments approved by the U.S. Food and Drug Administration (FDA) for rheumatoid arthritis have similar efficacy. Specific comparisons between biologics are limited to single head-to-head studies.
- Evidence for differences between biologic treatments for juvenile idiopathic arthritis is insufficient. No head-to-head trials were identified in children.
- Evidence for differences between biologic treatments for ankylosing spondylitis is insufficient. No head-to-head trials were identified.
- In adults, evidence remains insufficient to determine whether there are differences in efficacy for biologic treatments for psoriatic arthritis. Evidence from a single head-to-head clinical trial demonstrated equal efficacy between adalimumab, etanercept and infliximab in adults. No head-to-head trials were identified in children.
- In adults, evidence remains insufficient to determine whether there are differences in efficacy for FDA-approved biologic treatments for Crohn's disease. Evidence for differences in efficacy between biologic treatments is limited to low quality evidence based on one open-labeled study which did not find a difference between adalimumab and infliximab for clinical recurrence rates following curative ileocolonic resection. No head-to-head trials were identified in children.
- Evidence for differences between biologic treatments for ulcerative colitis is insufficient. No head-to-head trials were identified.

- In adults, evidence for differences in efficacy between FDA-approved biologic treatments for plaque psoriasis is limited to 4 head-to-head trials. These trials provide low quality evidence that secukinumab may be superior to ustekinumab; both secukinumab and ustekinumab may be superior to etanercept; and tofacitinib may be equally efficacious to etanercept for treatment of plaque psoriasis. No head-to-head trials were identified in children.

SAFETY COMPARISONS:

- Most comparative evidence available for harms outcomes is for the tumor necrosis factor (TNF) inhibitors adalimumab, etanercept and infliximab. There is moderate quality evidence that infliximab is associated with higher risk for serious infections and discontinuation of therapy due to adverse events than abatacept, adalimumab and etanercept. Specifically, risk for tuberculosis may be higher with adalimumab or infliximab compared to etanercept based on low quality evidence. Low quality evidence does not suggest any differences for risk of herpes zoster between TNF inhibitors.
- Low quality evidence suggests infliximab and adalimumab may be associated with more injection site or infusion reactions than abatacept. Low quality evidence also suggests etanercept may be associated with higher risk of injection site reactions than adalimumab, secukinumab and ustekinumab.
- Low quality evidence suggests no differences in risk for cancer between biologic treatments.
- There is high quality evidence that the combination of 2 biologic agents is associated with higher risk for serious adverse events, discontinuation due to adverse events, and serious infections without additional therapeutic benefit.
- There is insufficient evidence in children to make conclusions on differences in harms between biologic treatments.

SUBGROUP COMPARISONS:

- There is insufficient evidence to determine if differences in efficacy or harms exist between biologic treatments for the pre-specified subgroup populations.

Recommendations:

- Evidence from the Drug Effectiveness Review Project (DERP) report supports our current PDL. Review comparative drug costs in the executive session.
- Recommend minor modifications to the current prior authorization (PA) criteria (Appendix 2).

Previous Conclusions:

- There remains low to insufficient evidence of any difference in efficacy between biologics in the treatment of RA. The most obvious differences that might be clinically relevant involve dosage and administration (oral, intravenous, subcutaneous).
- There is insufficient comparative evidence for the efficacy of biologics in the treatment of juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis, and Crohn's disease.
- There is insufficient evidence based on one randomized controlled trial of no difference in efficacy between adalimumab, etanercept and infliximab for the treatment of psoriatic arthritis.
- There is insufficient evidence based on indirect comparisons of no difference between etanercept, adalimumab and abatacept in preventing disease flares for the treatment of juvenile idiopathic arthritis.
- For the treatment of Crohn's disease, TNF inhibitors (infliximab, adalimumab and certolizumab) were more effective than placebo at inducing remission (RR 1.8; 95% CI 1.4 to 2.4; moderate SOE). However, infliximab is the only biological consistently favored over placebo for multiple outcomes and at multiple time points for both induction and maintenance of remission.
- There is moderate quality evidence that apremilast 20 mg twice daily and apremilast 30 mg twice daily improves signs and symptoms of psoriatic arthritis, as measured by the ACR20 response, compared to placebo (32%, 37%, and 19%, respectively). There appears to be a small advantage of for apremilast 30 mg twice daily; however, it has not been proven to be statistically superior to 20 mg twice daily.

- There is moderate to high quality evidence that vedolizumab is significantly superior to placebo for induction of clinical remission, clinical improvement and prevention of clinical relapse in patients with moderate to severe ulcerative colitis with similar risk of adverse events.[3]
- There is moderate quality evidence of a significantly superior effect of vedolizumab on clinical remission compared to placebo, although the improvement was modest. In patients with previous failure of a TNF inhibitor, there is low quality evidence of no difference in clinical remission at week 6 between vedolizumab and placebo.
- There is low quality evidence that vedolizumab is significantly superior to placebo for maintenance of clinical remission at week 52 compared to placebo.

Previous Recommendations:
- Modify prior authorization criteria to include new FDA approved indications and new medications.
- Evaluate comparative costs of newly approved agents in executive session; Make golimumab non-preferred.

Methods:
The June 2016 Drug Class Update Report on Targeted Immune Modulators by the Drug Effectiveness Review Project (DERP) at the Pacific Northwest Evidence-based Practice Center at the Oregon Health & Science University (OHSU) was used to inform recommendations for this drug class.

The final original report is available to Oregon Pharmacy and Therapeutics Committee members upon request. An executive summary report is publically available in the agenda packet and on the DURM website.

The purpose of the DERP reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. OHSU does not recommend or endorse any guideline or recommendation developed by users of these reports.

Summary Findings:

At total of 3,828 citations were identified in this class update, which is the fifth update of the original DERP report. From these citations, 18 head-to-head randomized trials and 42 head-to-head observational studies were used to inform this report.

In summary, insufficient evidence exists for most comparisons of the efficacy, effectiveness, and harms between abatacept, alefacept, adalimumab, anakinra, apremilast, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, secukinumab, tocilizumab, tofacitinib, and ustekinumab for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis. The most obvious differences are around dosage and administration of these drugs:
- Apremilast and tofacitinib are the only approved orally administered drugs.
- Infliximab, golimumab, natalizumab, rituximab, and vedolizumab require intravenous administration.
- Abatacept, adalimumab, anakinra, canakinumab, certolizumab pegol, etanercept, golimumab, secukinumab, tocilizumab, and ustekinumab can be administered subcutaneously.
- Alefacept requires an intramuscular injection.

Furthermore, administration intervals between drugs substantially differ:

- Adalimumab requires an injection once every other week.
- Anakinra has to be administered daily.
- Etanercept is administered once a week.
- Certolizumab pegol is administered every 2 to 4 weeks.
- Tocilizumab is administered every 1 to 4 weeks.
- Golimumab is administered monthly.
- Ustekinumab is administered every 12 weeks.

See **Table 1** for a list of Biologic Immunosuppressants and their FDA-approved indications included in this DERP class update report.

Table 1. Indications for Biologic Immunosuppressants.

Drug Name	**Ankylosing Spondylitis**	**Crohn's Disease**	**Hidradenitis Suppurativa**	**Juvenile Idiopathic Arthritis**	**Plaque Psoriasis**	**Psoriatic Arthritis**	**Rheumatoid Arthritis**	**Ulcerative Colitis**	**Uveitis (non-infectious)**	**Other**
Abatacept **(ORENCIA)**				≥6 yo			≥18 yo			
Adalimumab **(HUMIRA)**	≥18 yo	≥6 yo	≥18 yo	≥2 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	
Alefacept **(AMEVIVE)**					≥18 yo					
Anakinra **(KINERET)**							≥18 yo			NOMID
Apremilast **(OTEZLA)**					≥18 yo	≥18 yo				
Canakinumab **(ILARIS)**				≥2 yo						FCAS ≥4 yo MWS ≥4 yo
Certolizumab **(CIMZIA)**	≥18 yo	≥18 yo				≥18 yo	≥18 yo			
Etanercept **(ENBREL)**	≥18 yo			≥2 yo	≥18 yo	≥18 yo	≥18 yo			
Golimumab **(SIMPONI)**	≥18 yo					≥18 yo	≥18 yo	≥18 yo		
Infliximab **(REMICADE)**	≥18 yo	≥6 yo			≥18 yo	≥18 yo	≥18 yo	≥6 yo		
Ixekizumab					≥18 yo					

(TALTZ)										
Natalizumab **(TYSABRI)**		≥18 yo								MS ≥18 yo
Rituximab **(RITUXAN)**							≥18 yo			CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo
Secukinumab **(COSENTYX)**	≥18 yo				≥18 yo	≥18 yo				
Tocilizumab **(ACTEMRA)**				≥2 yo			≥18 yo			
Tofacitinib **(XELJANZ)**							≥18 yo			
Ustekinumab **(STELARA)**					≥18 yo	≥18 yo				
Vedolizumab **(ENTYVIO)**		≥18 yo						≥18 yo		

Abbreviations: CLL = chronic lymphocytic leukemia; FCAS = familial cold autoinflammatory syndrome; GPA = granulomatosis with polyangiitis (Wegener's granulomatosis); MS = multiple sclerosis; MWS = Muckle-Wells syndrome; NHL = non-Hodgkin's lymphoma; NOMID = neonatal onset multi-systemic inflammatory disease; yo = years old.

Definitions of the evidence grades used in the DERP report are summarized in **Table 2**.

Table 2. Definitions of the Grades of the Overall Evidence.*

High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before conclusion.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

* This approach does not incorporate other factors that might be relevant to assess reliably the comparative efficacy, effectiveness, and harms; such considerations can include funding sources and comparable dosing. For this review, we reported these additional factors and highlighted any problems that could potentially bias our assessments (e.g., all studies funded by the same manufacturer).

EFFICACY COMPARISONS:

Head-to-Head Trials: Rheumatoid Arthritis

A total of 11 comparative trials were included. Ten head-to-head trials involved a TNF-inhibitor; 4 of the trials were open-labeled. All trials but one assessed efficacy outcomes in a narrowly defined population limited to less than 12 months of follow-up. All efficacy trials were funded by the manufacturer of one of the comparison drugs.

Enrolled patients suffered from active rheumatoid arthritis and most trials employed the American College of Rheumatology criteria to classify the diagnosis of rheumatoid arthritis. Some trials, however, used more strict eligibility criteria. Disease duration and concomitant treatments varied across studies. Most patients used nonsteroidal anti-inflammatory drugs or oral corticosteroids in addition to the study medication. The majority of trials enrolled patients who had failed at least 1 disease-modifying antirheumatic drug (DMARD) or who were on a stable dose of methotrexate with unsatisfactory response. Patients with other autoimmune diseases were generally excluded from studies.

All trials assessed response rates as defined by the American College of Rheumatology or by the European League against Rheumatism. These scales (American College of Rheumatology 20/50/70, Disease Activity Score28) combine measures of global disease activity with counts of tender and swollen joints and acute phase laboratory parameters. In addition, most studies evaluated health outcomes such as quality of life, functional capacity (e.g., Short Form 36 Health Survey, Health Assessment Questionnaire Disability Index, arthritis-specific health index), or discontinuation rates due to disease worsening.

Abatacept vs. adalimumab

Abatacept 125 mg weekly and adalimumab 40 mg every other week in combination with methotrexate may be equally efficacious based on one open-labeled randomized controlled trial. The study was designed to test the non-inferiority of abatacept compared with adalimumab and was funded by the producer of abatacept. The primary outcome measure was the American College of Rheumatology 20 (ACR 20) response at 12 months. At study endpoint, ACR 20 response rates were similar between patients treated with abatacept (64.8%) and adalimumab (63.4%). Secondary endpoints included ACR 50 response rates, Disease Activity Score 28 scores, and Health Assessment Questionnaire Disability Index scores were also similar between groups.

Abatacept vs. infliximab

Abatacept 10 mg/kg every 4 weeks may be superior treatment to a fixed dose of infliximab 3 mg/kg every 8 weeks, both in combination with methotrexate, based on one double-blind, placebo-controlled, head-to-head trial. The primary outcome was assessed at 6 months followed by a double-blinded extension phase for up to 1 year. No statistically significant differences in efficacy were found between treatments at 6 months (Disease Activity Score 28: abatacept –2.53, infliximab –2.25; p=NR). Results after 1 year favored abatacept over infliximab; however, because the infliximab dose was fixed and previous infliximab efficacy trials have shown that up to 30% of patients require dose increases; these results are biased towards a greater efficacy of abatacept.

Abatacept vs. rituximab

An open-label effectiveness trial in Dutch patients who had failed TNF-inhibitor treatment compared abatacept 500 mg, 750 mg or 1000 mg (based on body weight) every 4 weeks or rituximab 1000 mg at baseline, after 2 weeks, and optionally after 6 months. The only exclusion criterion for enrollment was contraindication for treatment. The primary outcome for effectiveness was the Disease Activity Score 28 over time. At 12 months, Disease Activity Score 28 scores were similar between treatment groups (3.8 for abatacept, 3.4 for rituximab; p=NS). Likewise, health-related quality of life measures (Health Assessment Questionnaire, Short Form 36 Health Survey) did not show any statistically significant differences between treatment groups.

Abatacept vs. TNF-inhibitors
An open-label effectiveness trial in Dutch patients who had failed TNF-inhibitor treatment compared abatacept 500 mg, 750 mg or 1000 mg (based on body weight) every 4 weeks or a TNF-inhibitor (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab according to approved dosages). The only exclusion criterion for enrollment was contraindication for treatment. The primary outcome for effectiveness was the Disease Activity Score 28 over time. At 12 months, Disease Activity Score 28 scores were similar between treatment groups (3.8 for abatacept, 3.5 for TNF-inhibitors; P=not significant). Likewise, health-related quality of life measures (Health Assessment Questionnaire, Short Form 36 Health Survey) did not show any statistically significant differences between treatment groups. The open-label study design significantly limits strength of evidence.

Adalimumab vs. etanercept
Evidence from one small, open-labeled randomized controlled trial suggests there is equal efficacy between adalimumab 40 mg every 2 weeks and etanercept 25 mg twice weekly based on similar improvements in the Health Assessment Questionnaire Disability Index score (0.69 vs. 0.68, respectively) and the Disease Activity Score 28-erythrocyte sedimentation rate (ESR) (-2.12 vs. -2.84) after 24 weeks .

Adalimumab vs. tocilizumab
Evidence from one double-blind randomized trial funded by the manufacturer of tocilizumab compared adalimumab 40 mg every 2 weeks with tocilizumab 8 mg/kg every 4 weeks (FDA-approved initial dose is 4 mg/kg every 4 weeks). After 24 weeks, patients treated with tocilizumab had statistically significantly greater improvements on the Disease Activity Score 28 than the adalimumab group (-3.3 vs. -1.8; $p<0.0001$). Because the dosing equivalence is questionable, these findings have to be interpreted cautiously. Evidence from a small, open-labeled randomized controlled trial found that patients in the adalimumab and the tocilizumab groups had similar improvements on the Health Assessment Questionnaire Disability Index score (0.69 vs. 0.70) and the Disease Activity Score 28-ESR (-2.12 vs. -2.10) after 24 weeks.

Adalimumab vs. tofacitinib
Evidence from 2 double-blinded randomized controlled trials show adalimumab 40 mg every other week and tofacitinib 5 mg or 10 mg twice daily may be equally efficacious. The primary endpoint was the change in Disease Activity Score 28 from baseline to week 24. At 6 months, patients treated with adalimumab or the 2 tofacitinib regimens had similar ACR 20 response rates (adalimumab: 47.2%: tofacitinib 5 mg: 51.5%; tofacitinib 10 mg: 52.6%). American College of Rheumatology 50/70 response rates and Health Assessment Questionnaire Disability Index scores were also similar between the 3 treatment groups.

Etanercept vs. infliximab
Evidence is from one small, open-labeled randomized controlled trial that compared etanercept 25 mg twice weekly with fixed-dose infliximab 3 mg/kg at weeks 0, 2, 6, and every 2 months in patients who did not adequately respond to DMARD therapy and remained on methotrexate. Although infliximab had a faster onset of action than etanercept, more patients on etanercept achieved ACR 20 response rates after 54 weeks (74.4% vs. 60%; p=NR). The same pattern existed for the Health Assessment Questionnaire Disability Index (-32.30 vs. -21.60; p=NR). However, infliximab was studied at a fixed-dose on the lower end of the recommended range which may bias the results to favor etanercept.

Etanercept vs. tocilizumab
Evidence is from one small, open-labeled randomized controlled trial that compared etanercept 25 mg twice weekly to tocilizumab 8 mg/kg every 4 weeks. After 24 weeks, patients in the etanercept and the tocilizumab groups had similar improvements on the Health Assessment Questionnaire Disability Index score (0.68 vs. 0.70) and the Disease Activity Score 28-ESR (-2.84 vs. -2.10).

Evidence based on 3 randomized controlled trials indicates that combination therapies etanercept and anakinra, etanercept and abatacept, and rituximab and anti-TNF drugs (adalimumab or etanercept) do not lead to additional benefits but cause significantly higher rates of adverse events.

Head-to-Head Trials: Juvenile Idiopathic Arthritis
No head-to-head randomized trials for the treatment of juvenile idiopathic arthritis were identified.

Head-to-Head Trials: Ankylosing Spondylitis
No head-to-head randomized trials for the treatment of ankylosing spondylitis were identified.

Head-to-Head Trials: Psoriatic Arthritis
One randomized, single-centered, Italian trial in adults with active psoriatic arthritis was identified. The trial compared adalimumab 40 mg every other week, etanercept 25 mg twice weekly and infliximab 5 mg/kg every 6-8 weeks.

Adalimumab vs. etanercept vs. infliximab
In this trial, 100 adult patients were randomized to receive 12 months of treatment. Dose adjustment was permitted for infliximab. Methods of randomization, allocation concealment, loss to follow-up and statistical analyses were poorly reported and baseline characteristics of the 3 groups differed. The patients had a mean age of 48.5 years with moderate disease severity. Patients who had previously used TNF-inhibitors were excluded, as were patients requiring more than 10 mg of prednisone per day or with escalating non-steroidal medication doses. Outcomes assessed were not designated as “primary” or “secondary” but included: American College of Rheumatology 20 response, Psoriasis Area and Severity Index, Health Assessment Questionnaire, tender joint count, swollen joint count, and adverse events. The efficacy results indicate that the 3 groups experienced similar improvements. The proportion of patients achieving an American College of Rheumatology 20 response at 12 months in the groups was: adalimumab 70%; etanercept 72%; infliximab 75%. The authors report on some differences in the other reported outcomes but they do not say whether adjustment for multiple testing was performed and they do not adjust for differences in baseline characteristics of the groups so these results are not reliable.

Head-to-Head Trials: Crohn’s Disease
Two open-label, randomized head-to-head clinical trials with poor methodological quality in adults with Crohn’s disease were identified: one study compared switching from infliximab to adalimumab or remaining on infliximab therapy in patients who had achieved a clinical response for at least 6 months on current infliximab therapy; the second study compared endoscopic, histologic or clinical recurrence after ileocolonic resection.

Adalimumab vs. infliximab
An open-label switch trials randomized patients stabilized on maintenance infliximab therapy to continue their current infliximab regimen (5 mg/kg every 6-8 weeks) for 56 weeks or switch to adalimumab (80 mg once, followed by 40 mg every other week) for 54 weeks. The primary outcome was the proportion of patients who needed rescue therapy with corticosteroids or dose escalation of the TNF-inhibitor or had to discontinue the treatment early. Secondary outcomes

were an increase in Crohn's Disease Activity Index of more than 100 compared to baseline. The Crohn's Disease Activity Index assesses 8 related variables (e.g., number of liquid or soft stools per day, severity of abdominal pain or cramping, general well-being, the presence or absence of extraintestinal manifestations of disease, the presence or absence of abdominal mass, the use or nonuse of antidiarrheal drugs, the hematocrit, and body weight) to yield a composite score between 0 and 600; scores below 150 indicate remission while scores above 450 indicate very severe illness. Response is commonly characterized by a Crohn's Disease Activity Index reduction greater than or equal to 70 points. During follow-up, significantly more patients in the adalimumab group required dose escalation compared with the infliximab group (47% vs. 16%, respectively; p=0.003). Likewise, significantly more patients in the adalimumab group terminated treatment early compared with the infliximab group (28% vs. 2%, respectively; p<0.01). An increase in Crohn's Disease Activity Index of 100 or more points was observed in 28% of patients treated with adalimumab compared with 19% in the infliximab group. Median Inflammatory Bowel Disease Questionnaire scores were similar between groups throughout the study.

A small, randomized controlled trial compared adalimumab to infliximab after ileocolonic resection by assessment of endoscopic, histological and clinical recurrence of disease. For the assessment of clinical recurrence patients were evaluated with the Harvey-Bradshaw index which is a shorter version of the Crohn's Disease Activity Index and consists of 5 clinical parameters. The study reported no statistically significant differences between adalimumab- and infliximab-treated patients regarding clinical (10% vs. 10%), endoscopic (10% vs. 20%), and histological (20% vs. 30%) recurrence after 12 months.

Head-to-Head Trials: Ulcerative Colitis
No head-to-head randomized trials for the treatment of ulcerative colitis were identified.

Head-to-Head Trials: Plaque Psoriasis
Four randomized, industry-sponsored, head-to-head clinical trials for the treatment of moderate-to-severe plaque psoriasis in adults were identified. Enrolled patients were adults with a 6 or 12 month history of moderate-to-severe plaque psoriasis with more than 10% BSA involvement and average baseline Psoriasis Area and Severity Index 75 scores between 20 and 23. The minimum Psoriasis Area and Severity Index score to meet inclusion criteria was 12 and patients were candidates for systemic treatment. Patients were excluded if they had nonplaque disease. The Psoriasis Area and Severity Index 75 results at 12 or 16 weeks from these 4 trials demonstrated that between 39.1% and 93.1% of patients achieved a response.

Etanercept vs. secukinumab
One randomized, double-blind, clinical trial compared etanercept 50 mg twice weekly from baseline to week 12, then once weekly through week 51 to secukinumab 150 mg or 300 mg weekly for 4 doses, and every 4 weeks until week 48. Enrolled patients were adults with moderate-to-severe plaque psoriasis of more than 6 months duration. The trial was sponsored by the manufacturer of secukinumab. The primary outcomes (Psoriasis Area and Severity Index 75 response) at week 12 was achieved in 77.1% of patients in the secukinumab 300 mg group, 67.0% in the 150 mg group, and 44.0% of patients in the etanercept group. The Psoriasis Area and Severity Index 75 response was maintained through to week 52 in 84.3% of the patients who received secukinumab 300 mg, 82.2% of the patients who received 150 mg secukinumab, and 72.5% of the patients who received etanercept.

Etanercept vs. tofacitinib
One randomized, non-inferiority 12-week trial compared etanercept 50 mg twice weekly with 2 doses of twice daily tofacitinib (5 mg or 10 mg) in adult patients with moderate-to-severe plaque psoriasis of at least 12 months duration. The trial was sponsored by the manufacturer of tofacitinib. The primary outcomes were a Psoriasis Area and Severity Index 75 and the Physician Global Assessment response. The results showed that a tofacitinib 10 mg, but not the 5 mg dose, is non-inferior to etanercept. At 12 weeks, 39.5% of the patients in the tofacitinib 5 mg group had achieved a Psoriasis Area and Severity Index 75 response,

compared with 63.6% of the patients in the 10 mg group and 58.8% of patients in the etanercept group. The results for Physician Global Assessment were similar: 47.1% achieved a response in the tofacitinib 5 mg group compared with 68.2% in the 10 mg group and 66.3% in the etanercept group. Tofacitinib does not have FDA-approval for use in plaque psoriasis.

Etanercept vs. ustekinumab
One randomized, single-blind, 12-week clinical trial compared etanercept 50 mg twice weekly with ustekinumab 45 mg or 90 mg at week 0 and week 4 in adults with moderate-to-severe plaque psoriasis. The trial was sponsored by the manufacturer of ustekinumab. Statistically significantly more patients in the ustekinumab 40 mg group and 90 mg group achieved the primary outcome of a Psoriasis Area and Severity Index 75 response compared with the etanercept group (67.5% vs. 73.8% vs. 56.8%, respectively; p<0.001). Similarly, statistically significantly more patients in both ustekinumab groups demonstrated cleared or minimal disease with the Physician Global Assessment (etanercept 50 mg, 49%; ustekinumab 45 mg, 65.1%; ustekinumab 90 mg, 70.6%; p<0.001).

Secukinumab vs. ustekinumab
One randomized, double-blind, controlled trial compared secukinumab 300 mg weekly for 4 weeks followed by every 4 weeks to ustekinumab 45 mg (≤100 kg patients) or 90 mg (>100 kg patients) at baseline, at week 4, then every 12 weeks in adult patients with moderate-to-severe plaque psoriasis. The trial was sponsored by the manufacturer of secukinumab. Results for the trial at time of DERP publication included data for up to 16 weeks of follow-up, but the trial is still ongoing and will provide results at up to 52 weeks duration. The primary outcome was Psoriasis Area and Severity Index 90 response at week 16. Secukinumab was statistically superior to ustekinumab: 79.0% of patients in the secukinumab group achieved a Psoriasis Area and Severity Index 90 response at week 16 compared with 57.6% of ustekinumab patients (p<0.0001). A total of 93.1% of secukinumab patients and 82.7% of ustekinumab patients achieved a Psoriasis Area and Severity Index 75 response at week 16 (p<0.0001).

SAFETY COMPARISONS:

Overall frequency of any adverse event
The majority of trials were conducted in patients with rheumatoid arthritis. The duration of trials varied from 12 weeks to 13 months and the rate of adverse events in the included trials varied from 15% to 87%, but it was generally greater than 50%.The most common adverse events that occurred in the included trials were: headache, urinary tract infection, respiratory infections, diarrhea and muscle pain. There was no statistically significant difference in the relative risk of overall adverse events between any of the biologic immunosuppressants included in the trials.

Withdrawal/discontinuation due to adverse events
In one trial, patients on abatacept had a statistically significant lower rate of discontinuations due to adverse events than patients on adalimumab (3.8% vs. 9.5%; relative risk [RR]: 0.4; 95% CI, 0.21 to 0.76) during 2 years of follow-up. Another trial reported that patients who received etanercept had a statistically significantly higher risk to discontinue the therapy because of adverse events than patients on tofacitinib 5mg twice daily (3% vs. 1%; RR 3.60; 95 CI, 1.01 to 12.79). Because of low event rates, these differences need to be viewed cautiously. There was no statistically significant difference in withdrawal due to adverse events for any other comparison based on the results from randomized trials. The majority of the trials, however, were not sufficiently large to detect a statistically significant difference.

Observational studies are generally larger than RCTs and therefore more able to detect rare outcomes and also may more accurately reflect real-world conditions. The DERP therefore reported on additional data of discontinuation of therapy from observational studies for this outcome. Seven observational

studies with more than 22,000 patients reported on the comparative risk of discontinuation of therapy due to adverse events; however, data were limited to the TNF-inhibitors adalimumab, etanercept and infliximab. Overall, infliximab was consistently associated with the highest risk of discontinuation due to adverse events in patients with rheumatoid arthritis. In several studies, the adjusted hazard ratio (HR) for discontinuation due to adverse events was significantly higher for infliximab compared with etanercept. In a British registry of psoriasis patients, the risk of discontinuation due to adverse events was also statistically significantly higher for infliximab than for adalimumab-treated patients (HR 2.82; 95% CI, 1.79-4.45). Patients taking ustekinumab were less likely to discontinue treatment due to adverse events than patients taking adalimumab (HR 0.60; 95% CI, 0.39-0.92). Likewise, in 3 observational studies the adjusted HR for discontinuation due to adverse events favored adalimumab over infliximab. The comparative evidence for adalimumab and etanercept was conflicting.

Serious adverse events
The number of serious adverse events reported was low (5% overall) resulting in wide confidence intervals. There was one statistically significant difference found from the head-to-head randomized controlled trials: the relative risk of serious adverse events for abatacept compared with infliximab is 0.45 (95% CI, 0.20 to 0.99) favoring abatacept. Importantly, the confidence interval for this estimate includes the possibility that there is no clinically relevant difference between abatacept and infliximab. Patients who received abatacept had a lower rate of serious adverse events than patients who received placebo (5.1% vs. 11.8%, respectively), which gives concern to the validity of the observations of serious adverse events in this study. Furthermore, for all of the other available comparisons, there were no statistically significant differences in incidence of serious adverse events across comparisons.

Injection site or infusion reactions
Infusion reactions consisted of mostly nonspecific symptoms such as headache, dizziness, nausea, pruritus, chills, or fever. A small proportion of infusion reactions resembled anaphylactic reactions or lead to convulsions. In contrast, injection site reactions mainly included erythema, pruritus, rash, and pain of mild to moderate severity.

Calculation of the relative risk for an infusion or injection site reaction revealed a significant difference between drugs. In one trial, abatacept has a lower risk of injection site reaction than adalimumab (RR 0.41; 95% CI, 0.22 to 0.79) and in a second trial the intravenous loading dose of abatacept had a lower risk of infusion reaction than infliximab (RR 0.28; 95% CI, 0.13 to 0.60). Etanercept consistently had higher risks of injections site reactions than comparator drugs. In trials, the risk of injection site reactions often were significantly higher for etanercept compared with adalimumab (RR 2.13; 95% CI, 1.04 to 4.35), secukinumab (RR 14.90; 95% CI, 6.70 to 33.16), and ustekinumab (RR 6.26; 95% CI, 4.00 to 9.81).

Mortality
Large observational studies and registries identified indicate that there is no statistically significant difference among the TNF-inhibitors adalimumab, infliximab, and etanercept. Mortality data for other biologic immunosuppressants are not adequate to make inferences.

Serious infections
Definitions of serious infections were typically deaths, hospitalizations, and use of intravenous antibiotics associated with infections. The number of overall serious infections was reported in 5 of the included randomized controlled trials providing direct comparative data for adalimumab versus tofacitinib, adalimumab versus tocilizumab, etanercept versus tofacitinib, and secukinumab versus ustekinumab. In all 5 trials, very few serious infections occurred which lends the data inadequate to sufficiently compare rates of serious infections. However, 14 observational studies containing data on the comparative risk between biologic immunosuppressants for serious infections were identified. For this outcome, comparative data on abatacept, rituximab, tocilizumab,

ustekinumab, and the TNF-inhibitors adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab were identified. Overall, infliximab was consistently associated with the highest risk of serious infections compared to abatacept, adalimumab, etanercept and rituximab.

Tuberculosis
Five retrospective studies that reported on the comparative risk of tuberculosis in patients taking biologic immunosuppressants were identified. The results of these 5 studies consistently showed that etanercept is associated with a lower risk of developing tuberculosis than adalimumab or infliximab although baseline risk of tuberculosis differed between settings.

Opportunistic infections
Data on opportunistic infections from once large observational study (n=48.349) indicated that infliximab has a higher hazard of opportunistic infections than etanercept (adjusted HR 2.9; 95% CI, 1.5 to 5.4). In the same study, the difference between adalimumab and etanercept was not statistically significant (adjusted HR 1.8; 95% CI 0.8 to 4.0). Overall, 80 opportunistic infections were diagnosed in patients on a TNF-inhibitor. The most common infections were pneumocystis and nocardiosis/actinomycosis.

Herpes zoster
In 2 randomized controlled trials that reported on herpes zoster, the incidence was similar for abatacept (2.8% over 2 years) and adalimumab (1.8% over 2 years), and for tofacitinib 5 mg (1 out of 329 in 12 weeks), tofacitinib 10 mg (2 out of 330 in 12 weeks), and etanercept (2 out of 335 in 12 weeks). The DERP did not identify any other data on the incidence of herpes zoster in randomized controlled trials because the trials were too small to detect such a rare adverse event; however, 4 observational studies were identified that provide evidence on the comparative risk of varicella zoster virus (herpes zoster, chicken pox, or shingles) in over 45,000 rheumatoid arthritis patients on TNF-inhibitors adalimumab, etanercept, and infliximab. Overall, most of the comparisons produced non-significant hazard ratios and therefore no conclusions could be made with any certainty that one TNF-inhibitor has a higher risk of herpes zoster than another agent.

Malignancies
Evidence regarding malignancies from randomized controlled trials was sparse. Several included trials reported the number of malignancies in active arms, but due to the low numbers overall, no significant differences between biologic immunosuppressants were detected. However, 6 large observational database studies were identified that analyzed the incidence of any malignancy (excluding melanoma and non-melanoma skin cancer) in patients with rheumatoid arthritis (n=31,418). Overall, there were no significant difference in the risk of malignancy between adalimumab, anakinra, etanercept, infliximab, and rituximab. Furthermore, when adjusted hazard or odds ratios were provided, the data were conflicting and favored different biologic immunosuppressants in different studies. This body of evidence is limited because of the rare nature of the event.

Non-melanoma skin cancer
Three large observational databases of rheumatoid arthritis patients (n=24,154) that calculated the risk of non-melanoma skin cancers or keratinocyte skin cancers (such as basal and squamous cell carcinomas) for patients on TNF-inhibitors adalimumab, etanercept, or infliximab were identified. No differences in the incidence of non-melanoma skin cancers between these drugs were found.

Melanoma skin cancer
One observational database study that reported on the comparative incidence of melanoma was identified. This analysis compared the rates of melanoma in patients receiving the TNF-inhibitors etanercept and infliximab. Overall, the odds ratios for melanoma for infliximab (OR 2.6; 95% CI, 1.0 to 6.7) and etanercept (OR 2.4; 95% CI, 1.0 to 5.8) were equal.

SUBGROUP COMPARISONS:

The majority of the trials did not contain any information about the effectiveness and harms of biologic immunosuppressants in one subgroup of patients compared with another subgroup or compared with the general population. No statistically significant or clinically meaningful difference could be determined for subgroups based on age, gender, race, co-morbidities, duration of rheumatoid arthritis (<2 vs. ≥2 years), or number of previous DMARDs (0-5).

Reference:
Gartlehner G, Glechner A, Kien C, et al. Targeted Immune Modulators Drug Class Review: Final Update 5 Report, June 2016. Drug Effectiveness Review Project at the Pacific Northwest Evidence Practice Center, Portland, Oregon, in partnership with Cecil G. Sheps Center for Health Services Research at RTI-UNC Evidence-based Practice Center, Chapel Hill, NC.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-Q	PEN IJ KIT	HUMIRA PEN	ADALIMUMAB	Y
SUB-Q	PEN IJ KIT	HUMIRA PEN CROHN'S-UC-HS	ADALIMUMAB	Y
SUB-Q	PEN IJ KIT	HUMIRA PEN PSORIASIS	ADALIMUMAB	Y
SUB-Q	PEN INJCTR	ENBREL	ETANERCEPT	Y
SUB-Q	SYRINGE	ENBREL	ETANERCEPT	Y
SUB-Q	SYRINGEKIT	HUMIRA	ADALIMUMAB	Y
SUB-Q	SYRINGEKIT	HUMIRA PEDIATRIC CROHN'S	ADALIMUMAB	Y
SUB-Q	VIAL	ENBREL	ETANERCEPT	Y
INTRAVEN	VIAL	ACTEMRA	TOCILIZUMAB	N
INTRAVEN	VIAL	ORENCIA	ABATACEPT/MALTOSE	N
INTRAVEN	VIAL	REMICADE	INFLIXIMAB	N
INTRAVEN	VIAL	RITUXAN	RITUXIMAB	N
INTRAVEN	VIAL	SIMPONI ARIA	GOLIMUMAB	N
ORAL	TAB DS PK	OTEZLA	APREMILAST	N
ORAL	TABLET	OTEZLA	APREMILAST	N
ORAL	TABLET	XELJANZ	TOFACITINIB CITRATE	N
SUB-Q	KIT	CIMZIA	CERTOLIZUMAB PEGOL	N
SUB-Q	PEN INJCTR	COSENTYX PEN	IXEUKINUMAB	N
SUB-Q	PEN INJCTR	COSENTYX PEN (2 PENS)	IXEUKINUMAB	N
SUB-Q	PEN INJCTR	SIMPONI	GOLIMUMAB	N
SUB-Q	SYRINGE	ACTEMRA	TOCILIZUMAB	N
SUB-Q	SYRINGE	COSENTYX (2 SYRINGES)	IXEUKINUMAB	N
SUB-Q	SYRINGE	COSENTYX SYRINGE	IXEUKINUMAB	N
SUB-Q	SYRINGE	KINERET	ANAKINRA	N
SUB-Q	SYRINGE	ORENCIA	ABATACEPT	N
SUB-Q	SYRINGE	SIMPONI	GOLIMUMAB	N
SUB-Q	PEN INJCTR	TALTZ	IXEKIZUMAB	N
SUB-Q	SYRINGE	STELARA	USTEKINUMAB	N
SUB-Q	SYRINGEKIT	CIMZIA	CERTOLIZUMAB PEGOL	N
INTRAVEN	VIAL	TYSABRI	NATALIZUMAB	N
INTRAVEN	VIAL	ENTYVIO	VEDOLIZUMAB	

Biologics for Autoimmune Diseases

Goal(s):

- Restrict use of biologics to OHP funded conditions and according to OHP guidelines for use.
- Promote use that is consistent with national clinical practice guidelines and medical evidence.
- Promote use of high value products.

Length of Authorization:

Up to 12 months

Requires PA:

- All biologics except for biologics approved by the FDA for the following indications:
  - Non-Hodgkin Lymphoma (ICD-10 C85.8x, C85.9x)
  - Chronic Lymphocytic Leukemia (ICD-10 C91.10, C91.11, C91.12)
  - Juvenile Idiopathic Arthritis (ICD-10 M08)
  - Multiple Sclerosis (ICD-10 G35)
  - Non-infectious posterior uveitis (ICD-10 H44.13)

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Table 1. Indications for Biologic Immunosuppressants.

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Hidradenitis Suppurativa	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Uveitis (non-infectious)	Other
Abatacept **(ORENCIA)**				≥6 yo			≥18 yo			
Adalimumab **(HUMIRA)**	≥18 yo	≥6 yo	≥18 yo	≥2 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	≥18 yo	
Alefacept **(AMEVIVE)**					≥18 yo					
Anakinra **(KINERET)**							≥18 yo			NOMID
Apremilast **(OTEZLA)**					≥18 yo	≥18 yo				
Canakinumab **(ILARIS)**				≥2 yo						FCAS ≥4 yo MWS ≥4 yo
Certolizumab **(CIMZIA)**	≥18 yo	≥18 yo				≥18 yo	≥18 yo			
Etanercept **(ENBREL)**	≥18 yo			≥2 yo	≥18 yo	≥18 yo	≥18 yo			
Golimumab **(SIMPONI)**	≥18 yo					≥18 yo	≥18 yo	≥18 yo		
Infliximab **(REMICADE)**	≥18 yo	≥6 yo			≥18 yo	≥18 yo	≥18 yo	≥6 yo		
Ixekizumab **(TALTZ)**					≥18 yo					
Natalizumab **(TYSABRI)**		≥18 yo								MS ≥18 yo
Rituximab **(RITUXAN)**							≥18 yo			CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo
Secukinumab **(COSENTYX)**	≥18 yo				≥18 yo	≥18 yo				
Tocilizumab **(ACTEMRA)**				≥2 yo			≥18 yo			
Tofacitinib **(XELJANZ)**							≥18 yo			
Ustekinumab **(STELARA)**					≥18 yo	≥18 yo				
Vedolizumab **(ENTYVIO)**		≥18 yo						≥18 yo		

Abbreviations: CLL = chronic lymphocytic leukemia; FCAS = familial cold autoinflammatory syndrome; GPA = granulomatosis with polyangiitis (Wegener's granulomatosis); MS = multiple sclerosis; MWS = Muckle-Wells syndrome; NHL = non-Hodgkin's lymphoma; NOMID = neonatal onset multi-systemic inflammatory disease; yo = years old.

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the diagnosis funded by OHP? Note: Medical treatment for Hidradenitis Suppurativa (ICD-10 L73.2) is not funded by the OHP.	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Will the prescriber change to a preferred product? <u>Message</u>: • Preferred products do not require a co-pay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Go to #4
4. Is the prescription for rituximab for Non-Hodgkin Lymphoma (ICD-10 C85.8x; C85.9x) or Chronic Lymphocytic Leukemia (ICD-10 C91.10; C91.11; C91.12)?	**Yes:** Approve for length of treatment.	**No:** Go to #5
5. Is the prescription for natalizumab, prescribed for the management of multiple sclerosis (ICD-10 G35)?	**Yes:** Approve for length of treatment.	**No:** Go to #6
6. Is the diagnosis juvenile idiopathic arthritis (ICD-10 M08), non-infectious posterior uveitis (ICD-10 H44.13), or ankylosing spondylitis (ICD-10 M459) and the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for length of treatment.	**No:** Go to #7

Approval Criteria		
7. Is the diagnosis plaque psoriasis (ICD-10 L400-404; L408-418; L448) and the request for a drug FDA-approved for this condition as defined in Table 1? Note: Only treatment for severe plaque psoriasis is funded by the OHP	**Yes:** Go to #8	**No**: Go to #10 Note: Seborrheic dermatitis (L2083; L210-219; L303), keroderma (L110; L83; L850-852; L870-872; L900-902; L906; L940; L943) or other hypertrophic and atrophic conditions of skin (L119; L572; L574; L664; L908-909; L918-919; L922; L985) are not funded by OHP.
8. Is the plaque psoriasis severe in nature, which has resulted in functional impairment (e.g., inability to use hands or feet for activities of daily living, or significant facial involvement preventing normal social interaction) and one or more of the following: • At least 10% body surface area involvement; or • Hand, foot or mucous membrane involvement?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; not funded by the OHP.
9. Has the patient failed to respond to each of the following first-line treatments: • Topical high potency corticosteroid (e.g., betamethasone dipropionate 0.05%, clobetasol propionate 0.05%, fluocinonide 0.05%, halcinonide 0.1%, halobetasol propionate 0.05%; triamcinolone 0.5%); and • At least one other topical agent: calcipotriene, tazarotene, anthralin; and • Phototherapy; and • At least one other systemic therapy: acitretin, cyclosporine, or methotrexate?	**Yes**: Document each therapy with dates: _____ Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
10. Is the diagnosis rheumatoid arthritis (ICD-10 M069; M0500; M0530; M0560; M061; M0800; M083; M0840; M1200; M0510; M064) or psoriatic arthritis (ICD-10 L4054; L4059) and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #11	**No:** Go to #14
11. Has the patient failed to respond to at least one of the following disease-modifying antirheumatic drugs (DMARD) for ≥6 months: • Methotrexate, leflunomide, or sulfasalazine or hydroxychloroquine; or • Have a documented intolerance or contraindication to DMARDs?	**Yes:** Document each therapy with dates: _____ If applicable, document intolerance or contraindication(s): _____ Go to #12	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the request for tofacitinib?	**Yes:** Go to #13	**No:** Approve for up to 12 months
13. Is the patient currently on DMARD therapy or on another potent immunosuppressant like azathioprine or cyclosporine?	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for up to 12 months
14. Is the diagnosis Crohn's disease (ICD-10 K5000; K5010; K5080; K5090) or ulcerative colitis (ICD-10 K5100; K5120; K5130; K5140; K5150; K5180; K5190) and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #15	**No:** Go to #16

Approval Criteria		
15. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for ≥6 months: • Mercaptopurine, azathioprine, or budesonide; or • Have a documented intolerance or contraindication to conventional therapy?	**Yes:** Document each therapy with dates: _____ If applicable, document intolerance or contraindication(s): _____ Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
16. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *induction* of remission?	**Yes:** Approve for length of treatment	**No:** Go to #19
17. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *maintenance* of remission?	**Yes:** Go to #18	**No:** Go to #19
18. Has the patient failed to respond to at least one of the following conventional immunosuppressive therapies for maintenance of remission, in conjunction with a low-dose corticosteroid, for ≥6 months: • Azathioprine, leflunomide, or methotrexate • Have a documented intolerance or contraindication to DMARDs?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.
19. Is the diagnosis a variant cryopyrin-associated periodic syndrome (Familial Cold Autoinflammatory Syndrome, Muckle-Wells Syndrome, or chronic infantile neurologic cutaneous articular syndrome [also known as neonatal onset multi-systemic inflammatory disease]) and the request for a drug FDA-approved for one of these conditions as defined in Table 1?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny; medical appropriateness.

Drug Class Review

Targeted Immune Modulators

Final Update 5 Report
Executive Summary

June 2016

The purpose of Drug Effectiveness Review Project reports is to make available information regarding the comparative clinical effectiveness and harms of different drugs. Reports are not usage guidelines, nor should they be read as an endorsement of or recommendation for any particular drug, use, or approach. Oregon Health & Science University does not recommend or endorse any guideline or recommendation developed by users of these reports.

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Update 5 Authors:

Gerald Gartlehner, MD, MPH
Anna Glechner, MD
Christina Kien, MSc
Peter Mahlknecht, MD
Bita Mesgarpour, PharmD, MPH, PhD
Kylie J. Thaler, MD, MPH

Produced by
RTI-UNC Evidence-based Practice Center
Cecil G. Sheps Center for Health Services Research
University of North Carolina at Chapel Hill
725 Martin Luther King Jr. Blvd, CB# 7590
Chapel Hill, NC 27599-7590
Dan Jonas, MD, MPH, Director

Drug Effectiveness Review Project
Marian McDonagh, PharmD, Principal Investigator

Pacific Northwest Evidence-based Practice Center
Roger Chou, MD, Director
Marian McDonagh, PharmD, Associate Director

INTRODUCTION

Targeted immune modulators (TIMs) are a relatively new category of medications used in the treatment of certain types of immunologic and inflammatory diseases, including rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ulcerative colitis. The US Food and Drug Administration approved the first of the TIMs (infliximab) in 1998 and approved 16 additional agents since that time for treating various chronic inflammatory and autoimmune disorders, including different types of arthritis, inflammatory bowel diseases, plaque psoriasis and multiple sclerosis: etanercept (1998), anakinra (2001), adalimumab (2002), alefacept (2003), abatacept (2005), rituximab (2006), natalizumab (2008), certolizumab pegol (2008), golimumab (2009), ustekinumab (2009), tocilizumab (2010), tofacitinib (2012), canakinumab (2013), apremilast (2014), vedolizumab (2014) and secukinumab (2015).

Scope and Key Questions

The purpose of this review is to help policymakers and clinicians make informed choices about the use of targeted immune modulators. Included drugs are shown in Table 1.

Table 1 Included drugs

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
Apremilast	Otezla® Celgene Corporation	PDE4 inhibitor	Adult moderate to severe plaque psoriasis and psoriatic arthritis	Day 1: 10 mg tablet in AM; Day 2: 10 mg AM and 10 mg PM; Day 3: 10 mg AM and 20 mg PM; Day 4: 20 mg AM and 20 mg PM; Day 5: 20 mg AM and 30 mg PM; Day 6 and thereafter: 30 mg AM and 30 mg PM (in patients with severe renal impairment AM doses only).
Abatacept	Orencia® Bristol Myers Squibb	CD80/86–CD28 T-cell co-stimulation modulator	Rheumatoid arthritis	Intravenous infusion should be administered in 30-minutes according to body weight (<60 kg = 500 mg; 60-100 kg = 750 mg; >100 kg = 1000 mg); dose repeated at 2 weeks and 4 weeks after initial dose, and every 4 weeks thereafter. Subcutaneous injection once weekly with or without an intravenous loading dose; Following single intravenous loading dose according to body weight specified above, the first 125 mg SC injection within 1 day, followed by 125 mg once weekly. Patients unable to receive an infusion may initiate weekly SC injections without an intravenous loading dose. Patients transitioning from intravenous therapy to SC administration should administer the first SC dose instead of next scheduled intravenous dose.
			Juvenile idiopathic arthritis (6 years and older)	10 mg/kg intravenously for patients <75 kg; adults schedule for patients >75kg (maximum dose 1000 mg) on weeks 0, 2, and 4 and then every 4 weeks thereafter.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
Adalimumab	Humira® AbbVie	TNF Inhibitor	Rheumatoid arthritis	40 mg every other week as SC injection; may increase to 40 mg weekly for adalimumab monotherapy.
			Psoriatic arthritis, ankylosing spondylitis	40 mg every other week as SC injection.
			Juvenile idiopathic arthritis (4 years of age and older)	Body weight:10 kg (22 lbs) to < 15 kg (33 lbs): 10 mg every other week. Body weight: 15 kg (33 lbs) to < 30 kg (66 lbs): 20 mg every other week. Body weight: ≥ 30 kg (66 lbs): 40 mg every other week.
			Adult Crohn's disease	Initial SC dose (Day 1) 160 mg (4 40 mg injections in 1 day or 2 40 mg injections daily for 2 consecutive days), followed by 80 mg 2 weeks later (Day 15). 2 weeks later (Day 29) begin a maintenance dose of 40 mg every other week.
			Pediatric Crohn's disease	Pediatric patients 6 years of age and older with body weight of: 17 kg (37 lbs) to < 40 kg (88 lbs): 80 mg (2 40 mg injections on Day 1) and 40 mg 2 weeks later (on Day 15), followed by a maintenance dose of 20 mg every other week. Body weight ≥ 40 kg (88 lbs): 160 mg on Day 1 (4 injections on 1 day or 2 40 mg injections per day for 2 consecutive days); and 80 mg (2 40 mg injections) 2 weeks later (on Day 15), followed by a maintenance dose of 40 mg every other week.
			Ulcerative colitis	Initial SC dose (Day 1) 160 mg (4 40 mg injections in 1 day or 2 40 mg injections daily for 2 consecutive days), followed by 80 mg 2 weeks later (Day 15). 2 weeks later (Day 29) continue with a dose of 40 mg every other week. Only continue in patients who have shown evidence of clinical remission by 8 weeks (Day 57) of therapy.
			Plaque psoriasis	80 mg initial SC dose followed by 40 mg every other week starting 1 week after initial dose (beyond 1 year has not been evaluated in controlled clinical studies).
Alefacept	Amevive® Astellas	CD2 antagonist	Plaque psoriasis	15 mg given once weekly as an intramuscular injection. Treatment should be continued for 12 weeks; re-treatment with an additional 12 week course may be initiated provided that CD4+ T lymphocytes counts are >250 cells/μL and a 12-week interval has passed since the end of the initial treatment cycle.
Anakinra	Kineret® Biovitrum/ Amgen	IL-1 Inhibitor	Rheumatoid arthritis	100 mg daily as SC injection; dose should be decreased to 100 mg every other day in renal insufficiency (CLcr< 30 mL/min).
			Neonatal-Onset Multisystem Inflammatory Disease (NOMID)	1-2 mg/kg initial SC dose (adjusted in 0.5 to 1.0 mg/kg to a maximum of 8 mg/kg daily), once or split into twice daily administrations.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
Canakinumab	Ilaris® Novartis	IL-1β Inhibitor	Systemic Juvenile Idiopathic Arthritis (2 years and older)	Body weight ≥ 7.5 kg: 4mg/kg SC injections (maximum of 300 mg) every 4 weeks.
Certolizumab pegol	Cimzia® UCB, Inc	TNF Inhibitor	Rheumatoid arthritis	400 mg (given as 2 SC injections of 200 mg each) initially and at weeks 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered.
			Crohn'sdisease	400 mg (given as 2 SC injections of 200 mg each) initially and at weeks 2 and 4. If response occurs, follow with 400 mg SC every 4 weeks.
			Psoriatic Arthritis	400 mg (given as 2 SC injections of 200 mg each) initially and at week 2 and 4, followed by 200 mg every other week; for maintenance dosing, 400 mg every 4 weeks can be considered.
			Ankylosing spondylitis	400 mg (given as 2 SC injections of 200 mg each) initially and at weeks 2 and 4, followed by 200 mg every other week or 400 mg every 4 weeks.
Etanercept	Enbrel® Amgen Pfizer Immunex	TNF Inhibitor	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis	50 mg SC injection once weekly.
			Juvenile idiopathic arthritis (2-17 years)	Body weight ≥ 63 kg (138 pounds): 50 mg SC injection weekly Body weight <63 kg (138 pounds): 0.8 mg/kg SC injection weekly.
			Plaque psoriasis	50 mg SC injection twice weekly for 3 months, followed by 50 mg once weekly.
Golimumab	Simponi ARIA® Janssen Biotech	TNF Inhibitor	Rheumatoid arthritis	2 mg/kg intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks in combination with methotrexate.
	Simponi® Janssen Biotech		Rheumatoid arthritis	50 mg SC injection once a month in combination with methotrexate.
			Psoriatic arthritis, ankylosing spondylitis	50 mg SC injection once a month with or without methotrexate or other DMARDs.
			Ulcerative colitis	200 mg initially administered by SC injection at week 0, followed by 100 mg at week 2 and then 100 mg every 4 weeks.
Infliximab	Remicade® Janssen Biotech	TNF Inhibitor	Rheumatoid arthritis	*Adult:* 3 mg/kg intravenous induction at 0, 2, and 6 weeks with methotrexate followed by maintenance every 8 weeks thereafter; may increase to maximum of 10 mg/kg or treating as often as every 4 weeks.
			Crohn's disease	5 mg/kg intravenous infusion at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter; patients without initial response may benefit from increasing to 10 mg/kg. *Pediatric*:5 mg/kg intravenous induction at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
			Psoriatic arthritis	5 mg/kg intravenous induction at 0, 2, and 6 weeks followed by maintenance every 8 weeks thereafter, with or without methotrexate.
			Ankylosing spondylitis	5 mg/kg intravenous induction at 0, 2, and 6 weeks followed by maintenance every 6 weeks thereafter.
			Ulcerative colitis	*Adult and pediatric:* 5 mg/kg intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter.
			Plaque psoriasis	5 mg/kg intravenous induction regimen at 0, 2, and 6 weeks followed by a maintenance regimen of 5 mg/kg every 8 weeks thereafter.
Natalizumab	Tysabri® Biogen-Idec	α4 integrin inhbitor	Crohn'sdisease	300 mg intravenous infusion over one hour every 4 weeks.
			Multiple sclerosis	300 mg intravenous infusion over one hour every four weeks.
Rituximab	Rituxan® Genentech Hoffman-La Roche[h]	Anti-CD 20 antibody	Rheumatoid arthritis	2 1000 mg intravenous infusion on days 1 and 15 in combination with methotrexate. Subsequent courses administered every 24 weeks or based on clinical evaluation but not sooner than every 16 weeks.
Secukinumab	Cosentyx® Novartis	IL-17A inhibitor	Plaque psoriasis	300 mg (2 SC injections of 150 mg) at Weeks 0, 1, 2, 3 and 4 followed by 300 mg every 4 weeks. For some patients, a dose of 150 mg may be acceptable.
Tocilizumab	Actemra® Genentech	IL-6 receptor inhibitor	Rheumatoid arthritis	Intravenous dosage (a 60-minute single intravenous drip infusion): 4 mg/kg every 4 weeks initially, followed by an increase to 8 mg/kg every 1 to 4 weeks based on clinical response, with or without DMARD. Reduction of dose from 8 mg/kg to 4 mg/kg is recommended for management of certain dose-related laboratory changes including elevated liver enzymes, neutropenia, and thrombocytopenia; Dose exceeding 800 mg/ infusion are not recommended. SC dosage: Body weight <100 kg: 162 mg every other week, followed by an increase to every week based on clinical response, with or without DMARD; Body weight ≥ 100 kg: 162 mg every week.
			Polyarticular juvenile idiopathic arthritis (2 years and older)	Body weight <30 kg: 10 mg/kg as a 60-minute single intravenous infusion every 4 weeks. Body weight ≥30 kg: 8 mg/kg as a 60-minute single intravenous infusion every 4 weeks.
			Systemic juvenile idiopathic arthritis (2 years and older)	Body weight <30 kg: 12 mg/kg as a 60-minute single intravenous infusion every 2 weeks. Body weight ≥30 kg: 8 mg/kg as a 60-minute single intravenous infusion every 2 weeks.
Tofacitinib	Xeljanz®/ Pfizer	JAK inhibitor	Rheumatoid arthritis	5 mg tablets twice daily in combination with methotrexate or other non-biologic DMARDs. Dose should be decreased to 5 mg once daily in moderate and severe renal impairment and moderate hepatic impairment.

Generic name	Trade name Manufacturer	Mechanism of action	Indication	Dosage and administration approved by the FDA
Ustekinumab	Stelara® Janssen Biotech	IL-12/23 p40 inhibitor	Plaque psoriasis	Body weight ≤100 kg (220 lbs), 45 mg SC injection initially and 4 weeks later, followed by 45 mg every 12 weeks by SC injection. Body weight >100 kg (220 pounds), 90 mg SC injection initially and 4 weeks later, followed by 90 mg every 12 weeks.
			Psoriatic arthritis	45 mg SC injection initially and 4 weeks later, followed by 45 mg every 12 weeks; in co-existent moderate-to-severe plaque psoriasis weighing >100 kg (220 lbs), 90 mg initially and 4 weeks later, followed by 90 mg every 12 weeks.
Vedolizumab	Entyvio® Takeda Pharmaceuticals America	α4β7 integrin inhibitor	Adult ulcerative colitis	300 mg intravenously over 30 minutes at 0, 2 and 6 weeks, then every 8 weeks thereafter.
			Adult Crohn's disease	

Abbreviations: AM, ante meridiem (before noon); AS, ankylosing spondylitis; CD, cluster of differentiation; CLcr, creatinine clearance; DMARD, disease-modifying antirheumatic drug; FDA, US Food and Drug Administration; IL, interleukin; JIA, juvenile idiopathic arthritis; JAK, Janus kinase; PDE4, phosphodiesterase 4; PM, post meridiem (after noon); PsA, psoriatic arthritis; RA, rheumatoid arthritis; SC, subcutaneous; UC, ulcerative colitis; TNF, tumor necrosis factor.

The participating organizations of the Drug Effectiveness Review Project approved the following key questions to guide the review for this report:

1. How do included drugs compare in their efficacy and long-term effectiveness for alleviating symptoms and stabilizing the disease in patients with rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis?

2. What are the comparative incidence and severity of harms associated with the use of these drugs?

3. Do the included drugs differ in effectiveness or harms in the following subgroups:
    - Different genders or different racial, age, or socioeconomic groups?
    - Patients with comorbidities?
    - Patients taking other commonly prescribed drugs?
    - Patients with early aggressive compared with persistent rheumatoid arthritis?

METHODS

Literature Search

To identify articles relevant to each key question, for Update 5 we searched PubMed, EMBASE, CINAHL, Centre for Reviews and Dissemination, The Cochrane Library, and International Pharmaceutical Abstracts from 2013 (November) to 2016 (January). We attempted to identify additional studies through hand searches of reference lists of included studies and reviews. In addition, we searched the US Food and Drug Administration website for medical and statistical reviews of individual drug products. Finally, we requested dossiers of published and unpublished information from the relevant pharmaceutical companies for this review. All received dossiers were screened for studies or data not found through other searches.

Validity Assessment

We assessed risk of bias (quality rating) of trials based on predefined criteria developed by the United States Preventive Services Task Force (ratings: good-fair-poor) and the National Health Service Centre for Reviews and Dissemination. External validity (generalizability) was assessed but did not influence quality ratings.

RESULTS

Overview

For Update 5, literature searches identified 3828 citations. In combination with previous searches, we have now identified 10 532 relevant citations in total over the history of this report. For this update, we received dossiers from 10 pharmaceutical manufacturers: Abbvie, Amgen, Biogen, Bristol-Myers Squibb, Celgene Corporation, Genentech, Janssen Scientific Affairs, Novartis Pharmaceutical Corporation, Takeda Pharmaceuticals International Inc., and UCB Inc.

Key Question 1. Efficacy and Effectiveness

Rheumatoid Arthritis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis: abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab, and tofacitinib.

We included 11 trials of which 4 were open-label randomized controlled trials. All but one included trials were efficacy studies, conducted in narrowly defined populations and/or limited to less than 12 months of follow-up. The only effectiveness study for rheumatoid arthritis compared abatacept, rituximab, or a TNF-inhibitor in patients who had inadequate responses to a previous TNF-inhibitor treatment. Of the 55 possible head-to-head comparisons for the approved drugs, we found direct head-to-head evidence from trials for 9 comparisons and 3 combination strategies. For most comparisons, the evidence is limited to a single, fair trial funded by the producer of one of the compared drugs.

Single trial evidence indicates that efficacy outcomes are similar between abatacept and adalimumab, abatacept and rituximab, adalimumab and etanercept, adalimumab and tofacitinib, and etanercept and tocilizumab. The evidence is mixed regarding differences in efficacy between adalimumab and tofacitinib. The strength of evidence for these comparisons is low or insufficient.

For the comparison of abatacept with infliximab the only double-blinded head-to-head trial indicated no differences in efficacy between patients treated with abatacept or infliximab after 6 months. The study did not allow for dose adjustments for infliximab, results after 1 year, therefore, are biased towards a greater efficacy of abatacept. For the comparison of adalimumab with tocilizumab, a fair double-blinded randomized controlled trial reported statistically significantly lower response rates for patients treated with adalimumab than tocilizumab. Tocilizumab, however, was used at a higher starting dose than FDA approved. The dosing equivalence in this study, therefore, is questionable and findings have to be interpreted cautiously.

In contrast, a small open-label randomized controlled trial, indicated no differences in treatment effects between adalimumab and tocilizumab. The strength of evidence is low.

A fair, small (n=32), open-label randomized controlled trial indicated greater response rates in patients treated with etanercept than with infliximab (74.4% compared with 60% after 54 weeks; *P*=NR). The strength of evidence is insufficient.

A poor, open-label effectiveness trial reported similar effectiveness between abatacept, rituximab, and TNF-inhibitors in patients who failed a previous treatment with a TNF-inhibitor. The strength of evidence is insufficient.

Evidence based on 3 fair randomized controlled trials indicates that combination therapies etanercept and anakinra, etanercept and abatacept, and rituximab and anti-TNF drugs (adalimumab, etanercept) do not lead to additional benefits but cause significantly higher rates of adverse events. Juvenile Idiopathic Arthritis

Currently abatacept, adalimumab, etanercept, canakinumab, and tocilizumab are approved by the US Food and Drug Administration for the treatment of juvenile idiopathic arthritis.

We did not find any head-to-head randomized trials for the treatment of juvenile idiopathic arthritis.

Juvenile Idiopathic Arthritis

Currently abatacept, adalimumab, etanercept, canakinumab, and tocilizumab are approved by the US Food and Drug Administration for the treatment of juvenile idiopathic arthritis.

We did not find any head-to-head randomized trials for the treatment of juvenile idiopathic arthritis.

Ankylosing Spondylitis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of ankylosing spondylitis: adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab.

We did not find any head-to-head trials of targeted immune modulators for ankylosing spondylitis.

Psoriatic Arthritis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of psoriatic arthritis: apremilast, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and ustekinumab.

We located 1 poor-quality randomized head-to-head trial of adalimumab, etanercept, and infliximab. In this trial, 100 psoriatic arthritis patients were randomized and received 12 months of treatment. The main methodological problems with this trial were that the methods of randomization, allocation concealment, loss to follow up, and statistical analysis are poorly reported and the baseline characteristics of the three groups differ. Nonetheless, the American College of Rheumatology 20 response rates were similar: adalimumab 70%; etanercept 72%; and infliximab 75%. Overall, the strength of evidence for this comparison was insufficient.
We did not locate any head-to-head evidence on other targeted immune modulators for psoriatic arthritis. We did not find any comparative effectiveness studies for psoriatic arthritis.

Psoriatic Arthritis in Children

No targeted immune modulators are currently approved for thetreatment of psoriatic arthritis in children.

We did not find any head-to-head randomized trials for the treatment of psoriatic arthritis in children.Crohn's Disease

The following drugs are currently approved by the US Food and Drug Administration for the treatment of Crohn's disease: adalimumab, certolizumab pegol, infliximab, natalizumab, and vedolizumab.

We located 2, open-label, randomized, head-to-head trials; one compared switching from infliximab to adalimumab in patients with complete clinical response for at least 6 months on infliximab therapy. The second study compared the risk of endoscopic, histologic, or clinical recurrence after ileocolonic resection. We rated 1 study as fair-, the other as poor quality. In the fair-quality trial 73 patients with a satisfactory response to infliximab therapy were randomized to continue infliximab for 56 weeks or to switch to adalimumab. Significantly more patients in the adalimumab group discontinued treatment for loss of response or adverse events compared with the infliximab group. Because of an interim analysis, recruitment was stopped early before reaching the planned sample size. The poor-quality trial randomized patients (n=20) after surgery to adalimumab or infliximab. After 1 year of follow-up, no statistically significant differences regarding endoscopic recurrence, histological disease activity, and clinical recurrence rates could be detected. We rated this study as poor because the method of randomization was not reported, groups at baseline were substantially different regarding prognostic factors, and patients, outcome assessors, and care providers were not blinded to the treatment. The strength of evidence for this comparison is insufficient.

We did not locate any head-to-head evidence on other targeted immune modulators for Crohn's disease.

Crohn's Disease in Children

Adalimumab and infliximab are currently approved by the US Food and Drug Administration for the treatment of Crohn's disease in children.

We did not find any head-to-head randomized trials for the treatment of Crohn's disease in children.

Ulcerative Colitis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of ulcerative colitis:adalimumab, golimumab, infliximab and vedolizumab.

We did not find any head-to-head randomized trials for the treatment of ulcerative colitis.

Ulcerative Colitis in Children

Infliximab is the only drug currently approved by the US Food and Drug Administration for the treatment of ulcerative colitis in children.

We did not find any head-to-head randomized trials for the treatment of ulcerative colitis in children.

Plaque Psoriasis

The following drugs are currently approved by the US Food and Drug Administration for the treatment of plaque psoriasis: adalimumab, alefacept, etanercept, infliximab, secukinumab and ustekinumab.

We located 4 fair-quality, randomized, head-to-head trials for the treatment of moderate-to-severe plaque psoriasis; 1 of etanercept compared with ustekinumab, 1 of etanercept compared with secukinumab, 1 of etanercept compared with tofacitinib, and 1 of secukinumab compared with ustekinumab.

The results of the 4 trials conducted in 3 991 patients indicate that: secukinumab is superior to ustekinumab; both secukinumab and ustekinumab are superior to etanercept; and that tofacitinib is equivalent to etanercept in treating plaque psoriasis. We did not conduct any statistical comparisons across the trials (network analysis) so we can't draw any conclusions about the comparison of secukinumab or ustekinumab with tofacitinib. Nor did we locate any evidence regarding other targeted immune modulators. The strength of evidence for all the direct comparisons is low.

The 4 trials included patients with a 6 or 12 month history of moderate-to-severe plaque psoriasis resistant to systemic treatment. The average baseline Psoriasis Area and Severity Index score in the trials was between 20 and 23. The Psoriasis Area and Severity Index 75 results at 12 or 16 weeks from these 4 trials show that between 39.1% and 93.1% of patients achieved a response.

We did not find any comparative effectiveness studies for plaque psoriasis.

Plaque Psoriasis in Children

No targeted immune modulators are currently approved for the treatment of plaque psoriasis in children.

We did not find any head-to-head randomized trials for the treatment of plaque psoriasis in children.

Key Question 2. Adverse Events

59 head-to-head trials or observational studies provided direct evidence on the harms associated with targeted immune modulators: 17 randomized trials and data from 42 head-to-head observational studies.

Most comparative evidence was available for the tumor necrosis factor inhibitors adalimumab, etanercept, and infliximab. We did not locate any direct comparative evidence from trials or observational studies on the following targeted immune modulators: apremilast, alefacept; canakinumab; natalizumab, secukinumab, tofacitinib, or vedolizumab.

In trials, the comparative rates of overall adverse events occurring with targeted immune modulators did not differ (or any differences did not reach statistical significance; low strength of evidence).

Overall, however, infliximab appears to have a higher risk for infections and discontinuations than other drugs. In observational studies, infliximab had a higher risk of patients discontinuing treatment due to adverse events compared with adalimumab and etanercept (moderate strength of evidence), Infliximab also had a higher comparative risk for serious infections compared with abatacept, adalimumab, and etanercept (moderate strength of evidence), and opportunistic infections compared with etanercept (low strength of evidence). For tuberculosis specifically, low strength evidence suggests a greater risk with adalimumab and infliximab compared with etanercept. For herpes zoster, low strength evidence suggests no differences.

Injection site and infusion reactions reactions were less frequent for patients receiving abatacept compared with both adalimumab and infliximab (both low strength of evidence) and greater for etanercept than adalimumab, secukinumab, and ustekinumab (low strength of evidence).

Evidence regarding malignancies and overall mortality was sparse. Overall, no significant differences between targeted immune modulators were detected for malignancies and mortality.

Comparative evidence for regimes where 2 targeted immune modulators were given in combination showed an increased risk of serious adverse events, withdrawal due to adverse events, and serious infections (high strength of evidence).

No direct evidence exists on the comparative risk of harms for targeted immune modulators for children.

Key Question 3. Subgroups

The majority of the trials did not contain any information about the effectiveness and harms of targeted immune modulators in 1 subgroup of patients compared with another or compared with the general population. 1 head-to-head trial analyzed the effect of potential baseline predictors of achieving a 70% improvement of American College of Rheumatology-criteria in patients with rheumatoid arthritis with either adalimumab or tocilizumab after 24 weeks. No statistically significant or clinically meaningful difference could be determined for subgroups based on age, gender, duration of rheumatoid arthritis (< 2 vs. ≥ 2 years), and number of previous disease-modifying antirheumatic drugs (0-5). No absolute numbers of the individual subgroup-analyses were available, because the results were illustrated graphically. Overall, the strength of evidence to determine differences of the effectiveness and harms among subgroups in patients treated with targeted immune modulators is insufficient.

SUMMARY

Our conclusions are based on the review of 6704 abstracts and the inclusion of a total of 53 publications (of 15 head-to-head randomized controlled trials and 22 head-to-head observational studies). Almost all of the included randomized trials were funded by the pharmaceutical industry and could be classified as efficacy trials with highly selected patients. We did not locate any trials that enrolled less selected, primary care based populations and that would be classified as providing evidence on effectiveness.

In summary, no or insufficient evidence exists for most comparisons about the efficacy, effectiveness, and harms of abatacept, adalimumab, alefacept, anakinra, apremilast, canakinumab, certolizumab pegol, etanercept, golimumab, infliximab, natalizumab, rituximab, secukinumab, tocilizumab, tofacitinib, and ustekinumab for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, Crohn's disease, ulcerative colitis, and plaque psoriasis.

The most obvious differences that might be clinically decisive for choosing a targeted immune modulator involve dosage and administration. Apremilast and tofacitinib are the only approved orally administered drugs. Infliximab, golimumab, natalizumab, rituximab, and vedolizumab require intravenous administration. Abatacept, adalimumab, anakinra, canakinumab, certolizumab pegol, etanercept, golimumab, secukinumab, tocilizumab, and ustekinumab can be administered subcutaneously. Alefacept requires an intramuscular injection. Furthermore, administration intervals differ substantially among drugs. The main findings with strength of evidence ratings are summarized in Table 2.

Table 2. Summary of the evidence by key question

Key question	Strength of evidence	Conclusion
1. Comparative efficacy for rheumatoid arthritis	Low	Based on 1 open-label randomized controlled trial, similar efficacy between abatacept and adalimumab.
	Low	Based on 1 randomized controlled trial, no difference in efficacy between abatacept and infliximab.
	Insufficient	Based on 1 randomized controlled effectiveness trial, no difference in effectiveness between abatacept, rituximab, or TNF-inhibitors in patients who had an inadequate response

Key question	Strength of evidence	Conclusion
		to a first-line TNF-inhibitor.
	Insufficient	Based on 1 small open-label randomized controlled trial similar efficacy between adalimumab and etanercept
	Low	Based on 1 randomized controlled trial with questionable dosing equivalence and a contradicting open-label trial lower efficacy of adalimumab than tocilizumab
	Low	Based on 1 randomized controlled trial and a contradicting dose ranging trial similar efficacy between adalimumab and tofacitinib.
	Insufficient	Based on 1 small open-label randomized controlled trial similar efficacy between etanercept and infliximab
	Insufficient	Based on 1 small open-label randomized controlled trial similar efficacy between etanercept and tocilizumab
	Moderate	Based on 3 RCTs combination strategies of etanercept with anakinra or abatacept, and rituximab with adalimumab or etanercept do not lead to additional benefits but cause more harms.
	Insufficient	No evidence available for all other comparisons.
1. Comparative effectiveness for juvenile idiopathic arthritis	Insufficient	No comparative evidence available.
1. Comparative effectiveness for ankylosing spondylitis	Insufficient	No comparative evidence available.
1. Comparative effectiveness for psoriatic arthritis	Insufficient	Based on 1 head-to-head RCT, no difference in efficacy between adalimumab, etanercept and infliximab.
1. Comparative effectiveness for Crohn's disease	Insufficient	Based on 1 head-to-head RCT, switching from infliximab to adalimumab had higher treatment discontinuation and termination rates compared with maintaining infliximab. Based on 1 head-to-head RCT, postoperative treatment with adalimumab or infliximab showed similar treatment effects.
1. Comparative effectiveness for ulcerative colitis	Insufficient	No comparative evidence available.
1. Comparative effectiveness for plaque psoriasis	Low	Based on 1 head-to-head RCT, ustekinumab is more efficacious than etanercept
	Low	Based on 1 head-to-head RCT, secukinumab is more efficacious than etanercept
	Low	Based on 1 head-to-head RCT, 10mg tofacitinib is similarly efficacious as etanercept; 5 mg tofacitinib is less efficacious
	Low	Based on preliminary data of 1 head-to-head RCT, secukinumab is more efficacious than ustekinumab
1. Comparative harms	Low	Overall adverse events for all comparisons: Based on 12 RCTs, likely no difference between TIMs
	Moderate	*Discontinuations due to adverse events*: Based on 7 observational studies, the rate is greater with infliximab than adalimumab or etanercept; the rate is greater with adalimumab than etanercept
	Insufficient	*Serious adverse events:* Based on 1 RCT, more serious adverse events with infliximab than abatacept; No differences for other comparisons
	Low	*Injection-site (infusion) reactions*:

Key question	Strength of evidence	Conclusion
		Based on 7 RCTs, lower risk for abtacept compared with adalimumab and infliximab; higher risk for etanercept than adalimumab, secukinumab, and ustekinumab
	Moderate	*Serious Infections:* Based on 5 RCTs and 8 observational studies, infliximab caused higher rates of serious infections than abatacept, adalimumab, etanercept
	Insufficient	*Based on 1 observational study, infliximab had higher rates rates of serious infections than rituximab*
	Insufficient	*Based on 1 observational study, abatacept had lower rates of serious infections than etanercept, infliximab, and rituximab*
	Insufficient	*Based on 1observational study, no differences between abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, tocilizumab*
	Low	*Mortality* Based on 3 observational studies no difference between adalimumab, etanercept, and infliximab
	Low	*Tuberculosis* Based on 4 observational studies increased risk with adalimumab and infliximab compared with etanercept
	Insufficient	Based on 1 observational study no difference among abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, rituximab, and tocilizumab
	Low	*Opportunistic infections* Based on 1 observational study, higher risk for infliximab than etanercept; no difference between adalimumab and etanercept
	Low	*Herpes zoster* *Based on 1 RCT, similar risks between abatacept and adalimumab* *Based on 1 RCT, similar risks between tofacitinib and etanercept*
	Low	Based on 4 observational studies no difference between adalimumab, etanercept, and infliximab
	Insufficient	*Skin infections* Based on 1 observational study no difference between adalimumab, etanercept, and infliximab
	Insufficient	*Septic arthritis* Based on 1 observational study no difference between adalimumab, etanercept, and infliximab
	Low	*Malignancy* Based on 6 observational studies no difference between adalimumab, anakinra, etanercept, and infliximab
	Insufficient	*Non-melanoma skin cancer and melanoma* Based on 3 observational studies no difference between adalimumab, etanercept, and infliximab
	Insufficient	*Cardiovascular harms* Based on 1 observational study no difference between etanercept and infliximab
	Insufficient	*Interstitial lung disease* Based on 2 observational study no difference between adalimumab, etanercept, and infliximab
	High	*Combination strategies* Increase in risk of serious adverse events, withdrawals, and serious infections with combination therapy
2. Subgroups – age	Insufficient	The evidence is insufficient to draw conclusions.
3. Subgroups – ethnicity	Insufficient	The evidence is insufficient to draw conclusions.

	Key question	Strength of evidence	Conclusion
3.	Subgroups – gender	Insufficient	The evidence is insufficient to draw conclusions.
3.	Subgroups – disease duration	Insufficient	The evidence is insufficient to draw conclusions.

Abbreviations: RCT, randomized controlled trial

CONCLUSION

Overall, data from mostly highly-selected and short-term randomized trials in patients with rheumatoid arthritis provides evidence on comparative efficacy and shows that the efficacy of the targeted immune modulator drugs is similar. For plaque psoriasis secukinumab and ustekinumab are more efficacious than etanercept. Most direct evidence on the comparative harms of targeted immune modulators exists for rheumatoid arthritis and for patients receiving adalimumab, etanercept, and infliximab. Overall, where differences between the agents were detected, infliximab is associated with a greater risk of serious adverse events, serious infections, and withdrawal due to adverse events.

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update: Substance Use Disorders

Date of Review: September 2016 **Date of Last Review:** January 2015

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
Increases in misuse and abuse of opioids and subsequent increases in accidental opioid-related deaths have caught the attention of policy makers in the United States (U.S.) and in Oregon. On July 22, 2016, the Comprehensive Addiction and Recovery Act (CARA) was enacted which authorizes the federal government to strengthen opioid prevention and treatment programs and improve community access to naloxone. Improved practices in opioid prescribing will likely lead to decreased prescribing of opioids but it may be at the expense of increased illicit opioid use (i.e., heroin, synthetic fentanyl, prescription opioids) for persons dependent on or addicted to opioids. Illicit opioid use is a major cause of mortality from acute causes (e.g., overdose, traffic accidents) and transmission of blood-borne infections like HIV and Hepatitis C due to injection drug use. A review of new published data and updated clinical practice guidelines for management of substance use disorders will help inform whether current Oregon Health Plan (OHP) policies remain appropriate to access to these medications.

Research Questions:
1. Is there new evidence for differences in efficacy between drug therapies for alcohol use disorder or opioid use disorder?
2. Is there new evidence for differences in harms between drug therapies for alcohol use disorder or opioid use disorder?
3. Are there subpopulations based on demographics (i.e., adolescents, elderly, women, criminal justice offenders) or practice settings (i.e., rehabilitation/addiction center, clinics, private physician offices or patient self-administration) in which a drug for alcohol use disorder or opioid use disorder may be more effective or less harmful than other drugs?

Conclusions:
- Treatment for opioid use disorder was last reviewed by the Pharmacy and Therapeutics Committee in January 2015 and treatment for alcohol use disorder was last reviewed in July 2014. Since then, two high quality systematic reviews from the Agency for Healthcare Research and Quality (AHRQ) and the Cochrane Collaboration, and one high quality clinical practice guideline from the Veterans Affairs and Department of Defense (VA/DoD) have been published.

Author: Andrew Gibler, PharmD Date: September 2016

Alcohol Use Disorder

- There is high quality evidence for use of acamprosate and oral naltrexone to decrease alcohol consumption in patients with alcohol use disorder when used concurrently with psychosocial interventions; however, there is insufficient evidence to support their use based on an improvement in clinically relevant health outcomes (i.e., morbidity or mortality) alone.
    - The number needed to treat [NNT] to prevent one person from returning to *any* drinking is 12 persons (95% Confidence Interval [CI], 8 to 26; 16 trials; n=4847) for acamprosate and 20 persons (95% CI, 11 to 500; 16 trials; n=2347) for oral naltrexone 50 mg daily.[1]
    - Oral naltrexone is associated with statistically significant improvement in prevention of returning to *heavy* drinking (NNT 12; 95% CI, 8 to 26; 19 trials; n=2875) but acamprosate is not associated with an improvement.[1]
    - There is no statistically significant association with return to *any* drinking or return to *heavy* drinking with extended-release injectable naltrexone; however, there was a statistically significant association with reduction in *heavy* drinking days (weighted mean difference [WMD] -4.6%; 95% CI, -8.5% to -0.56%; 2 trials; n=926), although it is unclear if this difference is clinically meaningful.[1]
    - There is insufficient evidence to adequately support an association between disulfiram use and preventing return to *any* drinking or improvement in other alcohol consumption outcomes.[1] However, blinded studies may be incapable of distinguishing a difference between disulfiram and control groups due to high attrition and fear for disulfiram-ethanol reactions. Blinded studies may be incompatible for disulfiram research; when data from open-labeled studies are pooled, there is moderate quality evidence that disulfiram is safe and efficacious for treatment of alcohol use disorder in supervised settings.[2]
    - There is low quality evidence that suggests off-label use of topiramate may be useful in decreasing alcohol consumption.[1]
- There is high quality evidence of no difference between acamprosate and oral naltrexone in return to *any* drinking (RD 0.02; 95% CI, -0.03 to 0.08); return to *heavy* drinking (RD 0.01; 95% CI, -0.05 to 0.06); or percent of drinking days (WMD -2.98%; 95% CI, -13.4 to 7.5%).[1] There is insufficient evidence to compare extended-release injectable naltrexone or disulfiram with other drugs for treatment of alcohol use disorder.
- There is insufficient evidence to demonstrate differences in harms for medications used to treat alcohol use disorder.
- The updated clinical practice guideline from the Veterans Affairs and Department of Defense (VA/DoD) for the management of substance abuse disorders strongly recommends that treatment choice between acamprosate, disulfiram, naltrexone (oral or extended-release injection) or topiramate be individualized based on specific needs and patient preferences.[3] In all cases, strong psychosocial interventions are needed to successfully treat patients with alcohol use disorder.[3]

Opioid Use Disorder

- Moderate quality evidence from 2 trials demonstrates no difference between methadone and buprenorphine maintenance treatment in terms of self-reported opioid use (risk ratio [RR] 0.37; 95% CI, 0.08 to 1.63) or positive opioid urine drug screens (RR 0.81; 95% CI, 0.56 to 1.18).[4] Low quality evidence from 3 trials demonstrates no difference in treatment retention between methadone and buprenorphine maintenance treatment programs (RR 0.69; 95% CI, 0.39 to 1.22).[4]
- Maintenance treatment with buprenorphine is more effective than detoxification treatment alone or psychosocial treatment alone, based on low quality evidence that assessed self-reported opioid use in the last 30 days (RR 0.54; 95% CI, 0.31 to 0.93), urine drug screens (RR 0.63; 95% CI, 0.43 to 0.91), and treatment retention (RR 0.33; 95% CI, 0.23 to 0.47).[4]
- There is moderate quality evidence from 2 trials of no difference in rates of adverse events between methadone and buprenorphine maintenance treatment (RR 1.10; 95% CI, 0.64 to 1.91).[4]

- For patients with a diagnosis of opioid use disorder, the VA/DoD strongly recommends buprenorphine/naloxone or methadone in an Opioid Treatment Program depending on specific patient needs or preferences.[3] Alternatively, buprenorphine without naloxone is strongly recommended to be used in patients who are pregnant, and extended-release injectable naloxone is recommended as an option for patients for whom buprenorphine/naloxone or methadone is contraindicated, unacceptable, or unavailable, and who have established opioid abstinence for a sufficient period of time. In all cases, strong psychosocial interventions are needed to successfully treat patients with alcohol use disorder.[3]

Sub-groups

- There is insufficient evidence to confirm which treatments for alcohol or opioid use disorders are more or less effective or safe in older or younger subgroups, different sex groups, racial or ethnic minorities, smokers or nonsmokers, and those with certain coexisting conditions.[1] However, the VA/DoD strongly recommend that sublingual buprenorphine (without naloxone) be reserved for pregnant patients when used to treat opioid use disorder.[3]
- When compared to non-pharmacological treatment, there is low quality evidence that opioid agonist treatment (methadone or buprenorphine) and naltrexone may not be effective reducing illicit drug use in criminal justice offenders.[6] However, there is moderate quality evidence that naltrexone treatment reduces criminal activity as evidenced by decreased re-incarceration rates.[6]
- There is moderate quality evidence that disulfiram is more effective in supervised settings.[2] Otherwise, there is insufficient evidence to know with certainty whether buprenorphine products are more effective or safer when given in designated Opioid Treatment Programs or in private physician offices, or whether daily supplies should be administered or multi-day supplies may be administered. Methadone is restricted to designated Opioid Treatment Programs.

Recommendations:

- Continue to require clinical prior authorization (PA) criteria for all buprenorphine products and the naltrexone extended-release injection product based on the proposed amendments in Appendix 4.
- Remove buprenorphine sublingual tablets from the OHP Preferred Drug List (PDL) and restrict use to pregnant females as required in the clinical PA criteria in Appendix 4.
- No other changes to the OHP PDL are recommended. Review comparative drug costs in the executive session.

Previous Conclusions:

- New evidence is still insufficient to determine if there is any difference in efficacy/effectiveness or safety between different opioid dependence treatments, including different buprenorphine formulations.
- New evidence is insufficient to determine if a specific subpopulation may benefit more with a specific drug or formulation approved for opioid dependence.

Previous Recommendations:

- No further review or research needed at this time.

Background:

Substance Use Disorders (SUD) can develop in individuals who use alcohol, opioids, or other addicting drugs in harmful quantities.[3] About 9% of adults in the U.S. have a non-tobacco SUD, and about 25% of all Americans will develop a non-tobacco SUD over the course of a lifetime.[3] Excessive alcohol use and illicit drug use, including illicit prescription drug use, costs $223.5 billion and $193.5 billion, respectively, each year in the U.S. according to the latest available estimates from

the Centers for Disease Control and Prevention (CDC) and U.S. Department of Justice.[3] Excessive alcohol use in the U.S. results in about 88,000 premature deaths each year from acute (e.g., alcohol poisoning, motor vehicle accidents) and chronic causes (e.g., liver disease, hypertension, heart disease, stroke, pancreatitis).[3] Illicit opioid use (heroin or prescription opioids) is also a major cause of mortality from acute causes (e.g., overdose, traffic accidents) and transmission of blood-borne infections like HIV and Hepatitis C due to injection drug use. An estimated 400,000 persons have used heroin in the past month in the U.S. and 4 million persons have reported nonmedical use of prescription pain relievers.[7] Worldwide, opioid use disorder has resulted in 11 million life-years lost from health problems, disabilities, and early death from opioid-related conditions.[7] When tobacco use is included, SUDs are the leading actual cause of death in the U.S.[3]

The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) specifically recognizes SUDs related to substances such as tobacco, alcohol, opioids, cannabis, sedative, anxiolytics, and 5 other substances.[8] According to the DSM-V, SUDs are associated with a pattern of inappropriate substance use that adversely affects one's personal or professional life or results in noticeable distress.[8] In persons with SUDs, there is an underlying change in the way the brain functions that may persist beyond detoxification that can result in repeated relapses and intense cravings when exposed to different drug-related stimuli.[8] These addictive substances alter brain circuitry involved in complex functions like motivation and decision-making and alter natural reward mechanisms for essential substances like food and water.[3] Pleasure normally experienced with stimuli such as food or social interactions are diminished with repeated use of addicting substances.[3]

Over 16 million adults in the U.S. had a diagnosis of alcohol use disorder in 2014 (10.6 million males and 5.7 million females).[9] In adolescents aged 12-17 years, it was estimated that 679,000 had alcohol use disorder which was fairly equally diagnosed between boys and girls.[9] Unfortunately, only 1 in 10 patients are treated for alcohol use disorder and treatment options remain underutilized despite their potential to improve health outcomes.[1] Treatments for alcohol use disorder include a combination of cognitive behavioral therapy, motivational enhancement therapy, 12-step programs (e.g., Alcoholic Anonymous), and pharmacotherapy. Pharmacotherapy options for patients with alcohol use disorder include oral options like disulfiram, acamprosate, and naltrexone, as well as an extended-release injectable naltrexone. All of these treatments have been approved by the U.S. Food and Drug Administration (FDA) for treatment of alcohol dependence in patients who are able to abstain from alcohol. Outcomes studied have been primarily limited to reduction in alcohol consumption: return to any drinking, return to heavy drinking, drinking days, heavy drinking days (≥4 drinks per day for women; ≥5 for men), or drinks per drinking day. Off-label use of topiramate and gabapentin for alcohol use disorder has also shown some benefit, whereas drugs like baclofen, buspirone, antidepressants, and antipsychotics have not consistently shown benefit.[3]

Opioid analgesics have been used for decades to manage pain, but they can also produce feelings of euphoria, tranquility and sedation that lead to substantial misuse and abuse of these drugs. A person will build tolerance to regular use of opioids, including heroin, which can result in the desire for higher and higher doses to achieve the intended effect but at the expense of serious adverse events such as respiratory suppression and death. With the recent dramatic increase in misuse of prescription opioids and ease of accessibility of opioids, including heroin, it is imperative that physicians understand how to diagnose and navigate treatment strategies with their patients. From 2007 to 2014, the number of private insurance claim lines with an opioid dependence diagnosis increased 3,203%, with most of the claims associated with persons between 19-35 years of age.[10] On July 22, 2016, the Comprehensive Addiction and Recovery Act (CARA) was enacted which authorizes the federal government to strengthen opioid prevention and treatment programs, and improve community access to naloxone.[11]

Medically supervised treatment of long-acting opioid agonists for acute withdrawal symptoms (i.e., detoxification) can improve a patient's health and facilitate participation in a rehabilitation program.[7] However, detoxification alone is not helpful to produce long-term recovery and may increase a patient's risk for overdose due to lost tolerance for opioids.[7] The most effective approach is to relieve symptoms of detoxification with methadone or buprenorphine and then gradually reduce the dose to allow the patient to adjust to the absence of an opioid.[7] However, only licensed addiction-treatment programs and physicians who

have completed specific training for opioid drugs can administer opioids to treat opioid use disorder. Some non-opioid medications, such as the centrally-acting α-2 agonist clonidine, are also used off-label to manage the autonomic over-activity associated with opioid withdrawal. Loperamide, prochlorperazine and nonsteroidal anti-inflammatory drugs (NSAIDs) can also be used in combination to manage other withdrawal symptoms.

Opioid maintenance treatment, with methadone or buprenorphine/naloxone most commonly utilized, reduces withdrawal and cravings and has long been used in the treatment of heroin or prescription opioid dependence for rehabilitation purposes.[7] Oral and extended-release injectable naltrexone formulations are also approved by the FDA for opioid dependence in patients who can abstain from opioids. The regular dosing of a long-acting opioid lessens the sense of euphoria or intoxication that is usually associated with each illicit drug dose and has demonstrated reduction in illicit opioid use, mortality, criminal activity, HIV risk behavior and seroconversion, as well as improved physical and mental health and social functioning.[4] Concurrent psychosocial support is essential to address some of the psychological and social problems that can be associated with opioid use disorder.[4]

Methadone is a mu-opioid agonist and an N-methyl-D-aspartate (NMDA) antagonist given as a single daily dose for opioid dependence in approved Opioid Treatment Programs (i.e., 'methadone clinics'). Previous data show that methadone has strong evidence that demonstrates effectiveness in reducing mortality and substance use, improving physical and mental health outcomes, reducing criminal activity and reducing risk for HIV and risk behaviors.[4] However, methadone is not without harms. Adverse effects may include prolonged QT interval which rarely result in Torsade de pointes, and respiratory depression associated with titrating the drug. Opioid Treatment Programs have strict guidelines for dosing, supervised treatment and associated services. The optimal dosage of methadone for retention in treatment is at least 60 mg daily but many patients will require higher doses.[7]

Buprenorphine is a partial opioid agonist and has lower intrinsic activity at the opioid receptor, but due to its very high affinity for the receptor, buprenorphine possesses antagonist properties that block the effects of other opioids. Buprenorphine has a favorable safety profile compared to methadone due to its limited effects on the respiratory system and also has evidence for reduced mortality similar to methadone.[4] Unlike methadone which is 100% bioavailable as an oral formulation, buprenorphine has poor bioavailability and must be developed in formulations that are not swallowed orally (e.g., sublingual, buccal, transdermal, etc.). For treatment of opioid-dependence (and not pain), a buprenorphine sublingual formulation is available and buprenorphine/naloxone buccal and sublingual formulations are available. Buprenorphine and naloxone are usually formulated in 4:1 to discourage injection of the drug. The low dose of naloxone does not precipitate withdrawal symptoms unless it is injected. These products (C-III) are not as highly controlled as methadone (C-II) and can be provided by physicians who have received a waiver from the Substance Abuse and Mental Health Services Administration (SAMSHA), have completed 8 hours of buprenorphine training, and have a special Drug Enforcement Administration (DEA) number.[7] Previously, these physicians were limited to caring for 30 patients at a time, but that number was increased to 275 patients in July 2016.[7]

There are no guidelines that specify when to refer a patient to an Opioid Treatment Program for methadone or buprenorphine maintenance treatment. Both drugs have demonstrated improvement in clinical outcomes in multiple randomized clinical trials (RCTs). High-quality evidence supports the use of medication-assisted treatment using methadone or buprenorphine/naloxone over psychosocial treatment alone to improve outcomes.[7] Choice of drug typically comes down to individual clinician and patient preferences. Methadone can be dispensed in Opioid Treatment Programs only, whereas buprenorphine can also be prescribed by physicians in office-based settings, including primary care, outpatient specialty SUD treatment facilities, and mental health clinics. Considerations include cost; concomitant medical (e.g., heart disease) and psychiatric conditions; the availability of methadone clinics; the availability of physicians trained in administering buprenorphine; and the risk of diversion when determining which option is most appropriate. For example, an office-based treatment program may not be suitable for patients with a concurrent substance abuse disorder (e.g., alcohol, sedatives, anxiolytics) or even patients who regularly use sedative-hypnotics like benzodiazepines.[5] Buprenorphine is more expensive than methadone, and the private office charges for buprenorphine might exceed the usual

costs of a methadone clinic.[7] However, buprenorphine may be safer than methadone during induction and early stabilization phases of treatment. Buprenorphine can also be administered in physician offices which can improve access to opioid maintenance treatment.[7]

Evidence from one RCT also shows that extended-release injectable opioid antagonist naloxone can be successfully used to treat opioid use disorder.[7] The long-acting formulation can be given in both general healthcare and specialty substance use disorder treatment settings. There is insufficient evidence at this time to recommend oral naltrexone because it requires a highly motivated patient to be successful and it has not consistently demonstrated superiority to control groups at treatment retention or in opioid consumption.[3] Patients who initiate naltrexone treatment must be free of opioid dependence (e.g., >7 days without acute withdrawal symptoms), which should be confirmed based on an opioid-free urine sample and a naloxone challenge (intramuscular or intravenous administration of 0.8 to 1.6 mg of naloxone; or alternatively, 50 mg or oral naloxone with no subsequent withdrawal symptoms).[7]

Clinically important outcomes for studies that assess efficacy of substance use disorders can include: treatment retention/completion; illicit substance use or any alcohol consumption; risk behaviors (injecting, sexual, polysubstance use, overdoses, hospital admissions); quality of life as assessed by validated scales (e.g., WHO Quality of Life scale), employment, physical health as assessed by validated scales (e.g., 36-item Short Form), adverse effects and aberrant opioid-related behaviors (e.g., multiple prescribers, lost medications, or unauthorized dose increases).[4]

Methods:
A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this review is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

<u>Alcohol Use Disorder</u>
The Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review on the efficacy of various medications used for the treatment of alcohol use disorder.[1] Eligible studies were double-blind RCTs that enrolled adults with alcohol use disorder that evaluated an FDA-approved medication or off-label medication (i.e., baclofen, buspirone, citalopram, fluoxetine, sertraline, topiramate, quetiapine, and others) for at least 12 weeks against placebo or another medication in an outpatient setting.[1] Studies were required to assess one of the following outcomes: 1) consumption – return to any drinking, return to heavy drinking, drinking days, heavy drinking days (≥4 drinks per day for women; ≥5 for men), drinks per drinking day; 2) health outcomes – accidents (i.e., motor vehicle crashes), injuries, quality of life, function, and mortality; or 3) adverse effects.[1] Adequacy of randomization, allocation concealment, similarity of groups and baseline, blinding, attrition, validity and reliability of measures, whether intention-to-treat analysis was used, and methods of handling missing data were considered in assessment of the risk of bias of the studies.[1] Meta-analyses of RCTs were conducted using random-effects models.[1] Weighted mean differences

(WMD) with 95% CIs were used for continuous outcomes.[1] Risk differences (RD) with 95% CI were conducted for binary outcomes.[1] Studies with high or unclear risk of bias were excluded from the main analaysis but were included in sensitivity analyses.[1] The I^2 statistic was calculated to assess for statistical heterogeneity.[1] Publication bias was assessed when possible (≥10 studies in a meta-analysis) by examination of funnel plots. Strength of evidence was graded as high, moderate, low or insufficient based on 4 key domains: risk of bias, consistency, directness and precision.[1] A total of 123 studies were included.[1] Most studies assessed acamprosate (27 studies; n=7519), naltrexone (53 studies, n=9140) or both.[1] Treatment duration ranged from 12 to 52 weeks.[1] In most cases, psychosocial interventions were also given to participants.[1] Most studies enrolled patients after detoxification or required a period of sobriety before randomization.[1]

Both acamprosate and oral naltrexone improve alcohol consumption outcomes.[1] The NNT to prevent one person from returning to any drinking is 12 persons (95% CI, 8 to 26; 16 trials; n=4847) for acamprosate and 20 persons (95% CI, 11 to 500; 16 trials; n=2347) for oral naltrexone 50 mg daily.[1] Acamprosate was not associated with an improvement in return to heavy drinking but oral naltrexone is associated with statistically significant improvement (NNT 12; 95% CI, 8 to 26; 19 trials; n=2875).[1] There was no statistically significant association with return to any drinking or return to heavy drinking with extended-release injectable naltrexone; however, there was a statistically significant association with reduction in heavy drinking days (WMD -4.6%; 95% CI, -8.5% to -0.56%; 2 trials; n=926).[1] There is insufficient evidence for disulfiram to adequately support an association with preventing return to any drinking or improvement in other alcohol consumption outcomes.[1] However, the largest disulfiram trial to date (n=605) did report fewer drinking days for patients who returned to drinking.[1] Meta-analyses of head-to-head RCTs that compared acamprosate with oral naltrexone did not find a statistically significant difference between these 2 medications in return to any drinking (RD 0.02; 95% CI, -0.03 to 0.08); return to heavy drinking (RD 0.01; 95% CI, -0.05 to 0.06) or percent of drinking days (WMD -2.98%; 95% CI, -13.4 to 7.5%).[1] There was insufficient evidence to support most medications used off label for alcohol use disorder.[1] The exceptions are topiramate and valproic acid.[1] Topiramate is associated with fewer drinking days (WMD -6.5%; 95% CI, -12.0% to -1.0%; 2 trials; n=541), heavy drinking days (WMD -9.0%; 95% CI, -15.3% to -2.7%; 3 trials; n=691) and drinks per drinking day (WMD -1.0; 95% CI, -1.6 to -0.48; 3 trials; n=691).[1] Valproic acid demonstrated some efficacy in consumption outcomes in patients with bipolar disorder.[1] Trials primarily focused on consumption outcomes; very few trials reported health outcomes and those that did were not powered to assess health outcomes.[1] There was also insufficient evidence to make fair estimations of potential adverse events with these agents due to inadequate precision.[1] In general, adverse events occurred more often in active treatment groups than placebo, but differences were not statistically significant.[1] In head-to-head trials of naltrexone and acamprosate, no statistically significant differences in withdrawal due to adverse events were observed.[1] Compared with placebo, patients treated with acamprosate had a higher risk of anxiety (number needed to harm [NNH] 7); diarrhea (NNH 11) and vomiting (NNH 42); patients treated with naltrexone had a higher risk for dizziness (NNH 16) and vomiting (NNH 24).[1]

Overall, acamprosate and oral naltrexone (50 mg/day) have the best evidence for treatment alcohol use disorder when used concurrently with psychosocial interventions; however, evidence is limited to alcohol consumption outcomes, including evidence for alcohol abstinence but health outcomes are still lacking.[1] A summary of the evidence extracted from the AHRQ report is summarized in **Table 1**. The mean age of participants was generally in the 40s.[1] There is insufficient evidence to confirm which treatments are more or less effective or safe in older or younger subgroups, different sex groups, racial or ethnic minorities, smokers or nonsmokers, and those with certain coexisting conditions.[1] Most trials of acamprosate were conducted in Europe while most trials of naltrexone were conducted in the U.S.[1] The few U.S.-based acamprosate trials did not find the drug to be efficacious, which may be related to the sources that the patients were recruited from (inpatient treatment programs vs. advertisements).[1] Overall, most trials were conducted in specialized outpatient treatment settings and very little evidence from primary care settings is available.[1]

Table 1. Summary of Findings and Strength of Evidence for the Efficacy of Medications use to Treat Alcohol Use Disorder Versus Placebo (*Agency for Healthcare Research and Quality*).[1]

Medication	Outcome	N (studies)	N (subjects)	Finding	Effect Size (95% CI)	NNT	SOE
Acamprosate vs. Placebo	Return to any drinking	16	4,847	Reduced by acamprosate	RD -0.09 (-0.14 to -0.04)	12	Moderate
	Return to heavy drinking	7	2,496	No difference	RD -0.01 (-0.04 to 0.03)	NA	Moderate
	Percentage of drinking days	13	4,485	Reduced by acamprosate	WMD -8.8 (-12.8 to -4.8)	NA	Moderate
Disulfiram vs Placebo	Return to any drinking	2	492	No difference	RD -0.04 (-0.11 to 0.03)	NA	Low
Naltrexone 50 mg oral vs. Placebo	Return to any drinking	16	2,347	Reduced by naltrexone	RD -0.05 (-0.10 to -0.00)	20	Moderate
	Return to heavy drinking	19	2,875	Reduced by naltrexone	RD -0.09 (-0.13 to -0.04)	12	Moderate
	Percentage of drinking days	15	1,992	Reduced by naltrexone	WMD -5.4 (-7.5 to -3.2)	NA	Moderate
	Percentage of heavy drinking days	6	521	Reduced by naltrexone	WND -4.1 (-7.6 to -0.61)	NA	Moderate
Naltrexone injection vs. Placebo	Return to any drinking	2	939	No difference	RD -0.04 (-0.10 to 0.03)	NA	Low
	Return to heavy drinking	2	615	No difference	RD -0.01 (-0.14 to 0.13)	NA	Low
	Percentage of heavy drinking days	2	926	Reduced by naltrexone	WMD -4.6 (-8.5 to -0.56)	NA	Low
Topiramate vs. Placebo	Percentage of drinking days	2	521	Reduced by topiramate	WMD -8.5 (-15.9 to -1.1)	NA	Moderate
	Percentage of heavy drinking days	2	521	Reduced by topiramate	WMD -11.5 (-18.3 to -4.8)	NA	Moderate
	Number of drinks per drinking day	2	521	Reduced by topiramate	WMD -1.1 (-1.7 to -0.4)	NA	Moderate
Other drugs	The evidence is insufficient to determine the efficacy of other medications because of inconsistency, imprecision, or lack of sufficient studies in the literature (e.g., amitriptyline, aripiprazole, atomoxetine, baclofen, buspirone, citalopram, desipramine, fluoxetine, fluvoxamine, gabapentin, imipramine, olanzapine, ondansetron, paroxetine, quetiapine, varenicline, viloxazine).						

Abbreviations: CI = confidence interval; N = number; NA = not applicable; NNT = number needed to treat; RD = risk difference; SOE = strength of evidence; WMD = weighted mean difference.

Disulfiram appears to be successful for alcohol use disorder in patients who are compliant or supervised in real-world settings, but the efficacy of disulfiram in clinical trials has been conflicting which has led to controversy around use of the drug based on poorly designed trials. A systematic review with meta-analysis was conducted to determine whether disulfiram treatment is more effective in open-label studies rather than in blinded trials because of the negative psychological impact participants may have in blinded trials because of fear of the disulfiram-ethanol reaction (DER).[2] The hypothesis was that blinded trials would not show a difference in efficacy between disulfiram and control groups because fear of DER would dissuade compliance in all groups.[2] All controlled trials that evaluated use of disulfiram in patients with alcohol use disorder were eligible for inclusion.[2] These studies included both blind and open-label designs, both supervised and unsupervised.[2] The methodological quality of the studies was analyzed according to the Cochrane Collaboration's tool for assessing risk of bias.[2] Efficacy outcomes were analyzed using a random-effects model, due to high heterogeneity in the studies, and by calculating the Hedge's *g* effect-size for each trial with the uncertainty of each result expressed by their 95% CIs.[2] An effect size of 0.2 to 0.3 is thought to be a 'small' treatment effect, about 0.5 a 'medium' treatment effect, and 0.8 to infinity a 'large' treatment effect.[2] Publication bias was assessed using funnel plots and heterogeneity was assessed by calculating the I^2 value (range 0% to 100%, with 0%-40% considered unimportant heterogeneity).[2] The primary endpoint of the meta-analysis was the combined effect-size at the end of treatment for the primary outcomes studied. Primary outcomes included: total abstinence; proportion of abstinent days to treatment days; mean days of alcohol use; no relapse; time to first heavy drinking day; or 3 or more weeks of consecutive abstinence.

Overall, 23 studies were eligible for inclusion in the meta-analysis.[2] The studies were published between 1973 and 2010; most were from the U.S. (10) study durations of 8 to 52 weeks.[2] Most participants in the studies were males and 2 studies evaluated adolescents.[2] In addition, 6 of the studies evaluated a population of cocaine abusers who also had an alcohol use disorder.[2] The results of the meta-analysis found significant success rate for disulfiram compared to controls (g=0.58; 95% CI, 0.35 to 0.82; I^2=72%).[2] A funnel plot analysis indicated possible publication bias but the summary effect size remained significant after correcting for missing studies (g=0.53 to g-0.63; p<0.001).[2] A subgroup analysis that compared blinded RCTs to open-label RCTs found that open-label RCTs found a significant superiority of disulfiram versus controls (g=0.70; 95% CI, 0.46 to 0.93; I^2=65%) whereas the blinded RCTs found no efficacy with disulfiram compared to controls (g=0.01; 95% CI, -0.29 to 0.32; I^2=43%).[2] When blinded trials were excluded, the funnel plot showed symmetry which demonstrated that there was no publication bias among those types of studies.[2] A subgroup analysis by supervision categories found disulfiram to be significantly superior to controls when medication compliance was supervised (g=0.82; 95% CI, 0.59 to 1.05; I2=46%) but not when treatment was unsupervised (g=0.26; 95% CI, -0.02 to 0.53).[2] No publication bias was found when studies were broken down by supervision categories.[2] In another subgroup analysis by control group, disulfiram was statistically significantly superior to naltrexone (g=0.77; 95% CI, 0.52 to 1.02; I^2=26%) and to acamprosate (g=0.76; 95% CI, 0.04 to 1.48; I^2=81%).[2] In terms of safety, disulfiram was associated with an increased risk for adverse events compared to controls (RR 1.40; 95% CI, 1.01 to 1.94).[2] Out of studies that reported adverse events totaling 962 participants, 8 subjects reported a serious adverse event that required hospitalization but most continued the disulfiram study after discharge.[2] A total of 13 deaths were reported (disulfiram groups = 6; control groups = 6; unspecified = 6).[2] The authors concluded that blinded studies were incapable of distinguishing a difference between treatment groups and thus are incompatible with disulfiram research.[2] Open-labeled trials in supervised settings have shown disulfiram to be safe and efficacious comparted to other abstinence supportive pharmacological treatments (naltrexone, acamprosate, topiramate) or to no disulfiram for alcohol use disorder.[2]

Opioid Use Disorder

The efficacy and safety of maintenance opioid agonist therapy for the treatment of pharmaceutical opioid dependence was recently evaluated in a systematic review by the Cochrane Collaboration.[4] All RCTs that evaluated at least 30 days of full opioid agonist maintenance treatment (i.e., methadone) against another full opioid agonist or partial opioid agonist (buprenorphine) for opioid use disorder were eligible for inclusion.[4] In addition, RCTs that evaluated full or partial opioid agonist maintenance therapy for opioid use disorder versus placebo, psychosocial treatment only (without opioid agonist treatment), or detoxification only were also eligible for inclusion.[4] Eligible RCTs had to enroll patients who were primarily dependent on prescription opioids rather than heroin.[4] The primary outcomes studied were 1) illicit opioid use; 2) illicit opioid use at end of treatment; and 3) retention. Overall, 6 RCTs met inclusion criteria (n=607).[4] Three studies compared methadone with buprenorphine and 3 studies compared buprenorphine to either buprenorphine taper or brief intervention and referral to treatment.[4] The mean duration of the studies was 105 days.[4] The mean age of participants was 31.6 years and 77% were male.[4] Five of the trials took place in the U.S. but the evidence was somewhat limited by their open-label design and small sample sizes (53 to 204 participants).[4] There was enough consistency in the way the trials collected and reported primary outcomes to pool data on key outcome measures.[4] Moderate quality evidence from 2 trials demonstrates no difference between methadone and buprenorphine maintenance treatment in terms of self-reported opioid use (risk ratio [RR] 0.37; 95% CI, 0.08 to 1.63) or positive opioid urine drug screens (RR 0.81; 95% CI, 0.56 to 1.18).[4] Low quality evidence from 3 trials demonstrates no difference in treatment retention between methadone and buprenorphine maintenance treatment programs (RR 0.69; 95% CI, 0.39 to 1.22).[4] In addition, there is moderate quality evidence from 2 trials of no difference in rates of adverse events between methadone and buprenorphine maintenance treatment (RR 1.10; 95% CI, 0.64 to 1.91).[4] Buprenorphine maintenance treatment may be superior to detoxification treatment alone or psychosocial treatment alone in terms of self-reported opioid use in the last 30 days (RR 0.54; 95% CI, 0.31 to 0.93) and positive opioid urine drug screens (RR 0.63; 95% CI, 0.43 to 0.91) based on low quality evidence.[4] In addition, buprenorphine maintenance treatment is superior to detoxification treatment alone or psychosocial treatment alone in terms of treatment retention (RR 0.33; 95% CI, 0.23 to 0.47) and adverse events (RR 0.19; 95% CI, 0.06 to 0.57) based on moderate quality evidence.[4] Overall, the authors concluded that

there is low to moderate quality evidence to support the use of methadone or buprenorphine maintenance therapy for opioid dependence but further research may change the overall findings from this review.[4]

The effectiveness of pharmacological interventions for illicit drug-using (abuse or dependence) offenders (i.e., subject to the criminal system) in reducing drug use, criminal activity, or both, was recently evaluated in a systematic review by the Cochrane Collaboration.[6] The systematic review was conducted because trials in the criminal justice setting are largely lacking, and continuity of care is critical for the treatment of individuals who transition between prison and the community.[6] All RCTs that assessed the efficacy of any pharmacological intervention that is designed to reduce, eliminate or prevent relapse of drug use or criminal activity, or both, in drug-using offenders were eligible for inclusion.[6] Control interventions could be no treatment, minimal treatment, waiting list, treatment as usual, or other treatment (pharmacological or psychosocial).[6] Where studies reported a number of different follow-up periods, the longest time reported was used to provide the most conservative estimate of effectiveness.[6] Alcohol and tobacco use was excluded from drug use outcomes data.[6] Fourteen (n=2647) trials lasting between 6 months and 4 years met inclusion criteria but most studies had small sample sizes.[6] Thirteen studies used methadone as an intervention and most trials were conducted in prison.[6] In general, the trials included evaluated methadone, buprenorphine, or naltrexone compared to no intervention, other non-pharmacological treatments (e.g., counselling) or other pharmacological drugs.[6] The methodological quality of the included trials was mostly unclear as methods were generally poorly described.[6] According to the investigators, the biggest threats to risk of bias were open label study designs (performance and detection bias) and incomplete outcome data (attrition bias).[6] Heterogeneity between studies prevented the ability to pool some data; however, 11 studies were included in the meta-analysis.[6] When compared to non-pharmacological treatment, there was low quality evidence that opioid agonist treatment (methadone or buprenorphine) was not effective at reducing drug use based on objective dichotomous data (i.e., hair and urine analysis) (RR 0.72; 95% CI, 0.51 to 1.00; n=237), self-reported subjective dichotomous data (yes/no) (RR 0.61; 95% CI, 0.31 to 1.18; n=317) or self-reported continuous data (SMD -0.62; 95% CI, -0.85 to -0.39; n=510).[6] No statistically significant differences in individual treatments were found between methadone and buprenorphine in self-reported dichotomous data of drug use (yes/no) (RR 1.04; 95% CI, 0.69 to 1.55; n=370) or continuous data of drug use (amount of drug use) (MD 0.70; 95% CI, -5.33 to 6.73; n=81) or in criminal activity (RR 1.25; 95% CI, 0.83 to 1.88).[6] There was also low quality evidence that naltrexone was not effective at reducing drug use (RR 0.69; 95% CI, 0.28 to 1.70; n=63) but there was moderate quality evidence that naltrexone treatment reduced criminal activity as evidenced by re-incarceration (RR 0.40; 95% CI, 0.21 to 0.74; n=114).[6] In a separate systematic review that looked specifically at female drug-using offenders, the only trial identified used buprenorphine which did not significantly reduce self-reported drug use compared to placebo in this population (RR 0.58; 95% CI, 0.25 to 1.35; n=36).[12] Low retention rates after prison release significantly limit adequate follow-up of all trials in these systematic reviews.

New Guidelines:

<u>VA/DoD Clinical Practice Guideline for the Management of Substance Abuse Disorders</u>[3]

The Department of Veterans Affairs (VA) and Department of Defense (DoD) Evidence-based Practice Work Group facilitates the development of clinical practice guideline for the VA and DoD populations. In December 2015, the VA/DoD published an update of their clinical practice guideline for the evaluation, treatment and management of substance abuse disorders.[3] The guideline workgroup used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of the evidence base and assign a grade for the strength of each recommendation.[3] For example, a strong recommendation indicates the workgroup was highly confident based on evidence that benefits related to the recommendation outweigh risks.[3] The VA/DoD emphasizes that medical management for substance abuse disorders is a shared decision-making process that must provide strategies to increase medication adherence, as well as monitoring of substance use and its consequences.[3] Management of substance use disorders must also support abstinence through education and referral to support groups.[3]

Alcohol Use Disorder

The VA/DoD recommend all patients in general medical and mental healthcare settings be screened for unhealthy alcohol use every year using the 3-item Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) questionnaire or the Single-item Alcohol Screening Questionnaire (SASQ) [*strong recommendation*].[3] A single initial intervention regarding alcohol-related risks and advice to abstain or drink within the established limits is recommended for patients without documented alcohol use disorder that screen positive for unhealthy alcohol use by the nationally established age and gender-specific limits for daily and weekly consumption in Table 2 [*strong recommendation*].[3]

Table 2. Nationally Established Age- and Gender-specific limits for Daily and Weekly Alcohol Consumption.[3]

▪ Men aged ≤65 y: ≤4 standard drinks per day and ≤14 per week
▪ Men aged >65 y and all women: ≤3 standard drinks per day and ≤7 per week
▪ Patients with contraindications including potential drug-drug interactions: 0 drinks per day

For patients with substance use disorders, there is insufficient evidence to recommend for or against using a standardized assessment that would determine initial intensity and setting of substance use disorder care rather than the clinical judgment of trained providers.[3]

In addition to offering one or more recognized non-pharmacological interventions (Behavioral Couples Therapy for alcohol use disorder; Cognitive Behavioral Therapy for substance abuse disorders; Community Reinforcement Approach; Motivational Enhancement Therapy; and/or 12-step Facilitation), any of the following specific pharmacotherapy options is recommended for moderate-severe alcohol use disorder based on RCTs and several systematic reviews/meta-analyses [*strong recommendation*][3]:

- Acamprosate
- Disulfiram
- Naltrexone (oral or extended-release)
- Topiramate

In the absence of contraindications, there is insufficient evidence to recommend routine use of one of the recommended medications over another; thus, treatment choice should be individualized based on specific needs and patient preferences.[3]

For management of moderate to severe alcohol withdrawal, a benzodiazepine is recommended with adequate monitoring [*strong recommendation*].[3] Pharmacotherapy strategies for managing alcohol withdrawal should include a predetermined fixed medication (i.e., given in advance of the emergence of anticipated withdrawal) with a tapering schedule and an additional medication available as needed; alternatively, treatment may be only given when signs or symptoms of withdrawal occur (e.g., as needed dosing) [*strong recommendation*].[3] Non-benzodiazepine alternatives such as carbamazepine, gabapentin, or valproic acid are recommended for managing mild to moderate alcohol withdrawal in patients from whom risks of benzodiazepines outweigh benefits (e.g., inadequate monitoring available, abuse liability, or allergy/adverse reactions) [weak recommendation].[3] The VA/DoD strongly recommend against the use of alcohol to manage medically supervised withdrawal.[3]

Opioid Use Disorder

For patients with a diagnosis of opioid use disorder, the VA/DoD recommends any of the following specific medications considering patient preferences [*strong recommendation*][3]:

- Buprenorphine/naloxone
- Methadone in an Opioid Treatment Program

Specific recommendations for treatment of opioid use disorder are also recommended[3]:

- Buprenorphine alone without naloxone in pregnant women for whom buprenorphine is indicated [*weak recommendation*]
- The method of buprenorphine treatment (i.e., Opioid Treatment Program or office-based) should be individualized for the patient [strong recommendation]
- Extended-release injectable naloxone is an option for patients for whom opioid agonist treatment is contraindicated, unacceptable, unavailable, or discontinued and who have established abstinence for a sufficient period of time [*strong recommendation*]
- There is insufficient evidence to recommend for or against oral naltrexone for the treatment of opioid use disorder
- Addiction-focused Medical Management alone or in conjunction with another psychosocial intervention is recommended at initiation of office-based buprenorphine [*strong recommendation*][3]

The VA/DoD do not recommend withdrawal management unless patients are stabilized from opioid use disorder because it substantially increases risk for relapse and overdose [*strong recommendation*].[3] In such cases, administration of long-term opioid agonists (methadone, buprenorphine) is preferred over short tapers because it is more effective and less harmful.[3] A taper of opioids using methadone or buprenorphine can be used if medically supervised in patients that 1) require abstinence from opioids; 2) wish to receive non-opioid agonist treatment (extended-release naloxone injection); 3) have minimal symptoms of opioid dependency; or 4) are in a profession that does not permit opioid agonist treatment [*strong recommendation*].[3] Clonidine may be used for withdrawal management as a second-line agent in patients with opioid use disorder who may have contraindications to methadone or buprenorphine [*strong recommendation*].[3]

The VA/DoD do not have specific pharmacotherapy recommendations for or against management of cannabis use disorder, cocaine use disorder or methamphetamine use disorder because of insufficient evidence.[3]

New Safety Alerts:
None identified.

New Formulations or Indications:
PROBUPHINE (buprenorphine) [C-III] implant device for subdermal use was approved by the FDA in May 2016.[13] The device is not available in retail pharmacies and must be inserted and removed by the certified prescriber.[13] The implants can only be obtained through a restricted Risk Evaluation and Mitigation Strategy (REMS) program that requires specialized training for physicians on insertion and removal techniques, as well as the risks for accidental overdose, misuse and abuse of opioids.[13] Certification for use of PROBUPHINE, which must be renewed every 12 months, must be achieved before use of the device.[13]

The approved indication is for the maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability of no more than 8 mg daily of a sublingual (SL) or buccal buprenorphine-containing product.[13] Treatment should accompany counseling and other psychosocial support.[13] Four implants are inserted subdermally in the upper arm for 6 months and are removed by the end of the sixth month.[13]

The efficacy of the implant is based on evidence from one double-blind, double-dummy, 6-month RCT (n=173) that compared the 4 simultaneous 80 mg buprenorphine implants with sublingual buprenorphine in adults who met DSM-IV-TR criteria for opioid dependence.[14] All patients in the trial were clinically stable on at least 6 months on SL buprenorphine at 8 mg per day or less.[14] Patients randomized to the SL buprenorphine group remained on their pre-enrollment dose (75% were taking 8 mg daily). Patients are eligible for the implant based on the enrollment in the clinical trial and manufacturer prescribing information[13]:

- no reported illicit opioid use
- no reports of significant withdrawal symptoms
- low to no desire/need to use illicit opioids
- no hospitalizations (addiction or mental health issues), emergency room visits, or crisis interventions in the past 90 days
- stable living environment, participation in a structured activity/job that contributes to the community, consistent participation in recommended cognitive behavioral therapy/peer support program
- consistent compliance with clinic visit requirements

The 4 implants contained 80 mg of buprenorphine each and yield similar plasma concentrations at a range (0.5-1.0 ng/mL) comparable to 8 mg per day or less of SL buprenorphine.[14] The primary efficacy end point was the difference in proportion of responders, defined as participants with at least *4 of 6 months* without evidence of illicit opioid use (based on urine test and self-report composites) by treatment group.[14] A total of 81/84 (96.4%) of patients in the implant group responded to therapy versus 78/89 (87.6%) patients in the SL group.[14] The difference was 8.8% (1-sided 97.5% CI, 0.009 to infinity; p<0.001 for noninferiority; p=0.03 for superiority) for the primary endpoint (NNT = 12).[14] In a sensitivity analysis for all randomized participants, with all missing urine samples imputed as positive for opioids and no illicit opioid use for all 6 months, 70/87 (80.5%) patients in the implant group and 60/90 (66.7%) in the SL buprenorphine group remained opioid-free, resulting in a proportion difference of 13.8% (1-sided 97.5% CI, 0.010 to infinity; p<0.001 for noninferiority; p=0.03 for superiority).[14] Drug-related adverse events were consistent with the known safety profile of buprenorphine and the subdermal implantation procedures (local site adverse events).[14]

Randomized Controlled Trials:

A total of 108 citations were manually reviewed from the literature search. After manual review, most citations were excluded because of wrong study design (i.e., observational), lack of control group, hospital setting, or outcome studied (i.e., non-clinical). The remaining trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 3: Description of Randomized Comparative Clinical Trials.

Alcohol Use Disorder				
Study	Comparison	Population	Primary Outcome	Results
O'Malley, et al.[15] DB, PC, PG, RCT 8 weeks N=128	1. Naltrexone 25 mg/d + naltrexone 25 mg PRN once per day (≥2 hrs prior to drinking situations). Max 50 mg/day. 2. Placebo targeted + placebo daily	Ages 18-25 years reporting ≥4 heavy drinking days (≥4 drinks/women or ≥5 drinks/men) in past 4 weeks.	Outcome 1: % days abstinent (PDA) Outcome 2 % heavy drinking days (PHDD) Self-reported drinking by web-based diary	PDA: 1. 56.6% (SD 22.52) 2. 62.5% (SD 15.57) LSMD -2.55; 95% CI, -8.46 to 3.36) PHDD: 1. 21.6% (SD 16.05) 2. 22.9% (SD 13.20) LSMD -1.44; 95% CI, -6.60 to 3.71)

Opioid Use Disorder				
D'Onofrio, et al.[16] SC, OL, RCT 30 days N=329	1. Referral to addiction services 2. Referral to addiction services + Brief Negotiation Interview (BNI) 3. Referral to addiction services + BNI + 3-day supply of buprenorphine (8 mg day 1, 16 mg days 2 and 3) to bridge until first clinic visit.	Ages ≥18 years reporting to ED with DSM-IV criteria for opioid dependence and positive UDS for opioids nonmedical prescription opioid or heroin use in past 30 days	Engagement in treatment (enrollment and receiving formal addiction treatment	1. 38/102 (37%; 95% CI, 28 to 47%) 2. 50/111 (45%; 95% CI, 36 to 54%) 3. 89/114 (78%; 95% CI, 70 to 85%; p<0.001 vs. other 2 comparisons)
Lee, et al.[17] MC, OL, RCT 6 months	1. VIVITROL (naltrexone ER) inj once per month 2. Usual care (brief counseling, referral to addiction services)	Criminal justice offenders ages 18-60 years with opioid dependence per DSM-IV criteria but currently opioid free per UDS and willing to try opioid-free treatment	Time to an opioid-relapse event during the 6-month treatment phase (defined as ≥10 days opioid use in a 28-day period)	Time to first relapse: 1. 10.5 weeks 2. 5.0 weeks (HR 0.49; 95% CI, 0.36 to 0.68) Total participants with relapse: 1. 66 (43%) 2. 99 (64%) (OR 0.43; 95% CI, 0.28 to 0.65)

Abbreviations: CO = cross-over; DB = double-blind; ED = emergency department; ER = extended-release; LSMD = least squares mean difference; MC = multi-centered; MD = mean difference; MME = morphine milligram equivalents; NRS = numerical rating scale (range 0-10); OL = open label; PC = placebo-controlled; PG = parallel group; RCT = randomized clinical trial; SC = single center; SD = standard deviation.

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Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET DR	ACAMPROSATE CALCIUM	ACAMPROSATE CALCIUM	Y
SUBLINGUAL	FILM	SUBOXONE	BUPRENORPHINE HCL/NALOXONE HCL	Y
SUBLINGUAL	TAB SUBL	BUPRENORPHINE HCL	BUPRENORPHINE HCL	Y
SUBLINGUAL	TAB SUBL	BUPRENORPHINE-NALOXONE	BUPRENORPHINE HCL/NALOXONE HCL	Y
SUBLINGUAL	TAB SUBL	ZUBSOLV	BUPRENORPHINE HCL/NALOXONE HCL	Y
ORAL	TABLET	NALTREXONE HCL	NALTREXONE HCL	Y
BUCCAL	FILM	BUNAVAIL	BUPRENORPHINE HCL/NALOXONE HCL	N
ORAL	TABLET	ANTABUSE	DISULFIRAM	N
ORAL	TABLET	DISULFIRAM	DISULFIRAM	N
INTRAMUSC	SUS ER REC	VIVITROL	NALTREXONE MICROSPHERES	N

Appendix 2: Abstracts of Clinical Trials

O'Malley, et al.
Reduction of Alcohol Drinking in Young Adults by Naltrexone: A Double-Blind, Placebo-Controlled, Randomized Clinical Trial of Efficacy and Safety. *J Clin Psychiatry* (2015).

Objective: Naltrexone, an opioid antagonist, may facilitate reduction in drinking among young adults. We compared the efficacy and safety of naltrexone administered daily plus targeted dosing with placebo to reduce drinking in heavy drinking young adults.
Methods: Randomized, double-blind, placebo-controlled study, outpatient research center, March 2008-January 2012. Participants were ages 18-25, reporting ≥4 heavy drinking days in the prior 4 weeks. Interventions included naltrexone 25 mg daily plus 25 mg targeted (at most daily) in anticipation of drinking (n=61) or daily/targeted placebo (n=67). All received a personalized feedback session and brief counseling every other week. Primary outcomes were percent days heavy drinking (PHDD) and percent days abstinent (PDA) over the 8-week treatment period. Secondary outcomes included drinks/drinking day and percent days with estimated blood alcohol levels ≥0.08 g/dL.
Results: Of 140 randomized, 128 began treatment, comprising the evaluable sample. During treatment, PHDD (Naltrexone M=21.60, SD=16.05; Placebo M=22.90, SD=13.20) (p=0.58) and PDA (Naltrexone M=56.60, SD=22.52; Placebo M=62.50, SD=15.75) (p=0.39) did not differ by group. Naltrexone significantly reduced drinks per drinking day (Naltrexone M=4.90, SD=2.28; Placebo M=5.90, SD=2.51) (p=0.009) and percentage of drinking days with estimated BAC ≥0.08 g/dL (Naltrexone M=35.36, SD=28.40; Placebo M=45.74, SD=26.80) (p=0.042). There were no serious adverse events. Sleepiness was more common with naltrexone.
Conclusions: Naltrexone did not reduce frequency of drinking or heavy drinking days, but reduced secondary measures of drinking intensity. While effects were modest, the risk-benefit ratio favors offering naltrexone to help young adult heavy drinkers reduce their drinking.

D'Onofrio, et al.
Emergency Department–Initiated Buprenorphine/Naloxone Treatment for Opioid Dependence: A Randomized Clinical Trial. *JAMA* (2015).

IMPORTANCE: Opioid-dependent patients often use the emergency department (ED) for medical care.
OBJECTIVE: To test the efficacy of 3 interventions for opioid dependence: (1) screening and referral to treatment (referral); (2) screening, brief intervention, and facilitated referral to community-based treatment services (brief intervention); and (3) screening, brief intervention, ED-initiated treatment with buprenorphine/naloxone, and referral to primary care for 10-week follow-up (buprenorphine).
DESIGN, SETTING, AND PARTICIPANTS: A randomized clinical trial involving 329 opioid-dependent patients who were treated at an urban teaching hospital ED from April 7, 2009, through June 25, 2013.
INTERVENTIONS: After screening, 104 patients were randomized to the referral group, 111 to the brief intervention group, and 114 to the buprenorphine treatment group.
MAIN OUTCOMES AND MEASURES: Enrollment in and receiving addiction treatment 30 days after randomization was the primary outcome. Self-reported days of illicit opioid use, urine testing for illicit opioids, human immunodeficiency virus (HIV) risk, and use of addiction treatment services were the secondary outcomes.
RESULTS: Seventy-eight percent of patients in the buprenorphine group (89 of 114 [95%CI, 70%-85%]) vs 37%in the referral group (38 of 102 [95% CI, 28%-47%]) and 45%in the brief intervention group (50 of 111 [95% CI, 36%-54%]) were engaged in addiction treatment on the 30th day after randomization (p< 0.001). The buprenorphine group reduced the number of days of illicit opioid use per week from 5.4 days (95% CI, 5.1-5.7) to 0.9 days (95% CI, 0.5-1.3) versus a reduction

from 5.4 days (95% CI, 5.1-5.7) to 2.3 days (95% CI, 1.7-3.0) in the referral group and from 5.6 days (95% CI, 5.3-5.9) to 2.4 days (95% CI, 1.8-3.0) in the brief intervention group (p<0.001 for both time and intervention effects; p=0.02 for the interaction effect). The rates of urine samples that tested negative for opioids did not differ statistically across groups, with 53.8% (95% CI, 42%-65%) in the referral group, 42.9% (95% CI, 31%-55%) in the brief intervention group, and 57.6% (95% CI, 47%-68%) in the buprenorphine group (p=0.17). There were no statistically significant differences in HIV risk across groups (p=0.66). Eleven percent of patients in the buprenorphine group (95% CI, 6%-19%) used inpatient addiction treatment services, whereas 37% in the referral group (95% CI, 27%-48%) and 35% in the brief intervention group (95% CI, 25%-37%) used inpatient addiction treatment services (p< .001).
CONCLUSIONS AND RELEVANCE: Among opioid-dependent patients, ED-initiated buprenorphine treatment vs brief intervention and referral significantly increased engagement in addiction treatment, reduced self-reported illicit opioid use, and decreased use of inpatient addiction treatment services but did not significantly decrease the rates of urine samples that tested positive for opioids or of HIV risk. These findings require replication in other centers before widespread adoption.

Lee, et al.
Extended-Release Naltrexone to Prevent Opioid Relapse in Criminal Justice Offenders. *N Engl J Med* (2016).

BACKGROUND: Extended-release naltrexone, a sustained-release monthly injectable formulation of the full mu-opioid receptor antagonist, is effective for the prevention of relapse to opioid dependence. Data supporting its effectiveness in U.S. criminal justice populations are limited.
METHODS: In this five-site, open-label, randomized trial, we compared a 24-week course of extended-release naltrexone (Vivitrol) with usual treatment, consisting of brief counseling and referrals for community treatment programs, for the prevention of opioid relapse among adult criminal justice offenders (i.e., persons involved in the U.S. criminal justice system) who had a history of opioid dependence and a preference for opioid-free rather than opioid maintenance treatments and who were abstinent from opioids at the time of randomization. The primary outcome was the time to an opioid-relapse event, which was defined as 10 or more days of opioid use in a 28-day period as assessed by self-report or by testing of urine samples obtained every 2 weeks; a positive or missing sample was computed as 5 days of opioid use. Post-treatment follow-up occurred at weeks 27, 52, and 78.
RESULTS: A total of 153 participants were assigned to extended-release naltrexone and 155 to usual treatment. During the 24-week treatment phase, participants assigned to extended-release naltrexone had a longer median time to relapse than did those assigned to usual treatment (10.5 vs. 5.0 weeks, P<0.001; hazard ratio, 0.49; 95% confidence interval [CI], 0.36 to 0.68), a lower rate of relapse (43% vs. 64% of participants, P<0.001; odds ratio, 0.43; 95% CI, 0.28 to 0.65), and a higher rate of opioid-negative urine samples (74% vs. 56%, P<0.001; odds ratio, 2.30; 95% CI, 1.48 to 3.54). At week 78 (approximately 1 year after the end of the treatment phase), rates of opioid-negative urine samples were equal (46% in each group, P = 0.91). The rates of other prespecified secondary outcome measures — self-reported cocaine, alcohol, and intravenous drug use, unsafe sex, and reincarceration — were not significantly lower with extended-release naltrexone than with usual treatment. Over the total 78 weeks observed, there were no overdose events in the extended-release naltrexone group and seven in the usual-treatment group (p= 0.02).
CONCLUSIONS: In this trial involving criminal justice offenders, extended-release naltrexone was associated with a rate of opioid relapse that was lower than that with usual treatment. Opioid-use prevention effects waned after treatment discontinuation.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week 2 2016

1 exp Buprenorphine, Naloxone Drug Combination/ or exp Buprenorphine/ 3133
2 exp Naltrexone/ 4363
3 exp Prescription Drug Misuse/ or exp Opioid-Related Disorders/ or exp Substance-Related Disorders/ 134079
4 1 or 2 7341
5 3 and 4 3247
6 limit 5 to (english language and humans and yr="2015 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 77

Ovid MEDLINE(R) without Revisions 1996 to July Week 2 2016

1 acamprosate.mp. 641
2 exp Disulfiram/ 760
3 exp Naltrexone/ 4363
4 exp Alcoholism/ 27319
5 exp Substance-Related Disorders/ 133713
6 exp Alcohol Deterrents/ 1461
7 1 or 2 1308
8 4 or 5 or 6 134283
9 7 and 8 1247
10 limit 9 to (english language and humans and yr="2014 -Current" and (clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 31

Buprenorphine and Buprenorphine/Naloxone Products

Goals:
- Encourage use of buprenorphine products on the Preferred Drug List.
- Restrict use of buprenorphine products under this PA to management of opioid use disorder.
- Restrict use of oral transmucosal buprenorphine monotherapy products (without naloxone) to pregnant patients or females actively trying to conceive.

Length of Authorization:
Up to 6 months

Requires PA:
- Buprenorphine sublingual tablets
- Buprenorphine/naloxone buccal film (Bunavail), sublingual film (Suboxone) and sublingual tablets (Zubsolv)
- Buprenorphine (Probuphine) subdermal implants

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the prescription for opioid use disorder (opioid dependence or addiction)?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
3. Is the patient part of a comprehensive treatment program for substance abuse that includes psychosocial support system(s)?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness. Buprenorphine therapy must be part of a comprehensive treatment program that includes psychosocial support.
4. Is the prescriber enrolled in the Oregon Prescription Drug Monitoring Program (www.orpdmp.com) and has the prescriber verified at least once in the past 6 months that the patient has not been prescribed any opioid analgesics from other prescribers?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Is the requested medication a preferred agent?	**Yes:** Go to #7	**No:** Go to #6
6. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #7
7. Is the request for the buprenorphine implant system (Probuphine)?	**Yes:** Go to #8	**No:** Go to #9
8. Has the patient been *clinically stable* on 8 mg daily or less of Suboxone or Subutex (or equivalent, see Table 1) for at least 6 months? Note: see Table 1 for definition of clinical stability and for equivalent dosing of other buprenorphine products.	**Yes:** if <u>all</u> criteria in Table 1 met, approve 4 implants for 6 months	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
9. Is the prescription for a transmucosal formulation of buprenorphine (film, tablet) with an average daily dose of more than 24 mg (e.g., more than 24 mg/day or 48 mg every other day)?	**Yes:** Pass to RPh. Deny; medical appropriateness	**No:** Go to #10
10. Is the prescribed product a buprenorphine monotherapy product (i.e., without naloxone)	**Yes:** Go to #11	**No:** Go to #13
11. Is the patient pregnant or a female actively trying to conceive?	**Yes:** Go to #13	**No:** Go to #12
12. Does the patient have a contraindication or intolerance to buprenorphine/naloxone combination products that prevents successful management of opioid use disorder?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness
13. What is the patients' pharmacy-of-choice? Document pharmacy name and NPI or address in PA record. Lock patient into their pharmacy-of-choice for 6 months.	Inform prescriber patient will be locked into a single pharmacy for all prescriptions. Go to #14	
14. What is the expected length of treatment?	Document length of therapy: _____ Approve for anticipated length of treatment or 6 months, whichever is shorter.	

Table 1. Criteria for Approved Use of Probuphine (buprenorphine implant).[1]

PROBUPHINE implants are only for use in patients who meet ALL of the following criteria:
• Patients should not be tapered to a lower dose for the sole purpose of transitioning to PROBUPHINE • Stable transmucosal buprenorphine dose (of 8 mg per day or less of a sublingual Subutex or Suboxone sublingual tablet or its transmucosal buprenorphine product equivalent) for 3 months or longer without any need for supplemental dosing or adjustments: o Examples of acceptable daily doses of transmucosal buprenorphine include: ▪ Subutex (buprenorphine) sublingual tablet (generic equivalent) 8 mg or less ▪ Suboxone (buprenorphine and naloxone) sublingual tablet (generic equivalent) 8 mg/2 mg or less ▪ Bunavail (buprenorphine and naloxone) buccal film 4.2 mg/0.7 mg or less ▪ Zubsolv (buprenorphine and naloxone) sublingual tablets 5.7 mg/1.4 mg or less

Consider the following factors in determining clinical stability and suitability for PROBUPHINE treatment: • no reported illicit opioid use • low to no desire/need to use illicit opioids • no reports of significant withdrawal symptoms • stable living environment • participation in a structured activity/job that contributes to the community • consistent participation in recommended cognitive behavioral therapy/peer support program • stability of living environment • participation in a structured activity/job
Reference: PROBUPHINE (buprenorphine implant for subdermal administration) [Prescribing Information]. Princeton, MJ: Braeburn Pharmaceuticals, Inc., May 2016.

P&T Review: *9/16 (AG); 1/15 (AG); 9/09; 5/09*
Implementation: *TBD; 9/1/13; 1/1/10*

Naltrexone Extended Release Inj. (Vivitrol®)

Goal(s):

- Promote safe and cost effective therapy for the treatment of alcohol and opioid dependence.

Length of Authorization:

Up to 12 months

Covered Alternatives:

- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Approval Criteria	
1. What diagnosis is being treated?	Record ICD10 code.

Approval Criteria		
2. Will the prescriber switch to a preferred product? Note: Preferred products are reviewed and designated as preferred agents by the Oregon Pharmacy & Therapeutics Committee based on published medical evidence for safety and efficacy.	**Yes:** Inform prescriber of covered alternatives in class.	**No:** Go to #3
3. Does the patient have a diagnosis of alcohol dependence (DSM-IV-TR) or alcohol use disorder (DSM-V)?	**Yes:** Go to #4	**No:** Go to #5
4. Has the requesting prescriber provided documentation and/or confirmation of abstinence from alcohol as assessed by the provider or by objective testing?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness. Patients must have demonstrated alcohol abstinence prior to administration.
5. Does the patient have a diagnosis of opioid dependence (DSM-IV-TR) or opioid use disorder (DSM-V)?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.
6. Is the patient physiologically free of opioid dependence for ≥7 days, as confirmed by: a. Negative urine drug screen for opioids (including heroin) and their metabolites; and b. Negative naloxone challenge test (0.8 to 1.6 mg of IM/IV naloxone; or alternatively, 50 mg or oral naloxone with no subsequent withdrawal symptoms)?	**Yes:** Go to #7	**No:** Pass to RPh. Deny; medical appropriateness.
7. Has the patient tried and failed first-line oral opioid agonists (buprenorphine/naloxone or methadone) if for the treatment of opioid dependency; or is the patient unable to take oral therapy or requires injectable therapy due to poor adherence?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
8. Is the patient part of a comprehensive treatment program for substance abuse that includes psychosocial support system(s)?	**Yes:** Approve one 380 mg injection every 4 weeks for up to 12 months.	**No:** Pass to RPh. Deny; medical appropriateness. Naltrexone extended-release injection therapy must be part of a comprehensive treatment program that includes psychosocial support.

P&T Review: *9/16 (AG); 1/15 (AG); 5/14; 11/13*
Implementation: *1/1/14*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Literature Scan: Growth Hormones

Date of Review: September 2016

Date of Last Review: September 2015
Literature Search: July 2016

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- There is no new evidence that there is any difference in efficacy/effectiveness or safety between the different somatropin (i.e., Growth Hormone) products and formulations.
- There is no new evidence that further describes efficacy outcomes associated with use of GH.
- The updated Rapid Response Report from the Canadian Agency for Drugs and Technologies in Health (CADTH) found low to moderate quality evidence that suggest improvement in body composition for patients with Prader-Willi Syndrome (PWS) that received growth hormone treatment. Furthermore, growth hormone therapy should be continued for as long as the demonstrated benefits outweigh the risks.

Recommendations:
- No change to the PDL recommended at this time. Evaluate comparative drug costs in the executive session.

Previous Conclusions:
- There is no new evidence that there is any difference in efficacy/effectiveness or safety between the different somatropin (i.e., Growth Hormone, GH) products and formulations.
- There is insufficient new evidence that further described efficacy outcomes associated with use of GH.
- There is low quality evidence that use of GH in childhood may increase all-cause mortality as an adult but has no significant effect on malignancy-related mortality or cardiovascular-related mortality.
- There is low quality evidence that use of GH in childhood may increase incidence of cancer as an adult and increase secondary malignancies in cancer survivors.

Previous Recommendations:
- No change to the PDL recommended at this time. Update clinical PA criteria to reflect Guideline Note 74.

Author: Deanna Moretz, PharmD, BCPS

Date: September 2016

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The Medline search strategy used for this literature scan is available in **Appendix 3**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:
In late 2015, CADTH updated a Rapid Response Report originally published in 2012. The focus of the report was to review of the efficacy and safety of human growth hormone (GH) treatment for PWS in adolescent and adult patients. The reviewers identified 189 citations from their search of published documents from January 1, 2012 through August 21, 2015. After screening the data they found 14 publications that met their inclusion criteria. The two research questions were:

1. What is the clinical effectiveness of human GH treatment for PWS in adolescent and adult patients?[1] The reviewers concluded studies were of low to moderate quality and suggested there is improvement in body composition such as body fat mass and lean body mass; however, results were not always significant and should be interpreted with caution.[1] Very few studies reviewed for the CADTH summary reported adverse events.
2. What are the evidence based guidelines for the use of human growth hormone treatment for PWS in adolescent and adult patients?[1] Patients with PWS should have a genetically confirmed diagnosis and multidisciplinary evaluation prior to starting GH therapy.[1] GH therapy should be continued as long as demonstrated benefits outweigh the risks.[1]

New Guidelines:
None identified.

New Formulations and Indications:
None identified.

New FDA Safety Alerts:
None identified.

References:
1. Human Growth Hormone Treatment for Prader-Willi Syndrome in Adolescent and Adult Patients: Clinical Evidence, Safety, and Guidelines | CADTH.ca. https://www.cadth.ca/human-growth-hormone-treatment-prader-willi-syndrome-adolescent-and-adult-patients-clinical-eviden-0. Accessed July 18, 2016.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SUB-Q	CARTRIDGE	SAIZEN	SOMATROPIN	Y
SUB-Q	PEN INJCTR	NORDITROPIN FLEXPRO	SOMATROPIN	Y
SUB-Q	VIAL	SAIZEN	SOMATROPIN	Y
INJECTION	CARTRIDGE	HUMATROPE	SOMATROPIN	N
INJECTION	VIAL	HUMATROPE	SOMATROPIN	N
SUB-Q	CARTRIDGE	NUTROPIN AQ	SOMATROPIN	N
SUB-Q	PEN INJCTR	NUTROPIN AQ NUSPIN	SOMATROPIN	N
SUB-Q	VIAL	SEROSTIM	SOMATROPIN	N
SUB-Q	VIAL	ZOMACTON	SOMATROPIN	N
SUB-Q	VIAL	ZORBTIVE	SOMATROPIN	N
SUB-Q	CARTRIDGE	GENOTROPIN	SOMATROPIN	
SUB-Q	CARTRIDGE	OMNITROPE	SOMATROPIN	
SUB-Q	SYRINGE	GENOTROPIN	SOMATROPIN	
SUB-Q	VIAL	OMNITROPE	SOMATROPIN	

Appendix 2: New Clinical Trials

A total of 69 citations resulted from initial literature search. After further review, all studies were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical).

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to July Week1 2016

1 exp Growth Hormone/ 22243
2 somatotropin.mp. 3271
3 somatropin.mp. 128
4 1 or 2 or 3 23442
5 limit 4 to (english language and yr="2015 -Current" and (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or multicenter study or pragmatic clinical trial or randomized controlled trial)) 81
6 limit 5 to humans 69

Author: Moretz Date: September 2016

Growth Hormones

Goal(s):
- Restrict use of growth hormone (GH) for funded diagnoses where there is medical evidence of effectiveness and safety.

NOTE: Treatment with growth hormone (GH) is included only for children with: pituitary dwarfism, Turner's syndrome, Prader-Willi-syndrome, Noonan's syndrome, short stature homeobox-containing gene (SHOX), chronic kidney disease (stage 3 or higher) and those with renal transplant. Treatment with GH should continue only until adult height as determined by bone age is achieved. Treatment is not included for isolated deficiency of human growth hormone or other conditions in adults.

Length of Authorization:
- Up to 12 months

Requires PA:
- All GH products require prior authorization for OHP coverage. GH treatment for adults is not funded by the OHP.

Covered Alternatives:
- Current PMPDP preferred drug list per OAR 410-121-0030 at www.orpdl.org
- Searchable site for Oregon FFS Drug Class listed at www.orpdl.org/drugs/

Initial Approval Criteria		
1. What is the diagnosis being treated?	Record ICD10 code	
2. Is the patient an adult (>18 years of age)?	**Yes:** Pass to RPh. Deny; not funded by the OHP	**No:** Go to #3
3. Is this a request for initiation of growth hormone?	**Yes:** Go to #4	**No:** Go to **Renewal Criteria**
4. Is the prescriber a pediatric endocrinologist or pediatric nephrologist?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness

Initial Approval Criteria		
5. Is the diagnosis promotion of growth delay in a child with 3rd degree burns?	**Yes:** Document and send to DHS Medical Director for review and pending approval	**No:** Go to #6
6. Is the diagnosis one of the following? • Turner's syndrome (ICD10 Q969) • Noonan's syndrome (ICD10 E7871-7872, Q872-873, Q875, Q8781, Q8789, Q898) • Prader-Willi syndrome (PWS) (ICD10 Q871) • Pituitary dwarfism (ICD10 E230) • Short stature homeobox-containing gene (SHOX) (ICD10 R6252) • Chronic kidney disease (CKD, Stage ≥3) (ICD10 N183-N185) • Renal transplant (ICD10 Z940)	**Yes:** Document and go to #7	**No:** Pass to RPh. Deny; not funded by the OHP.
7. If male, is bone age <16 years? If female, is bone age <14 years?	**Yes:** Go to #8	**No:** Pass to RPh. Deny; medical appropriateness
8. Is there evidence of non-closure of epiphyseal plate?	**Yes:** Go to #9	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the product requested preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #10
10. Will the prescriber consider a change to a preferred product? <u>Message</u>: • Preferred products to not require a copay. • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months.	**No:** Approve for up to 12 months

Renewal Criteria		
1. Document approximate date of initiation of therapy and diagnosis (if not already done).		
2. Is growth velocity greater than 2.5 cm per year?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
3. Is male bone age <16 years or female bone age <14 years?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Is the product requested preferred?	**Yes:** Approve for up to 12 months	**No:** Go to #5
5. Will the prescriber consider a change to a preferred product? Message: • Preferred products do not require a copay. • Preferred products are evidence based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics (P&T) Committee.	**Yes:** Inform prescriber of covered alternatives in class and approve for up to 12 months	**No:** Approve for up to 12 months

P&T Review: *9/16; 9/15; 9/14; 9/10; 5/10; 9/08; 2/06; 11/03; 9/03*
Implementation: *1/1/11, 7/1/10, 4/15/09, 10/1/03, 9/1/06; 10/1/03*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Literature Scan: Parenteral Antipsychotics

Date of Review: September 2016

Date of Last Review: May 2016 (all antipsychotics)
End Date of Literature Search: August 2016

Current Status of PDL Class:
See **Appendix 1**.

Conclusions:
- One new high quality systematic review was published since the parenteral antipsychotic agents were last reviewed in May 2016. Otherwise, no new clinical practice guidelines, formulations, indications, or safety alerts were identified.
- One systematic review with meta-analysis specifically evaluated long-acting injectable risperidone. Evidence shows the drug may have similar efficacy and harms as oral second-generation antipsychotics and other long-acting parenteral antipsychotics.

Recommendations:
- No further review or research needed at this time. Review comparative drug costs in the executive session.

Previous Conclusions:
- There is insufficient evidence of clinically meaningful differences between antipsychotic agents in efficacy or effectiveness or harms between antipsychotic agents for schizophrenia, bipolar mania or MDD.
- There is insufficient evidence to determine if brexpiprazole and cariprazine offer superior efficacy or safety to other antipsychotic agents for schizophrenia.
- There is insufficient evidence to determine if brexpiprazole offers superior efficacy or safety to other antipsychotic agents for MDD.
- There is insufficient evidence to determine if cariprazine offers superior efficacy or safety to other antipsychotic agents for bipolar mania.
- There is insufficient evidence to determine if new formulations of long-acting injectable aripiprazole and paliperidone offer improved safety or efficacy over other formulations of aripiprazole and paliperidone, or to other antipsychotic agents generally.

Previous Recommendations:
- Designate Rexulti (brexpiprazole), Vraylar (cariprazine), and new formulations of aripiprazole (Aristada) and paliperidone (Invega Trinza) voluntary non-preferred (no PA required) based on limited data.
- After executive session, make Latuda (lurasidone), Saphris (asenapine) and Abilify Maintenna (aripiprazole) preferred and make chlorpromazine voluntary non-preferred (no PA required).

Author: Andrew Gibler, PharmD Date: September 2016

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

Systematic Reviews:
The Cochrane Collaboration conducted a systematic review with meta-analysis to critically appraise the current evidence for risperidone by long-acting intramuscular injection for the treatment of schizophrenia or related psychoses.[1] The long-acting injectable formulation contains risperidone encapsulated within biodegradable polymer microspheres and suspended in an aqueous solution.[1] The polymers break down after intramuscular administration and the drug is released at a set rate that occurs over several weeks, with the highest plasma concentrations occurring at about one month after injection.[1] Randomized controlled trials that compared the long-acting risperidone injectable product with placebo, no treatment, or other oral or long-acting injectable formulations of antipsychotic agents in these populations were eligible for inclusion.[1] For dichotomous data, the risk ratio (RR) with 95% confidence intervals (CI) was calculated. For continuous data, mean difference (MD) was calculated. The GRADE approach was used to interpret the evidence after risk of bias was assessed. Primary outcomes included long-term relapse and long-term clinically important changes in mental state.[1] Several pre-specified secondary outcomes were also assessed, including early study withdrawal, severe adverse effects, and any adverse effects related to movement disorder, weight gain, prolactin levels and glucose metabolism.[1] All outcomes were reported for the short-term (up to 12 weeks), medium term (13-26 weeks), and long-term (>26 weeks).[1] Twelve studies (n=5723; mean age ~40 years) were included in the final analysis.[1] The prescribing of risperidone was consistent across all studies; 25 mg, 37.5 mg and 50 mg injections every 2 weeks were the most common dosages, with participants typically initiated on 25 mg every 2 weeks, which was then titrated by 12.5 mg increments if symptoms worsened.[1] All studies used the Diagnostic and Statistical Manual version 1V (DSM-IV) to define schizophrenia.[1] Exclusion criteria for all studies were fairly consistent: patients with a history of violence to themselves or others, recent suicide attempts, substance use disorders, or general ill health were all excluded.[1]

It is uncertain if long-acting injectable risperidone is any more effective than placebo in controlling symptoms of schizophrenia because outcomes of relapse and improvement in mental state were neither measured nor reported in placebo-controlled trials.[1] Compared to placebo, less patients who received risperidone withdrew from the study early by 12 weeks (RR 0.74; 95% CI, 0.63 to 0.88) and less risperidone-treated patients experienced severe short-term adverse events (RR 0.59; 95% CI, 0.38 to 0.93) based on low quality evidence.[1] However, low quality evidence suggests no difference in weight gain between long-acting injectable risperidone and placebo (RR 2.11; 95%CI, 0.48 to 9.18).[1]

Outcomes of improvement in mental state could not be reported when long-acting injectable risperidone was compared to oral antipsychotics because trials had such high attrition rates.[1] Most primary outcomes of these studies did not show a difference between treatment groups, including in trials that compared

injectable to oral risperidone.[1] However, more patients who received long-acting injectable risperidone experience nervous system disorders long-term compared to oral antipsychotics (RR 1.34; 95% CI, 1.13 to 1.58) based on low-quality evidence.[1]

In comparisons with other long-acting injectable second-generation antipsychotics, risperidone was primarily studied against paliperidone palmitate.[1] Relapse rates were not reported and rates of response using total Positive and Negative Syndrome Scale (PANSS), weight increase, prolactin-related adverse events and glucose-related adverse events were similar between groups.[1] Fewer patients in the risperidone group withdrew early due to lack of efficacy in one long-term study (RR 0.60; 95% CI, 0.45 to 0.81) based on low quality evidence, but more patients in the risperidone group required use of medications to manage extrapyramidal symptoms (RR 1.46; 95% CI, 1.18 to 1.8) based on moderate quality evidence.[1]

Outcomes of relapse, severe adverse events or movement disorders were not reported in trials that compared long-acting injectable risperidone to first-generation long-acting injectable antipsychotics.[1] Outcomes relating to improvement in mental state demonstrated no difference between groups based on low quality evidence.[1] However, more patients who received risperidone withdrew early in long-term studies compared to first-generation long-acting injectable antipsychotics (RR 3.05; 95% CI, 1.12 to 8.31) based on low quality evidence.[1]

New Guidelines:
None identified.

New Formulations or Indications:
None identified.

New FDA Safety Alerts:
None identified.

References:
1. Sampson S, Hosalli P, Furtado VA, Davis JM. Risperidone (depot) for schizophrenia. *Cochrane Database of Systematic* Reviews. 2016, Issue 4. Art. No.: CD004161. DOI: 10.1002/14651858.CD004161.pub2.

Appendix 1: Current Status on Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL	CARVEOUT
ANTIPSYCHOTICS, PARENTERAL					
INJECTION	AMPUL	CHLORPROMAZINE HCL	CHLORPROMAZINE HCL	Y	Y
INJECTION	AMPUL	HALDOL	HALOPERIDOL LACTATE	Y	Y
INJECTION	AMPUL	HALOPERIDOL	HALOPERIDOL LACTATE	Y	Y
INJECTION	VIAL	FLUPHENAZINE DECANOATE	FLUPHENAZINE DECANOATE	Y	Y
INJECTION	VIAL	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
INJECTION	VIAL	HALOPERIDOL LACTATE	HALOPERIDOL LACTATE	Y	Y
INTRAMUSC	AMPUL	HALDOL DECANOATE 100	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	AMPUL	HALDOL DECANOATE 50	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	AMPUL	HALOPERIDOL DECANOATE	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	AMPUL	HALOPERIDOL DECANOATE 100	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	SUSER SYR	ABILIFY MAINTENA	ARIPIPRAZOLE	V	Y
INTRAMUSC	SUSER SYR	ARISTADA	ARIPIPRAZOLE LAUROXIL	V	Y
INTRAMUSC	SUSER VIAL	ABILIFY MAINTENA	ARIPIPRAZOLE	V	Y
INTRAMUSC	SYRINGE	INVEGA SUSTENNA	PALIPERIDONE PALMITATE	V	Y
INTRAMUSC	SYRINGE	INVEGA TRINZA	PALIPERIDONE PALMITATE	V	Y
INTRAMUSC	SYRINGE	RISPERDAL CONSTA	RISPERIDONE MICROSPHERES	Y	Y
INTRAMUSC	VIAL	GEODON	ZIPRASIDONE MESYLATE	V	Y
INTRAMUSC	VIAL	HALOPERIDOL DECANOATE	HALOPERIDOL DECANOATE	Y	Y
INTRAMUSC	VIAL	OLANZAPINE	OLANZAPINE	V	Y
INTRAMUSC	VIAL	ZYPREXA	OLANZAPINE	V	Y
INTRAMUSC	VIAL	ZYPREXA RELPREVV	OLANZAPINE PAMOATE	V	Y

Appendix 2: New Clinical Trials

A total of 4 citations were manually reviewed from the literature search. After manual review, all trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical). Full abstracts are included in **Appendix 3**.

Appendix 3: Abstracts of Clinical Trials
Not applicable.

Appendix 4: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to August Week 2 2016

1 exp Chlorpromazine/ 1537
2 exp Haloperidol/ 5473
3 exp Fluphenazine/ 283
4 exp Aripiprazole/ 1773
5 exp Paliperidone Palmitate/ 523
6 exp Risperidone/ 5185
7 olanzapine.mp. 6908
8 1 or 2 or 3 or 4 or 5 or 6 or 7 17907
9 parent*.mp. 222873
10 inject*.mp. 403022
11 intramusc*.mp. 29455
12 intravenou*.mp. 198274
13 9 or 10 or 11 or 12 755591
14 8 and 13 2296
15 limit 14 to (english language and humans and yr="2016 -Current" and (clinical study or clinical trial, all or clinical trial or comparative study or controlled clinical trial or meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 4

Risperdal® Consta® Quantity Limit

Goal(s):

- To ensure the use of the appropriate billing quantity. This is a quantity initiative, **not a clinical initiative**. The vial contains 2 mL. The dispensing pharmacy must submit the quantity as 1 vial and not 2 mL.

Length of Authorization:

Date of service or 12 months, depending on criteria

Requires PA:

- Risperdal® Consta®

Approval Criteria		
1. Is the quantity being submitted by the pharmacy expressed correctly as # syringes?	**Yes:** Go to #2	**No:** Have pharmacy correct to number of syringes instead of number of mL.
2. Is the amount requested above 2 syringes per 18 days for one of the following reasons? • Medication lost • Medication dose contaminated • Increase in dose or decrease in dose • Medication stolen • Admission to a long term care facility • Any other reasonable explanation?	**Yes:** Approve for date of service only (use appropriate PA reason)	**No:** Go to #3
3. Is the pharmacy entering the dose correctly and is having to dispense more than 2 syringes per 18 days due to the directions being given on a weekly basis instead of every other week.	**Yes:** Approve for 1 year (use appropriate PA reason)	Note: This medication should NOT be denied for clinical reasons.

P&T Review: *9/16; 5/05*
Implementation: *11/18/04*

Drug Use Research & Management Program
Oregon State University, 500 Summer Street NE, E35
Salem, Oregon 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Class Update with New Drug Evaluations: Hepatitis C Direct-acting Antivirals

Date of Review: September 2016
Generic Name: elbasvir/grazoprevir
Generic Name: sofosbuvir/velpatasvir

End Date of Literature Search: August 2016
Brand Name (Manufacturer): Zepatier ® (Merck)
Brand Name (Manufacturer): Epclusa® (Gilead)
Dossiers Received: yes

Current Status of PDL Class:
See **Appendix 1**.

Purpose for Class Update:
To define place in therapy for 2 new direct-acting antivirals (DAAs) recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of chronic Hepatitis C (CHC) infection. In addition, new comparative evidence for existing DAAs will be reviewed.

Research Questions:
1. Does elbasvir/grazoprevir (EBR/GZR; Zepatier®) or sofosbuvir/velpatasvir (SOF/VEL; Epclusa®) have superior efficacy to placebo and are they more effective/efficacious than other DAAs for the treatment of CHC?
2. Is EBR/GZR or SOF/VEL safer than other DAAs for the treatment of CHC?
3. Is there new comparative evidence for differences in efficacy/effectiveness or harms between available DAAs for the treatment of CHC?
4. Are there specific subpopulations based on severity of disease, comorbidities, or level of fibrosis that may benefit from one particular DAA over another DAA?
5. What is the evidence to support use of non-invasive testing to stage fibrosis, and how do these tests differ in sensitivity and specificity compared to liver biopsies?
6. Is there evidence to support an optimal time to initiate treatment for CHC based on improved effectiveness or less harms?

Conclusions:
- There is moderate quality evidence that 12 weeks of EBR/GZR without ribavirin (RBV) produces a sustained virologic response (SVR) rate of approximately 95% in treatment-naïve CHC patients with genotype (GT) 1 or GT4 with or without HIV coinfection. SVR rates did not significantly differ between patients with or without cirrhosis. However, higher virologic failure occurred in patients with GT1a infection and baseline NS5a resistant amino acid variants (RAVs). Relapse may be reduced with baseline NS5A polymorphism screening.

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

- Low quality evidence suggests that 12 weeks of EBR/GZR + RBV may be efficacious in treatment-experienced patients with GT1 who previously failed triple therapy with pegylated interferon and ribavirin plus an early generation protease inhibitor (SVR 96.2%; 95% CI, 89.3 to 99.2%).
- There is low quality evidence for use of EBR/GZR in treatment-experienced patients with GT4, which makes it difficult to determine efficacy in this population. One unpublished trial included 37 treatment-experienced GT4 patients randomized to 12 or 16 weeks of EBR/GZR with or without RBV. SVR rates ranged from 60-100% with the highest SVR rates (8/8) in patients who received EBR/GZR + RBV for 16 weeks. The FDA recommends 16 weeks with RBV based on these data alone due to limited treatment options in treatment-experienced GT4 patients.
- There is low quality evidence based on a phase 3 trial that EBR/GZR can achieve high SVR rates (94.3%; 95% CI, 88.5-97.7%) in GT1 patients with stage 4 or 5 chronic kidney disease (CKD). Although EBR/GZR was generally safe in the population studied, the exclusion criteria were much more restrictive than the other GZR/EBR trials which limit the applicability of these results to real-world patients with CKD.
- GZR exposure is increased in decompensated cirrhosis. EBR/GZR is therefore contraindicated in Child-Pugh B and C cirrhosis due to increased risk for liver toxicity.
- There is low quality evidence that 12 weeks of SOF/VEL results in SVR rates of 95% or higher for treatment-naïve or treatment-experienced CHC patients with GT1, GT2, GT3, GT4, GT5 or GT6. SVR rates did not vary significantly based on age, race, or sex but were numerically lower for patients with GT3, patients with cirrhosis, and patients with prior treatment failure. Confidence intervals were imprecise for GT5 and GT6 due to the low number of patients studied with these 2 genotypes.
- There is low quality evidence that 12 weeks SOF/VEL may be modestly superior to 12 weeks SOF + RBV in patients with GT2 (SVR 99% vs. 95%, respectively; absolute difference 5.2%; 95% CI, 0.2-10.3%; p=0.02). Treatment with 24 weeks of SOF/VEL may also be superior to 24 weeks of SOF + RBV in patients with GT3 (SVR 95% vs. 80%; respectively; absolute difference 14.8%; 95% CI 9.6-20%; p<0.001). There are no other alternative treatment regimens approved for GT2 and there is insufficient comparative data for other treatments available for GT3 (LDV/SOF + RBV or DCV/SOF).
- There are still several limitations in the current evidence for the treatment of CHC:
    - There is still insufficient evidence for the optimal treatment of patients who have had a virologic failure to a previous NS5A or NS5B inhibitor. Risk of DAA resistance is a major concern in this population.
    - There is still a lack of head-to-head trials for most DAA regimens. In some populations, data on DAAs are limited to open-label, uncontrolled, or historically controlled trials.
    - Trials often exclude patients with chronic hepatitis B virus (HBV), HIV, cancer, hepatocellular carcinoma (HCC), decompensated cirrhosis, severe psychiatric, cardiac, pulmonary, or renal comorbidities, and severe alcohol or substance abuse. When decompensated cirrhosis is included, there are very little data in patients with Child-Pugh class C.
    - There is no direct evidence that treatment with antiviral therapy for CHC leads to improved long-term clinical outcomes in incidence of HCC, liver transplantation, or mortality.
- Given the high sensitivity and specificity of image tests to stage fibrosis (specifically, transient elastography [FibroScan], acoustic radiation force impulse imaging [ARFI], shear wave elastography [SWE]) and potential harms of liver biopsy, these less invasive options are favored for prescribers considering CHC treatment with a DAA.

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

Author: Megan Herink, Pharm.D Date: September 2016

- Limited data are available according to severity of fibrosis. Studies define patients by cirrhosis status. There is insufficient evidence from clinical trials that patients with early stages of disease (F0-F2) achieve higher SVR rates than those with more advanced disease, or whether delayed treatment leads to poorer long-term clinical outcomes. However, an assessment of the patient's readiness to treat and education on the importance of compliance and follow-up are vital for successful treatment. Factors to consider before deciding to treat early fibrosis stages (F0-F1) include: 1) the slow progression of disease to cirrhosis, 2)limited treatment options for the re-treatment of HCV in cases of relapse or reinfection, and 3) possibility of superior DAA regimens in the pipeline.

Recommendations:

- Approve amendments to clinical prior authorization (PA) criteria (**Appendix 4**) to allow for treatment of preferred DAA regimens in CHC patients with Metavir fibrosis stage 2 or higher.
- Approve SOF/VEL for 12 weeks as a preferred treatment regimen for patients with GT2.
- Evaluate comparative drug costs in the executive session to inform placement of other DAA regimens on the Oregon Health Plan (OHP) Preferred Drug List (PDL).

Previous Conclusions:

- DCV+SOF was FDA approved for the treatment of genotype 3 (GT3) CHC based on 1 open-label nonrandomized phase 3 trial. OMB/PTV-R was FDA approved for the treatment of genotype 4 (GT4) CHC based on one open label phase 2b trial. In addition, updated guidelines were released for the treatment of CHC.
- There is low quality evidence from one phase 3 trial with significant methodological flaws, but a high magnitude of effect, that DCV+SOF achieved an SVR of 89% in subjects with GT3 CHC. However, SVR rates were reduced in patients with cirrhosis (63%) compared to those without cirrhosis (96%). As a result, the optimal treatment duration for GT3 patients with cirrhosis is not established. Further data demonstrate that patients with cirrhosis may benefit from the addition of rivabirin (RBV) or an extended duration of 16 weeks. No other treatment options have shown to be more effective in this population: SOF + ribavirin (RBV) for 24 weeks resulted in lower SVR rates (84%), and ledipasvir/sofosbuvir (LDV/SOF; Harvoni®) + RBV for 12 weeks has only proven to be effective in non-cirrhotic patients.
- There is low quality to insufficient evidence that DCV+SOF is efficacious in GT 1 or GT2 CHC, and insufficient evidence for use in patients with cirrhosis with these genotypes. At this time, there is more evidence to support LDV/SOF in genotype 1 (GT1) and SOF+RBV in genotype 2 (GT2) CHC.
- There is low quality evidence from one phase 2b trial (PEARL-1), with significant methodological flaws, that OMB/PTV-R +/- RBV achieved an SVR of 91-100% in GT4 CHC without cirrhosis.
- There is insufficient evidence that OMB/PTV-R is efficacious in patients with cirrhosis, in patients with genotypes other than GT4, or in treatment-experienced patients with regimens other than pegylated interferon (PEG-IFN) with ribavirin.
- There is insufficient comparative evidence between direct-acting antiviral agents.
- HCV antiviral agents have insufficient evidence for long-term clinical outcomes such as liver transplantation, HCC, and mortality.
- There is low quality evidence that ombitasvir/paritaprevir/ritonavir with dasabuvir (OMB/PTV-R + DAS; Viekira Pak®) and OMB/PTV-R may cause serious liver injury, mostly in patients with underlying advanced liver disease. These agents should be used with caution in patients with cirrhosis and are contraindicated in decompensated liver disease.

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

Author: Megan Herink, Pharm.D Date: September 2016

Previous Recommendations:

- Continue to prioritize treatment for persons with advanced liver disease (METAVIR stage F3 or F4), as well as those at greatest risk of developing complications of liver disease, including:
    - All patients awaiting a liver transplantation
    - All patients post solid organ transplant
    - HIV coinfection with METAVIR stage F2 or greater
    - Patients with extrahepatic manifestations
- Make DCV preferred and replace LDV/SOF with DCV with SOF and RBV in current prior authorization (PA) for patients with GT3 CHC with cirrhosis.
- Due to extensive drug-drug interactions and safety concerns, make OMB/PTV-R + RBV and OMB/PTV-R + DAS non-preferred.
- Allow treatment approval if prescribed by or in consultation a hepatologist, gastroenterologist, or infectious disease specialist with experience of hepatitis C.
- Approve updated PA criteria.

Background:

Chronic hepatitis C infection is the leading cause of complications from chronic liver disease, including cirrhosis, liver failure, and hepatocellular carcinoma. It is also the leading indication for liver transplantation in the Western world.[1] The goal of treatment for CHC is to reduce the occurrence of end-stage liver disease and its related complications. However, results from clinical trials designed to evaluate long-term health outcomes are not available. In addition, only about 30% of people with CHC go on to develop cirrhosis and the time to progress to cirrhosis varies at an average of 40 years.[2]

The SVR rate is defined as the proportion of patients who experience a decline in HCV-RNA to undetectable levels following completion of antiviral treatment, as measured by a sensitive polymerase chain reaction assay. It is the standard marker of successful treatment in clinical trials and is associated with the long-term absence of viremia. There is some evidence based on observational data of an association of SVR and reductions in mortality, liver failure, and cancer.[1] The two major predictors of SVR are viral genotype and pre-treatment viral load.[3] Other factors associated with an increased likelihood of SVR include female sex, age less than 40 years, non-Black race, lower body weight, absence of insulin resistance, and absence of bridging fibrosis or cirrhosis on liver biopsy. Studies that include patients with decompensated cirrhosis, renal failure or other comorbidities, and minority racial or ethnic groups are lacking though these patients remain the most difficult to successfully treat.[4]

There are no published data to support a specific minimum length of abstinence from illicit substances or alcohol before treatment. In addition, no evidence is available that shows patients who use alcohol, illicit drugs, and marijuana are less likely to achieve SVR if they are adherent to therapy. However, substance use should be part of a readiness to treat assessment because of the higher risk of non-adherence and re-infection.

Trials have historically used SVR at week 24 of follow-up (SVR24) as a primary endpoint. SVR24 has been associated with improvements in quality of life, decreased decompensated liver disease, hepatocellular carcinoma, liver transplant, and all-cause mortality. More recent studies use SVR rate at 12 weeks

(SVR12) as the primary endpoint based on evidence that the majority of patients with SVR12 maintain SVR at 24 weeks.[5] SVR12 is generally considered a virologic cure in clinical trials.

Patients at greatest risk for progression to cirrhosis have detectable HCV-RNA and liver histology demonstrating fibrosis (METAVIR stage 2 or higher). Patients with compensated cirrhosis are at risk of progressing to decompensation, developing hepatocellular carcinoma, and are at higher risk for death. Urgency to treat patients with CHC is higher when risk of decompensated cirrhosis or death from liver-related diseases is higher; treatment urgency is also higher in liver transplant recipients with CHC in order to prolong graft survival. Disease progression varies greatly among patients with compensated liver disease and the number needed to treat to prevent adverse long-term outcomes is dependent on several factors. The newer DAAs will be most beneficial in patients at highest risk for cirrhosis-related events.[6] However, treatment of CHC with DAAs at earlier stages of fibrosis incur substantial upfront costs but can be cost-effective long-term if adverse events are avoided from cure.[7] Patients with decompensated liver disease are a challenging population to treat because of symptomatic complications related to cirrhosis (i.e., jaundice, ascites, variceal hemorrhage, or hepatic encephalopathy). Clinical trials define decompensated cirrhosis as Child-Turcotte-Pugh (CTP) class B or C cirrhosis; the majority of decompensated cirrhosis patients included in trials have CTP class B cirrhosis.[8]

Virologic failure is defined as confirmed HCV RNA level at or above the lower limit of quantification (LLOQ) during treatment after previously being below the LLOQ; relapse is defined as confirmed HCV RNA level at or above the LLOQ after treatment after previously achieving an SVR.[9] Virologic failure is typically associated with the emergence of resistance-associated variants (RAVs) that can cause cross resistance to other DAAs in the same class.[10] Baseline RAVs exist in a minority of patients and are found in most patients who fail to achieve SVR with DAA treatment. NS3 variants can cause high-level resistance to other protease inhibitors. In the U.S., the prevalence of baseline NS5A polymorphisms in patients with GT1a and GT1b infection is 8-12% and 11-12%, respectively.[11] Sofosbuvir (SOF), an NS5B inhibitor, appears to have the highest genetic barrier to resistance. Genetic polymorphisms that reduce drug susceptibility have been reported for the NS5A and NS3/4A (protease inhibitor) drug classes. The presence of baseline NS5A RAVs significantly reduce SVR12 rates in patients with GT3 treated with daclatasvir (DCV) plus SOF compared to patients without the NS4A RAV (SVR rates of 54% vs. 92%, respectively).[12]

In the U.S., GT1 infection is found in about 75% of patients with CHC; GT2 and GT3 represent about 20% of CHC patients.[1] Subgenotypes 1a and 1b are the most common subgenotypes of GT1. Cure rates for GT1a and 1b infection may differ depending on the treatment regimen. Data suggests that fibrosis progression occurs most rapidly in patients with GT3; DAA regimens have also been less effective in patients with this genotype.[8] Therapies to treat CHC have advanced significantly over the past several years. Prior to 2011, the combination of pegylated interferon (PEG-IFN) and ribavirin (RBV) was the standard of care and approximately only 55-60% of patients achieved a SVR. In 2011, the FDA approved the first generation DAAs boceprevir and telaprevir.[13] Since then, a variety of additional DAAs have been approved by the FDA resulting in interferon-free regimens, substantial improvement in adverse events and tolerability, and SVR12 rates that exceed 90% (Table 1). However, newer DAAs are associated with substantial cost. A significant challenge remains identifying patients who will most benefit from treatment since only 5-20% of CHC patients will develop cirrhosis over 20 years.[14] Additionally, the lack of head-to-head trials and the use of single-arm cohort studies make it difficult to compare the relative efficacy of the different DAA regimens available.

The Oregon Drug Use Review / Pharmacy & Therapeutics (P&T) Committee initially prioritized treatment for the fee-for-service population to patients in greatest need of treatment. Limited real-world experience and data, consideration for the number of patients waiting for treatment and limited provider expertise, and

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the limited number of alternative treatment options in cases of treatment resistance and patient comorbidities all played a role in prioritizing treatment. As more treatment options become available, real world experience increases, and the community standard evolves, the P&T Committee has opened up treatment in a step-wise fashion to patients with less severe disease. Current drug policies in place approve treatment for patients with fibrosis Metavir stage 3 or 4, or patients with extrahepatic manifestations at any stage of fibrosis, patients in the setting of solid organ transplant, and in patients with fibrosis Metavir stage 2 or greater coinfected with HIV.

Zepatier® (EBR/GZR) is a fixed dose-combination of 2 DAAs which contain 50 mg of elbasvir (EBR) and 100 mg of grazoprevir (GZR) approved for patients with GT1 or GT4. EBR is an NS5A inhibitor and GZR is an NS3/NS4A protease inhibitor.[15] EBR/GZR was also approved for GT1 patients with end stage renal disease (ESRD) on hemodialysis.[11]

Epclusa® (SOF/VEL) is a fixed-dose combination of 400 mg of SOF, a NS5B inhibitor, and 100 mg of velptasvir (VEL), a NS5A inhibitor approved for the treatment of CHC in adult patients with GT1, 2, 3, 4, 5 or 6 with or without cirrhosis, including decompensated cirrhosis.[16]

Table 1. Direct-acting Antiviral Regimens for Chronic Hepatitis C.

Drug Name	Indications	Strength/Route	Dose and Frequency
Daklinza®[17] and Solvaldi®[18]	CHC GT1; GT3	Daclatasvir 60 mg + sofosbuvir 400 mg	1 tablet of each daily x12 weeks
Epclusa®[16]	CHC GT1; GT2; GT3; GT4; GT5; GT6	Sofosbuvir 400 mg/velpatasvir 100 mg	1 tablet once daily x12 weeks
Harvoni®[19]	CHC GT1; GT4; GT5; GT6	Ledipasvir 90 mg/sofosbuvir 400 mg	1 tablet once daily x8, 12, or 24 weeks
Sovaldi®[18]	CHC GT1; GT2; GT3; GT4 Used in combination with other antivirals	Sofosbuvir 400 mg	1 tablet once daily with ribavirin and/or peginterferon alfa x12 weeks
Technivie®[20]	CHC GT4 Without cirrhosis	Ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg	2 tablets once daily x12 weeks
Viekira Pak®[21]	CHC GT1 Without cirrhosis or With compensated cirrhosis	Ombitasvir 12.5 mg/paritaprevir 75 mg/ritonavir 50 mg + dasabuvir 250 mg	2 tablets once daily + 1 dasabuvir tablet twice daily (+/- ribavirin) x12 or 24 weeks
Viekira XR®[22]	CHC GT1	Dasabuvir 200 mg/ombitasvir 8.33 mg/paritaprevir 50 mg/ritonavir 33.33 mg	3 tablets once daily x12 or 24 weeks
Zepatier®[15]	CHC GT1; GT4	Elbasvir 50 mg/ grazoprevir 100 mg	1 tablet once daily x12 or 16 weeks
Abbreviations: CHC = chronic hepatitis C; GT = genotype			

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Author: Megan Herink, Pharm.D Date: September 2016

Methods:
A Medline literature search for new systematic reviews and randomized controlled trials (RCTs) assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts. Finally, the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. Randomized controlled trials and abstracts are in **Appendix 2.**

Systematic Reviews:
1. The Canadian Agency for Drugs and Technologies in Health (CADTH) systematically assessed the comparative efficacy and safety of DAA regimens for the treatment of CHC infection (genotypes 1 to 6).[23] Due to a lack of head-to-head trials, a Bayesian network meta-analysis was performed to assess treatments based on indirect evidence. A total of 67 studies were included with the majority reporting on patients with GT1. The authors categorized the available evidence as adequate; however, all but 2 trials had at least one methodological domain with unclear risk of bias. The newest agents, EBR/GZR and SOF/VEL, were not included in this review.

The following conclusions were made for treatment of patients with GT1:
- For treatment-naive patients, SOF + ledipasvir (LDV), paritaprevir/ritonavir + ombitasvir + dasabvir (PAR/RIT + OMB + DAS) ± RBV, and DCV-based regimens were statistically superior to pegylated interferon and ribavirin (PEG-RBV) in achievement of SVR. Patients on SOF + LDV or PAR/RIT + OMB + DAS ± RBV also achieved SVR significantly more often than simeprevir (SIM) +PEG-RBV, SOF + PEG-RBV, and SOF + RBV.
- For treatment-experienced patients, all 3 regimens noted above were superior to PEG-RBV-based treatments, specifically SOF + LDV and PAR/RIT + OMB + DAS ± RBV. There was limited evidence for patients with cirrhosis. There were no significant differences between SOF + LDV and PAR/RIT + OMB + DAS ± RBV.
- For treatment-experienced patients with prior relapse, prior partial response, or null response, PAR/RIT + OMB + DAS ± RBV, SOF + LDV, and DCV-based regimens demonstrated improved SVR rates compared with PEG-RBV-based treatments.
- There was no evidence available for patients with genotype 1 infection and decompensated liver disease.
- Evidence for efficacy of treatments in patients previously treated unsuccessfully with DAA + PEG-RBV regimens were limited to 4 studies that reported SVR rates. The largest study found SVR rates in patients with GT1 and prior treatment failure on DAA + PEG-RBV were 94% with 12 weeks of SOF + LDV (n = 66); 97% with 12 weeks of SOF + LDV + RBV (n = 64); 98% with 24 weeks of SOF + LDV (n = 50); and 100% with 24 weeks of SOF + LDV + RBV (n = 51). Evidence was also available from one trial (n = 80) for the use of 12 weeks of SOF + PEG-RBV for patients with GT1 without cirrhosis and prior experience with DAA- PEG-RBV, in which the reported SVR rate was 79%. Only one study reported SVR rates for patients previously treated with an all-oral DAA

regimen. In this study, all 14 patients with GT1 previously treated with SOF + RBV achieved SVR with 12 weeks of SOF + LDV.

The following conclusions were made for treatment of patients with GTs 2, 3, 4, 5 and 6:

- For patients with GT2, 12 weeks of SOF + RBV significantly improved SVR rates over 24 weeks of PEG-RBV in treatment-naive patients, but 12 weeks of SOF + PEG-RBV did not. In treatment-experienced patients, neither 16 weeks of SOF + RBV nor 12 weeks of SOF + PEG-RBV were significantly different from 12 weeks of SOF + RBV.
- For patients with GT3 regardless of treatment experience, 24 weeks of SOF + RBV, 12 weeks of DCV + SOF, and 12 weeks of SOF + PEG-RBV significantly improved SVR compared with 48 weeks of PEG-RBV, and there were no significant differences between these regimens.
- For patients with GT4, 12 weeks of SOF + PEG-RBV and 24 weeks of SOF + RBV significantly improved SVR rates compared with 48 weeks of PEG-RBV in treatment-naive patients; 12 weeks of SOF + PEG-RBV was statistically superior to 12 weeks of SOF + RBV. There was no data to include 12 weeks of SOF + PEG-RBV in the analysis of treatment-experienced patients.
- Evidence is insufficient for patients with GT2, 3, or 4 and decompensated liver disease.
- Evidence is insufficient to determine the efficacy of DAA-based regimens in patients with GT2, 3, or 4 and previously unsuccessful treatment with a DAA-based regimen.

2. A systematic review evaluated what the effects of interferon-free treatments in treatment-naïve people with CHC with and without cirrhosis.[24] This systematic review was limited to comparisons to SOF (with or without RBV), SIM + SOF, and SOF/LDV. RCTs or systematic reviews of RCTs were eligible for inclusion. Therefore, the majority of the open-label trials, which were part of the FDA approval process, were excluded from this report. RCTs were only found in people with GT2 or 3 as there was insufficient evidence from RCTs for all other treatment regimens and genotypes. GRADE was applied to the evidence for GT 2 and 3. There was no RCT evidence evaluating long-term clinical outcomes including HCC, end-stage liver disease, mortality or quality of life; RCT evidence for any comparisons in subjects with cirrhosis was also insufficient.
    - SOF + RBV may be more effective than placebo at reducing HCV RNA levels at the end of treatment, and increasing SVR12 after the end of treatment in treatment-naïve people with GT2 or 3 without cirrhosis (low quality evidence).
    - SOF + RBV may be more effective than placebo at reducing HCV RNA levels at the end of treatment in treatment-naïve people with GT2 or 3 with cirrhosis (very low quality evidence).
    - SOF + RBV may be more effective than placebo at increasing SVR12 after the end of treatment in treatment-naïve people with GT2 and 3 with cirrhosis. However, this effect appears to be greater for patients with GT2 than for GT3 (very low quality evidence).
    - SOF + RBV appears to be safe and well tolerated with an adverse event profile consistent with RBV alone.

3. A systematic review with meta-analysis assessed HCV recurrence and reinfection rates by risk group.[25] The majority of studies in all groups included subjects treated with PEG/RBV and there has not been a review of the risk of reinfection after use of DAAs. Populations were categorized into 1) low risk populations (mono-HCV infected patients); 2) high-risk populations (≥1 risk factor for reinfection); and 3) HIV/HCV coinfection populations. Risk factors for reinfection were defined as current or former intravenous drug use, imprisonment, and men who have sex with men. Results were available from 59 studies (n=9049).

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In the low-risk population, the pooled estimate for the recurrence rate was 1.85/1000 person years of follow-up (PYFU) and the 5-year recurrence risk was 0.95%. In the high-risk population, the pooled estimate for recurrence was 22.32/1000 PYFU with a 5-year recurrence rate of 10.67% and was driven mainly by reinfection (19.06/1000 PYFU) rather than late relapse. There were only 4 studies that identified recurrence in HIV/HCV coinfected patients with a recurrence rate of 32.02/1000 PYFU and 5-year recurrence rate of 15.02%. The authors concluded that the 5-year recurrence risk was higher among high-risk patients (10.67%) and HIV coinfected patients (15.02%) but SVR appears durable in the majority of patients at 5 years post-treatment.

4. Draft guidance was developed by the Oregon Health Evidence Review Commission (HERC) evaluating if noninvasive testing, including imaging and blood tests, for liver fibrosis for CHC should be recommended.[26] No randomized controlled evidence on the use of noninvasive tests compared to liver biopsy was available However, studies were available that compared the diagnostic accuracy of noninvasive tests to the reference standard of liver biopsy and demonstrated good or excellent performance of non-invasive tests for the detection of various levels of fibrosis. Good to excellent performance was defined as an area under the receiver operating curve (AUROC) of ≥ 0.8. The AUROC is an overall measure of how well the noninvasive test compared to the reference standard of a liver biopsy. Imaging tests appear to have a greater ability to distinguish between intermediate stages of fibrosis (between F2 and F3), while blood tests appear to be effective in establishing the presence of significant fibrosis (≥F2) or cirrhosis. Using the GRADE framework, the authors concluded that given the good and excellent performance of the recommended noninvasive imaging tests and potential harms of liver biopsy, the evidence favors offering these tests as an option for those considering therapy with a DAA. Additional testing including a liver biopsy may be necessary for some patients since noninvasive tests sometimes return inconclusive results. Based on the available evidence, resource allocation and patient preferences and values, the authors recommended that:
   - If a fibrosis score of ≥F2 is the threshold for DAA treatment, the following are recommended for coverage (weak recommendation):
     - Imaging tests (Transient elastography [FibroScan®], Acoustic radiation force impulse imaging [AFRI], shear wave elastography (SWE)
     - Blood tests only if imaging tests are unavailable (Enhanced liver fibrosis (ELF), Fibrometer, FIBROSpect II
   - If a fibrosis score of ≥F3 is the threshold for DAA treatment, one of the following are recommended for coverage (strong recommendation):
     - Imaging tests (FibroScan, ARFI, SWE)
   - Magnetic resonance elastography (MRE), which is much more expensive than other imaging tests, is recommended for coverage only when at least one imaging tests has resulted in indeterminate results, and second imaging test is similarly indeterminate, contraindicated or unavailable (weak recommendation).
   - Noninvasive tests should be performed no more often than once per year (weak recommendation).
   - Other imaging and blood tests are not recommended for coverage (strong recommendation).

Clinical Practice Guidelines:

The World Health Organization (WHO) updated their guidelines for the screening care and treatment of persons with CHC in April 2016.[27] The Veterans Affairs (VA) National Hepatitis C Resource Center updated treatment guidelines in March 2016,[12] and the Guidelines from the American Association for the Study of Liver Diseases (AASLD) and Infectious Diseases Society of America (IDSA) updated their recommendations for testing, managing, and treating CHC in July 2016.[8] The AASLD/IDSA guidelines are routinely updated to reflect rapidly changing evidence with the DAAs.[8] The AASLD/IDSA guideline has many limitations with poor

methodological quality. The panel lacks non-specialist members and there is no assessment of risk of bias for individual studies. In addition, the authors and sponsors of the guideline has multiple conflicts of interest.

Publication of both the WHO and VA guidelines preceded the approval of SOF/VEL and this agent is only included in the AASLD/IDSA guidelines. The following recommendations are included in these guidelines:

When to Treat:
AASLD/IDSA: Treatment for all patients regardless of disease severity is recommended, except those with short life expectancy that cannot be remediated by treatment or transplantation.[8] Little evidence exists to support initiation of treatment in patients with limited life expectancy. Prior to treatment, the guideline continues to emphasize the need to assess the patient's understanding of treatment goals and provision of education on adherence and follow-up.

WHO: HCV treatment should be considered for all persons with CHC, including persons who inject drugs. Persons with cirrhosis should be prioritized for treatment because they are at increased risk of HCC and death due to liver failure.[27]

VA: All patients with CHC who did not have medical contraindications are potential candidates for treatment. Patients with advanced liver disease are likely to derive the greatest benefit from treatment.[12] The urgency of treatment should be based on the risk of developing decompensated cirrhosis or dying from liver or liver-related disease, and prolonging graft survival and in transplant recipients. In particular, patients with cirrhosis or advanced fibrosis, selected patients with HCC awaiting liver transplant, post-transplant recipients, patients with serious extra-hepatic manifestations of HCV, and women of childbearing potential who desire to conceive a child in the next 12 months should be considered for antiviral treatment in the near term. Patients with mild liver disease (METAVIR F0-2) have less urgency for treatment in the short-term, but should be informed of current treatments and the potential to cure HCV. Patients with mild liver disease (METAVIR F0-2) and no extra-hepatic manifestations can be treated in the near term if the patient desires treatment and is otherwise a candidate for HCV treatment.

Who Should Treat:
With all-oral shorter course regimens, treatment may be increasingly available outside of specialty clinics. Guidelines recommend that therapy should be managed by medical specialists with experience in the treatment of CHC infection and the physician prescribing should have knowledge of monitoring and ensuring patient adherence with therapy. The VA guideline states treatment can be provided by non-specialists trained in the management of CHC and who have access to specialists for support (Expert Opinion).[12] However, patients with decompensated cirrhosis should be seen by a specialist with experience in the management of advanced disease.

Alcohol and Drug Abuse Recommendations:
AASLD/IDSA: Abstinence from alcohol and, when appropriate, interventions to facilitate cessation of alcohol consumption should be advised for all persons with HCV infection.[8] Persons identified as abusing alcohol and having alcohol dependence require treatment and consideration for referral to an addiction specialist. For individuals with acute HCV infection who have a history of recent injection drug use, referral to an addiction medicine specialist is recommended when

appropriate.

WHO: An alcohol intake assessment is recommended for all persons with HCV infection followed by the offer of a behavioral alcohol reduction intervention for persons with moderate-to-high alcohol intake. Persons who inject drugs should be assessed for antiviral treatment. Persons who inject drugs are at increased risk of HCV-related disease and transmission, as well as for all-cause morbidity and mortality, and therefore require specialized care and should be considered as a priority for HCV treatment.[27]

VA: All patients should be evaluated for current alcohol and other substance use, with validated screening instruments such as AUDIT-C (www.hepatitis.va.gov/provider/tools/audit-c.asp).[12] Patients with a history of substance or alcohol use disorders should be considered for HCV antiviral therapy on a case-by-case basis. There are no published data supporting a minimum length of abstinence as an inclusion criterion for HCV antiviral treatment, while multiple studies show successful treatment of patients who have short durations of abstinence or infrequent use of alcohol. Thus, automatic disqualification of patients as treatment candidates based on length of abstinence is unwarranted and strongly discouraged. The presence of current heavy alcohol use (>14 drinks per week for men or >7 drinks per week for women), binge alcohol use (>4 drinks per occasion at least once a month), or active injection drug use warrants referral to an addiction specialist before treatment initiation. Patients with active substance or alcohol use disorders may be considered for therapy on a case-by-case basis, and care should be coordinated with substance use treatment specialists.[12]

Treatment Discontinuation Guidelines:
The VA guidelines are the only guidelines that recommend discontinuing HCV treatment based on lack of virologic response after 6 weeks of initial treatment. These treatment discontinuation recommendations based on HCV RNA levels are based only on expert opinion.[12]

Testing for Liver Cirrhosis:
AASLD/IDSA: Considers the use of biopsy, imaging, and/or noninvasive markers appropriate to evaluate advanced fibrosis in HCV patients planning on treatment (Class I, Level A).[8] They also recommend that a biopsy should be considered for any patient with discordant results between 2 modalities that would affect clinical decision making. If direct biomarkers or elastography are not available, the AST-to-platelet ratio index (APRI) or FIB-4 index score can help, although neither test is sensitive enough to rule out significant fibrosis.

WHO: In resource-limited settings, it is suggested that the APRI or FIB-4 test be used for the assessment of hepatic fibrosis rather than other noninvasive tests that require more resources such as elastography or FibroTest (Conditional recommendation, low quality of evidence).[27] FibroScan®, which is more accurate than APRI and FIB-4, may be preferable in settings where the equipment is available and the cost of the test is not a barrier to testing.[27]

VA: Includes clinical findings (low platelet count), abdominal imaging for features of portal hypertension, liver fibrosis imaging (FibroScan and Acoustic Radiation force impulse [APRI]), serum markers of fibrosis (APRI, FIB-4, FibroSure, FibroTest), and liver biopsy as options. Liver biopsy should be reserved for situations in which the risks and limitations of the procedure are outweighed by the benefits of obtaining information via this technique.[12]

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Decompensated Cirrhosis:
All guidelines recommend patients with decompensated cirrhosis be considered for treatment on a case by case basis and should involve an experienced specialist who is able to manage complications.

Recommendations for performing pre-treatment resistant testing:
The VA guidelines recommend that NS5A resistance-associated variants (RAV) testing should be performed at baseline prior to initial treatment for GT1a-infected patients who are being treated with EBR/GZR and for GT3 patients who are being treated with DCV.[12] Patients who fail DAA treatment usually have RAVs to one or more classes of DAAs and should have testing done for each of the drug classes before being considered for re-treatment.

Recommended Treatment Options:
Treatment options based on genotype and treatment history are included in the following table:

Table 2: Guideline Recommended Treatment Options

GT	Treatment History	Cirrhosis Status	Veterans Affairs Guidelines[12]	AASLD/IDSA Guidelines[8]	WHO Guidelines[27]
1	***Naïve or Experienced (PEG-INF/RBV only)***	***Non-cirrhotic***	EBR/GZR x 12 weeks ** LDV/SOF x 12 weeks	EBR/GZR x 12 weeks** LDV/SOF x 8-12 weeks OMB/PTV-R + DAS +/- RBV x 12 weeks SOF/VEL x 12 weeks DCV/SOF x 12 weeks	DCV/SOF x 12 weeks LDV/SOF x 8-12 weeks
1		***Cirrhotic***	LDV/SOF + RBV x 8-12 weeks	EBR/GZR x 12 weeks** LDV/SOF x 12 weeks SOF/VEL x 12 weeks	DCV/SOF +/- RBV x 12 weeks LDV/SOF +/- RBV x 12 weeks
1		***Decompensated Cirrhosis***	LDV/SOF + RBV x 12 weeks	LDV/SOF + RBV x 12 week SOF/VEL + RBV x 12 week DCV/SOF + RBV X 12 week	DCV/SOF x 12 weeks
1	***Experienced (prior sofosbuvir)***	***Non-cirrhotic or cirrhosis***	EBR/GZR x 12 weeks +/- RBV	LDV/SOF + RBV X 12 weeks – 24 weeks	N/A
1	***Experienced (Prior NS3A/4A inhibitor)***	***Non-cirrhotic (or cirrhotic CTP A)***	EBR/GZR + RBV x 12 weeks	LDV/SOF X 12 weeks SOF/VEL x 12 weeks DCV/SOF X 12 weeks EBR/GZR + RBV X 12 weeks	N/A
1	***Experienced (Prior NS5A-containing regimen or SMV)***		Test for RAPs to NS5A prior to re-treatment. Consult with an expert based on results.	Deferral of treatment, pending more data. Testing for RAVs should be done.	N/A
2	***Naïve***	***Non-cirrhotic***	SOF + RBV x 12 weeks	SOF/VEL x 12 weeks	SOF + RBV X 12 weeks
2		***Cirrhotic***	SOF + RBV x 16 weeks	SOF/VEL x 12 weeks	SOF + RBV x 16 weeks
2		***Decompensated***	SOF + RBV x 16 weeks	SOF/VEL + RBV X 12 weeks DCV/SOF + RBV X 12 weeks	SOF + RBV x 16 weeks
2	***Experienced (Prior PEG-IFN/RBV)***	***Non-cirrhotic or Cirrhotic***	SOF + RBV x 16 weeks	SOF/VEL x 12 weeks	N/A
2	***Experienced (SOF + RBV)***	***Non-cirrhotic or Cirrhotic***	The optimal DAA-based therapy for this patient population is not known. Consult with an expert	DCV/SOF x 24 weeks SOF/VEL + RBV X 12 weeks	N/A
3	***Naïve***	***Non-cirrhotic***	LDV/SOF + RBV x 12 weeks*	DCV/SOF x 12 weeks SOF/VEL X 12 weeks	DCV/SOF X 12 weeks

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3		***Cirrhotic***	DCV/SOF + RBV x 12 weeks	SOF/VEL + RBV X 12 weeks DCV/SOF + RBV X 12 weeks	DCV/SOF + RBV x 12 weeks
3		***Decompensated Cirrhosis***	DCV/SOF + RBV x 12-24 weeks	SOF/VEL + RBV X 12 weeks DCV/SOF + RBV X 12 weeks	N/A
3	***Experienced (Prior PEG-IFN/RBV only)***	***Non-cirrhotic***	LDV/SOF + RBV X 12 weeks*	DCV/SOF X 12 weeks SOF/VEL X 12 weeks	N/A
3		***Cirrhotic***	DCV/SOF + RBV X 12 weeks- 24 weeks	SOF/VEL x 12 weeks DCV/SOF x 24 weeks	DCV/SOF + RBV x 24 weeks
3	***Experienced (SOF + RBV)***	***Non-cirrhotic or Cirrhotic***	The optimal DAA-based therapy for this patient population is based on expert opinion. Recommend NS5A resistance testing.	DCV/SOF + RBV X 24 weeks SOF/VEL + RBV X 12 weeks	N/A
4	***Naïve***	***Non-cirrhotic***	EBV/GZR x 12 weeks LDV/SOF x 12 weeks	OMB/PTV-R + RBV x 12 weeks SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	DCV/SOF x 12 weeks LDV/SOF x 12 weeks
4		***Cirrhotic***	EBV/GZR x 12 weeks LDV/SOF x 12 weeks	OMB/PTV-R + RBV x 12 weeks SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	DCV/SOF x 24 weeks DCV/SOF + RBV x 12 weeks LDV/SOF x 24 weeks LDV/SOF + RBV x 12 weeks
4		***Decompensated Cirrhosis***	N/A	LDV/SOF + RBV x 12 weeks SOF/VEL + RBV x 12 week DCV/SOF + RBV X 12 week	N/A
4	***Experienced (Prior PEG-IFN/RBV only)***	***Non-cirrhotic or Cirrhotic***	OMB/PTV-R + RBV x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	OMB/PTV-R + RBV x 12 weeks SOF/VEL x 12 weeks EBV/GZR x 12 weeks LDV/SOF x 12 weeks	N/A
5/6	***Naïve or Experienced (Prior PEG-IFN/RBV only)***	***Non-cirrhotic or Cirrhotic***	N/A	SOF/VEL x 12 weeks LDV/SOF x 12 weeks	LDV/SOF X 12 weeks
**No baseline NS5A RAVs Abbreviations: DCV = dacltasvir; EBV/GZR = elbasvir/grazoprevir; LDV/SOF = ledipasvir/sofosbuvir; OMB/PTV-R + DAS = ombitasvir, paritaprevir and ritonavir with dasabuvir; PEG-IFN = pegylated interferon; VEL/SOF = velpatasvir/sofosbuvir; RBV = ribavirin; SOF = sofosbuvir					

New Indications:

In February 2016, DCV + SOF was granted FDA approval for the treatment of GT1, treatment of patients co-infected HIV, and those with decompensated cirrhosis (GT1 or 3).[17,28] The expanded approval was based on the ALLY-1[29] and ALLY-2[30] trials.

In February 2016, LDV/SOF also received approval for use in patients with GT1 with decompensated cirrhosis, including those who have undergone liver transplantation.[19] LDV/SOF is now FDA approved for GT1, 4, 5 and 6, HIV coinfection, GT1 and GT4 liver transplant recipients, and GT1 patients with decompensated cirrhosis. Approval was supported by data from the SOLAR-1[31] and SOLAR-2[32] trials.

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Author: Megan Herink, Pharm.D Date: September 2016

In July 2016 the FDA approved Viekira XR® as a single tablet version of Viekira Pak® for GT1 infection.[22] The new formulation includes ombitasvir, paritaprevir, and dasabuvir, along with ritonavir as a booster, which are the same ingredients of Viekira Pak®. It was approved based on 6 clinical trials that demonstrated safety and efficacy of the immediate-release formulation. The formulation is contraindicated in patients with moderate to severe hepatic impairment.

Elbasvir/Grazoprevir (EBR/GZR) NEW DRUG EVALUATION**:**

See **Appendix 3** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

The FDA approved EBR/GZR 100 mg/50 mg based on data from 2 phase 2, 1 phase 2/3, and 3 pivotal phase 3 trials in patients who were treatment naïve, treatment experienced, HIV co-infected, and those with CKD.[11] Additional phase 2 trials also supported efficacy analyses; however they were not included in the FDA's main analysis for approval. Trials included GT1, 4 and 6 patients, but the majority were GT1. SVR12 was the primary endpoint in all trials and was defined as HCV RNA less than lower limit of quantification 12 weeks after the cessation of treatment. Patients with and without cirrhosis were included in all of the trials. Two phase 3 trials were placebo controlled (C-EDGE TN and C-SURVER) to evaluate safety outcomes only and all of the trials were designed to compare SVR12 to historical rates from previously conducted trials of standard of care regimens to define efficacy. The FDA noted that comparisons to historical rates are considered appropriate.[11] In the trials, hepatic fibrosis was staged by biopsy or noninvasive assessment. Cirrhosis was defined as a liver biopsy showing METAVIR stage F4 at any time prior to entry; transient elastography (Fibroscan) performed within 12 months of entry yielding a result >12.5 kPa; or biochemical markers of liver fibrosis (FibroText or FibroSure) yielding a score of >0.75 along with an aspartate aminotransferase-platelet ratio index (APRI) > 2. The overall SVR12 rates in GT1 infected patients are included in Table 3:

Table 3: SVR rates for GT Treatment Naïve Patients[11]

	C-EDGE TN	**C-EDGE COINFECTION**	**C-SURVER (CKD)**
GT1 Overall	95% (273/288)	95% (179/189)	94% (115/122)
GT1a	92% (144/157)	94% (136/144)	97% (61/63
GT1b	98% (129/131)	96% (43/45)	92% (54/59)
GT1 No Cirrhosis	94% (207/220)	94$ (148/158)	95% (109/115)
GT1 Cirrhosis	97% (66/68)	100% (31/31)	86% (6/7)

SVR12 results overall ranged from 92-100% depending on the regimen, GT, and prior treatment history. Baseline NS5A resistance testing is strongly recommended for all GT 1a infected patients to decrease the risk of resistance. Overall, 96-97% of GT1a infected subjects with baseline NS5A polymorphisms who failed treatment developed additional resistant mutations, and 58% developed resistance to both NS5A inhibitors and NS3/4A PIs, limiting future treatment options.

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C-SALVAGE was an open-label, single-arm phase 2 clinical trial designed to evaluate EBR/GZR + RBV in patients with HCV GT 1 who had previously failed triple therapy with PR plus an earlier-generation PI (boceprevir, telaprevir, or simeprevir).[33] All subjects (n=79) had been unsuccessfully treated with an NS3/4A PI in the past and 66 (84%) of them had a history of virologic failure. The majority of subjects had received either boceprevir or telaprevir. SVR12 rates were 96.2% (95% CI 89.3-99.2%). Relapses occurred in 3 (3.8%) subjects, all of whom had baseline NS3 resistance-associated variants (RAVs). Overall, there were too few virologic failures in this trial to determine the impact of baseline NS5A polymorphism. In addition, it is too small to support an indication for subjects with baseline NS3 resistance substitutions.

C-EDGE TN was a phase 3 trial multinational evaluating EBR/GZR for 12 weeks (immediate treatment group [ITG) without RBV vs. placebo (deferred treatment group [DTG]) in treatment-naïve (TN) monoinfected patients with and without cirrhosis and with GT1, GT4, or GT6 infection.[34] The DGT received GZR/EBR for 12 weeks following unblinding at week 4. Approximately half of the clinical sites (49%) were in the United States and the majority of patients had HCV GT 1. Overall, SVR12 rates were 95% in the immediate treatment group. SVR12 rates were 92% in patients with GT1a, 99% in those with GT1b, 100% (18/18) with GT4, and 80% (8/10) in those with GT6. SVR12 was achieved in 97% of cirrhotic patients (68/70) and 94% of noncirrhotic patients (231/246). Overall, the majority of patients had less severe disease (66% F0-F2) partly due to extensive exclusion criteria. However, 92 (22%) of patients did have cirrhosis. Subgroup analysis did not identify meaningful effects of age, sex, race, ethnicity, or IL28B genotype on treatment outcome. Virologic failure occurred in 13 (4%) patients, including 1 breakthrough and 12 relapses. NS3 resistance variants were detected in 57% of patients with GT1a and 19% of those with GT1b; however, there did not seem to be an association between baseline NS4 resistance and virologic failure. NS5A resistance variants were identified in 19 (12%) of GT1a infected patients and SVR12 was only achieved in 11 of 19 (58%) of these patients compared with 99% of patients without baseline NS5A resistance variants, suggesting an association between virologic failure (> 5 fold loss of EBR susceptibility) and baseline NS5A resistance. SVR12 rates were 91% in those with cirrhosis.

C-EDGE COINFECTION was a phase 3 open-label trial that assessed EBR/GZR for 12 weeks in TN cirrhotic and non-cirrhotic subjects with HCV GT 1, 4, or 6 and HIV coinfection.[35] This was a non-randomized, single arm trial that compared SVR12 to the historical rate of 70%, derived from the phase 2 trial of sofosbuvir in HCV GT1 subjects with HIV (Photon-1). However, the SVR rate among TN patients with GT 1 was 76% in the Photon-1 trial.[36] The majority of patients were male, white with F0-F2 disease. Sixteen percent of subjects had cirrhosis and 11% with advanced fibrosis (F3). Overall, 207/218 (95%) achieved SVR12. Seven (3.2%) subjects experienced virologic failure, all due to relapse and all of whom were non-cirrhotic. All 35 subjects with cirrhosis achieved SVR12 and SVR rates in GT 1a and 1b were similar, unlike the C-EDGE TN trial. Baseline NS4 resistance-associated variants (RAV) were detected in 41% (74) of subjects with GT1, but did not seem to effect rates of SVR12. In patients with GT1, 13/15 patients with baseline NS5A RAV achieved SVR12 (87%) compared to 98% without.

C-SURFER is a randomized, phase 2/3 placebo-controlled trial in stage 4 or 5 CKD patients with GT 1 HCV, with or without prior treatment experience (majority were TN) and with or without cirrhosis.[37] This is the first trial of a DAA in patients with advanced CDK (76.2% on dialysis). The most common etiologies of renal disease were hypertension (39.1%) and type 2 diabetes (19.6%). Similar to other trials, those with decompensated liver disease were excluded as well as subjects receiving peritoneal dialysis or new or worsening cardiovascular or cerebrovascular disease or uncontrolled diabetes (HgA1C > 8.5%). Subjects were randomized to ITG or DGT (unblended after receiving placebo during the initial 4 weeks). The placebo comparison was for safety and efficacy data remains observational. SVR rates were compared to a historical rate of 45% based on studies of HCV subjects with stage 3-5 CKD treated with interferon monotherapy and non-CKD subjects treated with PR. The exclusion criteria were much more restrictive than the other GZR/EBR trials (see evidence table) and limit the generalizability of

these results to real world patients with CKD. There was a larger representative of black patients (45%) and fewer cirrhotics (6%) compared to other trials. Overall 115 subjects achieved SVR12 (94%). One subject (0.9%) failed due to relapse. The remaining 6 virologic failures were due to missing data for reasons unrelated to treatment. Two additional relapses were found after follow-up through week 24.[11] All 3 patients who relapsed had at least one of the key RAVs at baseline.

Additional Trials:
A phase III, open label recently published RCT compared GZR/EBR to SOF plus pegylated interferon/ribavirin in patients with HCV GT 1 or 4 infection.[38] Since pegylated interferon/ribavirin is no longer considered standard of care for HCV GT 1 or 4, the clinical relevance of this trial is low. Patients were either treatment naïve or failed treatment with pegylated interferon/ribavirin and both cirrhotic and noncirrhotic patients were included. Those with HIV, HBV, decompensated liver disease or HCC were excluded. Overall SVR12 rates were 99.2% (129/129; 95% CI 95.6-99.9) and 90.5% (114/126; 95% CI 84-95) in the EBR/GZR and SOF groups, respectively establishing both noninferiority and superiority of EBR/GZR. As expected, there were significantly higher rates of adverse events reported in those receiving pegylated interferon/ribavirin (92.9%) compared to EBR/GZR (51.9%).

EBR/GZR was studied in a double-blind, placebo-controlled RCT in 301 treatment naïve patients with CHC GT 1, 4, or 6 who were receiving opioid agonist therapy (methadone, buprenorphine, or buprenorphine-naloxone) in persons who inject drugs. Patients actively using drugs of potential abuse while receiving opioid agonist therapy were excluded from the trial. Patients were randomly assigned to the ITG group (blinded EBR/GZR for 12 weeks; n=201) or the DTG (placebo for 12 weeks followed by 12 weeks of open label treatment with EBR/GZR; n=100). To ensure adherence, study medication was dispensed every 2 weeks and patients were asked to complete an electronic study medication diary. In clinical practice, replicating this kind of follow-up is difficult in this patient population and therefore SVR results and adherence may be lower than results seen in clinical trials. The SVR12 rate was 91.5% (184/201; 95% CI 86.8 to 95) in the ITG and 89.5% (95% CI 81.5 to 94.8) in the DTG. Five patients in the ITG had probable reinfection and 1 patient in the DTG. Through follow-up week 24, the reinfection rate was 4.6 reinfections (95% CI 1.7 to 10) per 100 person years. This increased risk of reinfection is a considerable concern in high-risk populations. Over 50% of patients had positive results on a urine drug screen with no meaningful differences in SVR between those that did not.

Unpublished Trials:
C-EDGE TE was a phase 3 randomized, parallel-group, open-label clinical trial.[11,39] It remains unpublished and cannot be assessed for quality. The trial compared GZR/EBR +/- RBV for 12 weeks to EBR/GZR +/- RBV for 16 weeks (n=420). The patient population consisted of TE cirrhotic and non-cirrhotic subjects who failed prior treatment with PR (43% null responders, 21% partial responders, 35% relapsers). Discontinuations due to adverse events were higher in subjects on RBV and on extended therapy for 16 weeks (3.8%). There was an imbalance across groups with respect to HCV GT and race. There were higher rates of black subjects in the 12 week treatment groups (22.5%) compared to 16 week treatment groups (11.4%) and a higher number of Asian subjects in the 16 week group. Asian race is associated with higher GZR exposures, which may impact safety. Similar to previous studies, there were very few subjects with either GT4 or GT6. SVR12 results and number of subjects experiencing virologic failure are included in Table 4:

Table 4: SVR12 rates of EBR/GZR +/- RBV for 12 to 16 weeks

Treatment Duration	12 weeks		16 weeks	
	EBR/GZR (n=105)	EBR/GZR + RBV (104)	EBR/GZR (n=105)	EBR/GZR + RBV (N=106)
SVR Achieved (%) 95% CI	97 (92.4%) 85.5-96.7	98 (94.2%) 87.9-97.9	97 (92.4%) 85.5-96.7	103 (97.2%) 92-99.4
Virologic failure	6 (5.6%)	6 (5.8%)	7 (6.7%)	0 (0%)
SVR Achieved (%) • GT 1a • GT 1b • GT 4	 90.2% (79.8-96.3) 100% (89.7-100) 77.8% (40-97.2)	 93.3% (83.8-98.2) 96.6% (82.2-99.9) 93.3% (68.1-99.8)	 93.8% (82.8-98.7) 95.8% (85.8-99.5) 60.0% (14.7-94.7)	 94.8% (85.6-98.9) 100% (90.3-100) 100% (63.1-100)
Abbreviations: EBR = elbasvir; GZR = grazoprevir; RBV = ribavirin; SVR = sustained virologic response				

All of the virologic failures in the 12 week groups were due to relapse; the majority with GT 1a. Four of the 7 failures in the 16 week treatment group without RBV were due to relapse. The longer treatment duration of 16 weeks in addition to RBV appeared to improve efficacy and minimize the risk of relapse and overcome the effect of baseline NS5A polymorphisms as SVR 12 rate remained 100% even in those with resistance variants. Similar to the previous trial, the presence of baseline NS5A polymorphisms appears to explain the majority of virologic failures. There was a higher SVR12 rate in the 16 week + RBV arm for GT4 subjects. However, the number of subjects was relatively small overall (37) and imbalanced between groups.

C-SCAPE was a phase 2 open-label clinical trial that assessed the efficacy and safety of EBR/GZR +/- RBV for 12 weeks in TN non-cirrhotic subjects with HCV GT 4, 5, and 6 infection (n=19).[11,40] This was a small study with one discontinuation due to an adverse event and one due to lack of efficacy. The majority of subjects had HCV GT 4 (n=38) and SVR rates were 100% and 90% with and without RBV, respectively. It is hard to determine if the addition of RBV was beneficial in this population as groups were not balanced at baseline. There were more patients with severe fibrosis (F3) in the RBV group compared to the majority of subjects not receiving RBV with F0-F2 fibrosis. This trial helped support efficacy in GT 4 infected subjects (52.6%), but overall the trial enrolled very few numbers. Virologic failure occurred in ¾ of HCV GT 5-infected subjects and as a result, subsequent studies did not enroll GT 5 subjects.

Clinical Safety:

EBR/GZR was generally well tolerated in short term studies with the most significant concern being increased transaminase elevations occurring at or after 8 weeks of treatment initiation, occurring in less than 1% of patients with the FDA approved dose. Phase 2 trials demonstrated higher rates of increases with higher doses that were studies. GZR exposure is increased in decompensated cirrhosis and therefore EBR/GZR is contraindicated in Child-Pugh B and C cirrhosis due to an increased risk of liver toxicity.

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The most common reported adverse events (>5%) in clinical trials with EBR/GZR were fatigue, headache, and nausea (Table). These rates were similar in the trial including subjects on hemodialysis. In patients receiving EBR/GZR + RBV for 16 weeks, the most common adverse events were anemia (8%) and headache (6%). During clinical trials with EBR/GZR ± RBV, 1% of patients experienced ALT elevations of >5 times the ULN, generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing or completion of therapy. Higher rates of late ALT elevations occurred in the following subgroups: females (2% [10/608]), Asian race (2% [4/164]), and age 65 years or older (2% [3/177]).

Table 5. Adverse Reactions Reported In ≥5% of Treatment-Naïve Subjects with HCV

Adverse Reaction	EBR/GZR (n=316)	Placebo (n=105)
Fatigue	11%	10%
Headache	10%	9%
Nausea	9%	8%

GZR is a substrate of OATP1B1/3 transporters and drugs that inhibit these transporters may result in a significant increase in the plasma concentrations of GZR. In addition, EBR and GZR are substrates of CYP3A and P-gp.

Table 6: Pharmacology and Pharmacokinetic Properties: [41]

Parameter	
Mechanism of Action	GZR is an NS3/4A Protease Inhibitor, and EBR is an NS5A replication inhibitor. GZR/EBR is a fixed dose combination of direct-acting antiviral agents against the hepatitis C virus.
Distribution and Protein Binding	Extensively bound to plasma proteins (EBR > 99.9%, GZR > 98.8%), both bind to albumin and alpha1-acid glycoprotein. VD 680 L (EBR) and 1250 L (GZR).
Metabolism	Partially eliminated by oxidative metabolism, primarily by CYP3A.
Half-Life	24 hours (EBR) and 31 hours (GZR)
Elimination	Primary route of elimination is through feces

Abbreviations: IL-5 = interleukin 5; kg = kilograms; L = liters; Vd = volume of distribution

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Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Hepatocellular Carcinoma
2) Mortality
3) Liver Transplant
4) Decompensated Liver Disease
5) Discontinuation Rates Due to Adverse Events
6) Severe Adverse Events

Primary Study Endpoints:
1) Sustained Virologic Response at 12 after the end of treatment (SVR12)

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Author: Megan Herink, Pharm.D

Date: September 2016

Table 7. Clinical Efficacy Evidence Table (EBR/EZR)

Ref./ Study Design	Drug Regimen/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARI/ NNH	Quality Rating Risk of Bias/Applicability
1. Buti, et al.[33,42] Open-label, single arm C-SALVAGE Phase 2	1. EBR 50 mg/GZR 100 mg daily + weight based RBV twice daily 12 weeks	Demographics: Treatment-experienced Mean age 54.4 42% women 43% cirrhotics 38% GT 1a Key Inclusion Criteria: -HCV GT1, prior regimen containing an approved DAA + PR, HCV RNA > 10,000 IU/ml Key Exclusion Criteria: -Decompensated liver disease, hepatocellular carcinoma, HIV or hepatitis B co-infection, uncontrolled DM (HgA1C > 10%), elevated PT, CrCl < 50ml/min, Hg < 95 g/L, thrombocytopenia, ALT > 10 x ULN, hypoalbuminemia, clinically-relevant drug or alcohol abuse within 12 months	FAS 1. 79 Attrition 1. 0%	Primary Endpoint: SVR12 76 (96.2%; 95% CI 89.3-99.2) *Patients with prior virologic failure:* 63 (95.5%; 95% CI 87.3-00.1)	N/A	Safety Outcomes D/C due to AE: 1 (1.2%) Serious AE: 5 (6.3%)	NA for all	**Risk of Bias** Selection bias: (high) non-randomized Performance bias: (high) open-label. Detection bias: (unclear) open-label; objective outcome Attrition bias: (low) overall attrition low and similar across groups based on mITT analysis; missing outcome data were imputed as failures unless flanked by visits where HCV RNA levels were both < 15 IU/ml. Reporting bias: (unclear) funded by Merck. Merck involved in trial design, study execution, data collection, statistical analyses, and drafting of the report. **Applicability**: Patient: extensive exclusion criteria may limit applicability of study results to patients with more severe disease. Intervention: Optimal treatment duration unknown other phase 3 trial in TE patients explored 16 weeks with or without ribavirin. Comparator: This study lacked an active comparator control. . Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: 77.2% (61) of the sites were not in the U.S.

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2. Zeuzem, et al.[34] RCT, PC, PG C-EDGE	1. EBR/GZR daily (ITG) 2. Placebo* followed by deferred EBR/GZR x 12 weeks (DTG) 12 weeks *Placebo was used for safety comparison only	Demographics: Treatment-naïve Mean age 52.6 46% women 37% nonwhite 91% GT1 22% Cirrhosis 66% F0-F2 Key Inclusion Criteria: -age ≥18 y, HCV RNA levels > 10^4 IU/ml Key Exclusion Criteria: -Decompensated liver disease, hepatocellular carcinoma, HIV or hepatitis B co-infection, uncontrolled DM (HgA1C > 10%), elevated PT, CrCl < 50ml/min, Hg < 95 g/L, thrombocytopenia, ALT > 10 x ULN, hypoalbuminemia	mITT 1. 316 2. 105 Attrition 1. 0% 2. 0%	Primary Endpoint: SVR12 1. 299 (95%) P<0.0001 -GT 1a: 144/157 (92%) -GT1b: 129/131 (99%) -GT4: 18/18 (100%) -GT6: 68/70 (97%) *Cirrhosis:* Yes: 68/70 (97%) No: 231/246 (93.9%)	NA for all	Safety Outcomes D/C due to AE: 1. 1% 2. 1% Serious AE: 1. 9 (2.8%) 2. 3 (2.9%)	 NS NS	**Risk of Bias** Selection bias: (low) randomized 3:1 to immediate (tx) or deferred (placebo) therapy through a central interactive voice-response system and a computer-generated random allocation schedule. Baseline characteristics similar between groups, except almost twice as many elderly subjects in the DTG Performance bias: (low) Matching placebo used. Patients, clinical site, and sponsor personnel were blinded for first 4 weeks. 4 weeks after treatment, treatment allocation was unblended and patients in placebo group received open-label treatment. Detection bias: (unclear): Unblinded medical team monitored virologic failures and serious adverse events. However, primary outcome objective so less likely to be effected by unblinding. Attrition bias: (low) overall attrition low and similar across groups based on mITT analysis; missing outcome data were imputed as failures uless the values immediately before and after the missing result were both successes, in which case the absent value was imputed as a success. Appropriate statistical tests used. Reporting bias: (unclear) funded by Merck. Merck involved in trial design, study execution, data collection, statistical analyses, and drafting of the report. **Applicability**: Patient: extensive exclusion criteria may limit applicability of study results to patients with more severe disease. Very little representation of non-GT1 patients. Intervention: No concerns Comparator: This study lacked an active comparator control. Historical comparator of SVR rate of 73% was used but not applicable today as peginterferon no longer preferred treatement option. Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: 60 centers in Australia, Czech Republic, France, Germany, Israel, Puerto Rico, South Korea, Sweden, Taiwan, and the U.S. (24)

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

3. Rockstroh et al.[35] Open-label, single arm, MC Phase 3 C-EDGE CO-INFECTION	EBR/GZR Daily 12 weeks	Baseline Demographics: Mean age: 49 y Female: 16% White 77%, Black 17% HCV GT 1a 66%, GT 1b 20%, GT 4 13%, GT 6 0.5% F0-F2 73% Key Inclusion Criteria: -age ≥18 y, HCV RNA levels > 10,000 IU/ml, HIV coinfection, either naïve to ART or on stable ART with tenofovir or abacavir, and either emtricitabine or lamibudine plus raltegravir, dolutegravir, or rilpivirine Key Exclusion Criteria: -decompensated liver disease, Child-Pugh class B or C, or with a Child-Turcotte-Pugh score of >6 points, HBV, HCC, h/o malignant disease, clinically-relevant drug or alcohol abuse within 12 months, CrCl <50 ml/min, Hg < 9.5 g/dl, platelets < 50 x 10^3 uL, albumin < 3.0 g/dl, INR > 1.7, HbA1c > 10%, ALT/AST >10x ULN, use of CYP3A/P-gp inducers, OATB inhibitors, statins	FAS 218 Attrition 0	Primary Endpoint: SVR12: 207/218 (95%; 95% CI 91.2-97.5%) P<0.0001* -GT 1a: 136/144 (94.4%) -GT1b: 42/44 (95.5%) -GT4: 27/28 (96.4%) *Cirrhosis:* Yes: 35/35 (100%) No: 23(172/183) (94%) *compared to historical rate of 73% Secondary Endpoints: SVR24	NA for all	Safety Outcomes D/C due to AE: 0 Serious AE: 6 (0.3%)	NA for all	**Risk of Bias** Selection bias: (high) non-randomized Performance bias: (high) open-label Detection bias: (low) statisticians and GSK personnel blinded to data. Power assumptions appropriate. Appropriate statistical tests utilized. Attrition bias: (low) overall attrition low and similar across groups based on mITT analysis; imputation of missing data unclear but few dropped out early. Appropriate statistical tests used. Reporting bias: (unclear) funded by GSK; data analyzed by GSK. Pre-specified primary outcome reported as relative risk reduction. **Applicability**: Patient: Over 70% of patients with F0-F2; results have limited applicability to patients with more severe disease. Intervention: Unclear if addition of RBV or extended duration would benefit HIV coinfected patients. Comparator: No comparator group. Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: 37 centers across Austrlia (2), Canada (2), Denmark (3), France (3), Germany (3), Israel (3), Spain (3), United Kingdom (2) and the U.S. (18).

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

4. Roth et al.[37] RCT, PC Phase 2/c C-SURVER	1. EBR/GZR daily (ITG) 2. Placebo* followed by deferred EBR/GZR x 12 weeks (DTG) 12 weeks *Placebo was used for safety comparison only	Demographics: Treatment-naïve Mean age 56 26.8% women 53.7% nonwhite 51.9% GT1a 6% Cirrhosis 69.4% F0-F2 76.2% dialysis Key Inclusion Criteria: -age ≥18 y, HCV RNA levels > 10^4 IU/ml, liver disease staging with either liver biopsy, fibroscan, or FibroSure AND APRI, CKD Key Exclusion Criteria: -Decompensated liver disease, peritoneal dialysis, hepatocellular carcinoma, HIV or hepatitis B co-infection, uncontrolled DM (HgA1C > 8.5%), significant CV disorder, severe active peripheral vascular disease, recent stroke, elevated PT, Hg < 95 g/L, thrombocytopenia, ALT > 10 x ULN, hypoalbuminemia, taking a prohibited medication**, substance abuse to any of the following: alcohol, IV drugs, inhalational (not including marijuana), psychotropics, narcotics, cocaine, OTC or prescription drugs within 1 year	mITT 1. 122 2. 113 Attrition 0 (0%)	Primary Endpoint: SVR12 (ITG only) 1. 115 (94.3%; 95% CI 88.5-97.7) P<0.001* *Compared to historical rate of 45%	NA	Safety Outcomes D/C due to AE: 1. 0 (0%) 2. 5 (4.4%) Serious AE: 1. 16 (14%) 2. 19 (17%)	NA for all	**Risk of Bias** : Selection bias: (low) randomized 1:1 to immediate (tx) or deferred (placebo) therapy through a central interactive voice-response system and a computer-generated random allocation schedule. Baseline characteristics similar between groups. Performance bias: (high) Matching placebo used. Patients, clinical site, and sponsor personnel were blinded for first 4 weeks. 4 weeks after treatment, treatment allocation was unblended and patients in placebo group received open-label treatment. Detection bias: (low) Unblinded medical team monitored virologic failures and serious adverse events. However, primary outcome objective so less likely to be effected by unblinding. Attrition bias: (low) overall attrition low. Reporting bias: (unclear) funded by Merck. Merck involved in trial design, study execution, data collection, statistical analyses, and drafting of the report. **Applicability**: Patient: extensive exclusion criteria may limit applicability of study results to patients with more severe disease as well as patients with severe DM or CVD. Small number of TE and cirrhotic subjects. Intervention: The lack of RBV does not seem to compromise efficacy in this population. Unclear if extending to 16 weeks in those with RAVs would be beneficial. Limited treatment options for those with CKD. Comparator: This study lacked an active comparator control. Historical comparator of SVR rate of 45% was used but not applicable today as peginterferon no longer preferred treatement option. Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: Multinational trial in 79 centers in 12 countries: U.S. (48 sites), Canada, Israel, France, Lithuania, Spain, Australia, Estonia, Korea, Netherlands, Sweden, Argentina

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

Abbreviations: AE = adverse events; ALT = alanine aminotransferase; APRI = AST to platelet ratio index; ARI = absolute risk increase; ARR = absolute risk reduction; CI = confidence interval; CKD = chronic kidney disease; CrCl = creatinine clearance; CV = cardiovascular; DB = double-blind; DAA = direct acting antiviral; D/C = discontinue; DM = diabetes mellitus; DTG = deferred treatment group; EBR = elbasvir; EF = ejection fraction; FAS = full analysis set; FDA = U.S. Food and Drug Administration; GT = genotype; GZR = grazoprevir; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; h/o = history of; HG = hemoglobin; ICS = inhaled corticosteroid; ITG = immediate treatment group; ITT = intention to treat; IV = intravenous; MC = multi-centered; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; OR = odds ratio; PC = placebo-controlled; PBO = placebo;; PG = parallel group; PP = per protocol; PT=prothrombin time; RBV = ribavirin; RCT = randomized controlled trial; RR = relative risk; RRR = relative risk reduction; SAE = serious adverse event; SE = standard error; SVR12 = sustained virologic response at 12 weeks after therapy completed; TE = treatment experienced; TN = treatment naïve; ULN = upper limit of normal; wk = weeks; wt = weight; y = years; µL = microliters.
*derived from phase 3 trials of simeprevir/peginterferon + ribavirin in treatment-naïve monoinfected patients
** Known hepatotoxic drugs (etofoxine, isoniazid, nitrofurantoin, phenytoin), herbal supplements, strong CYP3A4/P=gp inhibitors (clarithromycin, erythromycin, telithromycin, azole antifungals, nifedipine, nefazodone), strong and moderate CYYP4A/P=gp inducers (nafcillin, rifampin, carbamazepine, phenytoin, phenobarbital, bosentan, modafinil, St. John's Wort), OATP inhibitors (cyclosporine, rifampin, gemfibrozil, eltrombopag, lapatinib), HIV medications, statins (simvastatin, fluvastatin, rosuvastatin, atorvastatin, pitavastatin, pravastatin doses > 10 mg).

Sofosbuvir/Velpatasvir NEW DRUG EVALUATION**:**

See **Appendix 1** for **Highlights of Prescribing Information** from the manufacturer, including indications, dosage and administration, formulations, contraindications, warnings and precautions, adverse reactions, drug interactions and use in specific populations.

Clinical Efficacy:

Three phase 3 trials evaluated the safety and efficacy of SOF/VEL that contributed to FDA approval.[43] ASTRAL-1 included GT 1, 2, 4, 5 or 6 and two additional phase 3 trials were conducted in patients with GT 2 (ASTRAL 2), and GT 3 (ASTRAL-3).[43] The FDA requested studies with an active comparator for both GT 2 and 3. Cirrhosis was defined as: liver biopsy showing cirrhosis (Metavir score = 4 or Ishak score ≥ 5), FibroTest score > 0.75 AND an APRI > 2, or Fibroscan with a result of > 12.5 kPa. In the absence of a definitive diagnosis, liver biopsy or Fibroscan was required. In addition, a long list of medications were not allowed or advised to use with caution, including proton-pump inhibitors and statins, respectively. VEL solubility decreases as pH increases and drugs that increase gastric pH are expected to decrease concentration of VEL. This includes antacids, H2-receptor antagonists, and proton pump inhibitors.[16] Pooled analysis of these 3 trials resulted in SVR12 rates of 95% of higher in subjects without decompensated cirrhosis. SVR12 rates were comparable with the exception of GT3. Subgroup analysis showed that cirrhosis, prior treatment failure, and the presence of baseline NS5A polymorphisms were associated with numerically higher rates of treatment failure. [43]

The ASTRAL-1 trial is a phase 3 randomized, double-blind, placebo controlled trial, comparing an immediate treatment group (ITG) with SOF/VEL for 12 weeks to a deferred treatment group (DTG) of placebo followed by treatment with SOF/VEL in subjects with GT 1, 2, 4 or 6.[44] Due to the low prevalence of GT 5 infection, these subjects were not randomized but placed directly in the ITG. Subjects in the placebo group were eligible for deferred treatment after the 12 week blinded period. The placebo group was included to evaluate the safety profile of SOF/VEL. The efficacy analysis was designed to compare SVR of SOF/VEL to a performance goal of 85% which was not a historical control but rather a benchmark based on general trend of treatment. The clinical relevance of this ambiguous value is unclear. Both TN and TE patients were included in the trial and 19% had cirrhosis. Of the 32% who had received previous treatment, 28% received PR plus a protease inhibitor and 61% had received PR. Subjects previously on a NS5A or NS5B inhibitor were excluded from the trial. Overall SVR rates were 98% to 100% regardless of HCV genotype (See evidence table). Confidence intervals were wider for subjects with GT 5 or GT 6, consistent with the low number of subjects included in the trial with these genotypes. Only 2 subjects experienced a virologic failure, both of whom had baseline NS5A RAVs. This trial

had extensive exclusion criteria and excluded medications (see evidence table) that limits the overall generalizability of results. The majority of subjects were from the US which increases applicability but resulted in lower recruitment of non-GT1 HCV genotypes, which are less common in the US.

The ASTRAL-2 and ASTRAL-3 trials were two identical randomized, phase 3, open-label noninferiority studies involving HCV GT 2 or 3, respectively.[45] Patients who had previously failed treatment with PEG +/- RBV and treatment naïve patients were included, as well as those with compensated cirrhosis. SOF/VEL for 12 weeks was compared to SOF + RBV for 12 or 24 weeks for GT 2 and 3, respectively. Non-inferiority using a margin of 10% was used for each comparison. Previous studies with SOF + RBV for 12 weeks in GT 2 HCV have demonstrated SVR12 rates of 95% in treatment naïve and 82% in treatment experienced subjects. In patients with GT 2, VEL/SOF was found to be superior to SOF/RBV for 12 weeks in SVR rates (99% vs. 94%; absolute difference 5.2 percentage points; 95% CI 0.02 to 10.3; p=0.02). There were no virologic failures among subjects receiving SOF/VEL and 6 in the SOF + RBV group. In subjects with GT 3, SOF/VEL for 12 weeks was superior to SOF + RBV for 24 weeks in achieving SVR (95% vs. 80%; absolute difference of 14.8 percentage points; 95% CI 9.6 to 20.0; p<0.001). Eleven subjects receiving SOF/VEL had virologic failure. Across all groups, SVR rates were lowest among those with cirrhosis and previous treatment and in GT 3 subjects. In GT3, those with cirrhosis had SVR rates of 91.3% and 66.3% for the SOF/VEL and SOF/RBV groups, respectively. SVR rates for treatment experienced with GT 3 were 90.1% and 63.4%. All clinical sites for ASTRAL-2 were in the US, while approximately 75% of subjects in ASTRAL-3 were enrolled in sites in Europe and Australia/New Zealand where GT3 HCV is more prevalent. This resulted in an underrepresentation of Black subjects. All subjects with a baseline NS5A polymorphism responded favorably to treatment and there does not seem to be a role for NS5A screening prior to treatment. There is insufficient evidence if the addition of RBV may benefit subjects with GT3 HCV or if extending treatment for cirrhotics will be effective in reducing relapse. The FDA requested a further clinical trial to evaluate for a clinically meaningful difference between SOF/VEL and SOF/VEL + RBV in GT3 cirrhotics.[43]

The ASTRAL-4 trial was a phase 3 open-label trial assessing SOF/VEL with or without ribavirin for 12 or 24 weeks in patients with HCV genotypes 1 through 6 and with decompensated cirrhosis (Child-Pugh-Turcotte [CPT] class B).[46] Patients were randomized to receive: 1) SOF/VEL x 12 weeks, 2) SOF/VEL + RBV x 12 weeks, or 3) SOF/VEL x 24 weeks. The primary outcome was SVR12 and the secondary end point was change from baseline in the CPT and Model for End-Stage Liver Disease (MELD) scores at 12 weeks after the end of treatment. For SVR rates, each treatment group was compared to the assumed spontaneous rate of 1%; however, the study was not designed or powered to detect significant differences in rates of SVR among the treatment groups. A post-hoc comparison did not detect any significant differences in rates of SVR between the 3 treatment groups. Twenty two (8.2%) of patients had virologic failure; the majority of subjects had a relapse. Of those with virologic failure, 9 patients had baseline NS5A or NS5B RAVs. There were too few subjects with genotypes 4, 5, or 6 to make generalizing conclusions in these subgroups. Overall SVR rates were 83%, 94% and 86% for those receiving SOF/VEL for 12 weeks, SOF/VEL + RBV for 12 weeks, and SOF/VEL for 24 weeks, respectively. SVR rates were lowest in those with GT3 (50-85%), but rates were improved with the addition of RBV. Forty seven percent of patients had an improvement in the CPT score over baseline and 51% had an improved MELD score. Only patients with moderate hepatic decompensation were included in the study; results cannot be generalized to those with more severe liver disease. In addition, all 47 sites were within the US which resulted in the majority of patients having GT 1. Severely decompensated patients (CPT C) were not included in study.

Clinical Safety:

Phase 3 trials evaluated over 1300 patients treated with SOF/VEL. The most common adverse events were headache, fatigue, nausea, insomnia, nasopharyngitis and diarrhea and subjects who received RBV experienced higher rates of adverse events associated to RBV therapy. [16,43] Adverse reactions observed in at least 5% of patients and more commonly than placebo are included in table 8. Most rates were comparable in both groups. In subjects with decompensated cirrhosis, the most common adverse events were fatigue (32%), anemia (26%), nausea (15%), headache (21%), insomnia (11%), and diarrhea (10%). Decreases in

hemoglobin to less than 10g/dl and 8.5 g/dl were observed in 23% and 7% of subjects treated with SOF/VEL and ribavirin, respectively. There were low rates of discontinuations due to adverse events (<2%) and serious adverse events when given without RBV (2%). In patients with decompensated cirrhosis, there were much higher rates of serious adverse events (17%), consistent with advanced underlying liver disease. Still, few subjects discontinued SOF/VEL due to adverse events (3% overall).

Table 8. Adverse Reactions Reported In ≥5% of Subjects and More Commonly than Placebo

Adverse Reaction	SOF/VEL 12 week (n=1035)	Placebo (n=116)
Headache	296 (29%)	33 (28%)
Fatigue	217 (21%)	23 (20%)
Nausea	135 (13%)	13 (11%)
Nasopharyngitis	121 (12%)	12 (10%)
Insomnia	87 (8%)	11 (9%)
Asthenia	58 (6%)	9 (8%)
Cough	57 (6%)	4 (3%)
Upper respiratory tract infection	50 (5%)	3 (3%)
Irritability	49 (5%)	4 (3%)
Constipation	47 (5%)	3 (3%)

Similar to SOF, there is a safety warning regarding the risk of serious symptomatic bradycardia related to co-administration of SOF with amiodarone and another DAA. Both SOF and VEL are substrates for P=glycoprotein (P-gp) and breast cancer resistance protein (BCRP). VEL is also a substrate of CYP2B6, CYP2C8 and CYP3A as well as an inhibitor of P-gp, BCRP and OATP2B1. Therefore, there are many potential drug-drug interactions to be aware of and concomitant drugs that were not included in clinical trials.

Table 9: Pharmacology and Pharmacokinetic Properties:

Parameter	
Mechanism of Action	SOF is a NS5B inhibitor, and VEL is an NS5A replication inhibitor. SOF/VEL is a fixed dose combination of direct-acting antiviral agents against the hepatitis C virus.
Distribution and Protein Binding	SOF 61-65% protein bound; VEL > 99.5%
Metabolism	SOF: Cathepsin A, CES1, HINT1; VEL: CYP2B6, CYP2C8, CYP3A4
Half-Life	SOF: 0.5 h; VEL: 15 h
Elimination	SOF: glomerular filtration and active tubular secretion, 80% excreted in urine; VEL: biliary excretion as parent; 94% excreted in feces

Abbreviations: IL-5 = interleukin 5; L = liters; ml =milliliters

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Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Hepatocellular Carcinoma
2) Mortality
3) Liver Transplant
4) Decompensated Liver Disease
5) Discontinuation Rates Due to Adverse Events
6) Serious Adverse Events

Primary Study Endpoints:
2) Sustained Virologic Response at 12 after the end of treatment (SVR12)

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Table 10. Clinical Evidence Table (SOF/VEL)

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Feld et al.[44] DB, PC, MC Phase 3 ASTRAL-1	1. SOF/VEL (ITG) 2. Placebo (DTG) 12 weeks	Demographics: 34% GT 1a 19% GT 1b 17% GT 2 19% GT 4 6% GT 5 7% GT 6 79% white 60% male 19% Cirrhosis Key Inclusion Criteria: -age ≥18 y, HCV RNA levels > 10^4 IU/ml Key Exclusion Criteria: -Clinically-significant illness, decompensated cirrhosis, HCC, psychiatric hospitalization, suicide attempt or period of disability within last 5 years, malignancy, ALT/AST > 10 x ULN, bilirubin > 1.5 x ULN, Platelets < 50,000/uL, HbA1c > 8.5%, CrCl < 60 ml/min, Hg < 11 g/dL-12 g/dl, albumin < 3 g/dL, INR > 1.5 x ULN, prior tx with SOF or other NS5B/NS5A inhibitor, HBV or HIV, clinically-relevant alcohol or drug abuse within 12 months, use of prohibited concomitant medications*	ITT: 1. 624 2. 116 Attrition: 1. 0 2. 0	Primary Endpoint: SVR12 (ITG only) 1. 99% (95% CI 98 to > 99) P<0.001* *Compared to performance goal of 85% *GT 1a 98% (95 to >99)* *GT 1b 99% (95to 100)* *GT 2 100% (97 to 100)* *GT 4 100% (97 to 100)* *GT 5 97% (85 to >99)* *GT 6 100% (91 to 100)* *Cirrhosis:* 99% (95 to >99)	N/A	Outcome: D/C due to AE: 1. 1 (0.2%) 2. 2 (2%) Serious AE: 1. 15 (2%) 2. 0 (0%)	NS NS	**Risk of Bias**: Selection Bias: (low) randomized 5:1 by computerized central randomization and interactive response technology. Subjects with GT 5 not randomized. Groups generally well balanced; however efficacy comparison not done between groups so differences unlikely to bias results. Performance Bias: (low) patients and investigators remained masked. SOF/VEL and placebo identical in appearance. Detection Bias: (unclear) Funder's clinical staff masked until analysis; unclear of outcome assessors blinded. Attrition Bias: (low) overall attrition low and similar across groups Reporting Bias: (unclear) Funded and designed by Gilead Sciences. Gilead was involved in data collection, study conduct, and statistical analyses, as well as writing of the manuscript. **Applicability**: Patient: Extensive and elusive exclusion criteria limits applicability of study results. Only patients with moderate liver disease were included (CPT B). Severely decompensated patients (CPT C) not included in study. Few patients with GTs 5 & 6 and mostly younger white men. Intervention: No concerns Comparator: Primary efficacy endpoint compared to performance goal of 85%. It is unclear how this goal was decided on. Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: 81 sites in the U.S., Canada, Europe, and Hong Kong; 51% in Europe and 46% in North America.

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2. Foster et al.[45] Open-label, phase 3, noninferiority trial Astral-2 & Astral-3	ASTRAL-2 (GT2) 1. SOF/VEL 2. SOF/RBV 12 weeks ASTRAL:-3 (GT3) 1. SOF/VEL x 12 weeks 2. SOF/RBV x 24 weeks	Demographics: *GT2:* 14% cirrhosis 15% previous treatment *GT3:* 30% cirrhosis 26% previous treatment Key Inclusion Criteria: -age ≥18 y, HCV RNA levels > 10^4 IU/ml, GT 2 (ASTRAL-2), GT3 (ASTRAL-3), Key Exclusion Criteria: See Feld, et al.	ITT: 1. 135 2. 134 Attrition: 1. 1 2. 2 ITT: 1. 278 2. 280 Attrition: 1. 1 2. 5	Primary Endpoint: SVR12 *Genotype 2:* Sof/Vel: 133/134 (99%; 95% CI 96-100) Sof/RBV: 124 (94%; 95% CI 88-97) Absolute difference 5.2%; 95% CI 0.2to 10.3 P=0.02 *Genotype 3:* 1. 264/277 (95%; 95% CI 92-98) 2. 221/275 (80%; 95% CI 75-85) Absolute difference 14.8%; 95% CI 9.6 to 20.0 P<0.001 Relapse: *Genotype 2:* Sof/Vel: 0 (0%) Sof/Rbv: 6 (5%) *Genotype 3:* 1. 11 (4%) 38 (14%)	NS for all	Outcome: D/C due to AE: 1. 1 (%) 2. 0 (0%) Serious AE: 1. 2 (1.5%) 2. 2 (1.5%) GT3: D/C due to AE: 1. 0 (0%) 2. 9 (3%) Serious AE: 1. 6 (2%) 2. 15 (5%)	NS for all	**Risk of Bias:** Selection Bias: (low) randomized 1:1 by computerized central randomization and interactive response technology. Groups similar at baseline. Performance Bias: (high) open-label study Detection Bias: (high) open-label study Attrition Bias: (low) overall attrition low and similar across groups; full analysis set used for efficacy analysis. Missing data counted as a success only if data point preceded and followed by values that are deemed successes, otherwise counted as a failure. Reporting Bias: (unclear) Funded and designed by Gilead Sciences. Gilead was involved in data collection, study conduct, and statistical analyses, as well as writing of the manuscript. **Applicability**: Patient: Extensive and elusive exclusion criteria limits applicability of study results. Mostly white males. Patients previously treated with another NS5A or NS5B inhibitor were excluded; unknown the effect of newer DAA's in this population. Intervention: No concerns; appropriate dose of SOF and VEL based on phase 2 studies. Comparator: SOF+RBV current standard of care for GT2, but other agents now available and used for GT3 Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: ASTRAL-2: 51 sites in the US; ASTRAL-3: 76 sites in the US, Canada, Europe, Australia, and New Zealand

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3. Curry et al.[46] Open-label Phase 3 ASTRAL-4	1. SOF/VEL x 12 weeks 2. SOF/VEL + RBV x 12 weeks 3. SOF/VEL x 24 weeks	Demographics: 60% GT 1a 18% GT 1b 4% GT 2 15% GT 3 3% GT 4 Mean age 58 Key Inclusion Criteria: -age ≥18 y, HCV RNA levels > 10^4 IU/ml, decompensated cirrhosis Key Exclusion Criteria: -Clinically-significant illness, HCC, significant pulmonary disease or cardiac disease, psychiatric hospitalization, suicide attempt or period of disability within last 5 years, malignancy, ALT/AST > 10 x ULN, bilirubin > 5 mg/dl, Platelets < 30,000/uL, CrCl < 50 ml/min, Hg <10g/dl, albumin < 3 g/dL, INR > 1.5 x ULN, prior tx with SOF or other NS5B/NS5A inhibitor, HBV or HIV, clinically-relevant alcohol or drug abuse within 12 months, use of prohibited concomitant medications*	ITT: 1. 90 2. 87 3. 90 Attrition: 1. 0 2. 0 3. 0	Primary Endpoint: SVR12 (ITG only) 1. 83%; 95% CI 74 to 90) 2. 94%; 95% CI 87 to 98) 3. 86%; 95% CI 77 to 98) P<0.001 for all comparisons* *Compared to assumed spontaneous rate of HCV clearance of 1%	NA for all	Outcome: D/C due to AE: 1. 1 (1.1%) 2. 4 (4.6%) 3. 4 (4.4%) Serious AE: 1. 17 (19.9%) 2. 14 (16.1%) 3. 16 (17.8%)	NS for all	**Risk of Bias**: Selection Bias: (low) randomized but unclear on method of randomization used. Fewer males in Group 1. However efficacy comparison not done between groups so differences unlikely to bias results. Performance Bias: (high) open-label Detection Bias: (high) open-label; objective primary outcome used for efficacy analysis Attrition Bias: (low) overall attrition low and similar across groups; if missing data point was preceded and followed by values deemed successes, then the missing data point was termed a success; otherwise it was termed a failure. Reporting Bias: (unclear) Funded and designed by Gilead Sciences. Gilead was involved in data collection, study conduct, and statistical analyses, as well as writing of the manuscript. **Applicability**: Patient: Extensive and elusive exclusion criteria limits applicability of study results. Only moderate liver disease; majority of GT 1 patients included, possibly because only study sites in the U.S. were included. Intervention: No concerns Comparator: Primary efficacy endpoint compared to assumed spontaneous rate of 1%. More relevant if study would have compared treatment regimens to each other. Outcomes: Surrogate outcome of SVR 12 used to evaluate efficacy. Setting: 47 sites in the U.S.

Abbreviations: AE = adverse events; ALT = alanine aminotransferase; APRI = AST to platelet ratio index; ARI = absolute risk increase; ARR = absolute risk reduction; CI = confidence interval; CKD = chronic kidney disease; CPT = child turcotte-pugh; CrCl = creatinine clearance; CV = cardiovascular; DB = double-blind; DAA = direct acting antiviral; D/C = discontinue; DM = diabetes mellitus; DTG = deferred treatment group; EF = ejection fraction; FAS = full analysis set; FDA = U.S. Food and Drug Administration; GT = genotype; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; h/o = history of; HG = hemoglobin; ICS = inhaled corticosteroid; ITG = immediate treatment group; ITT = intention to treat; IV = intravenous; MC = multi-centered; MD = mean difference; mITT = modified intention to treat; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not statistically significant; OR = odds ratio; PC = placebo-controlled; PBO = placebo;; PG = parallel group; PP = per protocol; PT=prothrombin time; RBV = ribavirin; RCT = randomized controlled trial; RR = relative risk; RRR = relative risk reduction; SAE =

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serious adverse event; SE = standard error; SOF = sofosbuvir; SVR12 = sustained virologic response at 12 weeks after therapy completed; TE = treatment experienced; TN = treatment naïve; ULN = upper limit of normal; VEL = velpatasvir; wk = weeks; wt = weight; y = years; µL = microliters.
*Hematologic stimulating agents (erythropoiesis-stimulating agents, granulocyte colony stimulating factor), chronic immunosuppressants, herbal supplements, inhibitors or inducers of P-gyp or CYP, proton-pump inhibitors, anticonvulsants, modafinil, sulfasalazine, methotrexate,

Decompensated cirrhosis defined by child-pugh-turcotte class B

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Appendix 1: Current Preferred Drug List

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TABLET	DAKLINZA	DACLATASVIR DIHYDROCHLORIDE	Y
ORAL	TABLET	DAKLINZA	DACLATASVIR DIHYDROCHLORIDE	Y
ORAL	TABLET	HARVONI	LEDIPASVIR/SOFOSBUVIR	Y
ORAL	TABLET	SOVALDI	SOFOSBUVIR	Y
ORAL	TAB DS PK	VIEKIRA PAK	OMBITA/PARITAP/RITON/DASABUVIR	N
ORAL	TABLET	TECHNIVIE	OMBITASVIR/PARITAPREV/RITONAV	N
ORAL	TABLET	ZEPATIER	ELBASVIR/GRAZOPREVIR	N
ORAL	CAPSULE	OLYSIO	SIMEPREVIR SODIUM	N

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Appendix 2: Summary of Randomized Controlled Trials

Randomized Controlled Trials:

A total of 10 citations were manually reviewed from the literature search. After further review, 5 trials were excluded because of wrong study design (observational), comparator (placebo), or outcome studied (non-clinical) or because of unapproved medication. Trials covered in the new drug evaluation sections were also excluded and are summarized above. The remaining 5 trials are briefly described in the table below.

Table 1: Description of Randomized Comparative Clinical Trials

Study	Comparison	Population	Results (Primary Outcome; SVR12)	
ALLY-1[29] Open-label, phase 3	DCV/SOF + RBV x 12 weeks	Compensated/decompensated cirrhosis (n=60) or post-liver transplantation (n=53) (treatment naïve or experienced) HCV GT 1, 2, 3, 4, 5 or 6	SVR12: *Advanced Cirrhosis:* 50/60 (83%; 95% CI 71.5-91.7)	*Posttransplantation:* 50/53 (94%; 95% CI 84.3-98.8)
ELECTRON-2[47] Open-label, phase 2	LDV/SOF vs. LDV/SOF + RBV x 12 weeks	HCV GT 3 or 6 (n=126), treatment naïve and treatment experienced	SVR12: *Treatment Naïve GT3* LDV/SOF: 16/25 (64%; 95% CI 43-82) LDV/SOF + RBV: 26/26 (100%; 95% CI 87-100) *Treatment Experienced GT3* LDV/SOF + RBV: 41/50 (82%; 95% CI 69-91)	*GT 6 (Treatment Naïve and Experienced)* LDV/SOF: 24/25 (96%; 95% CI 80-100)
Wilson, et al.[48] Phase 2, open-label	LDV/SOF x 12 weeks	HCV GT 1 with treatment failure to short course LDV/SOF based regimens without liver cirrhosis (n=34)	SVR12: 31/34 (91.2%)	
OPTIMIST-2[49] Open-label, phase 3	SMV/SOF x 12 weeks	HCV GT1 and compensated cirrhosis, treatment-naïve and treatment experienced	SVR12: 83% (95% CI 76-91)	
SOLAR-2[32] Phase 2, open label	LDV/SOF + RBV for 12 -24 weeks	Cohort A (decompensated cirrhosis CTP B or C) Cohort B (post liver transplantation) GT 1 or 4	SVR12: *Cohort A; GT 1; CTP B* 12 wks: 20 (87%; 90% CI 70-96) 24 wks: 22 (96%; 81-100)	*Cohort A; GT 1; CTP C* 12 wks: 17 (85%; 66-96) 24 wks: 18 (78%; 60-91) *Cohort B; GT1; without cirrhosis* 12 wks: 42 (93%; 84-98) 24 wks: 44 (100%; 84-98)

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

Abstracts of Randomized Controlled Trials:

1. Poordad F, Schiff Er, Vierling JM, et al. Daclatasvir with sofosbuvir and ribavirin for hepatitis C virus infection with advanced cirrhosis or post-liver transplantation recurrence. *Hepatology. 2*016 May;63(5):1493-505. Epub 2016 Mar 7.

Abstract: Chronic hepatitis C virus (HCV) infection with advanced cirrhosis or post-liver transplantation recurrence represents a high unmet medical need with no approved therapies effective across all HCV genotypes. The open-label ALLY-1 study assessed the safety and efficacy of a 60-mg once-daily dosage of daclatasvir (pan-genotypic NS5A inhibitor) in combination with sofosbuvir at 400 mg once daily (NS5B inhibitor) and ribavirin at 600 mg/day for 12 weeks with a 24-week follow-up in two cohorts of patients with chronic HCV infection of any genotype and either compensated/decompensated cirrhosis or posttransplantation recurrence. Patients with on-treatment transplantation were eligible to receive 12 additional weeks of treatment immediately after transplantation. The primary efficacy measure was sustained virologic response at posttreatment week 12 (SVR12) in patients with a genotype 1 infection in each cohort. Sixty patients with advanced cirrhosis and 53 with posttransplantation recurrence were enrolled; HCV genotypes 1 (76%), 2, 3, 4, and 6 were represented. Child-Pugh classifications in the advanced cirrhosis cohort were 20% A, 53% B, and 27% C. In patients with cirrhosis, 82% (95% confidence interval [CI], 67.9%-92.0%) with genotype 1 infection achieved SVR12, whereas the corresponding rates in those with genotypes 2, 3, and 4 were 80%, 83%, and 100%, respectively; SVR12 rates were higher in patients with Child-Pugh class A or B, 93%, versus class C, 56%. In transplant recipients, SVR12 was achieved by 95% (95% CI, 83.5%-99.4%) and 91% of patients with genotype 1 and 3 infection, respectively. Three patients received peritransplantation treatment with minimal dose interruption and achieved SVR12. There were no treatment-related serious adverse events.

Conclusion: The pan-genotypic combination of daclatasvir, sofosbuvir, and ribavirin was safe and well tolerated. High SVR rates across multiple HCV genotypes were achieved by patients with post-liver transplantation recurrence or advanced cirrhosis.

2. Gane EJ, Hyland RH, An D, et al. Efficacy of ledipasvir and sofosbuvir, with or without ribavirin, for 12 weeks in patients with HCV genotype 3 or 6 infection. *Gastroenterology.* 2015 Nov;149(6):1454-1461.e1. doi: 10.1053/j.gastro.2015.07.063. Epub 2015 Aug 7.

BACKGROUND & AIMS: We performed a phase 2 clinical trial to evaluate the efficacy and safety of ledipasvir and sofosbuvir, with or without ribavirin, in patients infected with hepatitis C virus (HCV) genotype 3 or 6.

METHODS: We performed an open-label study of 126 patients with HCV genotype 3 or 6 infections at 2 centers in New Zealand from April 2013 through October 2014. Subjects were assigned 1 of 4 groups that received 12 weeks of treatment. Previously untreated patients with HCV genotype 3 were randomly assigned to groups given fixed-dose combination tablet of ledipasvir and sofosbuvir (n = 25) or ledipasvir and sofosbuvir along with ribavirin (n = 26). Treatment-experienced patients with HCV genotype 3 (n = 50) received ledipasvir and sofosbuvir and ribavirin. Treatment-naïve or treatment-experienced patients with HCV genotype 6 (n = 25) received ledipasvir and sofosbuvir. The primary end point was the percentage of patients with HCV RNA ≤15 IU/mL 12 weeks after stopping therapy (sustained virologic response at 12 weeks [SVR12]).

RESULTS: Among treatment-naïve genotype 3 patients, 16 of 25 (64%) receiving ledipasvir and sofosbuvir alone achieved SVR12 compared with all 26 patients (100%) receiving ledipasvir and sofosbuvir and ribavirin. Among treatment-experienced patients with HCV genotype 3, forty-one of fifty achieved an SVR12 (82%). Among patients with HCV genotype 6, the rate of SVR12 was 96% (24 of 25 patients). The most common adverse events were headache, upper respiratory infection, and fatigue. One patient with HCV genotype 3 discontinued ledipasvir and sofosbuvir because of an adverse event (diverticular perforation), which was not considered treatment related.

CONCLUSIONS: In an uncontrolled, open-label trial, high rates of SVR12 were achieved by patients with HCV genotype 3 infection who received 12 weeks of ledipasvir and sofosbuvir plus ribavirin, and by patients with HCV genotype 6 infection who received 12 weeks of sofosbuvir and ledipasvir without ribavirin. Current guidelines do not recommend the use of ledipasvir and sofosbuvir, with or without ribavirin, in patients with HCV genotype 3 infection.

3. Luetkemeyer AF, McDonald C, Ramgopal M, Noviello S, Bhore R, Ackerman P. 12 Weeks of Daclatasvir in Combination With Sofosbuvir for HIV-HCV Coinfection (ALLY-2 Study): Efficacy and Safety by HIV Combination Antiretroviral Regimens. *Clin Infect Dis.* 2016 Jun 15;62(12):1489-96. doi: 10.1093/cid/ciw163. Epub 2016 Mar 29.

   BACKGROUND: Highly effective hepatitis C virus (HCV) direct-acting antiviral therapies that do not require modification of human immunodeficiency virus (HIV) antiretroviral regimens are needed. We evaluated the efficacy and safety of daclatasvir + sofosbuvir (DCV + SOF) for 12 weeks by antiretroviral (ARV) regimen in HIV-HCV-coinfected patients.

   METHODS: In the randomized, open-label ALLY-2 study, HIV-HCV-coinfected patients received 8 or 12 weeks of once-daily DCV 60 mg (dose-adjusted as-necessary for concomitant ARVs) + SOF 400 mg. Results were stratified by ARV class for the 151 patients who received 12 weeks of DCV + SOF.

   RESULTS: Fifty-one patients were HCV treatment experienced, 100 were treatment naive, 89% male and 33% black. HCV genotypes were: genotype 1a (GT1a; 69%), GT1b (15%), GT2 (8%), GT3 (6%), and GT4 (2%). Sustained virologic response 12 weeks post-treatment (SVR12) was 97% and was similar across ARV regimens (P = .774): protease inhibitor-based, 97% (95% confidence interval [CI], 90%-99.7%); nonnucleoside reverse transcriptase inhibitor-based, 100% (95% CI, 91%-100%); and integrase inhibitor based, 95% (95% CI, 83%-99.4%). SVR12 among patients receiving either tenofovir disoproxil fumarate or abacavir as part of their antiretroviral therapy regimen was 98% (95% CI, 93%-99.5%) and 100% (95% CI, 85%-100%), respectively. Age, gender, race, cirrhosis, HCV treatment history, GT , and baseline HCV RNA did not affect SVR12. No discontinuations were attributed to treatment-related adverse events.

   CONCLUSIONS: DCV + SOF x12 weeks is a highly efficacious, all-oral, pan-GT HCV treatment for HIV-HCV coinfected patients across a broad range of ARV regimens.

4. Wilson EM, Kattakuzhy S, Sidharthan S, Sims Z, Tang L, McLaughlin M, et al. Successful Retreatment of Chronic HCV Genotype-1 Infection With Ledipasvir and Sofosbuvir After Initial Short Course Therapy With Direct-Acting Antiviral Regimens. *Clin Infect Dis*. 2016 Feb 1;62(3):280-8. doi: 10.1093/cid/civ874. Epub 2015 Oct 31.

BACKGROUND: The optimal retreatment strategy for chronic hepatitis C virus (HCV) patients who fail directly-acting antiviral agent (DAA)-based treatment is unknown. In this study, we assessed the efficacy and safety of ledipasvir (LDV) and sofosbuvir (SOF) for 12 weeks in HCV genotype-1 (GT-1) patients who failed LDV/SOF-containing therapy.

METHODS: In this single-center, open-label, phase 2a trial, 34 participants with HCV (GT-1) and early-stage liver fibrosis who previously failed 4-6 weeks of LDV/SOF with GS-9669 and/or GS-9451 received LDV/SOF for 12 weeks. The primary endpoint was HCV viral load below the lower limit of quantification 12 weeks after completion of therapy (sustained virological response [SVR]12). Deep sequencing of the NS3, NS5A, and NS5B regions were performed at baseline, at initial relapse, prior to retreatment, and at second relapse with Illumina next-generation sequencing technology.

RESULTS: Thirty-two of 34 enrolled participants completed therapy. Two patients withdrew after day 0. Participants were predominantly male and black, with median baseline HCV viral load of 1.3 × 10(6) IU/mL and Metavir fibrosis stage 1 and genotype-1a. Median time from relapse to retreatment was 22 weeks. Prior to retreatment, 29 patients (85%) had NS5A-resistant variants. The SVR12 rate was 91% (31/34; intention to treat, ITT) after retreatment. One patient relapsed.

CONCLUSIONS: In patients who previously failed short-course combination DAA therapy, we demonstrate a high SVR rate in response to 12 weeks of LDV/SOF, even for patients with NS5A resistance-associated variants

5. Manns M, Samuel D, Gane EJ, Mutimer D, McCaughan G, et al. Ledipasvir and sofosbuvir plus ribavirin in patients with genotype 1 or 4 hepatitis C virus infection and advanced liver disease: a multicentre, open-label, randomised, phase 2 trial. Lancet Infect Dis. 2016 Jun;16(6):685-97. doi: 10.1016/S1473-3099(16)00052-9. Epub 2016 Feb 18.

BACKGROUND: Treatment options are limited for patients infected by hepatitis C virus (HCV) with advanced liver disease. We assessed the safety and efficacy of ledipasvir, sofosbuvir, and ribavirin in patients with HCV genotype 1 or 4 and advanced liver disease.

METHODS: We did an open-label study at 34 sites in Europe, Canada, Australia, and New Zealand. Cohort A included patients with Child-Turcotte-Pugh class B (CTP-B) or CTP-C cirrhosis who had not undergone liver transplantation. Cohort B included post-transplantation patients who had either no cirrhosis; CTP-A, CTP-B, or CTP-C cirrhosis; or fibrosing cholestatic hepatitis. Patients in each group were randomly assigned (1:1) using a computer-generated randomisation sequence to receive 12 or 24 weeks of ledipasvir (90 mg) and sofosbuvir (400 mg) once daily (combination tablet), plus ribavirin (600-1200 mg daily). The primary endpoint was the proportion of patients achieving a sustained virological response 12 weeks after treatment (SVR12). All patients who received at least one dose of study drug were included in the safety analysis and all patients who received at least one dose of study drug and did not undergo liver transplantation during treatment were included in the efficacy analyses. Estimates of SVR12 and relapse rates and their two-sided 90% CI (Clopper-Pearson method) were provided. This exploratory phase 2 study was not powered for formal comparisons among treatment groups; no statistical hypothesis testing was planned or conducted. The trial is registered with EudraCT (number 2013-002802-30) and ClinicalTrials.gov (number NCT02010255).

FINDINGS: Between Jan 14, 2014, and Aug 19, 2014, 398 patients were screened. Of 333 patients who received treatment, 296 had genotype 1 HCV and 37 had genotype 4 HCV. In cohort A, among patients with genotype 1 HCV, SVR12 was achieved by 20 (87%, 90% CI 70-96) of 23 CTP-B patients with 12 weeks of treatment; 22 (96%, 81-100) of 23 CTP-B patients with 24 weeks of treatment; 17 (85%, 66-96) of 20 CTP-C patients (12 weeks treatment); and 18 (78%, 60-91) of 23 CTP-C patients (24 weeks treatment). In cohort B, among patients with genotype 1 HCV, SVR12 was achieved by 42 (93%, 84-98) of 45 patients without

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cirrhosis (12 weeks treatment); 44 (100%, 93-100) of 44 patients without cirrhosis (24 weeks treatment); 30 (100%, 91-100) of 30 CTP-A patients (12 weeks treatment); 27 (96%, 84-100) of 28 CTP-A patients (24 weeks treatment); 19 (95%, 78-100) of 20 CTP-B patients (12 weeks treatment); 20 (100%, 86-100) of 20 CTP-B patients (24 weeks treatment); one (50%, 3-98) of two CTP-C patients (12 weeks treatment); and four (80%, 34-99) of five CTP-C patients (24 weeks treatment). All five patients with fibrosing cholestatic hepatitis achieved SVR12 (100%, 90% CI 55-100). Among all patients with genotype 4 HCV, SVR12 was achieved by 14 (78%, 56-92) of 18 patients (12 weeks treatment) and 16 (94%, 75-100) of 17 patients (24 weeks treatment). Seven patients (2%) discontinued ledipasvir-sofosbuvir prematurely due to adverse events. 17 patients died, mainly from complications of hepatic decompensation.

INTERPRETATION: Ledipasvir-sofosbuvir and ribavirin provided high rates of SVR12 for patients with advanced liver disease, including those with decompensated cirrhosis before or after liver transplantation.

Appendix 3: Highlights of Prescribing Information

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ZEPATIER safely and effectively. See full prescribing information for ZEPATIER.

ZEPATIER™ (elbasvir and grazoprevir) tablets, for oral use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------
ZEPATIER is a fixed-dose combination product containing elbasvir, a hepatitis C virus (HCV) NS5A inhibitor, and grazoprevir, an HCV NS3/4A protease inhibitor, and is indicated with or without ribavirin for treatment of chronic HCV genotypes 1 or 4 infection in adults. (1)

----------DOSAGE AND ADMINISTRATION----------
- Testing prior to initiation:
  - Genotype 1a: Testing for the presence of virus with NS5A resistance-associated polymorphisms is recommended. (2.1)
  - Obtain hepatic laboratory testing. (2.1)
- Recommended dosage: One tablet taken orally once daily with or without food. (2.2)

Dosage Regimens and Durations for ZEPATIER in Patients with Genotype 1 or 4 HCV with or without Cirrhosis

Patient Population	Treatment	Duration
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* without baseline NS5A polymorphisms†	ZEPATIER	12 weeks
Genotype 1a: Treatment-naïve or PegIFN/RBV-experienced* with baseline NS5A polymorphisms†	ZEPATIER + ribavirin	16 weeks
Genotype 1b: Treatment-naïve or PegIFN/RBV-experienced*	ZEPATIER	12 weeks
Genotype 1a or 1b: PegIFN/RBV/PI-experienced‡	ZEPATIER + ribavirin	12 weeks
Genotype 4: Treatment-naïve	ZEPATIER	12 weeks
Genotype 4: PegIFN/RBV-experienced*	ZEPATIER + ribavirin	16 weeks

*Peginterferon alfa + ribavirin.
†Polymorphisms at amino acid positions 28, 30, 31, or 93.
‡Peginterferon alfa + ribavirin + HCV NS3/4A protease inhibitor.

- HCV/HIV-1 co-infection: Follow the dosage recommendations in the table above. (2.2)
- Renal Impairment, including hemodialysis: No dosage adjustment of ZEPATIER is recommended. Refer to ribavirin prescribing information for ribavirin dosing and dosage modifications. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------
- Tablets: 50 mg elbasvir and 100 mg grazoprevir (3)

----------CONTRAINDICATIONS----------
- Patients with moderate or severe hepatic impairment (Child-Pugh B or C). (4)
- OATP1B1/3 inhibitors, strong CYP3A inducers, and efavirenz. (4)
- If ZEPATIER is administered with ribavirin, the contraindications to ribavirin also apply. (4)

----------WARNINGS AND PRECAUTIONS----------
- ALT elevations: Perform hepatic laboratory testing prior to therapy, at treatment week 8, and as clinically indicated. For patients receiving 16 weeks of therapy, perform additional hepatic laboratory testing at treatment week 12. For ALT elevations on ZEPATIER, follow recommendations in full prescribing information. (5.1)
- Risk associated with ribavirin combination treatment: If ZEPATIER is administered with ribavirin, the warnings and precautions for ribavirin also apply. (5.2)

----------ADVERSE REACTIONS----------
In subjects receiving ZEPATIER for 12 weeks, the most commonly reported adverse reactions of all intensity (greater than or equal to 5% in placebo-controlled trials) were fatigue, headache, and nausea. In subjects receiving ZEPATIER with ribavirin for 16 weeks, the most commonly reported adverse reactions of moderate or severe intensity (greater than or equal to 5%) were anemia and headache. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., at 1-877-888-4231 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
- Co-administration of ZEPATIER with moderate CYP3A inducers is not recommended as they may decrease the plasma concentration of ZEPATIER. (7)
- Co-administration of ZEPATIER with certain strong CYP3A inhibitors is not recommended as they may increase the plasma concentration of ZEPATIER. (7)
- Consult the full prescribing information prior to and during treatment for potential drug interactions. (4, 5.3, 7, 12.3)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 1/2016

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HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use EPCLUSA safely and effectively. See full prescribing information for EPCLUSA.

EPCLUSA® (sofosbuvir and velpatasvir) tablets, for oral use
Initial U.S. Approval: 2016

----------INDICATIONS AND USAGE----------
EPCLUSA is a fixed-dose combination of sofosbuvir, a hepatitis C virus (HCV) nucleotide analog NS5B polymerase inhibitor, and velpatasvir, an HCV NS5A inhibitor, and is indicated for the treatment of adult patients with chronic HCV genotype 1, 2, 3, 4, 5, or 6 infection (1):

- without cirrhosis or with compensated cirrhosis
- with decompensated cirrhosis for use in combination with ribavirin

----------DOSAGE AND ADMINISTRATION----------

- Recommended dosage: One tablet (400 mg of sofosbuvir and 100 mg of velpatasvir) taken orally once daily with or without food (2.1)
- See recommended treatment regimen and duration in patients with genotypes 1, 2, 3, 4, 5, or 6 HCV in table below: (2.1)

Patient Population	Recommended Treatment Regimen
Patients without cirrhosis and patients with compensated cirrhosis (Child-Pugh A)	EPCLUSA for 12 weeks
Patients with decompensated cirrhosis (Child-Pugh B and C)	EPCLUSA + ribavirin for 12 weeks

- A dosage recommendation cannot be made for patients with severe renal impairment or end stage renal disease (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Tablets: 400 mg sofosbuvir and 100 mg velpatasvir (3)

----------CONTRAINDICATIONS----------
EPCLUSA and ribavirin combination regimen is contraindicated in patients for whom ribavirin is contraindicated (4)

----------WARNINGS AND PRECAUTIONS----------
Bradycardia with amiodarone coadministration: Serious symptomatic bradycardia may occur in patients taking amiodarone, particularly in patients also receiving beta blockers, or those with underlying cardiac comorbidities and/or advanced liver disease. Coadministration of amiodarone with EPCLUSA is not recommended. In patients without alternative viable treatment options, cardiac monitoring is recommended. (5.1, 7.3)

----------ADVERSE REACTIONS----------

- The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with EPCLUSA for 12 weeks are headache and fatigue. (6.1)
- The most common adverse reactions (incidence greater than or equal to 10%, all grades) observed with treatment with EPCLUSA and ribavirin for 12 weeks in patients with decompensated cirrhosis are fatigue, anemia, nausea, headache, insomnia, and diarrhea. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Gilead Sciences, Inc. at 1-800-GILEAD-5 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

- P-gp inducers and/or moderate to potent CYP inducers (e.g., rifampin, St. John's wort, carbamazepine): May decrease concentrations of sofosbuvir and/or velpatasvir. Use of EPCLUSA with P-gp inducers and/or moderate to potent CYP inducers is not recommended (5.2, 7)
- Consult the full prescribing information prior to use for potential drug interactions (5.1, 5.2, 7)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 06/2016

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Appendix 4: Proposed Prior Authorization Criteria

Hepatitis C Direct-Acting Antivirals

Goals:

- Approve use of cost-effective treatments supported by the medical evidence.
- Provide consistent patient evaluations across all hepatitis C treatments.
- Ensure appropriate patient selection based on disease severity, genotype, and patient comorbidities.

Length of Authorization:

- 8-12 weeks

Requires PA:

- All direct-acting antivirals for treatment of Hepatitis C

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code.	
2. Is the request for treatment of chronic Hepatitis C infection?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness.
3. Is expected survival from non-HCV-associated morbidities more than 1 year?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness.
4. Has all of the following pre-treatment testing been performed: a. Genotype testing in past 3 years; b. Baseline HCV RNA level in past 6 months; c. Current HIV status of patient; d. Pregnancy test in past 30 days for a woman of child-bearing age; and e. History of previous HCV treatment and outcome?	**Yes:** Record results of each test and go to #5	**No**: Pass to RPh. Request updated testing.

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Approval Criteria		
5. Has the patient failed treatment with <u>any</u> of the following HCV NS5A inhibitors: a) Daclatasvir plus sofosubvir; b) Ledipasvir/sofosbuvir; c) Paritaprevir/ritonavir/ombitasvir plus dasabuvir; d) Elbasvir/grazoprevir; <u>or</u> e) sofosbuvir/velpatasvir)? <u>Note</u>: Patients who failed treatment with sofosbuvir +/- ribavirin or pegylated interferon can be retreated (see table below).	**Yes:** Pass to RPh. Deny; medical appropriateness. Note: If urgent retreatment is needed, resistance testing must be done to indicate susceptibility to prescribed regimen. Refer to medical director for review.	**No:** Go to #6
6. Which regimen is requested?	Document and go to #7	
7. Does the patient have: a) A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]) to indicate advanced fibrosis (METAVIR F3) or cirrhosis (METAVIR F4); <u>or</u> b) Clinical, radiologic or laboratory evidence of complications of advanced cirrhosis (ascites, portal hypertension, hepatic encephalopathy, hepatocellular carcinoma)**?**	**Yes:** Go to #8 Note: Other imaging and blood tests are not recommended based on insufficient evidence for high sensitivity and specificity compared to a liver biopsy	**No:** Go to #9
8. Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist with experience in treatment of Hepatitis C?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness. Forward to DMAP for further manual review to determine appropriateness of prescriber.

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Approval Criteria		
9. Does the patient have: A biopsy, imaging test (transient elastography [FibroScan®], acoustic radiation force impulse imaging [ARFI], or shear wave elastography [SWE]), or serum test if the above are not available (enhanced liver fibrosis [ELF]; Fibrometer; FIBROSpect II) to indicate fibrosis (METAVIR F2)?	**Yes:** Go to #10 Note: Other imaging and blood tests are not recommended based on insufficient evidence for high sensitivity and specificity compared to a liver biopsy	**No:** Go to #11
10. Is the regimen prescribed by, or in consultation with, a hepatologist, gastroenterologist, or infectious disease specialist with experience in treatment of Hepatitis C? **OR** A provider with documented experience in HCV treatment or directly involved in the Oregon ECHO program?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.
11. Does the patient have one of the following extrahepatic manifestations of Hepatitis C (with documentation from a relevant specialist that their condition is related to HCV)? a) Type 2 or 3 cryoglobulinemia with end-organ manifestations (i.e., leukocytoclastic vasculitis); or b) Proteinuria, nephrotic syndrome, or membranoproliferative glomerulonephritis; or c) Porphyria cutanea tarda	**Yes:** Go to #13	**No:** Go to #12
12. Is the patient in one of the following the transplant settings: a) Listed for a transplant and it is essential to prevent recurrent hepatitis C infection post-transplant; or b) Post solid organ transplant?	**Yes:** Go to #13	**No:** Pass to RPh. Deny; medical appropriateness.

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Approval Criteria		
13. In the previous 6 months: • Has the patient actively abused alcohol (>14 drinks per week for men or >7 drinks per week for women or binge alcohol use (>4 drinks per occasion at least once a month)); OR • Has the patient been diagnosed with a substance use disorder; OR • Is the prescriber aware of current alcohol abuse or illicit injectable drug use?	**Yes:** Go to #14	**No:** Go to #15
14. Is the patient enrolled in a treatment program under the care of an addiction/substance use treatment specialist?	**Yes:** Go to #15	**No:** Pass to RPh. Deny; medical appropriateness.
15. Will the patient and provider comply with all case management interventions and adhere to monitoring requirements required by the Oregon Health Authority, including measuring and reporting of a post-treatment viral load?	**Yes**: Go to #16	**No:** Pass to RPh. Deny; medical appropriateness.
16. Is the prescribed drug: a) Elbasvir/grazoprevir for GT 1a infection; or b) Daclatasvir + sofosbuvir for GT 3 infection?	**Yes**: Go to #17	**No:** Go to #18
17. Has the patient had a baseline NS5a resistance test show a resistant variant to one of the agents in #16?	**Yes:** Pass to RPh; deny for appropriateness	**No:** Go to #18

Direct Acting Antiviral Abbreviations: **DCV/SOF** (Daclatasvir + sofosbuvir): Daklinza® + Sovaldi®; **EBR/GZR** (elbasvir/grazoprevir): Zepatier®; **LDV/SOF** (ledipasvir/sofosbuvir): Harvoni®; **OMB/PTV-R + DAS** (ombitasvir, paritaprevir and ritonavir with dasabuvir): Viekira Pak®/Viekira XR®; **OMB/PTV-R** (ombitasvir, paritaprevir and ritonavir): Technivie®; **SOF/VEL** (sofosbuvir/velpatasvir): Epclusa®; **SOF** (sofosbuvir): Sovaldi®

Approval Criteria		
18. Is the prescribed drug regimen a recommended regimen based on the patient's genotype and cirrhosis status (see Table 1)?	**Yes:** Approve for 8-12 weeks based on duration of treatment indicated for approved regimen (Table 1)	**No:** Pass to RPh. Deny; medical appropriateness.

Table 1: Recommended Treatment Regimens for Chronic Hepatitis C.

[Pending P&T Committee Recommendations]

P&T Review: *9/16 (MH); 1/16; 5/15; 3/15; 1/15; 9/14; 1/14*
Implementation: *TBD; 2/12/16; 4/15; 1/15*

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