Drug Use Research & Management Program
OHA Division of Medical Assistance Programs
500 Summer Street NE, E35; Salem, OR 97301-1079
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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, January 25, 2018 1:00 - 5:00 PM
Barbara Roberts Human Services Building
500 Summer St. NE
Salem, OR 97301
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. Roles and Responsibilities of Committee Members	T. Douglass (OHA)
	C. Conflict of Interest Declaration	R. Citron (OSU)
	D. Election of Chair & Vice Chair	R. Citron (OSU)
	E. Department and Legislative Update	T. Douglass (OHA)
	F. Approval of Agenda and Minutes	
	II. CONSENT AGENDA TOPICS	R. Citron (OSU)
1:25 PM	A. Noctiva® (desmopressin) Abbreviated Drug Review	
	B. Drugs for Asthma and COPD Literature Scan	
	1. Public Comment	
	III. DUR NEW BUSINESS	
1:30 PM	A. Hepatitis C Direct-Acting Antivirals Policy Discussion	R. Citron (OSU)
	1. Prior Authorization Criteria	A. Seaman (OHSU)
	2. Treatment of Hepatitis C in People who Inject Drugs	
	3. Public Comment	
	4. Discussion of Clinical Recommendations to OHA	
	IV. PREFERRED DRUG LIST NEW BUSINESS	
2:05 PM	A. Biologics for Autoimmune Conditions Class Update	J. Page (OSU)
	1. Class Update/Prior Authorization Criteria	
	2. Kevzara® (sarilumab) New Drug Evaluation	

3. Tremfya® (guselkumab) New Drug Evaluation
4. Prior Authorization Criteria
5. Public Comment
6. Discussion of Clinical Recommendations to OHA

2:35 PM B. Vesicular Monoamine Transporter 2 Inhibitors Class Review — K. Sentena (OSU)
1. Class Review/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

2:55 PM BREAK

3:10 PM C. Oral First and Second Generation Antipsychotics Class Update — S. Servid (OSU)
1. Class Update/Safety Edits
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

3:30 PM D. PCSK-9 Inhibitors Class Update — M. Herink (OSU)
1. Class Update/Prior Authorization Criteria
2. Public Comment
3. Discussion of Clinical Recommendations to OHA

V. DUR ACTIVITIES

3:50 PM A. Quarterly Utilization Reports — R. Citron (OSU)
B. ProDUR Report — R. Holsapple (DXC)
C. RetroDUR Report — R. Citron (OSU)
D. Oregon State Drug Reviews — K. Sentena (OSU)
1. Recently Published Reviews
a. Marketing Claims of Newer Drugs and the Evidence
2. Future Topic Recommendations

4:00 PM VI. EXECUTIVE SESSION

4:50 PM VII. RECONVENE for PUBLIC RECOMMENDATIONS

VIII. ADJOURN

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OHA Health Systems Division
500 Summer Street NE, E35; Salem, OR 97301-1079
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Oregon Pharmacy and Therapeutics Committee – Appointed members

Name	Title	Profession	Location	Term Expiration
William Origer, M.D.	Physician	Residency Faculty	Albany	December 2020
Caryn Mickelson, Pharm.D.	Pharmacist	Pharmacy Director	Coos Bay	December 2020
Tracy Klein, Ph.D., F.N.P.	Public	Nurse Practitioner	Portland	December 2020
James Slater, Pharm.D.	Pharmacist	Pharmacy Director	Beaverton	December 2020
Kelley Burnett, D.O.	Physician	Pediatric Medical Director	Grants Pass	December 2019
Dave Pass, M.D.	Physician	Medical Director	West Linn	December 2019
Stacy Ramirez, Pharm.D.	Pharmacist	Community Pharmacist	Corvallis	December 2019
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

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, November 30, 2017, 1:00-5:00 PM
Human Services Building
Salem, OR 97301

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: Tracy Klein, PhD, FNP; Caryn Mickelson, PharmD; Cathy Zehrung, RPh; Stacy Ramirez, PharmD; Kelley Burnett, DO; Phil Levin, PhD; William Origer, MD; James Slater, PharmD; Rich Clark, MD, MPH; Walter Hardin, DO, MBA

Members Present by Phone:

Staff Present: Richard Holsapple, RPh; Roger Citron, RPh; Dee Weston; Sarah Servid, PharmD; Lindsay Newton; Dave Engen, PharmD, CGP; Kathy Sentena, PharmD; Kim Wentz, MD; Julia Verhulst, PharmD; Deanna Moretz, PharmD

Staff Present by Phone: Dean Haxby, PharmD

Audience: *Margaret Olmon, AbbVie; Jeana Colabianchi, Sunovion; *Mary Kemhus, Novartis; Jennifer Shidler, Genzyme; Lisa Boyle, WVP Health; Bobbi Jo Drum, BMS; Karen Jackson, Trividia; Russ Rahmidah, PTC Therapeutics; Tera Gardol, PTC Therapeutics; Jeremy Guard, Alexion; Bill McDougall; Braden Purke; Chris Johnson, Spark; Diann Matthews, Merz; Nicolas Nguyen, Sunovion; Bill Francis; Rick Frees, Vertex; Joe Schreck, Allergan; Mike Donabedia, Sarepta; *Niren Shah, PTC Therapeutics; *Stan Cohan, Providence Hospital; *Lynda Finch, BioGen; Todd Hudson, PTC Therapeutics; *Kelley Maynard, Little Hercules; *Paul Cosgrove; Maiceya Gonzalez, Salud Pharmacy; Gregg Gittus, Alkermes; Tim McFerron, Alkermes; *Christine Curry, Genetech; David Barhoum, Genetech; Darren Coffman, HERC; Holly Bourgeois, OSU; *Meganne Leach, OHSU; Patrick Moty, Horizon Pharma; Joe Glassmire, Portola; *Andrea Dumont, Portola; Amy Burns, AllCare Health;

(*) Provided verbal testimony

Written testimony provided: Kyle Pinion, MSAA; PTC Therapeutics

I. CALL TO ORDER

A. The meeting was called to order at approximately 1:05 pm. Introductions were made by Committee members and staff.

B. Mr. Citron reported there were no new conflicts of interest to declare.
C. Approval of agenda and July minutes presented by Mr. Citron. (pages 5-9)

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

II. DUR ACTIVITIES

A. Quarterly Utilization Reports – Mr. Citron presented the Quarterly Utilization report.
B. ProDUR Report – Mr. Holsapple presented the ProDUR report.
C. RetroDUR Report – Dr. Engen presented the RetroDUR report
D. RetroDUR Project Proposals - Dr. Engen presented the proposals.
E. Oregon State Drug Reviews
    1. Recently published reviews
        i. Tramadol and Codeine Use in Pediatrics
        ii. Oral Anticoagulation Update
    2. Future Topic Recommendations

Dr. Sentena presented two recently published newsletters, thanked the Committee for reviewing the draft versions and solicited ideas for future newsletters.

F. Provider Education Opportunities
    1. Proton Pump Inhibitors

Dr. Sentena presented a draft of the Proton Pump Inhibitor provider education proposal.

III. P&T Operating Procedures Update

A. Operating Procedures Update-Presented by Mr. Citron and Dr. Servid
    1. Consent Agenda
    2. New Drug Policy
    3. Biosimilar Policy
    4. Public Comment
    5. Discussion of Recommendations to OHA

The Committee approved the specific items regarding consent agenda, biosimilar policy and the new drug policy after amending the proposed PA criteria to a $5,000 per claim or per month threshold instead of $10,000 and to require FDA approved dosing.

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

The proposed changes to the operating procedures and evidence grading methods was deferred for future study and a P&T subcommittee was requested to be convened to meet and bring edits back to January meeting.

IV. DUR OLD BUSINESS

A. Drugs for Duchenne Muscular Dystrophy (pages 45 - 46)
Dr. Servid presented the proposal of updating the PA criteria to:

1. Require that the requested treatment is funded by the OHP for that condition.

ACTION: Amend PA criteria to include link to the HERC prioritized list. Motion to approve, 2nd. All in favor. Approved.

B. Antiemetics (pages 47-49)
Dr. Sentena presented the proposal to update the PA criteria to:

1. Eliminate quantity limits for all drugs in the class except for dronabinol.

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

C. Low-Dose Quetiapine (pages 50-54)
Dr. Servid presented the proposal to modify the safety edit to:

1. Apply to only patients with a daily dose of 50 mg or less.

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

V. DUR NEW BUSINESS

A. Pediatric Antipsychotic Drug Use Evaluation (pages 55 - 85)
Dr. Servid presented the drug use evaluation and recommendation to:

1. Develop a RetroDUR program that provides new start patients access to care coordination and referral for expert consultation.

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

VI. PREFERRED DRUG LIST NEW BUSINESS

A. Bevyxxa (betrixaban) New Drug Evaluation (pages 86-93)
Dr. Sentena presented the new drug evaluation, with the recommendation to:

1. Maintain betrixaban as a non-preferred drug in the anticoagulant PDL class
2. Subject betrixaban to the non-preferred drug prior authorization (PA) criteria.

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

B. Multiple Sclerosis Class Update (pages 94-129)
Dr. Moretz presented the class update, with the recommendation to:

1. Apply clinical prior authorization (PA) criteria to ocrelizumab for both physician administered and point of sale pharmacy claims and limit use to:
   - Funded MS conditions
   - History of inadequate response to at least 2 disease modifying agents (DMA) approved for MS; and
   - Prescribed by a neurologist.
2. Create clinical PA criteria for natalizumab separate from the biologic PA criteria.
3. Amend PA criteria for oral multiple sclerosis drugs to remove requirement of failure of a trial of interferon beta 1a or interferon 1b, and glatiramer.
4. Consider referring ocrelizumab for PPMS to the Health Evidence Review Commission (HERC) for prioritization consideration.

ACTION: Amend PA criteria for ocrelizumab to add a question verifying Hepatitis B status. Amend PA criteria for oral multiple sclerosis drugs to change the approval duration to 6 months. Amend PA criteria for natalizumab to require screening for tuberculosis only for Crohn's disease and not for multiple sclerosis. Refer ocrelizumab, when prescribed for primary progressive MS, to the Health Evidence Review Commission (HERC) for prioritization consideration Motion to approve, 2nd. All in favor. Approved.

C. Antidepressant DERP Summary Review (pages 130-155)
Dr. Verhulst presented the summary review and recommendation:

1. Due to clinical concerns with the Initial Pediatric SSRI Antidepressant-Daily Dose Limit PA that has not yet been implemented, evaluate for potential intervention (possibly education, retro-DUR, or case management focused) to be brought back to the committee and implemented instead of a PA.

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

VII. EXECUTIVE SESSION

VIII. RECONVENE FOR PUBLIC RECOMMENDATIONS * After executive session

A. Multiple Sclerosis Class Update (pages 94 - 129)
*__ACTION:__ No changes to the PMPDP
Motion, 2nd, All in Favor. Approved.
B. Antidepressant DERP Summary Review (pages 130 - 155)
*__ACTION:__ No changes to the PMPDP.
Motion, 2nd, All in Favor. Approved.

VIIII. ADJOURN

Trade Name (generic)

Noctiva™ (desmopressin acetate) nasal spray, 0.83 mcg and 1.66 mcg

Indications

- Desmopressin nasal spray is indicated for treating nocturia due to nocturnal polyuria in adults who awaken ≥2 times nightly to void. This formulation of desmopressin has not been studied in patients younger than 50 years of age.

Dosage

- Patients <65 years old who are not at increased risk for hyponatremia: One spray of 1.66 mcg in either nostril nightly about 30 minutes before bedtime
- Patients <65 years old at risk of hyponatremia or ≥65 years old: One spray of 0.83 mcg nightly (if needed, may step-up to 1.66 mcg spray after ≥7 days if serum sodium still normal)

Background

- Desmopressin, a synthetic analog of vasopressin and selective V2 receptor agonist, stimulates water re-absorption in the kidneys, which leads to reduced urine production.

Efficacy

The FDA approved desmopressin acetate nasal spray based on two 12-week randomized, double-blind, placebo-controlled, multi-center, phase 3 trials in adults 50 to 90 years old with nocturia. The mean age was 67 years. Included patients had a six-month history of an average of ≥2 nocturic episodes per night at baseline and ≥13 documented nocturia episodes over 6 nights during screening. Most patients were Caucasian (79%) males (57%). Patients with nocturia (n=1337) were randomized to receive either desmopressin 1.66 mcg or 0.83 mcg or placebo. Results of post-hoc subgroup analysis of patients with nocturia due to nocturnal polyuria for the two co-primary efficacy endpoints were as follows:[1]

	Desmopressin 1.66 mcg		Desmopressin 0.83 mcg		Placebo	
Co-primary endpoints (from baseline to Week 12):	Trial 1 (n=199)	Trial 2 (n=143)	Trial 1 (n=209)	Trial 2 (n=145)	Trial 1 (n=204)	Trial 2 (n=145)
Change in mean # of nocturic episodes/night *(baseline mean #: 3.2-3.4)*	-1.5	-1.5	-1.5	-1.4	-1.2	-1.1
difference from placebo (95% CI)	-0.3 (-0.5 to -0.1)	-0.4 (-0.6 to -0.2)	-0.3 (-0.4 to -0.0)	-0.3 (-0.5 to -0.1)	--	--
% patients with ≥50% reduction in mean # of nocturia episodes/night	47%	49%	35%	41%	27%	29%
difference from placebo (95% CI)	21% (12 to 30)	20% (9 to 31)	8% (**NS**)	12% (1 to 23)	--	--

Safety

Black box warning: Desmopressin can cause hyponatremia (life-threatening if severe) and is contraindicated in patients at risk for severe hyponatremia; confirm serum sodium is normal before starting or resuming desmopressin; measure serum sodium ≤7 days and about 1 month after therapy initiation or dose increases, and periodically thereafter and more often in patients ≥65 years old or at risk for hyponatremia; consider temporarily or permanently discontinuing desmopressin if hyponatremia occurs.
Common adverse reactions: Nasal discomfort, nasal congestion, nasopharyngitis, sneezing, hypertension/blood pressure increase, back pain, epistaxis, bronchitis, dizziness
Contraindications: Current/history of hyponatremia; polydipsia; primary nocturnal enuresis; use with loop diuretics or systemic or inhaled glucocorticoids; eGFR <50 mL/min/1.73 m^2; syndrome of inappropriate antidiuretic hormone secretion; use during illness that can cause fluid or electrolyte imbalance; NYHA Class II-IV CHF; uncontrolled hypertension
Warnings and precautions: Not recommended in patients at risk of increased intracranial pressure or history of urinary retention; monitor volume status in patients with NYHA Class I CHF; discontinue in patients with concurrent nasal conditions that may increase absorption, until resolved; monitor serum sodium more frequently when desmopressin is used with drugs that may cause water retention and increased risk for hyponatremia; moderate fluid intake in the evening and night-time to decrease the risk of hyponatremia
Avoid use: in pregnancy; in pediatric patients; with other intranasal drugs

Evidence Gaps/Limitations

No additional studies found to support evidence for use in the treatment of Oregon Health Plan (OHP) funded conditions or co-morbidities.

Recommendation

Restrict use for OHP-funded conditions through Prior Authorization.

References

1. Noctiva (desmopressin) [Prescribing Information]. Milford, PA: Serenity Pharmaceuticals, LLC, March 2017.
2. FDA Center for Drug Evaluation and Research. Summary Review. Application Number: 201656. Available at: https://www.accessdata.fda.gov/scripts/cder/daf/. Accessed 3/19/3017

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Drug Class Literature Scan: Asthma and COPD Maintenance Medications

Date of Review: November 2017

Date of Last Review: September 2016
Literature Search: 06/01/16 – 09/01/17

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

Conclusions:

- Since the last review, the following evidence has been identified: 3 new guidelines[1–3], 5 new systematic reviews and meta-analyses[4–8], 6 new randomized-controlled studies[9–14], 4 new formulations[15–18] and 2 new indications[19,20]. Important indicators of pharmacological efficacy for asthma and COPD are mortality benefits, hospitalizations, exacerbation, exercise tolerance, symptoms and quality of life. There is no new evidence that has demonstrated a mortality benefit of pharmacotherapy in asthma or COPD patients. The surrogate endpoint of change in FEV_1 is often used in clinical trials to demonstrate efficacy; however, measurements do not always correlate with clinical relevant outcomes. A change in FEV_1 of 100-140 ml is suggested as a minimal clinically relevant change.
- New asthma management guidelines and recommendations by the National Institute for Health and Care Excellence (NICE), 2017 Global Initiative for Chronic Obstructive Lung Disease (GOLD) and European Respiratory Society/American Thoracic Society (ERS/ATS), in addition to the five high-quality systematic reviews, support our current preferred drug list (PDL) and prior authorization (PA) criteria.[1–3]

ASTHMA

- A high-quality systematic review and meta-analysis found moderate evidence that adding tiotropium to long-acting beta-agonist/inhaled corticosteroid (LABA/ICS) resulted in fewer exacerbations requiring oral corticosteroids compared to LABA/ICS in adult patients with severe asthma; however, the confidence intervals do not rule out that there may be no difference between the groups (OR 0.76; 95% CI, 0.57 to 1.02).[4] There was no significant difference in the number of patients with an exacerbation requiring hospital admission based on an incidence of 2.5% in patients taking tiotropium + LABA/ICS and an incidence of 4.3% in the LABA/ICS group (risk difference -0.01; 95%CI, -0.04 to 0.01).
- A high quality systematic review and meta-analysis compared increased ICS doses and stable ICS doses in children and adult patients with chronic asthma experiencing an exacerbation and found moderate evidence of similar rates of treatment failure (need for oral corticosteroids), odds ratio (OR) 0.89 (95% confidence interval [CI], 0.68 to 1.18).[5] The risk of unscheduled physician visits were similar between treatment strategies, OR 0.96 (95% CI, 0.66 to 1.41), suggesting no clear benefit of either treatment based on low quality of evidence. The incidence of unscheduled acute care, emergency department (ED) visit or hospital admission was 18 per 1000 patients for both groups (OR 0.98; 95% CI, 0.24 to 3.98).[5]

CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

- Studies in patients with COPD taking LABA/ICS + tiotropium compared to tiotropium + placebo for at least 6 months were included in a high-quality review. The systematic review and meta-analysis found moderate evidence, based off of two studies with low risk of bias, that mortality occurred in 7 patients taking

combination therapy compared to 4 patients taking tiotropium + placebo (OR 1.80; 95% CI, 0.55 to 5.91). Wide confidence intervals prevent meaningful conclusions. Exacerbations were not analyzed due to a high degree of heterogeneity.[6]

- Long-acting muscarinic antagonists+long-acting beta-agonists (LAMA+LABA) were compared to LABA+ICS in patients with moderate to severe, stable COPD in a high quality systematic review and meta-analysis. Low quality evidence found LABA+LAMA to have less risk of exacerbations compared to LABA+ICS in trials lasting up to 52 weeks (ARR=3%/NNT=33; OR 0.82; 95% CI, 0.70 to 0.96; P=0.01). Pneumonia events occurred 61 times in patients treated with LABA+LAMA compared to 109 events in patients treated with LABA+ICS (ARR=1.2%/number needed to harm [NNH]=83) (low quality of evidence). [7]
- A fair quality, randomized, placebo-controlled study in patients with moderate COPD and an increased risk of cardiovascular disease found no effect of the combination of fluticasone furoate 100mcg/vilanterol 25 mcg on all-cause mortality rates compared to placebo (hazard ratio [HR] 0.88 (95%CI, 0.74 to 1.04; P=0.137).[13]

NEW FORMULATIONS/APPROVALS

- Four new products were approved since the last review. These include fluticasone propionate (Armonair™ RespiClick®) and fluticasone propionate/salmeterol (AirDuo™ RespiClick®) which are copy products of current formulations and beclomethasone dipropionate HFA (Qvar® Redihaler™), which will replace the current Qvar® formulation.[15,16,18] A fourth new product is a 3-drug combination of fluticasone furoate, umeclidinium, and vilanterol (Trelegy Ellipta) which is approved for patients with COPD.[17]
- Tiotropium (Spiriva® Respimat®) received approval for treatment of long-term, once-daily, maintenance treatment of asthma in patients 6 years and older and budesonide and formoterol (Symbicort®) received an indication for maintenance treatment of airflow obstruction and exacerbations in patients with COPD.[19,20]
- The evidence in this scan has high applicability to the Medicaid population. The highest prevalence of COPD is in patients 60 years and older which is older than the average Medicaid patient. No sub-group analyses were available for data specific to Medicaid patients.

Recommendations:

- Recommend no changes to the PDL for asthma and COPD maintenance drugs based on efficacy data.
- Recommend keeping new formulations as non-preferred drugs and subject to PA criteria with corresponding changes to the LAMA/LABA PA criteria to accommodate Trelegy Ellipta based on evidence.
- Recommend removing the coverage of uncomplicated chronic bronchitis from the ICS, LABA, LABA/ICS and LAMA/LABA PA criteria as this is no longer a funded diagnosis.
- No further review or research is needed at this time. Evaluate comparative drug costs in executive session.

Previous 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]

Previous Recommendations:

- The Committee agreed that no further research is needed at this time and recommended no changes to the PMPDP based on the clinical evidence. The Committee recommended continuation of the current clinical PA criteria after amending to add “without COPD” to #3 in the LAMA/LABA criteria. After

comparative cost consideration in executive session the Committee recommended making Ipratropium/Albuterol (Combivent Respimat®) non-preferred while grandfathering current users for 6 months and to make Ventolin® HFA Preferred on the PMPDP.

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), the Cochrane Collaboration, 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:

ASTHMA

Cochrane – LAMA Added to Combination LABA and ICS versus LABA/ICS for Adults with Asthma
In adults with asthma, the efficacy of adding a LAMA (tiotropium) to LABA/ICS was studied in a systematic review and meta-analysis.[4] Four double-blind studies lasting at least 12 weeks in duration were included. Patients enrolled in the trials were taking a LABA/ICS and had a mean FEV_1 of 55% of their predicted values, suggesting severe asthma.

Adding tiotropium to LABA/ICS resulted in an exacerbation requiring oral corticosteroids in 27% of patients compared to 33% in patients taking LABA/ICS (OR 0.76; 95% CI, 0.57 to 1.02) over 48 weeks, based on moderate evidence.[4] Imprecision in the effect and wide confidence intervals suggest that no difference between therapies could still exist. There was high quality evidence that there was no clinically significant difference between the quality of life scores, measured by at least a 0.5 difference on the Asthma Quality of Life Questionnaire (AQLA) 1 to 7 point scale, between LABA/ICS and the addition of tiotropium to LABA/ICS, mean score of 5.116 and 5.03, respectively.[4] There was imprecision in the results of risk of serious adverse events when LAMA was added to LABA/ICS and therefore no conclusions could be determined (low-quality evidence). Lung function, measured by trough FEV_1, was 0.07 L higher compared to LABA/ICS, 0.08 L and 0.15 L, respectively. There was insufficient data to determine the effect of LAMA added to LABA/ICS compared LABA/ICS on frequency of hospital admissions.

Cochrane – Increased versus Stable Doses of Inhaled Corticosteroids for Exacerbations of Chronic Asthma in Adults and Children
The effect of two ICS dosing strategies were compared in the management of exacerbations in children and adults.[5] Eight randomized trials comparing increased versus stable doses of ICS studied in patients managing exacerbations at home were included. Children and adults with persistent asthma who were receiving

maintenance ICS were included. Patients (n=1669) had mild to moderate asthma. Studies were found to be at low risk of bias. Seven of the eight studies followed patients for 6-12 months.

Outcomes studied were odds of treatment failure (need for oral corticosteroids), risk of unscheduled physician visits, unscheduled acute care (ED visits or hospital admission), duration of exacerbation and serious adverse events. The odds of treatment failure were similar between patients with increased ICS doses and stable ICS doses with an OR of 0.89 (95% CI, 0.68 to 1.18) (moderate quality evidence).[5] Treatment failure occurred 752 times in patients taking an increased dose of ICS compared to 768 events in patients taking stable ICS doses. Low quality evidence found increased doses of ICS did not reduce the risk of unscheduled physician visits (OR 0.96; 95% CI, 0.66 to 1.41) or acute visits (peto OR 0.98; 95% CI 0.24 to 3.98) compared to stable doses of ICS.[5] The peto OR is an alternative way of pooling data instead of using the traditional Mantel-Haenszel method. The peto OR is appropriate in many scenarios except when the control and treatment groups are significantly different in size, which may introduce bias. The evidence for durations of exacerbations was rated as moderate quality but due to the limitations of only one study providing data, there was insufficient evidence to draw conclusions between groups. Serious and non-serious adverse events were similar between groups based on moderate quality of evidence. Subgroup analyses on the impact of age, time to treatment initiation, doses used, smoking history and the fold increase of ICS on magnitude of effect were not done due to lack of studies.

Cochrane – Vilanterol and Fluticasone Furoate for Asthma

A systematic review and meta-analysis was done to compare the effect of vilanterol (VI) and fluticasone furoate (FF) compared to placebo or other ICS and/or LABA on the outcomes of acute exacerbations (hospital admissions or treatment with oral corticosteroids), health-related quality of life (HRQL) and severe adverse events in children and adults with chronic asthma.[8] Fourteen good-quality studies lasting between two and 78 weeks and enrolling 6641 patients were included. Doses studied were VI and FF 100/25 mcg (7 studies) and three studies of VI and FF 200/25 mcg. Comparators were placebo, FF 25 mcg, VI 100 mcg, fluticasone propionate (FP) 500 mcg twice-daily, fluticasone propionate/salmeterol (FP/SAL) 250/50 mcg twice-daily, FP 250/25 mcg twice-daily and FP/SAL 500/50.

One study found the HRQL to be improved with the use of VI/FF 100/25 mcg compared to placebo based on moderate evidence (mean difference [MD] 0.30; 95% CI, 0.14 to 0.46).[8] FEV_1 was improved with VI/FF compared to placebo with a MD of 0.17 (95% CI, 0.09 to 0.26) based on 2 studies (n= 393) with moderate quality of evidence. Peak expiratory flow was higher in VI/FF compared to placebo based on moderate quality evidence from one study (MD 33.30 L/min; 95% CI, 26.59 to 40.01). Asthma symptoms were lower for VI/FF compared to placebo based on moderate evidence (MD 17.90; 95% CI, 11.95 to 23.85).[8] Only very low quality of evidence was available for the outcomes of exacerbations and serious adverse events (results not estimable). There was insufficient data to determine the difference in efficacy outcomes between VI/FF and FP/SAL.

In conclusion, VI/FF was more effective than placebo for outcomes of lung function and HRQL based on moderate evidence. Evidence on active treatment comparisons was insufficient to draw conclusions.[8]

COPD

Cochrane – Combination of ICS and LABA in Addition to Tiotropium versus Tiotropium or LABA/ICS for COPD

A systematic review and meta-analysis was done to compare the effects of two maintenance treatment regimens in the management of COPD.[6] Two different regimens were compared. One comparison was between tiotropium + LABA/ICS (combined therapy) and tiotropium and the other comparison studied tiotropium

+ LABA/ICS (combined therapy) and LABA/ICS. Studied outcomes were exacerbations, symptoms, quality of life and lung function. Six randomized trials lasting at least three months were identified. Only one of the six studies compared combined therapy to LABA/ICS.

The analysis of two studies at low risk of bias found that there were no differences in mortality between combined therapy compared to tiotropium (OR 1.80; 95% CI, 0.55 to 5.91) based on moderate quality evidence.[6] There were 41 hospitalizations in patients taking combined therapy compared to tiotropium which was associated with 50 events, suggesting no difference between groups with an OR of 0.84 (95% CI, 0.53 to 1.33) (low quality evidence). Analysis of exacerbations could not be analyzed due to a high degree of heterogeneity. The SGRQ was used to measure quality of life and was found to be improved in patients taking combined therapy compared to tiotropium with a MD of -3.46 (95% CI, -5.05 to -1.87) based on four studies lasting up to six months based on low quality of evidence.[6] Lung function was found to be improved with combination therapy but changes were not clinically significant. There was insufficient evidence for exercise tolerance. Analysis of adverse events found no difference between groups for serious adverse events, adverse events and pneumonia.

The one study that evaluated combination therapy compared to LABA/ICS was underpowered and therefore no conclusions were made.[6]

Cochrane – LAMA + LABA versus LABA + ICS for stable COPD

In patients with COPD, a systematic review and meta-analysis compared the effect of LAMA+LABA to LABA+ICS.[7] Patients with moderate to severe COPD and no recent exacerbations in studies lasting at least one month were identified in 11 studies. The exception was one large trial (representing 37% of the participants) which enrolled COPD patients with recent exacerbations. Patients were diagnosed with the following grades of GOLD: Category B (5 studies), Category D (1 study), Category A/B (2 studies) and any category (3 studies). Ten studies were industry funded. Study follow-up was from 6-52 weeks.

The outcome results of the meta-analysis comparison of LAMA+LABA to LABA+ICS are presented in Table 1. Patients taking LAMA + LABA were found to have 1562 exacerbations compared to 1683 events in patients taking LABA/ICS (ARR=3%/NNT=33 studies lasting up to 52 weeks). Improvements in trough FEV_1 were higher with LAMA/LABA compared to LABA/ICS.[7] Quality of life scores were clinically improved for LAMA + LABA, as demonstrated by a 4 point or greater improvement in SGRQ, with LAMA + LABA compared to LABA + ICS. Risk of pneumonia was also found to be lower with LABA + LAMA compared to LABA + ICS (ARR=1.2%/NNH=83).

Table 1. Pooled Results of Meta-analysis Comparison Between LAMA + LABA and LABA + ICS[7]

Treatment	Comparator	Outcome	Results	Evidence Quality
LAMA+LABA	LABA+ICS	Exacerbations	OR 0.82 (95% CI, 0.70 to 0.96; P=0.01)	Low
		Serious Adverse Events	OR 0.91 (95% CI, 0.79 to 1.05, P = 0.18	Moderate
		SGRQ	MD -1.22 (95% CI, -2.52 to 0.07, P = 0.06)	Low
		Trough FEV_1 change from baseline	MD 0.08 L (95% CI, 0.06 to 0.09, P < 0.0001)	Moderate
		Pneumonia	OR 0.57 (95% CI, 0.42 to 0.79, P = 0.0006)	Low
		All-cause death	OR 1.01 (95% CI, 0.61 to 1.67, P = 0.88)	Low
		SGRQ change from baseline of 4 points or greater	OR 1.25 (95% CI, 1.09 to 1.44, P = 0.002)	Moderate

Abbreviations: CI – confidence interval; ICS – inhaled corticosteroid; LABA – long-acting beta-agonist; LAMA – long-acting muscarinic antagonist; MD – mean difference: OR – odds ratio; SGRQ – St. George's Respiratory Questionnaire

New Guidelines:

NICE – Asthma Management

A draft guidance on the treatment of asthma was published by NICE in 2016.[1] A pharmacological treatment pathway outlines the treatment recommendations based on a review of the evidence. Treatment pathways were divided up by age: adults (over 16 years), children and young people (5-16 years of age) and children (under 5 years of age).

Recommendations

Initial Therapy[1]

1. In *adults* SABA should be offered as reliever therapy with newly diagnosed asthma. SABA treatment should be used with maintenance therapy regimens except maintenance and reliever therapy (MART) regimens.
2. Newly diagnosed *children and young people* should receive SABA as reliever therapy. SABA treatment should be used with maintenance therapy regimens except MART regimens.
3. In *children under 5 years of age* with suspected asthma, SABA should be offered as reliever therapy. SABA should be used with all maintenance therapy regimens.

The above recommendations were consensus based recommendations due to insufficient clinical evidence.

First-*line Prevention Therapy in Patients with Poor Asthma Control*[1]

1. Low-dose ICS should be offered as a first-line maintenance therapy for *adults* with uncontrolled asthma on SABA.
2. *Children and young people* should be offered low-dose ICS as the first-line maintenance therapy that is uncontrolled on SABA alone.
3. An 8-week trial of pediatric moderate dose ICS should be considered in *children under 5* with suspected asthma that is uncontrolled with SABA. Treatment should be reevaluated after 8-weeks.
    a. If symptoms did not improve consider an alternative diagnosis.
    b. If symptoms initially resolved but returned within 4 weeks, consider starting a pediatric low dose ICS for first-line maintenance therapy.
    c. If symptoms returned after 4 weeks of stopping ICS then restart 8-week trial of pediatric moderate dose ICS.
    d. Asthma dose should be confirmed once the child is old enough for testing.

The above recommendations are based on low to very quality of evidence due to bias and imprecision. The exception was evidence for adults which had moderate quality of evidence for reliever use, lung function and quality of life outcomes. There was moderate quality evidence for children and young people for FEV_1, reliever medication and AQLQ. High quality evidence was used for the outcomes of reliever use in children under the age of 5. Lack of evidence in children under 5 for most outcomes caused reliance on consensus and experience driven recommendations.

<u>Escalating Pharmacological Treatment in Patients Poorly Controlled on Low-dose ICS</u>[1]

1. *Adults* with uncontrolled asthma on low-dose ICS as maintenance therapy should be offered a leukotriene receptor antagonist (LTRA) in addition to ICS.
2. In *adults* that remained uncontrolled on combination therapy of low-dose ICS and LTRA, a LABA should be added to ICS and consider the following for LTRA treatment:

a. Consider patient preference on continuing LTRA
b. Evaluate patient response to LTRA

3. Consider a LTRA in combination with low-dose ICS in *children and young people* with uncontrolled asthma on pediatric low-dose ICS maintenance therapy.
4. In *children and young people* who have uncontrolled asthma on pediatric low-dose ICS and an LTRA as maintenance treatment, stop the LTRA and consider adding a LABA to ICS.
5. If *patients younger than 5* are suspected of having uncontrolled asthma on a pediatric low-dose ICS, consider a LTRA in combination with ICS.
6. If *patients younger than 5* continue to have uncontrolled asthma on the above, stop the LTRA refer the child to an asthma specialist.

The evidence for the above recommendations ranged from high quality to very low quality. There was insufficient evidence in children under 5 and limited data in children and young people.

Comparison of ICS + LABA as Preventer and Reliever Therapy Compared to ICS + LABA as Preventer and SABA as Reliever Therapy[1]

1. In *adult patients* who are uncontrolled on low-dose ICS and a LABA, with or without an LTRA, as maintenance therapy, suggest changing the therapy to a MART regimen with low-dose maintenance ICS.
2. If the *adult patient* remains uncontrolled on the above regimen, with or without an LTRA, consider increasing the ICS to a moderate maintenance dose. The patient can continue on the MART regimen or change to a fixed-dose ICS and LABA with a SABA reliever.
3. If asthma is uncontrolled in *children and young people* on pediatric low-dose ICS and a LABA, consider changing them to a MART regimen with pediatric low-dose maintenance ICS.
4. If *children or young people* continue to have uncontrolled asthma on the above, consider increasing the ICS to a pediatric moderate maintenance dose. The patient can continue on MART or change to a fixed dose ICS and LABA with SABA reliever therapy.

The majority of evidence used for the previous recommendation was of moderate or high quality.

Therapy for Patients Who Remain Uncontrolled on Optimal Preventer Therapy Beyond Low-dose ICS[1]

1. In *adults* who are uncontrolled on moderate maintenance ICS with LABA, either as MART or fixed dose regimen, and with or without LTRA, recommend increasing the ICS dose to high maintenance. This should be given as part of a fixed-dose regimen with a SABA reliever.
    a. NICE found low quality of evidence that the addition of LAMA to moderate-strength ICS compared to moderate-strength ICS to have a clinically important benefit on exacerbations based on 1 study and moderate quality evidence of benefit in severe exacerbations. There were no clinically important differences found for quality of life, asthma control, or lung function (moderate to high quality evidence).
2. In *children and young people* with uncontrolled asthma despite pediatric moderate maintenance ICS dose with LABA, either as MART or a fixed dose regimen, consider increasing the ICS to a pediatric high maintenance dose. Recommend in conjunction with a fixed-dose regimen with a SABA.
    a. The quality of evidence for this recommendation ranged from very low to high. The majority of the evidence was of low or moderate quality.

Therapy for children, young people and adults with asthma on ICS preventer therapy or requiring ICS

1. Recommend daily versus intermittent inhaled ICS, if required, to patients with asthma who require ICS maintenance treatment.
    a. Evidence for this recommendation was derived from mostly low or very low quality evidence. High quality evidence was available for treatment of adults but with only one study contributing to each outcome.

GOLD – COPD Guidelines

The GOLD annual update was released in January 2017.[2] Evidence was reviewed and assigned an evidence grade (Table 2). New recommendations pertaining to the assessment and treatment of COPD include refinement of the ABCD tool to rely on respiratory symptoms and exacerbations alone to determine the ABCD category. In patients with stable COPD, assessment of symptoms and risk of exacerbations is recommended to determine the pharmacological treatment approach. One of the changes to the recommendations is the inclusion of escalation and de-escalation strategies which are often required when caring for patients with COPD (Figure 1.).[2]

Table 2. Description of the Level of Evidence. [2]

Evidence Category	Sources of Evidence	Definition
A	• Randomized controlled trials (RCTs) • Rich body of high quality evidence without any significant limitation or bias	- Evidence is from endpoints of well-designed RCTs that provide consistent findings in the population for which the recommendation is made without any important limitations. - Requires high quality evidence from ≥2 clinical trials involving substantial number of subjects, or a single high quality RCT involving substantial numbers of patients without any bias.
B	• Randomized controlled trials (RCTs) with important limitations • Limited body of evidence	- Evidence is from RCTs that include only a limited number of patients, post hoc or subgroup analyses of RCTs or meta-analyses of RCTs. - Also pertains when few RCTs exist, or important limitations are evident (methodological flaws, small numbers, short duration, undertaken in a population that differs from the target population of the recommendation or the results are somewhat inconsistent.
C	• Non-randomized trials • Observational studies	- Evidence is from outcomes of uncontrolled or non-randomized trials or from observational studies.
D	• Panel consensus judgement	- Provision of guidance is deemed valuable but clinical literature addressing the subject is insufficient. - Panel consensus is based on clinical experience or knowledge that does not meet the above stated criteria.

Evidence for Treatment Selection

The management of stable COPD is accomplished through short- and long-acting maintenance therapies. No pharmacological treatment has demonstrated a reduction in the risk of long-term decline in lung function in patients with COPD. Short-acting and long-acting bronchodilator therapy is recommended for patients with COPD. The following recommendations are based on level A evidence for the treatment of stable COPD.[2]

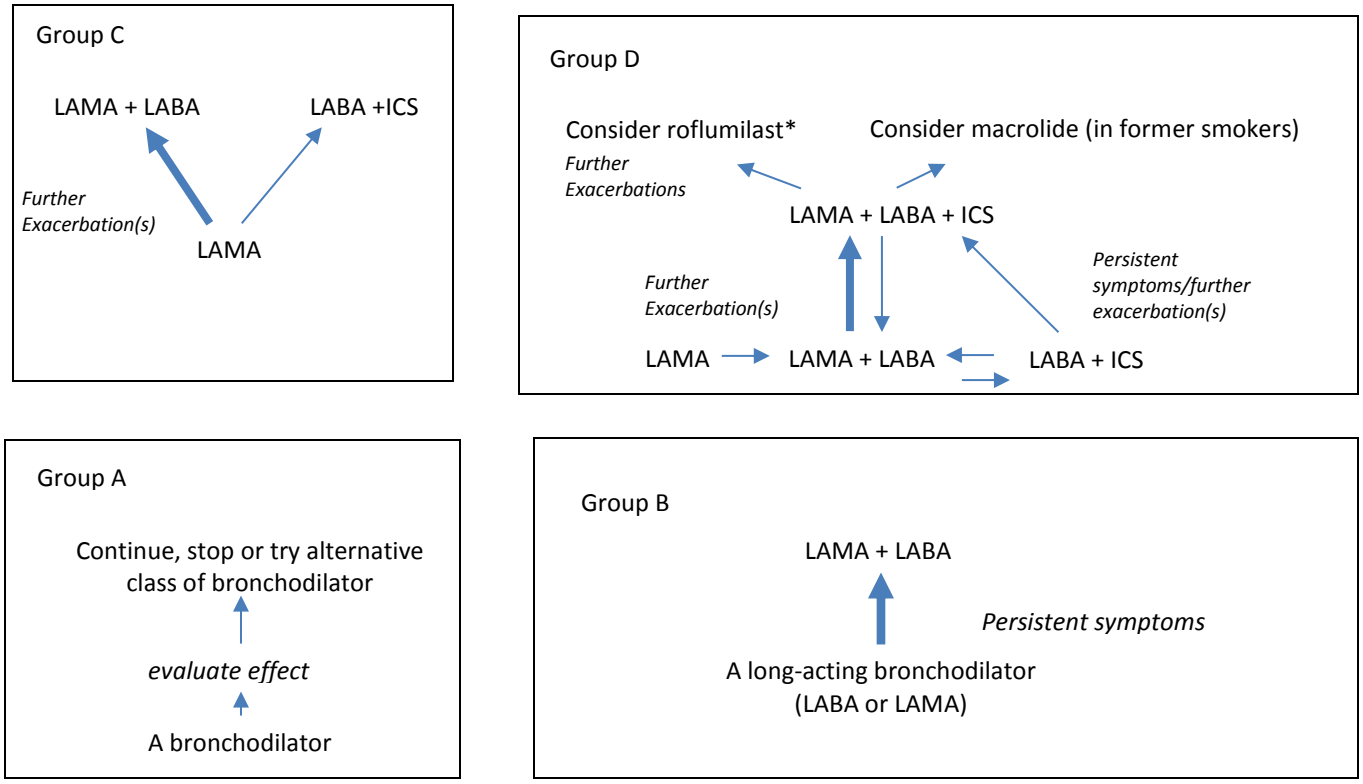
- Inhaled bronchodilators are used for symptom management and given on a regular basis in many patients to prevent or reduce symptoms.
- Improvement in FEV_1 and symptoms has been demonstrated with regular and as-needed use of SABA and SAMA.
- FEV_1 and symptom improvement is greater with combination therapy of SABA and SAMA compared to either medication alone.
- Lung function, dyspnea, health status, and reduced exacerbation rates have been shown to significantly improve with LAMAs and LABAs.
- Combination of LAMA and LABA is more effective than monotherapy at increasing FEV_1 and reducing symptoms.

LAMAs have been shown to reduce exacerbation risk (Evidence A) and decrease hospitalizations (Evidence B) more than LABAs. Combinations of LABA and LAMAs have been shown to reduce exacerbations more than monotherapy of either component (Evidence B) and more than ICS/LABA (Evidence B).[2] Tiotropium has been shown to improve the effectiveness of pulmonary rehabilitation by increasing exercise performance (Evidence B). Modest symptomatic benefit has been demonstrated with theophylline in patients with stable COPD based on level B evidence and bronchodilation based on level A evidence.

The effect of ICS on COPD outcomes has lacked precision. GOLD guidelines recommend combination ICS/LABA compared to the individual components based on improved lung function and health status and exacerbation reduction in patients with exacerbations and moderate to severe COPD (Evidence A).[2] Regular use of ICS has been shown to increase the risk of pneumonia in patient with COPD especially in patients with severe COPD (Evidence A). Improvement in lung function, symptoms and health status have been demonstrated with triple therapy with ICS/LAMA/LABA (Evidence A) compared to ICS/LABA or LAMA monotherapy. Reduced risk of exacerbations was found with triple therapy ICS/LAMA/LABA compared to ICS/LABA or LAMA monotherapy (Evidence B).

The GOLD guidelines have some methodological issues that limit interpretation and application of the clinical evidence. The recommendations are given an evidence grade based on the source of the evidence but strength of the evidence is not provided. There is no objective determinant for the quantification of symptoms and exacerbations to determine escalation and de-escalation of therapy. While funding of the guideline comes from sales of the GOLD documents, a statement of any conflicts of interest with committee members was not available.

Figure 1. Treatment Algorithms by GOLD Grade[2]



* If FEV_1 < 50% predicated and patient has chronic bronchitis
Thick arrows = preferred treatment

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Date: November 2017

ERS/ATS – Prevention of COPD Exacerbations

The ERS/ATS published guidelines on preventing COPD exacerbations in 2017.[3] Literature was systematically reviewed and the evidence was graded using the GRADE approach. Recommendations pertaining to the role of maintenance medications in the prevention of COPD exacerbations were as follows:

1. In patients with moderate to severe airflow obstruction and a history of one or more COPD exacerbation during the previous year, the guidelines recommend LAMA over LABA monotherapy to prevent future exacerbations (strong recommendation, moderate quality of evidence).

The recommendation was based off of meta-analysis data that found a risk of a moderate to severe COPD exacerbation in 30.9% of LAMA treated patients compared 34.6% of LABA treated (RR 0.89; 95% CI, 0.85 to 0.94).[3] One trial found the risk of hospitalization to be lower with LAMA compared to LABA, 7.1% versus 9.2%, respectively (RR 0.77; 95%CI, 0.66 to 0.90). There were no significant differences in adverse events between LAMA and LABA treated patients.

New Formulations/Indications:

Beclomethasone: The inhaled corticosteroid beclomethasone dipropionate HFA (Qvar® Redihaler™) was approved for the maintenance treatment of asthma as prophylactic therapy in patients 4 years of age and older at a dose of 40 or 80 mcg twice daily, which is to replace the current formulation of Qvar® inhaler.[18] Approval was based off of one 12-week, randomized, placebo-controlled, parallel-group study in patients 4-11 years of age (n=568) with persistent symptomatic asthma despite treatment with non-corticosteroid or low dose ICS (with or without LABA). Beclomethasone Redihaler 40 or 80 mcg, beclomethasone MDI 40 or 80 mcg or placebo was given as one inhalation twice daily. Patients 4-5 years old who were unable to perform spirometry were included in the safety population only. The primary endpoint, change from baseline in trough percent predicted FEV_1 area under the effect curve (AUEC) (0-12 weeks) was not statistically different between beclomethasone and placebo. Change in weekly average of daily morning peak expiratory flow (PEF, L/min) over the 12-week period was 11.3 (95% CI, 5.58 to 17.06) for beclomethasone 80 mcg/day and 8.5 (95% CI, 2.71 to 14.24) for beclomethasone 180 mcg/day which was nominally significant.[18]

Fluticasone propionate and fluticasone propionate and salmeterol: A copy of Flovent Diskus (fluticasone) and Advair (fluticasone/salmeterol) were approved by the FDA in January 2017 to be marketed by Teva Pharmaceuticals called Armonair™ RespiClick® and AirDuo™ RespiClick®, respectively.[15,16] Both products were studied together for the approval of treatment of asthma in patients aged 12 years and older. Recommended dosing for fluticasone is based on prior asthma therapy and available via one inhalation twice daily in concentrations of 55 mcg, 113 mcg and 232 mcg. The combination fluticasone/salmeterol combination is available as one inhalation twice daily in 3 concentrations: 55/14 mcg, 113/14 mcg, or 232/14 mcg.

Approval for both products was based on 2 phase 3, double-blind, parallel-group, 12-week studies in adolescents and adults with asthma not controlled on their current asthma regimen. Studies compared fluticasone/salmeterol 55/14 mcg and 113/14 mcg (1 inhalation twice daily) to fluticasone 55 mcg and 113 mcg and placebo in the first study. The second study compared fluticasone propionate 113 mcg and 232 mcg (1 inhalation twice daily) to fluticasone/salmeterol 113/14 mcg and 232/14 mcg (1 inhalation twice daily) and placebo. The primary endpoint was change in baseline trough FEV_1 at week 12 and standardized baseline-adjusted FEV_1 AUC 0-12h at week 12 for a subset of patients with post-dose serial spirometry.

In the first study the least squares (LS) mean change of 0.319 L was seen with fluticasone/salmeterol 55/14 mcg, LS mean change of 0.315 L with fluticasone/salmeterol 113/14 mcg and LS mean change of 0.175 L with fluticasone 55 mcg and a LS mean change of 0.204 L for fluticasone 113 mcg. The mean differences are presented in Table 3. The results of the second study were similar to study 1 and are presented in Table 4.

Table 3. Mean Difference Between Treatments in Study 1 based on the Primary Endpoint of Change in Trough FEV_1 at Week 12.[15,16]

Treatment	Comparator	Estimated Mean Difference
Fluticasone/salmeterol 55/14 mcg	Placebo	0.266 L (95% CI, 0.172 to 0.360)
Fluticasone 55 mcg	Placebo	0.119 L (95% CI, 0.025 to 0.212)*
Fluticasone/salmeterol 55/14 mcg	Fluticasone 55 mcg	0.147 (95% CI, 0.053 to 0.242)*
Fluticasone/salmeterol 113/14 mcg	Placebo	0.262 L (95% CI, 0.168 to 0.356)
Fluticasone 113 mcg	Placebo	0.151 L (95% CI, 0.057 to 0.244)*
Fluticasone/salmeterol 113/14 mcg	Fluticasone 113 mcg	0.111 L (95% CI, 0.017 to 0.206)*

* Results statistically significant (p-value not provided) for treatment

Table 4. Mean Difference Between Treatments in Study 2 based on the Primary Endpoint of Change in Trough FEV_1 at Week 12.[15,16]

Treatment	Comparator	Estimated Mean Difference
Fluticasone/salmeterol 113/14 mcg	Placebo	0.274 L (95% CI, 0.189 to 0.360)
Fluticasone 113 mcg	Placebo	0.123 L (95% CI, 0.038 to 0.208)*
Fluticasone/salmeterol 113/14 mcg	Fluticasone 113 mcg	0.152 (95% CI, 0.066 to 0.237)*
Fluticasone/salmeterol 232/14 mcg	Placebo	0.276 L (95% CI, 0.191 to 0.361)
Fluticasone 232 mcg	Placebo	0.183 L (95% CI, 0.098 to 0.268)*
Fluticasone/salmeterol 232/14 mcg	Fluticasone 232 mcg	0.093 (95% CI, 0.009 to 0.178)*

* Results statistically significant (p-value not provided) for treatment

Tiotropium: A new indication was approved for tiotropium bromide (Spiriva® Respimat®) in early 2017 for the long-term, once-daily, maintenance treatment of asthma in patients 6 years and older.[20] The recommended dose is 2 inhalations of the 1.25 mcg dose once-daily. Approval of the use of tiotropium in pediatric patients was based on two double-blind, randomized, placebo-controlled studies lasting 12 and 48 weeks. Patients treated for 12-weeks had severe asthma and were using an ICS plus one or more controller medication. The 48-week study was in patients with moderate asthma and on at least an ICS for maintenance therapy. The primary outcome was change in pre-treatment baseline in peak FEV_1, 0-3 h. The mean age was 9 years, 68% were male, and 87% were Caucasian. The results for the studies were imprecise. The 12-week study found no significant difference between tiotropium 2.5 mcg and placebo with a mean difference of 0.04 L (95% CI, -0.03 to 0.10) at 12 weeks. In the 48-week study the primary endpoint was measured at week 24 and found a mean difference of 0.17 L (95% CI, 0.11 to 0.23) between tiotropium 2.5 mcg and placebo.

Budesonide and formoterol fumarate dehydrate: The combination ICS/LABA product of budesonide and formoterol (Symbicort®) received approval for the long-term maintenance treatment of asthma in patients 6 years of age and older.[19] This approval was based on one 12-week efficacy and safety study in patients 6 to less than 12 years of age. The study was a randomized, double-blind, multicenter study in 184 pediatric patients. The result of the primary efficacy endpoint, change from baseline in 1-hour post-dose FEV_1, was improved by 0.28 L in patients receiving budesonide/formoterol 80/4.5 mcg compared to a change of 0.17 L in patients receiving budesonide 80 mcg (MD 0.12 L; 95% CI, 0.03 to 0.20; p=0.006).

This combination also received an indication to support the use of budesonide/formoterol (B/F) to reduce exacerbations in patients with COPD.[19] Two, randomized, double-blind, placebo-controlled studies were used for evidence. In the first study patients were a mean age of 64 years with a mean post-bronchodilator percent predicted normal FEV_1 of48.7%. The study evaluated B/F 160/4.5 compared to formoterol 4.5, 2 inhalations twice daily for 6 months. Patients randomized to B/F 160/4.5 had an annual rate estimate of 0.94 exacerbations compared to formoterol which had 1.27 (rate ratio of 0.74; 95% CI, 0.61 to 0.91). In a second study comparing B/F 160/4.5 to formoterol 4.5 mcg, 2 inhalations twice daily, for 12 months the patients were a mean age of 63 years with a mean post-bronchodilator percent predicted normal FEV_1 of 37.8%. Patients treated with combination therapy had an annual rate estimate of exacerbations of 0.68 compared to 1.05 in the formoterol 4.5 mcg group (rate ratio 0.65; 95% CI, 0.53 to 0.80).

Fluticasone furoate, umeclidinium and vilanterol: A new 3-drug combination product, of previously reviewed therapies, was recently approved by the FDA. The fluticasone furoate, umeclidinium and vilanterol (FF/U/V) (Trelegy Ellipta) is indicated for the long-term, once-daily maintenance treatment for patients with COPD, including chronic bronchitis and/or emphysema, who are on a fixed-dose combination of fluticasone furoate and vilanterol for airflow obstruction and reducing exacerbations in whom additional treatment of airflow obstruction is desired or for patients already receiving umeclidinium and a fixed-dose combination of fluticasone furoate and vilanterol. Clinical studies found a difference of 124 ml increase in trough FEV_1 from baseline in patients receiving umeclidinium + FF/VI compared to patients receiving placebo + FF/VI in one study and a difference of 122 ml in a second study both lasting 12-weeks.

New FDA Safety Alerts:
No new safety updates.

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19. Symbicort Prescribing Information. AstraZeneca Pharmaceuticals LP, Wilmington, DE; 2017.

20. Spiriva Respimat Prescribing Information. Boehringer Ingelheim Pharmaceuticals, Inc. Ridgefield, CT; 2017.

Appendix 1: Current 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
INHALATION	PWD INHAL	UTIBRON NEOHALER	INDACATEROL/GLYCOPYRROLATE	N
INHALATION	MIST INHAL	BEVESPI AEROSPHERE	GLYCOPYRROLATE/FORMOTEROL	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

Miscellaneous Pulmonary Agents

ROUTE	FORMULATION	BRAND	GENERIC	PDL
ORAL	TAB CHEW	MONTELUKAST SODIUM	MONTELUKAST SODIUM	Y
ORAL	TAB CHEW	SINGULAIR	MONTELUKAST SODIUM	Y
ORAL	TABLET	MONTELUKAST SODIUM	MONTELUKAST SODIUM	Y
ORAL	TABLET	SINGULAIR	MONTELUKAST SODIUM	Y
ORAL	TABLET	DALIRESP	ROFLUMILAST	N
ORAL	GRAN PACK	MONTELUKAST SODIUM	MONTELUKAST SODIUM	N
ORAL	GRAN PACK	SINGULAIR	MONTELUKAST SODIUM	N
ORAL	TABLET	ACCOLATE	ZAFIRLUKAST	N
ORAL	TABLET	ZAFIRLUKAST	ZAFIRLUKAST	N
ORAL	TABLET	ZYFLO	ZILEUTON	N
ORAL	TBMP 12HR	ZYFLO CR	ZILEUTON	N

Appendix 2: New Comparative Clinical Trials

A total of 489 citations were manually reviewed from the initial literature search. After further review, 483 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining 6 trials are summarized in the table below. Full abstracts are included in **Appendix 3**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Stempel, et al[10] RCT, DB, PG	Fluticasone propionate + Salmeterol (100/50 mcg or 250/50 mcg) Vs. Fluticasone (100 or 200 mcg) 26 weeks	Children (4-11 years) with asthma requiring daily maintenance therapy and a history of asthma exacerbations N=6208	First serious asthma-related event (death, endotracheal intubation, or hospitalization)	Fluticasone/Salmeterol: 27 (0.9%) Fluticasone: 21 (0.7%) HR 1.28 (95% CI, 0.73 to 2.27) P=0.006 for non-inferiority
Hamelmann, et al[14] RCT, DB, PC, PG	Tiotropium 2.5 or 5.0 mcg * Vs. Placebo* * With ICS ± LRA 24 weeks	Adolescent patients (12-17 years) with moderate symptomatic asthma N=398	Peak $FEV_{1(0\text{-}3h)}$ Improvement at 24 weeks	Tiotropium 2.5 mcg: 484 mL Tiotropium 5.0 mcg: 524 mL Placebo: 350 mL Tiotropium 2.5 mcg vs. Placebo: 134 mL (95% CI, 34-234; P<0.01) Tiotropium 5.0 mcg vs. Placebo: 174 mL (95% CI, 76-272; P<0.001)
Vestbo, et al[13] (SUMMIT) RCT, DB, PC, PG	Fluticasone furoate 100 mcg Vs. Vilanterol 25 mcg Vs.	Adult patients (40-80 years) with moderate COPD and heightened CV risk N=16,485	All-cause mortality	Fluticasone furoate: 251 (6.1%) Vilanterol: 265 (6.4%) Combination Therapy: 246 (6.0%) Placebo: 275 (6.7%) Fluticasone vs. Placebo: HR 0.91 (95%CI, 0.77 to 1.08; P=0.284)

	Fluticasone furoate 100 mcg + Vilanterol 25 mcg Vs. Placebo * All given as one inhalation daily Median follow-up 1.8 years			Vilanterol vs. Placebo: HR 0.96 (95%CI, 0.81 to 1.14; P=0.655) Combination Therapy vs. Placebo: HR 0.88 (95%CI, 0.74 to 1.04; P=0.137)
Singh, et al[11] (TRILOGY) RCT, DB, PG	Beclomethasone dipropionate + formoterol fumarate + glycpyrronium bromide (BDP/FF/GB)* Vs. Beclomethasone dipropionate + formoterol fumarate (BDP/FF) * As a single inhaler 52 weeks	Adult patients 40 year and older with COPD, post-bronchodilator FEV_1 of less than 50%, one or more moderate-to-severe COPD exacerbation in the previous 12 months, COPD Assessment Test Score of 10 or more and Baseline Dyspnea Index focal score of 10 or less. N=1368	Three co-primary endpoints were pre-dose FEV_1, 2 h post-dose FEV_1 and Transition Dyspnea Index (TDI) focal score all measured at week 26	Pre-dose FEV_1: BDP/FF/GB: 0.082 L BDP/FF: 0.001 L MD 0.081 L (95% CI, 0.052 to 0.109; p<0.001) 2-h Post-dose FEV_1: BDP/FF/GB: 0.261 L BDP/FF: 0.145 L MD 0.117 : (0.086 to 0.147; p<0.001) Mean TDI Focal Scores*: BDP/FF/GB: 1.71 BDP/FF: 1.50 MD 0.21 (95% CI, -0.08 to 0.51; p=0.160)
Stempel, et al[12] (AUSTRI) RCT, DB, PG	Fluticasone + salmeterol Vs.	Adolescents and adults (12 and older) with persistent asthma and	First serious asthma-related event (death, endotracheal intubation, or hospitalization).	Fluticasone/Salmeterol: 36 events Fluticasone: 38 events HR 1.03 (95% CI, 0.64 to 1.66; P=0.003 for noninferiority)

	Fluticasone 26 weeks	history of severe asthma exacerbation within the last year but not previous month		
Wedzicha, et al[9] (FLAME) RCT, DB, DD, PG	Indacaterol 110 mcg + glycopyrronium 50 mcg once daily (I/G) Vs. Salmeterol 50 mcg + fluticasone 500 mcg twice daily (S/F) 52 weeks	Patients with a history of COPD and at least one exacerbation during the previous year N=3,362	Annual rate of COPD exacerbations	I/G: 3.59 S/F: 4.03 RR 0.89 (95% CI, 0.83 to 0.96; P=0.003 for noninferiority)

Abbreviations: CV – cardiovascular risk; DB – double-blind: DD – double-dummy; FEV_1- forced expiratory flow volume in one second; ICS – inhaled corticosteroid; LRA – leukotriene receptor antagonist; PC – placebo-controlled; PG – parallel group; RCT - randomized clinical trial.
*TDI – a score of 1 or more is considered the minimal clinically important difference.

Appendix 3: Abstracts of Comparative Clinical Trials

Safety of Adding Salmeterol to Fluticasone Propionate in Children with Asthma.
Stempel DA, Szefler SJ, Pedersen S, Zeiger RS, Yeakey AM, Lee LA, Liu AH, Mitchell H, Kral KM, Raphiou IH, Prillaman BA, Buaron KS, Yun Kirby S, Pascoe SJ; VESTRI Investigators.

BACKGROUND: Long-acting beta-agonists (LABAs) have been shown to increase the risk of asthma-related death among adults and the risk of asthma-related hospitalization among children. It is unknown whether the concomitant use of inhaled glucocorticoids with LABAs mitigates those risks. This trial prospectively evaluated the safety of the LABA salmeterol, added to fluticasone propionate, in a fixed-dose combination in children. METHODS: We randomly assigned, in a 1:1 ratio, children 4 to 11 years of age who required daily asthma medications and had a history of asthma exacerbations in the previous year to receive fluticasone propionate plus salmeterol or fluticasone alone for 26 weeks. The primary safety end point was the first serious asthma-related event (death, endotracheal intubation, or hospitalization), as assessed in a time-to-event analysis. The statistical design specified that noninferiority would be shown if the upper boundary of the 95% confidence interval of the hazard ratio for the primary safety end point was less than 2.675. The main efficacy end point was the first severe asthma exacerbation that led to treatment with systemic glucocorticoids, as assessed in a time-to-event analysis. RESULTS: Among the 6208 patients, 27 patients in the fluticasone-salmeterol group and 21 in the fluticasone-alone group had a serious asthma-related event (all were hospitalizations); the hazard ratio with fluticasone-salmeterol versus fluticasone alone was 1.28 (95% confidence interval [CI], 0.73 to 2.27), which showed the noninferiority of fluticasone-salmeterol (P=0.006). A total of 265 patients (8.5%) in the fluticasone-salmeterol group and 309 (10.0%) in the fluticasone-alone group had a severe asthma exacerbation (hazard ratio, 0.86; 95% CI, 0.73 to 1.01). CONCLUSIONS: In this trial involving children with asthma, salmeterol in a fixed-dose combination with fluticasone was associated with the risk of a serious asthma-related event that was similar to the risk with fluticasone alone.

Tiotropium add-on therapy in adolescents with moderate asthma: A 1-year randomized controlled trial.
Hamelmann E, Bateman ED, Vogelberg C, Szefler SJ, Vandewalker M, Moroni-Zentgraf P, Avis M, Unseld A, Engel M, Boner AL.

BACKGROUND: Results from phase III clinical trials in adults and phase II clinical trials in children and adolescents demonstrate that tiotropium is an effective treatment when added to inhaled corticosteroid (ICS) maintenance therapy. OBJECTIVE: We sought to assess the efficacy and safety of once-daily tiotropium Respimat added to ICSs with or without a leukotriene receptor antagonist in a phase III trial in adolescent patients with moderate symptomatic asthma. METHODS: In this 48-week, double-blind, placebo-controlled, parallel-group study, 398 patients aged 12 to 17 years were randomized to receive 5 μg (2 puffs of 2.5 μg) or 2.5 μg (2 puffs of 1.25 μg) of once-daily tiotropium or placebo (2 puffs) administered through the Respimat device every evening, each as add-on treatment to ICS background therapy, with or without a leukotriene receptor antagonist; long-acting β2-agonist therapy was not permitted during the study. RESULTS: Improvement in peak FEV1 within 3 hours after dosing at 24 weeks (primary end point) was statistically significant with both tiotropium doses compared with placebo: 5 μg of tiotropium, 174 mL (95% CI, 76-272 mL); 2.5 μg of tiotropium, 134 mL (95% CI, 34-234 mL). Significant improvements in trough FEV1 at week 24 (a secondary end point) were observed with the 5-μg dose only. Trends for improvement in asthma control and health-related quality of life over the 48-week treatment period were observed. CONCLUSIONS: Once-daily tiotropium significantly improved lung function and was safe and well tolerated when added to at least ICS maintenance therapy in adolescent patients with moderate symptomatic asthma. Larger responses were observed with the 5-μg tiotropium dose.

Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial.

Vestbo J, Anderson JA, Brook RD, Calverley PM, Celli BR, Crim C, Martinez F, Yates J, Newby DE; SUMMIT Investigators.

BACKGROUND: Chronic obstructive pulmonary disease (COPD) often coexists with cardiovascular disease. Treatments for airflow limitation might improve survival and both respiratory and cardiovascular outcomes. The aim of this study was to assess whether inhaled treatment with a combined treatment of the corticosteroid, fluticasone furoate, and the long-acting β agonist, vilanterol could improve survival compared with placebo in patients with moderate COPD and heightened cardiovascular risk. METHODS: In this double-blind randomised controlled trial (SUMMIT) done in 1368 centres in 43 countries, eligible patients were aged 40-80 years and had a post-bronchodilator forced expiratory volume in 1 s (FEV1) between 50% and 70% of the predicted value, a ratio of post-bronchodilator FEV1 to forced vital capacity (FVC) of 0·70 or less, a smoking history of at least 10 pack-years, and a score of 2 or greater on the modified Medical Research Council dyspnoea scale. Patients had to have a history, or be at increased risk, of cardiovascular disease. Enrolled patients were randomly assigned (1:1:1:1) through a centralised randomisation service in permuted blocks to receive once daily inhaled placebo, fluticasone furoate (100 µg), vilanterol (25 µg), or the combination of fluticasone furoate (100 µg) and vilanterol (25 µg). The primary outcome was all-cause mortality, and secondary outcomes were on-treatment rate of decline in forced expiratory volume in 1 s (FEV1) and a composite of cardiovascular events. Safety analyses were performed on the safety population (all patients who took at least one dose of study drug) and efficacy analyses were performed on the intention-to-treat population (safety population minus sites excluded with Good Clinical Practice violations). This study is registered with ClinicalTrials.gov, number NCT01313676. FINDINGS: Between Jan 24, 2011, and March 12, 2014, 23 835 patients were screened, of whom 16 590 were randomised. 16 485 patients were included in the intention-to-treat efficacy population; 4111 in the placebo group, 4135 in the fluticasone furoate group, 4118 in the vilanterol group, and 4121 in the combination group. Compared with placebo, all-cause mortality was unaffected by combination therapy (hazard ratio [HR] 0·88 [95% CI 0·74-1·04]; 12% relative reduction; p=0·137) or the components (fluticasone furoate, HR 0·91 [0·77-1·08]; p=0·284; vilanterol, 0·96 [0·81-1·14]; p=0·655), and therefore secondary outcomes should be interpreted with caution. Rate of decline in FEV1 was reduced by combination therapy (38 mL per year [SE 2·4] vs 46 mL per year [2·5] for placebo, difference 8 mL per year [95% CI 1-15]) with similar findings for fluticasone furoate (difference 8 mL per year [95% CI 1-14]), but not vilanterol (difference -2 mL per year [95% CI -8 to 5]). Combination therapy had no effect on composite cardiovascular events (HR 0·93 [95% CI 0·75-1·14]) with similar findings for fluticasone furoate (0·90 [0·72-1·11]) and vilanterol (0·99 [0·80-1·22]). All treatments reduced the rate of moderate and severe exacerbation. No reported excess risks of pneumonia (5% in the placebo group, 6% in the combination group, 5% in the fluticasone furoate group, and 4% in the vilanterol group) or adverse cardiac events (17% in the placebo group, 18% in the combination group, and 17% in the fluticasone furoate group, and 17% in the vilanterol group) were noted in the treatment groups.INTERPRETATION: In patients with moderate COPD and heightened cardiovascular risk, treatment with fluticasone furoate and vilanterol did not affect mortality or cardiovascular outcomes, reduced exacerbations, and was well tolerated. Fluticasone furoate, alone or in combination with vilanterol, seemed to reduce FEV1 decline.

Single inhaler triple therapy versus inhaled corticosteroid plus long-acting β2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial.
Singh D, Papi A, Corradi M, Pavlišová I, Montagna I, Francisco C, Cohuet G, Vezzoli S, Scuri M, Vestbo J.

BACKGROUND: Few data are available for the efficacy of "triple therapy" with two long-acting bronchodilators and an inhaled corticosteroid in chronic obstructive pulmonary disease (COPD). We designed this study to assess efficacy of single-inhaler combination of an extra fine formulation of beclometasone dipropionate, formoterol fumarate, and glycopyrronium bromide (BDP/FF/GB) in COPD compared with beclometasone dipropionate and formoterol fumarate (BDP/FF) treatment. METHODS: TRILOGY was a randomised, parallel group, double-blind, active-controlled study done in 159 sites across 14 countries. The sites were a mixture of primary, secondary, and tertiary care providers, and specialist investigation units. Eligible patients with COPD had post-bronchodilator forced expiratory volume in 1 s (FEV1) of lower than 50%, one or more moderate-to-severe COPD exacerbation in the previous 12 months, COPD Assessment Test total score of 10 or more, and a Baseline Dyspnea Index focal score of 10 or less. Patients who met the inclusion and exclusion criteria at screening entered a 2-week open-label run-in period where they received beclometasone dipropionate (100 µg) and formoterol fumarate (6 µg) in two actuations twice daily. Patients were then randomly assigned (1:1) with an interactive response technology system to either continue BDP (100 µg) and FF (6 µg) or step-up to BDP (100 µg), FF (6 µg), and GB (12·5 µg) in two actuations twice daily for 52 weeks via pressurised metered-dose inhaler. The three co-primary endpoints were pre-dose FEV1, 2-h post-dose FEV1, and Transition Dyspnea Index (TDI) focal score, all measured at week 26 in the intention-to-treat population (all patients who were randomly assigned and received at least one dose of study drug and had at least one post-baseline efficacy assessment). Safety outcomes were measured in the safety population (all patients who were randomly assigned and received at least one dose of study drug). Secondary endpoints included moderate-to-severe COPD exacerbation rate over 52 weeks. This study is registered with ClinicalTrials.gov number NCT01917331. FINDINGS: Between March 21, 2014, and Jan 14, 2016, 1368 patients received either BDP/FF/GB (n=687) or BDP/FF (n=681). At week 26, BDP/FF/GB improved pre-dose FEV1 by 0·081 L (95% CI 0·052-0·109; p<0·001) and 2-h post-dose FEV1 by 0·117 L (0·086-0·147; p<0·001) compared with BDP/FF. Mean TDI focal scores at week 26 were 1·71 for BDP/FF/GB and 1·50 for BDP/FF, with a difference of 0·21 (95% CI -0·08 to 0·51; p=0·160). Adjusted annual moderate-to-severe exacerbation frequencies were 0·41 for BDP/FF/GB and 0·53 for BDP/FF (rate ratio 0·77 [95% CI 0·65-0·92]; p=0·005), corresponding to a 23% reduction in exacerbations with BDP/FF/GB compared with BDP/FF. Adverse events were reported by 368 (54%) patients with BDP/FF/GB and 379 (56%) with BDP/FF. One serious treatment-related adverse event occurred (atrial fibrillation) in a patient in the BDP/FF/GB group. INTERPRETATION: We provide evidence for the clinical benefits of stepping up patients with COPD from an inhaled corticosteroid/long-acting β2-agonist combination treatment to triple therapy using a single inhaler.

Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone.
Stempel DA, Raphiou IH, Kral KM, Yeakey AM, Emmett AH, Prazma CM, Buaron KS, Pascoe SJ; AUSTRI Investigators.

BACKGROUND: The safe and appropriate use of long-acting beta-agonists (LABAs) for the treatment of asthma has been widely debated. In two large clinical trials, investigators found a potential risk of serious asthma-related events associated with LABAs. This study was designed to evaluate the risk of administering the LABA salmeterol in combination with an inhaled glucocorticoid, fluticasone propionate. METHODS: In this multicenter, randomized, double-blind trial, adolescent and adult patients (age, ≥12 years) with persistent asthma were assigned to receive either fluticasone with salmeterol or fluticasone alone for 26 weeks. All the patients had a history of a severe asthma exacerbation in the year before randomization but not during the previous month. Patients were excluded from the trial if they had a history of life-threatening or unstable asthma. The primary safety end point was the first serious asthma-related event (death, endotracheal intubation, or hospitalization). Noninferiority of fluticasone-salmeterol to fluticasone alone was defined as an upper boundary of the 95%

confidence interval for the risk of the primary safety end point of less than 2.0. The efficacy end point was the first severe asthma exacerbation. RESULTS: Of 11,679 patients who were enrolled, 67 had 74 serious asthma-related events, with 36 events in 34 patients in the fluticasone-salmeterol group and 38 events in 33 patients in the fluticasone-only group. The hazard ratio for a serious asthma-related event in the fluticasone-salmeterol group was 1.03 (95% confidence interval [CI], 0.64 to 1.66), and noninferiority was achieved (P=0.003). There were no asthma-related deaths; 2 patients in the fluticasone-only group underwent asthma-related intubation. The risk of a severe asthma exacerbation was 21% lower in the fluticasone-salmeterol group than in the fluticasone-only group (hazard ratio, 0.79; 95% CI, 0.70 to 0.89), with at least one severe asthma exacerbation occurring in 480 of 5834 patients (8%) in the fluticasone-salmeterol group, as compared with 597 of 5845 patients (10%) in the fluticasone-only group (P<0.001). CONCLUSIONS: Patients who received salmeterol in a fixed-dose combination with fluticasone did not have a significantly higher risk of serious asthma-related events than did those who received fluticasone alone. Patients receiving fluticasone-salmeterol had fewer severe asthma exacerbations than did those in the fluticasone-only group.

Indacaterol-Glycopyrronium versus Salmeterol-Fluticasone for COPD.
Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, Thach C, Fogel R, Patalano F, Vogelmeier CF; FLAME Investigators.

BACKGROUND: Most guidelines recommend either a long-acting beta-agonist (LABA) plus an inhaled glucocorticoid or a long-acting muscarinic antagonist (LAMA) as the first-choice treatment for patients with chronic obstructive pulmonary disease (COPD) who have a high risk of exacerbations. The role of treatment with a LABA-LAMA regimen in these patients is unclear. METHODS: We conducted a 52-week, randomized, double-blind, double-dummy, noninferiority trial. Patients who had COPD with a history of at least one exacerbation during the previous year were randomly assigned to receive, by inhalation, either the LABA indacaterol (110 µg) plus the LAMA glycopyrronium (50 µg) once daily or the LABA salmeterol (50 µg) plus the inhaled glucocorticoid fluticasone (500 µg) twice daily. The primary outcome was the annual rate of all COPD exacerbations. RESULTS: A total of 1680 patients were assigned to the indacaterol-glycopyrronium group, and 1682 to the salmeterol-fluticasone group. Indacaterol-glycopyrronium showed not only noninferiority but also superiority to salmeterol-fluticasone in reducing the annual rate of all COPD exacerbations; the rate was 11% lower in the indacaterol-glycopyrronium group than in the salmeterol-fluticasone group (3.59 vs. 4.03; rate ratio, 0.89; 95% confidence interval [CI], 0.83 to 0.96; P=0.003). The indacaterol-glycopyrronium group had a longer time to the first exacerbation than did the salmeterol-fluticasone group (71 days [95% CI, 60 to 82] vs. 51 days [95% CI, 46 to 57]; hazard ratio, 0.84 [95% CI, 0.78 to 0.91], representing a 16% lower risk; P<0.001). The annual rate of moderate or severe exacerbations was lower in the indacaterol-glycopyrronium group than in the salmeterol-fluticasone group (0.98 vs. 1.19; rate ratio, 0.83; 95% CI, 0.75 to 0.91; P<0.001), and the time to the first moderate or severe exacerbation was longer in the indacaterol-glycopyrronium group than in the salmeterol-fluticasone group (hazard ratio, 0.78; 95% CI, 0.70 to 0.86; P<0.001), as was the time to the first severe exacerbation (hazard ratio, 0.81; 95% CI, 0.66 to 1.00; P=0.046). The effect of indacaterol-glycopyrronium versus salmeterol-fluticasone on the rate of COPD exacerbations was independent of the baseline blood eosinophil count. The incidence of adverse events and deaths was similar in the two groups. The incidence of pneumonia was 3.2% in the indacaterol-glycopyrronium group and 4.8% in the salmeterol-fluticasone group (P=0.02). CONCLUSIONS: Indacaterol-glycopyrronium was more effective than salmeterol-fluticasone in preventing COPD exacerbations in patients with a history of exacerbation during the previous year. (Funded by Novartis; FLAME ClinicalTrials.gov number, NCT01782326.).

Appendix 4: Medline Search Strategy

Database(s): Ovid MEDLINE(R) without Revisions 1996 to August Week 5 2017
Search Strategy:

#	Searches	Results
1	Tiotropium Bromide/	920
2	aclidinium bromide.mp.	112
3	umeclidinium.mp.	102
4	glycopyrrolate.mp. or Glycopyrrolate/	633
5	Budesonide, Formoterol Fumarate Drug Combination/ or Budesonide/ or budesonide.mp.	4344
6	fluticasone propionate.mp. or Fluticasone/	3066
7	beclomethasone dipropionate.mp. or Beclomethasone/	1756
8	mometasone furoate.mp. or Mometasone Furoate/	730
9	fluticasone furoate.mp.	211
10	ciclesonide.mp.	306
11	salmeterol xinafoate.mp. or Salmeterol Xinafoate/	1797
12	formoterol fumarate.mp. or Formoterol Fumarate/	1432
13	arformoterol tartrate.mp.	11
14	indacaterol maleate.mp.	11
15	olodaterol.mp.	85
16	vilanterol.mp.	180
17	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16	11729
18	limit 17 to (english language and humans and yr="2016 -Current")	489
19	limit 18 to (clinical study or clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comment or controlled clinical trial or meta-analysis or practice guideline or randomized controlled trial or systematic reviews)	

Author: Kathy Sentena, PharmD Date: November 2017

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

Approval Criteria		
2. Will the prescriber consider a change to a preferred product? Message: ~~• Preferred products do not require PA or a copay.~~ • Preferred products are 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 #3
3. Does the patient have a diagnosis of asthma or reactive airway disease (ICD10 J45.20-J45.22, J45.901-45.998)?	**Yes:** Go to #7	**No:** Go to #4
4. Does the patient have a diagnosis of COPD (ICD10 J44.9), mucopurulent chronic bronchitis (ICD10 J41.1~~J410-418, J42, J440-449~~) and/or emphysema (ICD10 J43.9)?	**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. Chronic bronchitis is unfunded (ICD10 J40, J41.0, J41.8, J42).
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/DUR Review: *11/17 (KS); 9/16 ~~(KS)~~; 9/15*
Implementation: *10/13/16; 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 are 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 #3

Approval Criteria		
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
4. Does the patient have a diagnosis of COPD (ICD10 J449), mucopurulent chronic bronchitis (ICD10 J41.1~~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. Chronic bronchitis is unfunded (ICD10 J40, J41.0, J41.8, J42).
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/DUR Review: *11/17 (KS);* *9/16* ~~*(KS)*~~*; 9/15); 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 are reviewed for comparative effectiveness and safety by the Oregon 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), mucopurulent chronic bronchitis (ICD10 J41.1~~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. Chronic bronchitis is unfunded (ICD10 J40, J41.0, J41.8, J42).
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/DUR Review: *11/17 (KS);* *9/16* ~~*(KS)*~~*; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*

Author: Kathy Sentena, PharmD

Date: November 2017

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 and LAMA/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 prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon 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) without COPD?	**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), mucopurulent chronic bronchitis (ICD10 J41.1 ~~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. Chronic bronchitis is unfunded (ICD10 J40, J41.0, J41.8, J42).
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 the request for the combination product fluticasone furoate, umeclidinium and vilanterol (Trelegy Ellipta)?	**Yes:** Go to #7	**No:** Go to #8
7. Has the patient been assessed with GOLD C/D COPD?	**Yes:** Approve for up to 12 months. Stop coverage of all other LAMA, LABA and ICS inhalers.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
~~6.~~8. 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 #9~~7~~
~~7.~~9. 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.

P&T Review: *11/17 (KS);* *9/16 ~~(KS)~~; 11/15; 9/15; 11/14; 11/13; 5/12; 9/09; 2/06*
Implementation: *10/13/16; 1/1/16; 1/15; 1/14; 9/12; 1/10*

Treatment of Hepatitis C in People Who Inject Drugs (PWIDs)

Andrew Seaman, MD
OHA P&T Meeting
January, 2017

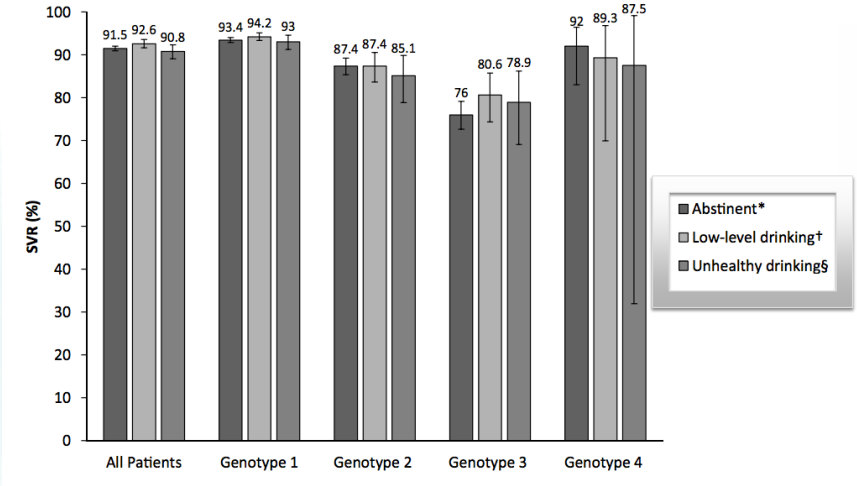
Conflicts of interest

- Receive <8% of my salary from an investigator initiated, Merck funded trial (makers of elbasvir/grazoprevir)
- I am highly influenced by the opinions, life experience, and knowledge my patients bring to the table (many of whom inject drugs)

Objectives

- Review of published and some unpublished data on PWIDs from colleagues in New York, Australia, Europe
- Brief review of the Old Town Clinic / Outside In / OHSU pilot trial for HCV treatment in People Who Inject Drugs

Alcohol use does not affect SVR12



Tsui et al. Drug Alcohol Depend. 2016 Dec 1;169:101-109.

C-EDGE CO-STAR Trial

- Multicenter-RCT tx w/ Elb-Graz with 301 PWIDs
- Patients with GT 1, 4, or 6 HCV on either methadone (81%) or buprenorphine (19%) for comorbid opioid use disorder
- Randomized 2:1 to immediate treatment group vs delayed treatment group (12wks placebo + 4 weeks de-randomization + 12 weeks treatment)
- Primary outcome SVR 12 assuming re-infection as cure

Intention-to-treat analysis

Dore et al. Ann Intern Med. 2016;165:625-634

C-EDGE CO-STAR Trial

Imm. Treat. Group (n=201)	SVR 12	SVR 24
Assuming Re-infections are Responses	**94% (89.8-96.9)**	85% (78.8-89) *2/201 additional relapses
Assuming Re-infections = Treatment Failure	91.5% (CI 86.8-95%)	87%
Probable Reinfection	5/201	5/201
Lost to Follow Up	3	**15**
Adherence >95%	~95%	95%

****2 year f/u re-infection data 2.3/100pyrs**

Dore et al. Ann Intern Med. 2016;165:625-634

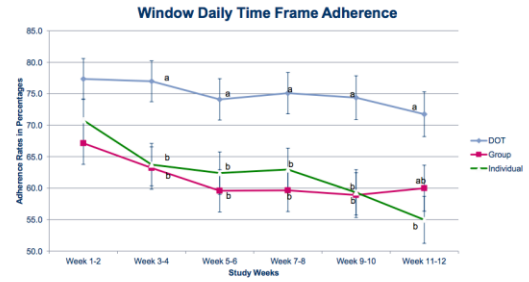
SIMPLIFY trial (pre-publication)

- Multicenter, international RCT with recent (<6mo) PWIDs
- 103 participants w/ GT 1-6 HCV
- Treated w/ Sof/Vel x 12 weeks
- Primary endpoint SVR12, secondary Adherence > 90%
- Results
  - 70% injecting in last month
  - 57% receiving opioid substitution therapy
  - End Treatment Response – 94% (NO confirmed VL failures – 6% loss to f/u)
  - SVR12 and Adherence data pending
  - Reinfection data pending (f/u 3 years)

Grebely et al. Hepatology. 2017Volume 66, Issue 1, Supplement, Page S513

Intensive management of HCV tx in PWIDs: Montefiore trial

Adherence higher in DOT vs. both Individual (p=0.0008) and Group (p=0.0003)



Overall adherence: DOT (75.0%) vs. Group (61.4%) vs. Individual (62.4%)

Montefiore

SVR12 high in all 3 arms (p=0.24)

Study Arm	ETR	SVR12
DOT	98.0% (50/51)	98.0% (50/51)
Group	93.8% (45/48)	93.8% (45/48)
Individual	96.1% (49/51)	90.2% (46/51)
Total	**96.0% (144/150)** (95% CI 92% - 99%)	**94.0% (141/150)** (95% CI 89% - 97%)

PREVAIL study: Unpublished data from INHSU. LINK to slides.

OTC – OI – OHSU Pilot Study

- Prospective, non-randomized real world clinical trial using elb/graz to treat people who inject drugs with GT 1 or 4 HCV and an APRI <0.7 who:
  - Arm 1: engage with Medication Assisted Therapy (Methadone/Bupe), n=25, Old Town Clinic
  - Arm 2: are actively using and engage with needle exchange program, n=25, Outside In
  - Arm 3: matched cohort in OHSU hepatology clinic, n=50

Endpoints

- Primary
  - SVR 12 and 48
- Secondary
  - Primary Tx failure (+RNA 24wks)
  - Secondary Tx Failure (+RNA 60wks)
  - Adherence
  - Discontinuation rate
  - NS5a resistance
  - Substance use relapse

OHSU-OTC-OI Study Progress: Enrollment

- Old Town Clinic / MAT:
  - 25/25 enrolled
  - Adherence greater than 95% (All patients completed by Jan, SVR data by April 1)
- Outside In
  - 14/25 enrolled
  - Adherence good except 2/10 lost-to f/u (? Sampling error)
- OHSU
  - Pending

Limitations

- Power
  - Powered to detect a difference of 20% in primary endpoint; this is not clinically ideal
- Group Disparities
  - Comparing prospective trial w/ very specific inclusion criteria to chart biopsy based cohort
  - Difference in un-measurables between people in MAT program and needle exchange (and university setting)
  - Differences in pre-screening process

Old Town Clinic Treatment Program

- Multidisciplinary
  - Medical director + two providers
  - HCV coordinator
  - Clinical pharmacist
  - CADC
- Weekly committee meetings
  - Decision made on need for treatment candidacy, Substance Used Disorder support, adherence support
  - Drug, labs ordered and PA process started by coordinator
  - First, last, and SVR visit by provider, remainder by pharmacist

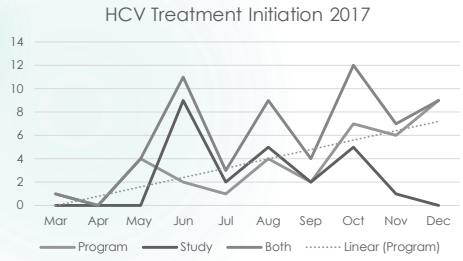
We treat… everyone

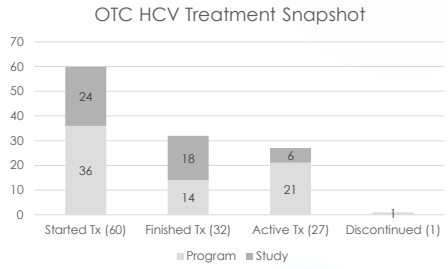
- Treatment candidacy
  - Made 2/3 last appointments or subjective adherence measure (whichever lower barrier)
  - Desires treatment
  - Meets their insurance eligibility criteria*

*We consider any SUDs support as treatment and have had great success with insurers

Our capacity

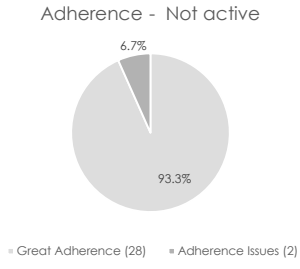
- A total of 60 patients have initiated treatment in the last 9.5 months (24 study/36 non-study).
- We expect to treat many more in 2018.





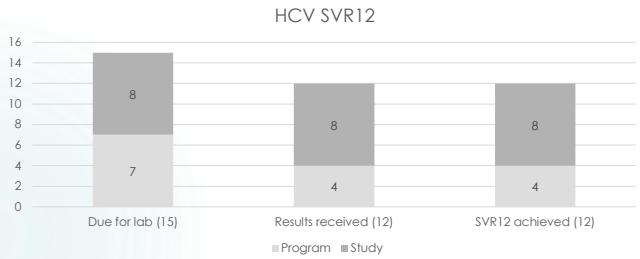
Adherence

- Adherence has been near perfect in almost all cases.
- The 4 exceptions are: #1 'completed' 1 month interruption, #2 'discontinued' completed 8 weeks, #3 'active' 15 day interruption & #4 'active' 24 day interruption.



Treatment efficacy

- Everyone that completed a SVR12 viral load has been undetectable.



Treatment as prevention depends on treating PWIDs

- Despite reinfection risk, not treating leads to a greater public health risk
- If we are not treating a patient population with at least some re-infection risk we are not treating the population that transmits this virus
- Multiple models suggest that we must treat PWIDs if we are to successfully address the HCV epidemic[9,10]

In Summary: We can and must treat hep C in PWIDs

- There is no evidence of different hepatitis C treatment outcomes among people with or without substance use disorders
- The WHO and others recommend we *prioritize* rather than restrict treatment in PWIDs
- Mathematical models and common sense suggest we cannot treat this epidemic unless we treat the people transmitting the virus
- Where is the rational for denying people with substance use disorders?? The rational for "6 months sobriety?"
  - (Why not deny diabetics? People with metabolic syndrome? Tobaccoism?)

HCVguidelines.org

Questions?

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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 Class Update: Biologics for Autoimmune Conditions

Date of Review: January 2018

Date of Last Review: July 2017
End Date of Literature Search: 10/30/2017

Generic Name: sarilumab **Brand Name (Manufacturer)/Dossier Received:** Kevzara® (Sanofi and Regeneron Pharmaceuticals, Inc.)/Yes
Generic Name: guselkumab **Brand Name (Manufacturer)/Dossier Received:** Tremfya® (Janssen)/Yes

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

Purpose for Class Update:
To define place in therapy and review comparative biologic response modifier evidence for 2 new biologic response modifiers recently approved by the United States (U.S.) Food and Drug Administration (FDA): sarilumab for the treatment of moderate to severe rheumatoid arthritis and guselkumab for the treatment of moderate to severe plaque psoriasis. In addition, new comparative evidence between biologics for autoimmune conditions will be reviewed.

Research Questions:
1. Is there new comparative evidence that biologics for autoimmune conditions differ in efficacy or effectiveness for alleviating symptoms and stabilizing disease in adults or children with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), ankylosing spondylitis (AS), psoriatic arthritis (PsA), Crohn's disease (CD), ulcerative colitis (UC), or plaque psoriasis (PsO)?
2. Is there new comparative evidence that biologics for autoimmune conditions differ in serious adverse events or tolerability when used to manage adults or children with RA, JIA, AS, PsA, CD, UC, or PsO?
3. Are there specific subpopulations based on age, gender, race, disease severity, or concomitant therapies for which one biologic is better tolerated or more effective than other available biologics for specific autoimmune conditions?

Conclusions:
CLASS UPDATE
- One systematic review (Cochrane Collaboration on RA)[1], 5 new clinical practice guidelines from the National Institute for Health and Care Excellence (NICE) and the European League Against Rheumatism (EULAR) [2-6], 8 new indications approved by the FDA[7-12], and one new formulation approved by the FDA[13] were identified which provide clinically meaningful new evidence for these drugs. The evidence is applicable to Medicaid patients; however, no subgroup analyses specific to Medicaid patients were provided in any of the studies reviewed. Several systematic reviews and meta-analyses were excluded from this review due to poor quality.[14-17]

- There is insufficient new evidence to determine if biologics differ in effectiveness for alleviating symptoms and stabilizing patients with JIA, AS, PsA, CD, UC, or PsO. There is moderate quality evidence that compares sarilumab and adalimumab in RA as discussed below.[18]
- Compared with placebo, there is high quality evidence from one systematic review that American College of Rheumatology (ACR) 50% improvement criteria (ACR50) is improved with certolizumab pegol 200 mg every other week in RA (relative risk [RR] 3.80; 95% confidence interval [CI] 2.42-5.95; absolute risk reduction [ARR] 25%; number needed to treat [NNT] 4 at 24 weeks).[1] There is insufficient new evidence to determine comparative efficacy of certolizumab pegol versus other biologic modifiers.
- There is insufficient new comparative evidence to determine if biologics differ in harms except for the comparison of sarilumab and adalimumab which is discussed below.[18]
- There is insufficient new comparative evidence to determine if there are specific subpopulations for which one biologic agent is better tolerated or more effective than other available agents.
- New high quality guidelines identified for CD, PsO, PsA, and RA support the current PDL and PA criteria.[2-6]

SARILUMAB

- There is moderate quality evidence that treatment with sarilumab 150 mg subcutaneously (SC) every 2 weeks and sarilumab 200 mg SC every 2 weeks results in a statistically significant improvement in symptoms compared to placebo as evaluated by ACR 20% improvement criteria (ACR20) at 24 weeks in patients with RA (ARR 22.1-35.6% and 27.2-44.0%, respectively; NNT 3-5 and 3-4, respectively; studies = 2).[19,20] There is also moderate quality evidence that treatment with sarilumab 200 mg SC every 2 weeks results in a statistically significant change from baseline in Disease Activity Score-28 (DAS-28)-Erythrocyte Sedimentation Rate (ESR) at week 24 (-3.28 vs. -2.20; 95% CI -1.36 to -0.79; p<0.0001) as well as achievement of ACR20/50/70 at week 24 (71.7% vs. 58.4%/45.7% vs. 29.7%/23.4% vs. 11.9%, respectively) compared to adalimumab 40 mg SC every 2 weeks in patients with RA.[18] A significant difference also was found in the secondary endpoint of mean improvement in HAQ-DI score from baseline to week 24 for sarilumab compared to adalimumab (-0.61 vs. -0.43; 95% CI -0.31 to -0.06; p=0.0037).[18] There is insufficient comparative evidence for RA radiographic progression for sarilumab and adalimumab as this was not studied in the trial.[18]
- There is moderate quality evidence that adalimumab 40 mg every 2 weeks and sarilumab 200 mg every 2 weeks have similar risk of infections (27.7% vs. 28.8%) and serious adverse events (6.5% vs. 4.9%) but that sarilumab has a higher risk of neutropenia (13.6% vs. 0.5%) based on data from a 24 week study which was not powered to determine differences in adverse effects.[18] There is insufficient evidence to determine long-term safety of sarilumab compared to other treatments for moderate-to-severe RA.
- There is insufficient evidence to determine differences in efficacy or safety of sarilumab compared to other biologic agents for specific subpopulations.

GUSELKUMAB

- Moderate quality evidence from 2 Phase 3 trials (VOYAGE 1 and VOYAGE 2) demonstrated comparative efficacy of guselkumab with adalimumab in treating PsO.[21, 22] At week 16 in the VOYAGE 1 trial, patients who received guselkumab demonstrated higher achievement in the Psoriasis Area and Severity Index (PASI) 90 (73.3% vs. 49.7%; ARR = 23.6%, NNT = 5; p <0.001), and Investigator's Global Assessment (IGA) 0/1 (85.1% vs. 65.9%; ARR = 19.2%; NNT =6; p< 0.001) scores than patients treated with adalimumab.[21] Similar results were observed at week 16 when guselkumab was compared to adalimumab during the VOYAGE 2 trial. During the withdrawal and retreatment phase of VOYAGE 2, adalimumab non-responders started on guselkumab had PASI 90 response rates of 66% at week 48.[22] Both Phase 3 trials demonstrated the effectiveness of guselkumab 100mg in treating patients with moderate to severe PsO when compared to placebo and the active comparator, adalimumab.
- The most common adverse events for guselkumab observed during clinical trials were upper respiratory tract infections, injection-site reactions, and headaches. Rates of adverse events and serious adverse events observed with guselkumab were comparable to placebo and adalimumab. In the Voyage

1 trial, discontinuation rates through 48 weeks due to adverse effects with guselkumab were 2.7% compared to 3.6% with adalimumab.[21] A higher proportion of adalimumab patients had injection site reactions (6.9% vs 4.5%) compared to guselkumab.[23] Pooled data from VOYAGE 1 and VOYAGE 2 did not demonstrate an increased risk of suicidal ideation or adverse cardiovascular events with guselkumab.[23]

- There is insufficient evidence to determine long term safety with guselkumab due to limited duration of published clinical trials. VOYAGE 1 and 2 have extended open-label treatment arms that are currently investigating treatment with guselkumab through 252 weeks.

Recommendations:

- Modify PA criteria as follows:
  - Add new and updated indications for previously approved drugs to the approved indications table
  - Add guselkumab to the PA criteria for use in moderate-to-severe plaque psoriasis for ages ≥18 years
  - Add sarilumab to the PA criteria for use in moderate-to-severe rheumatoid arthritis for ages ≥18 years
  - Remove natalizumab (Tysabri) from biologic PA criteria as separate natalizumab criteria were approved at the November 2017 P and T meeting
- Evaluate comparative costs in executive session.

Previous Conclusions:

- For the treatment of RA, four systematic reviews provide moderate quality evidence to support the efficacy of abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab and tofacitinib in improving disease activity and function compared to conventional disease modifying antirheumatic drug (DMARD) therapy. In head-to-head trials of biologic therapy combined with a DMARD versus adalimumab monotherapy, adalimumab was similar to abatacept, tofacitinib, and certolizumab pegol in rates of remission achieved, American College of Rheumatology (ACR) response, and improvement in Health Assessment Questionnaire-Disability Index (HAQ-DI).
- Compared with placebo, there is high quality evidence that patients on a tumor necrosis factor (TNF) inhibitor are 3 to 4 times more likely to achieve an improvement in ankylosing spondylitis (AS) clinical symptoms as measured by Assessment of Spondyloarthritis (ASAS) 40 response within 6 months (adalimumab: RR 3.53, 95% CI 2.49 to 4.91; etanercept: RR 3.31, 95% CI 2.38 to 4.53; golimumab: RR 2.90, 95% CI 1.90 to 4.23; infliximab: RR 4.07, 95% CI 2.80 to 5.74, with a 25% to 40% absolute difference between treatment and placebo groups. There is a lack of head to head trials to define superiority of one agent over another for the treatment of AS.
- In 6 direct comparative trials evaluating treatment of adults with PsO ustekinumab, secukinumab, and ixekizumab were superior to etanercept for disease severity, measured by the Psoriasis Area Severity Index (PASI) 90 and 100. Secukinumab and brodalumab were superior to ustekinumab in PASI 90 and 100. Refer to Table 6 for specific results of the six different head-to-head trials. One-year follow-up of pivotal trials demonstrate that etanercept, ustekinumab, secukinumab, and brodalumab have comparable safety profiles when used for the treatment of psoriasis. There is limited comparative data in pediatric patients.
- There is moderate to high quality evidence of no increase in the risks of breast cancer, lymphoma, or non-melanoma skin cancer (NMSC) with TNF inhibitors compared to placebo in RA studies. There is insufficient evidence on total malignancy risk. In IBD, PsA, and PsO patients, TNF inhibitors were not associated with elevated cancer risk compared to control groups.
- Evidence is inconclusive for withdrawals due to adverse events, rates of cancer occurrence, and rates of serious adverse events with biological response modifiers compared to conventional therapy.

- There is moderate quality evidence that treatment with brodalumab 210 mg every 2 weeks results in a statistically significant improvement in symptoms compared to placebo (as evaluated by PASI75) in patients with moderate to severe PsO (absolute risk reduction [ARR] of 79 to 81%, number-needed-to-treat [NNT] 2). Evaluation of symptoms using a static physician's global assessment (sPGA) score of 0 or 1 corresponding to clear or almost clear skin, resulted in similar improvements.
- There is moderate quality evidence that compared to ustekinumab, more patients with PsO treated with brodalumab achieved complete disease clearance (PASI100 or sPGA of 0) at 12 weeks (37-44% vs. 19-22%; ARR 18-22%, NNT 5-6). The proportion of PsO patients with 75% improvement in PASI score was also improved with brodalumab treatment compared to ustekinumab (low quality evidence).
- There is insufficient evidence to determine differences in long-term efficacy, remission rates, health-related quality of life, or functional improvement with brodalumab compared to other treatments for moderate to severe PsO.
- There is insufficient evidence to determine long-term safety of brodalumab or differences in safety compared to currently available treatments for moderate to severe plaque psoriasis. During the clinical trial program, 10 patients treated with brodalumab attempted suicide, and 6 patients had completed suicides. In order to mitigate and further monitor these safety concerns including increased risk for suicidality, brodalumab is only available through a Risk Evaluation and Mitigation Strategy (REMS) program. Furthermore, due to significant safety concerns associated with long-term treatment, discontinuation of brodalumab is recommended if adequate response is not achieved within 12 to 16 weeks.
- There is insufficient evidence to determine differences in efficacy or safety of brodalumab compared to other biologic agents for specific demographics or populations including subgroups based on age, gender, ethnicity, prior treatment or concurrent psoriasis treatments, disease duration or severity, or concomitant psoriatic arthritis.
- There is no evidence regarding the efficacy or safety of brodalumab for conditions other than moderate to severe plaque psoriasis. It has also been evaluated in clinical trials for the treatment of psoriatic arthritis and axial spondyloarthritis though trials were discontinued with due to safety concerns associated with brodalumab use.

Previous Recommendations:

- Modify PA criteria to reflect updated indications and age ranges for specific biologic response modifiers as follows:
    - Decrease age for abatacept to ≥ 2 years old for juvenile idiopathic arthritis
    - Decrease age for etanercept to ≥ 4 years old for plaque psoriasis
    - Add Crohn's Disease indication for ustekinumab for patients ≥ 18 years
- Remove alefacept from PA criteria as it is no longer marketed in the United States.
- Require trial and failure of adalimumab or enteracept for arthritic or psoriatic conditions or ankylosing spondylitis before advancing to another biologic agent. Require trial and failure of adalimumab before advancing to another biologic for Crohn's Disease.
- Modify the PA criteria to required TB screening prior to initial approval and renewal criteria to ascertain patient response to therapy.
- Because brodalumab is associated with significant safety concerns including suicidal ideation and behavior, add brodalumab as a non-preferred drug to the PDL. Modify PA criteria to include brodalumab for use in moderate to severe plaque psoriasis.
- After evaluation of comparative costs in executive session, no PDL changes were recommended.

Background:

Rheumatoid Arthritis

RA is an autoimmune inflammatory disease that causes cartilage damage, bone erosions, and eventually joint deformity. Other tissues and organs, including the heart, kidney, and lungs, may also be affected. Inflammation in RA is mediated by activation of T-cells, B-cells, and macrophages which leads to expression of cytokines such as tumor necrosis factor and interleukins. In 2005, the prevalence of RA in the U.S. was estimated to be 0.6% of the adult population.[24] The diagnosis of RA increases after the fourth decade of life and is 3 times more likely in women than men.[25] According to the ACR, first-line treatment of early RA is an oral nonbiologic disease-modifying antirheumatic drug (DMARD) such as methotrexate (MTX), leflunomide, sulfasalazine, or hydroxychloroquine.[26] Monotherapy with MTX is the preferred therapy.[26] This recommendation is based on low quality evidence, but has strong support from the ACR panel due to ease of patient access and relatively low cost of therapy.[26] For patients with established RA with continued disease activity despite DMARD therapy, biologics are recommended to improve function and control RA symptoms.[26] The TNF inhibitors adalimumab, certolizumab, etanercept, golimumab, and infliximab are approved by FDA to manage RA. Other injectable biologics approved to manage RA are abatacept, anakinra, rituximab, sarilumab, and tocilizumab. One oral agent, tofacitinib, a janus kinase inhibitor, was approved by FDA for RA in 2012. No head-to-head comparative effectiveness trials have been conducted in this drug class with the exception of one trial that compared adalimumab with sarilumab.[18] This trial is discussed in the drug evaluation for sarilumab.[18,27]

Primary endpoints used in RA clinical trials are ACR response, the Health Assessment Questionnaire Disability Index (HAQ-DI), and the DAS-28. The ACR response is considered a measure of efficacy and evaluates tender joint count, swollen joint count, patient's assessment of pain, patient's and physician's global assessments of disease activity, patient's assessment of physical function, and laboratory evaluation of an acute-phase reactant (erythrocyte sedimentation rate [ESR] or C-reactive protein level [CRP]).[28] ACR20 criteria is met when patients have at least 20% improvement in tender and swollen joint counts and at least 20% improvement in at least 3 of the 7 domains.[27] ACR50 and ACR70 criteria correspond to improvement of at least 50% and 70%, respectively, in tender and swollen joints and at least 50% and 70% improvement, respectively, at least 3 of the 7 domains.[27] The HAQ-DI is a self-reported measure of functional capacity (total score 0 to 3).[27] Scores of 0 to 1 are generally considered mild to moderate disability, 1 to 2 moderate to severe disability, and 2 to 3 severe to very severe disability.[27] A decreases 0.22-0.25 is generally considered the minimum clinically important difference for this scale.[29] However, one study has also indicated that a greater decrease of -0.375 may be needed to be clinically significant.[30] The DAS-28 is another index of disease activity (similar to the ACR response) which assesses 28 joints in swelling, tenderness, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP, and patient global assessment of health.[27,31] A DAS-28 score greater than 5.1 corresponds to high disease activity and less than 3.2 corresponds to low disease activity.[27] A DAS-28 score of 2.6 is considered to correspond to remission.[27]

Juvenile Idiopathic Arthritis

JIA is diagnosed in children under the age of 16 years who present with joint inflammation of unknown etiology lasting longer than 6 weeks.[32] In 2001, the International League of Associations of Rheumatology (ILAR) proposed classification criteria for chronic childhood arthritis to enhance diagnosis and optimize treatment.[32] The umbrella term "juvenile idiopathic arthritis" was chosen and the disease was subdivided into 7 categories according to clinical presentation and disease course.[32] The 7 categories are: systemic arthritis, oligoarthritis, rheumatoid factor (RF) negative polyarthritis, RF positive polyarthritis, psoriatic arthritis, enthesitis-related arthritis, and undifferentiated arthritis.[32] The oligoarticular subtype is the most common.[33] JIA is the most common pediatric rheumatic disease and prevalence rates have been reported as 1.6 to 86.0 cases per 100,000 children.[33] JIA treatment goals include: suppression of inflammation, achievement of remission, relief of pain, maintenance of function and minimizing toxicity.[34] Nonsteroidal anti-inflammatory drugs (NSAIDs) have a role in treating pain associated with mild disease.[34] Intra-articular steroid injections are most commonly used in patients with oligoarticular JIA.[34] Disease-modifying agents such as MTX have demonstrated efficacy and safety; however some patients do not respond to DMARD therapy and progress to treatment with biologic

agents.[34] Biologic agents are selected according to the presenting symptoms such as active joint counts and JIA stratification by presence of active systemic features such as fever, evanescent rash, lymphadenopathy, hepatomegaly, splenomegaly, or serositis.[35] Effective therapies include TNF inhibitors (adalimumab, etanercept and infliximab) and abatacept (a T-cell inhibitor).[35] Interleukin inhibitors such as canakinumab and tocilizumab are two additional agents used to manage the systemic form of JIA.[35]

Ankylosing Spondylitis

AS is a chronic rheumatic disorder that primarily affects the sacroiliac joints and spine.[36] Bone inflammation results in inflammation of entheses, or attachment points between tendon, ligament, and bone.[36] Cytokine production released during inflammation affects osteoclast and osteoblast activity which can lead to paradoxical systemic bone loss, despite new bone formation which causes fusion of joints or the spine.[37] Prevalence estimates in the US are between 0.9 to 1.4% of the adult population.[38] AS is more common in males than females by 5 to 1, with a peak age of onset between 15 to 35 years of age.[36] Diagnosis is based on radiologic confirmation of sacroiliitis and the presence of at least one clinical symptom: low back pain for at least 3 months, limited lumbar spine motion, or decreased chest expansion for age and sex.[39] Patients who have chronic pain and other features suggestive of spondyloarthritis (SpA) without radiologic changes are classified as having nonradiographic axial SpA.[40] Organ involvement can result in uveitis, psoriasis, and inflammatory bowel disease (IBD).[38] Guidelines for management of AS were updated in 2010 by the Assessments in Ankylosing Spondylitis International Society (ASA) and the European League against Rheumatism (EULAR).[41] NSAIDs and exercise are recommended as first-line therapies to alleviate pain and stiffness.[38,41] TNF inhibitors are recommended for patients with persistent disease activity despite conventional treatment.[41] Five TNF inhibitors including infliximab, etanercept, adalimumab, certolizumab, and golimumab are proven to provide sustained improvement in disease activity and patient functioning as assessed by the Bath Ankylosing Spondylitis Disease Activity Index (BASDI) and Functional Index (BASFI) scores.[38] The anti–interleukin monoclonal antibody secukinumab has also demonstrated efficacy in treating AS.[38] There is no evidence for the efficacy of systemic glucocorticoids or disease-modifying antirheumatic drugs (DMARDs) in the treatment of AS, although sulfasalazine may be considered for patients with peripheral arthritis.[41]

Plaque Psoriasis

PsO is a chronic, inflammatory, immune-mediated skin disorder resulting in formation of erythematous, scaly papules or plaques on the skin.[42] Psoriasis affects men and women equally, with the onset peaking between the ages 30 and 50 years, and affects about 2% of the U.S. population.[43,44] The disease often has a negative impact on quality of life and is estimated to account for more than $5 billion in total direct medical expenses.[45] People with psoriasis, especially those with severe disease, are also at increased risk of cardiovascular disease, diabetes, and depression.[42] The cause of psoriasis is not yet fully understood, but several risk factors have been identified, including a family history of psoriasis, smoking, infections, drugs, obesity, stress, and alcohol consumption.[46] Typically, PsO is classified as mild, moderate or severe. Mild disease involves less than 5% of the body surface area involved and has little to no impact on quality of life or function. Per NICE guidance, topical medications including corticosteriods and vitamin D analogs, such as calcipotriene, or coal tar are first-line agents for PsO.[47] Phototherapy is an option for moderate-to-severe plaque psoriasis that has not responded to topical therapy. Systemic nonbiologic treatments are recommended for moderate-to-severe PSO unresponsive to topical or phototherapy and include MTX, cyclosporine, or acitretin. Biologics such as apremilast, etanercept, adalimumab, infliximab, secukinumab, ixekizumab, brodalumab or ustekinumab are added for moderate-to-severe PsO not controlled by other therapies. A new biologic agent, guselkumab, was approved by the FDA in 2017 for the treatment of adult patients with moderate-to-severe PsO who are candidates for systemic therapy or phototherapy.[23]

Several tools have been developed to evaluate symptom improvement and quality of life in patients with psoriasis. In clinical trials, symptom improvement is often evaluated using the psoriasis area and severity index (PASI), the static physician's global assessment scale (sPGA), or the psoriasis symptom inventory (PSI).

There is no consensus on the most reliable scale, but the PASI is used most often in clinical trials and is considered the most validated scale.[48,49] The PASI ranges from 0 to 72 points and evaluates body surface area involvement, induration, scaling, and erythema. Because the PASI only evaluates skin involvement on the trunk, head and extremities, the PASI has limited sensitivity in patients with mild to moderate disease or limited BSA involvement.[48,49] It does not take into account symptoms affecting hands, feet, face or genitals. Because the PASI scale is not linear, small changes in BSA involvement can result in a significant improvement of the overall score without change in other symptoms.[42] In addition, though the PASI evaluates symptoms on a range of 0 to 72 points, in clinical practice, patients often do not have scores greater than 40.[49] The most commonly reported outcome in clinical trials is improvement of greater than 75% in the PASI score. However, 100% improvement indicating complete disease clearance, is considered more clinically significant.[50] In 2013, a 5-point Investigator's Global Assessment (IGA) was developed to assist in overcoming the limitations of disease severity assessment of the PASI scoring tool.[51] In clinical trials that assessed secukinumab, the IGA was utilized as an outcome measure in responder analyses by determining the proportion of patients with scores ranging from 0 (clear), 1 (minimal), 2 (mild), 3 (moderate) or 4 (severe).[51] At a given point in time, psoriatic lesions are graded by the investigator for induration, erythema, and scaling on the 5-point scale.[51] The IGA does not measure the extent of psoriasis and small changes in symptom severity may not be distinguishable.[51]

Psoriatic Arthritis

PsA is a spondyloarthropathy characterized by synovitis, enthesitis, dactylitis, and skin and nail psoriasis.[52] PsA most commonly appears between the ages of 30 and 50 years but it can develop at any time including childhood.[44] Men and women are affected equally and PsA symptoms include stiffness, pain, swelling, and tenderness of the joints and surrounding ligaments and tendons.[44] Common locations include the insertion sites of the plantar fascia, the Achilles' tendons, and ligamentous attachments to the ribs, spine, and pelvis.[44] Dactylitis is a combination of enthesitis of the tendons and ligaments and synovitis involving a whole digit.[44] The prevalence of PsA in the U.S. population ranges from 6 to 25 cases per 10,000 people.[53] Approximately 30% of patients with psoriasis with have symptoms of PsA.[53] Initially, management of PsA was extrapolated from experiences in managing RA.[54] The European League against Rheumatism (EULAR) developed PsA management recommendations in 2011 to improve management of this disease.[55] First-line treatment recommendations include NSAID therapy to alleviate joint pain, but it is recognized that NSAIDs cannot improve skin lesions.[55] DMARD therapy (MTX, sulfasalazine or leflunomide) should be initiated in patients with active disease (one or more inflamed joints) and poor prognosis (>5 actively inflamed joints).[55] If DMARD therapy is not effective, TNF inhibitors (adalimumab, etanercept, golimumab, or infliximab) should be added to improve skin and joint symptoms and to prevent radiographic damage.[55] More recent guidelines advocate for the use of secukinumab, ustekinumab, and apremilast for PsA in patients who do not respond to TNF inhibitors.[54,56]

Crohn's Disease

CD is characterized by transmural inflammation of any part of the gastrointestinal tract, but most often affects the small bowel and colon.[57] Symptoms of CD include abdominal pain, chronic diarrhea, and gastrointestinal bleeding.[58] The prevalence of CD in the U.S. is estimated at 50 cases per 100,000 persons.[59] CD is incurable; it begins in young people between the ages of 10 and 30 years and continues throughout life.[59] Among patients with CD, surgery is required for the majority and some require multiple operations.[57] Approved biologics to manage CD are adalimumab, certolizumab, infliximab, natalizumab, ustekinumab, and vedolizumab. AHRQ clinical practice guidelines for CD recommend taking into account the disease location, severity, complications, and extraintestinal manifestations when choosing a treatment strategy.[58] Treatment is largely directed at symptom relief rather than cure, and active treatment of acute disease (inducing remission) should be distinguished from preventing relapse (maintaining remission).[58] There is controversy between two treatment strategies: "top-down therapy," when biologics are used early in therapy, versus "step-up therapy," when biologics are taken after prolonged corticosteroid.[58] There is insufficient evidence to guide which strategy is most appropriate but currently the "step-up" strategy is standard of care.[58] A recent randomized controlled trial compared conventional "step-up" therapy to early combined immunosuppression therapy with a TNF inhibitor ("top-down" therapy) and found no statistically significant difference in remission rates between the two strategies. The "step-up" strategy was associated with a lower rate of major adverse outcomes for the

combined therapy.[60] The American Gastroenterological Association (AGA) strongly recommends induction with an anti-TNF drug in patients who have moderately severe CD despite standard therapies, and to maintain remission.[61] NICE guidelines recommend TNF inhibitors for induction, but only after failure of conventional therapy with corticosteroids, azathioprine or mercaptopurine, and should only be used for maintenance if there is clear evidence of active disease.[62]

Ulcerative Colitis

UC is a relapsing and remitting form of IBD, with inflammation typically restricted to the colon and rectum.[63,64] Symptoms include bloody diarrhea with or without mucus, abdominal pain, weight loss, fatigue, rectal urgency and tenesmus.[65] Unlike CD, UC is limited to the colon and does not usually present with fistulas or strictures.[65] The onset of symptoms and diagnosis of UC usually occurs in young to middle-aged adults. The peak age of onset is between 15 and 30 years of age.[64] The prevalence in the U.S. is approximately 205 to 240 cases per 100,000 people.[64] Smoking is protective for UC but it is a risk factor for CD.[64] Colectomy rates range from 5% to 20% of patients.[65] Acute severe ulcerative colitis (ASUC) is a potentially life-threatening condition.[66] The lifetime risk of a severe exacerbation requiring hospitalization is around 25%.[66] Severe flares of UC are associated with considerable morbidity and a mortality rate of approximately 1%.[67] Treatment for UC aims to relieve symptoms during a flare-up and then to maintain remission.[68] The American College of Gastroenterology (ACG) and the NICE Guidelines recommend the use of biologic agents (infliximab, adalimumab, vedolizumab, golimumab) for treating moderately to severely active UC in adults whose disease has responded inadequately to, or have intolerance or contraindications to conventional therapy including mesalamine, corticosteroids, mercaptopurine, or azathioprine.[63,69,70] Continuation of these agents is only recommended if there is clear evidence of response.[63,70] As placebo-controlled trials are common, a 2017 Cochrane Collaboration systematic review evaluated placebo responses for various treatments for ulcerative colitis in adults and found that trials of biologics had the highest placebo response rate (35%; 95% confidence interval [CI] 31-38%; trials = 29; I^2 = 52%; I^2 p value <0.001).[71]

Fee-for-Service Utilization July 1, 2017 to September 30, 2017

In the third quarter of 2017 there were approximately 148 pharmacy claims for biologic agents in the fee-for-service (FFS) population. Seventy-two percent of the claims were for the preferred agents of etanercept or adalimumab. For the non-preferred agents, there were 1-2 claims for tocilizumab, abatacept, golimumab, anakinra, natalizumab and 4-10 claims for certolizumab, apremilast, ustekinumab, tofacitinib, and secukinumab. There were no pharmacy claims for brodalumab, canakinumab, infliximab, ixekizumab, rituximab, tocilizumab, or vedolizumab. Seventy-one percent of the submitted prior authorization (PA) requests were approved. No PA request was submitted for 16% of the claims that were not paid.

Table 1. Approved Indications of Biologics for Autoimmune Conditions.[72]

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo		
Adalimumab (HUMIRA) and biosimilars	≥18 yo	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo(Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥18 yo	Uveitis (non-infectious) ≥18 yo (Humira) HS ≥18 yo (Humira)
Anakinra (KINERET)						≥18 yo		NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo			
Broadalumab (SILIQ)				≥18 yo				
Canakinumab (ILARIS)			≥2 yo					FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4yo HIDS≥ 4 yo MKD≥ 4 yo FMF≥ 4 yo
Certolizumab (CIMZIA)	≥18 yo	≥18 yo			≥18 yo	≥18 yo		
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥18 yo (biosimilars)	≥18 yo	≥18 yo		
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo				≥18 yo	≥18 yo	≥18 yo (SIMPONI)	
Guselkumab (TREMFYA)				≥18 yo				
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo (Remicade) ≥18 yo (biosimilars)	
Ixekizumab (TALTZ)				≥18 yo	≥18 yo			
Natalizumab (TYSABRI)		≥18 yo						MS ≥18 yo
Rituximab (RITUXAN)						≥18 yo		CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo
Sarilumab (KEVZARA)						≥18 yo		
Secukinumab (COSENTYX)	≥18 yo			≥18 yo	≥18 yo			
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo		CRS ≥2 yo GCA ≥18 yo
Tofacitinib (XELJANZ)					≥18 yo	≥18 yo		
Ustekinumab (STELARA)		≥ 18 yo		≥12 yo	≥18 yo			
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo	

Abbreviations: CLL = Chronic Lymphocytic Leukemia; CRS = Cytokine Release Syndrome; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; HS = Hidradenitis Suppurativa; MKD = Mevalonate Kinase Deficiency; MS =

Multiple Sclerosis; MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; SLE = Systemic Lupus Erythematosus; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic Syndrome; yo = years old.

Table 2. Mechanisms of Action, Dosing and Formulations of Biologics for Autoimmune Conditions.[72]

Generic Name	Maintenance Dosing	How Supplied
CD-20 Inhibitor		
Rituximab	1000 mg IV every 2 weeks x 2 doses (one course) repeated every 24 weeks	100 and 500 mg IV vials
Integrin Receptor Antagonist		
Natalizumab	300 mg IV every 4 weeks	300 mg IV vial
Vedolizumab	300 mg IV every 8 weeks	300 mg IV vial
IL-1 Receptor Antagonist		
Anakinra	100 mg SC once daily	100 mg SC Injection
Canakinumab	4 mg/kg SC every 4 weeks	150 mg SC Injection
IL-6 Receptor Antagonist		
Tocilizumab	**Adults:** 4 to 8 mg/kg IV every 4 weeks OR 162 mg SC every week or every other week based on clinical response **Pediatrics**: 8-12 mg IV Infusion depending on indication and weight Cytokine Release Syndrome: IV dose varies by weight (12 mg/kg for <30 kg; 8 mg/kg for ≥30 kg)	80, 200 and 400 mg IV vials and 162 mg SC Injection
Sarilumab	200 mg SC every 2 weeks	150 mg and 200 mg prefilled syringes
IL-12 and IL-23 Inhibitor		
Ustekinumab	Psoriasis: SC dosing varies by weight for adolescents (0.75 mg/kg if <60 kg; 45 mg if 60-100 kg; 90 mg if >100 kg) and adults (45 mg if ≤100 kg; 90 mg if >100 kg) every 12 weeks Psoriatic Arthritis: 45 mg SC every 12 weeks; if co-existent moderate-to-severe plaque psoriasis and weight of >100 kg, 90 mg every 12 weeks Crohn's Disease: Initial weight-based IV infusion x1 followed by 90 mg SC every 8 weeks	45 and 90 mg SC pre-filled syringe, 45 mg SC vial, and 130 mg IV vial
IL-17 Receptor Antagonist		
Brodalumab	210 mg SC every 2 weeks	210 mg SC Injection
Ixekizumab	80 mg SC every 4 weeks	80 mg SC Injection
Secukinumab	SC dosing varies by indication	150 mg SC Injection
IL-23 Inhibitor		
Guselkumab	100 mg SC every 8 weeks	100 mg prefilled syringe
Janus Kinase Inhibitor		
Tofacitinib	5 mg po twice daily OR 11 mg XR po once daily	5 mg oral immediate release and 11 mg XR
PDE-4 Inhibitor		
Apremilast	30 mg orally twice daily	10, 20 and 30 mg tablets
T Lymphocyte Inhibitor		
Abatacept	**Adults:** 500 mg to 1000 mg (dose varies by weight) IV every 4 weeks OR 125 mg SC once weekly **Pediatrics**: 10 mg/kg IV every 4 weeks (≥6 yo) OR 50 -125 mg (weight based) SC once weekly (≥2 yo)	250 mg IV vial and 125 mg SC Injection
TNF inhibitor		
Adalimumab	SC dosing varies by indication	10, 20, 40 and 80 mg SC Injection

Certolizumab	SC dosing varies by indication	200 mg SC Injection
Etanercept	50 mg SC once weekly	50 mg SC Injection
Golimumab	SC dosing varies by indication IV: 2 mg/kg via IV infusion every 8 weeks	50 and 100 mg SC Injection, 50 mg/4 mL IV vial
Infliximab	3-10 mg/kg via IV infusion – dose and interval varies by indication	100 mg IV vial

Abbreviations: IL = interleukin; IM= intramuscular; IV = intravenous; kg = kilogram; mg = milligram; PDE = phosphodiesterase; po = oral; SC = subcutaneous; TNF = tumor necrosis factor; XR = extended release

Table 3. Selected Outcomes Used for Assessment of Disease Progression in Clinical Trials[73,74]

Ankylosing Spondylitis		
Outcome Measure	**Domains**	**Scale and Scoring**
Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)	Level of symptoms: 1. Fatigue 2. Pain in hips, back and neck 3. Pain in joints other than hips, back or neck 4. Discomfort in areas tender to touch or pressure Mean measurements of: 5. Intensity of morning stiffness 6. Duration of morning stiffness (0 to 2 hours scored on a 0-10 scale)	VAS scale 0-10: 0 is no symptoms, 10 is very severe BASADI score calculation: 1.Add scores for first 4 questions 2. Add one half of the sum of question 5 and 6 3. Divide the result by 5 A BASDI score ≥ 4 (on a scale of 0-10) indicates active disease that warrants consideration of therapy
BASDI 50	• ≥ 50% improvement in BASDAI	
Bath Ankylosing Spondylitis Functional Index (BASFI)	Severity of 10 functional abilities: 1. Putting on socks 2. Bend from the waist to pick up a pen from the floor 3. Reaching up to a high shelf 4. Getting up from an armless chair 5. Getting up off the floor 6. Standing unsupported 7. Climbing 12-15 steps unaided 8. Looking over shoulder 9. Doing physically demanding activities 10. Doing a full day's activities	VAS scale 0-10: easy (0) to impossible (10) BASFI score calculation: Total all 10 items and divide by 10 for final score Reported as change in score from baseline
Assessment of Spondyloarthritis International Society (ASAS) Response	Combines measures of symptoms and disability in 4 disease measures: 1. Spinal inflammation (BASDI questions 5 and 6) 2. Spinal pain 3. Patient global assessment of spondylitis 4. Functional impairment (BASFI score)	Scale of 0-10: 0 is no symptoms, 10 is very severe
ASAS20	• Improvement of ≥ 20% and ≥ 1 unit in ≥ 3 of disease measures above • No worsening of ≥ 20% and ≥ 1 unit in remaining unimproved measure	Assessment of response to therapy by percent in symptom improvement
ASAS40	• Improvement of ≥ 40% and ≥ 2 units in ≥ 3 of disease measures above • No worsening at all in remaining measure	
ASAS Partial Remission	• Reflects low disease activity	Value of ≤ 2 in each of the 4 domains

Ankylosing Spondylitis Disease Activity Score (ASDAS) ASDAS Calculator: http://www.asas-group.org/clinical-instruments/asdas_calculator/asdas.html	Measures severity of symptoms and signs of inflammation including: 1. Back pain 2. Patient global assessment of spondylitis 3. Peripheral pain and swelling (BASDAI score) 4. Duration of morning stiffness (BASDI score) 5. CRP or ESR	Scale of 0-10: 0 is no symptoms, 10 is very severe ASDAS scores: < 1.3 – Inactive Disease 1.4 to 2.1 – Moderate Disease Activity 2.2 to 3.4 – High Disease Activity >3.5 – Very High Disease Activity Improvement Criteria: Change ≥ 1.1 – Clinically Important Improvement Change ≥ 2.0 – Major Improvement
Psoriasis		
Outcome Measure	**Domains**	**Scale and Scoring**
Static Physician's Global Assessment Scale (sPGA)	The static PGA is a 0-5 ordinal rating ranging from "clear" to "very severe psoriasis" as evaluated by the provider	Scale of 0 – 5: 0 = clear; scores 1–5 = increasing severity Response to therapy indicated by a score of 0 or 1
Psoriasis Symptom Inventory (PSI)	Patient reported outcome in 8 areas: 1. Itch 2. Redness 3. Scaling 4. Burning 5. Cracking 6. Stinging 7. Flaking 8. Pain of Lesions	Scale of 0-4: 0 = not at all severe, 1 = mild, 2 = moderate, 3 = severe, and 4 = very severe Score ranges from 0 – 32 Response to therapy indicated by scores < 8 with no single item rated higher than 1
Psoriasis Area and Severity Index (PASI) PASI-75	Measure of overall psoriasis severity and coverage on Head, Upper Extremities, Trunk and Lower Extremities • Erythema • Induration • Scaling 75% Improvement in PASI score	Scale of 0-4: 0 is clear, 1-4 increasing severity PASI score: 1. Sum rows 1, 2, and 3 for each area of the body using 0-4 scale 2. Add an area score based on percentage involvement from 0 (clear) to 6 (≥90% coverage) 3. Multiply score as rated for each body area (0.1, 0.2, 0.3, 0.4 for head, arms, trunk, and legs, respectively) 4. Add all the scores together Composite score ranges from 0 -72: 0 = normal 72 = maximal disease
PsA Response Criteria (PsARC)	Used by the National Institute of Health Care Excellence (NICE) to continue TNF inhibitor therapy with an assessment at baseline and 12 weeks 1. 66 swollen joint score 2. 68 tender joint score 3. Patient global assessment 4. Physician global assessment	**Response** = improvement in ≥ 2 of the 4 tests: -One of which must be the joint tenderness or swelling score -No worsening in any of the four measures • **Improvement** is defined as a decrease ≥ 30% in the swollen or tender joint score and ≥1 in either of the global assessments

Dermatology Quality of Life (DQLI)	10 question patient self-reported assessment 1. How itchy has your skin been? 2. How embarrassed are because of your skin? 3. Has your skin interfered with activities? 4. Has your skin influenced the clothes you wear/ 5. Has your skin affected social activities? 6. How your skin impacted your ability to participate in a sport? 7. Has your skin prevented you from working? 8. Has your skin caused any problems with friends? 9. Has your skin impacted sexual activities? 10. How much has the treatment for your skin affected your daily activities?	Scale of 0-3: 0 not at all, 1 a little, 2 a lot, and 3 very much Interpretation of DQLI score: 0 – 1 no effect at all on patient's life 2 – 5 small effect on patient's life 6 – 10 moderate effect on patient's life 11 – 20 very large effect on patient's life 21 – 30 extremely large effect on patient's life
Rheumatoid Arthritis		
Outcome Measure	**Domains**	**Scale and Scoring**
Disease Activity Score(DAS)-28 DAS-28 calculator https://www.das-score.nl/das28/DAScalculators/dasculators.html	Clinical assessment of disease activity in combination with an acute phase reactant level 1. Assessment of 28 joints for swelling and tenderness - swollen joint count (SJC) - tender joint count (TJC) 2. General health (GH) - patient assessment of disease on a 0-100 scale where 100 means maximal disease activity 3. Either ESR or CRP adjusted with SJC and TJC scores	DAS-28 scoring ranges from 0 to 9.4: <2.6: Remission ≥2.6 and ≤3.2: Low Disease Activity >3.2 and ≤5.1: Moderate Disease Activity >5.1: High disease activity • DAS-28 reduction by 0.6 represents a moderate improvement. • DAS-28 reduction more than 1.2 represents a major improvement.
Health Assessment Questionnaire Disability Index (HAQ-DI)	Assess 8 domains of daily activity – patient self-reported 1. Dressing and Grooming 2. Arising 3. Eating 4. Walking 5. Hygiene 6. Reach 7. Grip 8. Chores or Activities	Scored 0 to 3: 0 - no difficulty 1 - with some difficulty 2- with much difficulty 3 - unable to do HAQ-DI calculation: Sum of all domains then divided by 8 to give total score ranging from 0 (best) to 3 (worst)

American College of Rheumatology (ACR)
 	
ACR 20
 	
ACR 50
 	
ACR 70
	Definition of improvement in RA symptoms
	
	• 20% improvement in tender and swollen joint counts
	• 20% improvement in 3 of 5 remaining ACR core set measures
	  ○ patient global assessment (VAS score)
	  ○ physician global assessment (VAS score)
	  ○ self-reported physical disability (HAQ score)
	  ○ an acute phase reactant (ESR or CRP)
	  ○ patient pain assessment (VAS score)
	
	• 50% improvement in tender and swollen joint counts
	• 50% improvement in 3 of 5 remaining ACR core set measures
	
	• 70% improvement in tender and swollen joint counts
	• 70% improvement in 3 of 5 remaining ACR core set measures
		
		20% improvement
		
		50% improvement
		
		70% improvement

Crohn's Disease		
Outcome Measure	**Domains**	**Scale and Scoring**
Crohn's Disease Activity Score (CDAI)	Evaluation of 8 clinical factors (each weighted and summed to reach a total score) 1. Number of liquid or soft stools each day for 1 week (weight x2) 2. Abdominal pain (graded on a severity scale of 0-3) for 1 week (weight x5) 3. General Well-being (subjective score of 0-4) for 1 week (weight x7) 4. Presence of complications (weight x20) 5. Use of Lomotil or opiates for diarrhea (weight x30) 6. Presence of abdominal mass (graded as 0 [none], 2 [questionable] or 5 [definite]) (weight x10) 7. Absolute deviation of Hematocrit from 47% (men) or 42% (women) (weight x6) 8. Percentage deviation from standard weight (weight x1)	Each factor is weighted and summed to achieve a total score • Scores ≤150 indicate minimal disease • Scores >150 indicate active disease • Scores >450 indicate extremely severe disease

Abbreviations: CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; VAS = visual analog scale

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 review is available in **Appendix 2**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), the Cochrane Collaboration, 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 evidence-based clinical practice 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:

Rheumatoid Arthritis

Cochrane Collaboration

A 2017 update of a 2014 Cochrane Review assessed the efficacy and safety of certolizumab pegol (with or without MTX) compared to placebo (with or without MTX) in RA for adult patients who had not responded to conventional DMARDs.[1] This review included 14 trials (12 for efficacy, n=5422; 13 for safety, n=5273) with at least 3 months of follow-up.[1] The major outcomes investigated included ACR50, HAQ or Short Form Health Survey (SF-36), DAS28, radiological changes, serious adverse events (SAEs), early study withdrawals, and early study withdrawals due to adverse events.[1] Both the 200 mg and 400 mg doses were investigated, but 200 mg every other week dose will be focused on as that is the usual dose for RA maintenance therapy.[1,75] ACR50 was achieved in a significantly higher proportion of certolizumab-treated patients compared to placebo-treated patients based on high quality evidence (RR 3.80; 95% CI 2.42-5.95; ARR 25%; NNT 4).[1] A significant benefit in change in HAQ from baseline was also found with certolizumab based on moderate quality evidence (mean difference [MD] -0.35; 95% CI -0.43 to -0.26).[1] High quality evidence showed a statistically significant benefit in DAS28 with certolizumab and moderate quality evidence showed a statistically significant benefit in radiological changes with certolizumab.[1] An increase in SAE (ARR 3%; NNH 33) as well as an increase in withdrawals due to adverse events (ARR 2%; NNH 58) was found with certolizumab based on high quality evidence.[1] Additionally, a higher number of withdrawals was seen with certolizumab (RR 0.47; 95% CI 0.39-0.56; ARR -29%; NNH 3) based on moderate quality evidence.[1] The authors concluded that these findings confirm that certolizumab is clinically beneficial based on greater efficacy outweighing greater risk of harms in management of RA compared to placebo.[1] There were no head-to-head comparator trials between certolizumab pegol and other anti-TNFs to evaluate.[1]

New Guidelines:

Crohn's Disease

National Institute for Health and Care Excellence

NICE guidance for treating adults with moderate to severe CD after previous treatment with ustekinumab was updated July 2017.[5] Recommendations based on clinical and cost effectiveness which take into consideration evidence and expert opinion are as follows:

- Ustekinumab is recommended as an option for treating moderate to severe active CD for adults who have had an inadequate response with, lost response to, have a contraindication to, or were intolerant of, conventional therapy or a TNF-alpha inhibitor.[5]
- The choice of treatment with ustekinumab or another biologic should be individualized based on a discussion between the patient and provider after weighing risks and benefits.[5] The least expensive option should be chosen if more than one option is acceptable.[5]
- Ustekinumab should be given until treatment failure (including necessity of surgery) or until 12 months after treatment initiation, whichever is shorter.[5] The disease severity should be reassessed at that time to determine if treatment should continue.[5]

Plaque Psoriasis

National Institute for Health and Care Excellence

NICE guidance for treating plaque psoriasis in children and young people with adalimumab, etanercept, and ustekinumab was also updated in July 2017.[6] Recommendations based on clinical and cost effectiveness which take into consideration evidence and expert opinion are as follows:

- Adalimumab is recommended as an option for plaque psoriasis in children and young people age 4 and older if the disease is severe (defined by PASI of 10 or more) and has not responded to standard systemic therapy (cyclosporine, methotrexate, or phototherapy) or if those options are contraindicated or not tolerated.[6]

- Etanercept is recommended as an option for plaque psoriasis in children and young people age 6 and older if the disease is severe (defined by PASI of 10 or more) and has not responded to standard systemic therapy (cyclosporine, methotrexate, or phototherapy) or if those options are contraindicated or not tolerated.[6]
- Ustekinumab is recommended as an option for plaque psoriasis in children and young people age 12 and older if the disease is severe (defined by PASI of 10 or more) and has not responded to standard systemic therapy (cyclosporine, methotrexate, or phototherapy) or if those options are contraindicated or not tolerated.[6]
- Treatment should be discontinued for etanercept at 12 weeks, and adalimumab and ustekinumab at 16 weeks if the psoriasis has not responded adequately (defined as 75% reduction in PASI score from treatment initiation).[6]
- The choice of treatment should be made on an individual patient basis after discussion of advantages and disadvantages of treatments available. The lowest cost option, including the consideration of biosimilars, should be started first after taking administration cost, dose, and product cost per dose into consideration.[6]

Psoriatic Arthritis

National Institute for Health and Care Excellence

NICE guidance for treating adults with active PsA after inadequate response to DMARDs with certolizumab pegol and secukinumab was updated May 2017.[4] Recommendations based on clinical and cost effectiveness which take into consideration evidence and expert opinion are as follows:

- Certolizumab pegol monotherapy or in combination with MTX is recommended for treating active PsA if:
    - It is used as described in the NICE technology appraisal guidance on etanercept, infliximab, and adalimumab for the treatment of PsA;[76] or
    - The patient has a history of TNF-alpha inhibitor treatment but they no longer had a response to the treatment after the first 12 weeks.[4]
- Secukinumab monotherapy or in combination with MTX is recommended for treating active PsA if:
    - It is used as described in the NICE technology appraisal guidance on etanercept, infliximab, and adalimumab for the treatment of PsA;[76] or
    - The patient has a history of TNF-alpha inhibitor treatment but they no longer had a response to the treatment after the first 12 weeks; or
    - TNF-alpha inhibitors are contraindicated but would otherwise be considered as described in the NICE technology appraisal guidance on etanercept, infliximab, and adalimumab for the treatment of PsA.[4,76]
- Assessment of response to certolizumab pegol and secukinumab should be completed after 12 weeks and 16 weeks, respectively.[4] Treatment should only be continued if there is clear evidence of response.[4]

Rheumatoid Arthritis

National Institute for Health and Care Excellence

NICE guidance for treating adults with moderate to severe RA with tofacitinib was updated October 2017.[3] Recommendations based on clinical and cost effectiveness which take into consideration evidence and expert opinion are as follows:

- Tofacitinib in combination with MTX is recommended as an option to treat active RA in adults who have not adequately responded to a combination of conventional DMARDs if the disease is severe (DAS28 >5.1).[3]
- Tofacitinib in combination with MTX is recommended as option to treat active RA in adults who have not adequately responded to other DMARDs, including at least 1 biologic DMARD if the disease is severe (DAS28 >5.1) and the patient cannot have rituximab.[3]
- Tofacitinib monotherapy may be used in adults when MTX is contraindicated or not tolerated when the two criteria above are met.[3]

- Treatment should be continued only if there is a moderate response measured using European League Against Rheumatism (EULAR) criteria at 6 months after initiation.[3] After an initial response, discontinue treatment if at least a moderate EULAR response is not maintained.[3]

European League Against Rheumatism (EULAR)
A 2016 update of the 2013 EULAR recommendations for the management of RA was published in 2017.[2] Recommendations regarding biologics will be the focus of this summary and are as follows:

- If the treatment target is not achieved with the first conventional DMARD, and when poor prognostic factors are present, addition of a biologic or targeted synthetic DMARD (tsDMARD; defined by the guidelines as tofacitinib or baricitinib) should be considered (Level A Strength of Evidence indicating evidence from RCTs or meta-analyses of RCTs); current practice would be to start a biologic (Level D Strength of Evidence indicating expert opinion or extrapolated recommendation from evidence from nonrandomized trials or descriptive studies).[2]
    - This recommendation was expanded to include tsDMARDs such as tofacitinib and baricitinib (which is not currently approved in the U.S.[72]).[2]
- Biologics or tsDMARDs should be combined with a DMARD. In patients who cannot use a concomitant DMARD, IL-6 pathway inhibitors and tsDMARDs may have some advantages compared with other biologics (Level A Strength of Evidence).[2]
    - This recommendation was updated to include tsDMARDs similarly to above as increasing evidence has been published supporting combination therapy.[2]
- If a biologic (Level A Strength of Evidence) or tsDMARD (Level D Strength of Evidence) has failed, treatment with another biologic or tsDMARD should be considered. If one TNF-inhibitor therapy has failed, patients may receive another TNF-inhibitor or an agent with another mode of action.[2]
- If a patient is in persistent remission after having tapered corticosteriods, tapering the biologic may be considered (Level B Strength of evidence indicating either evidence from nonrandomized studies or quasi-experimental studies or recommendations extrapolated from RCTs or meta-analyses of RCTs).[2]

This guideline was rated as high quality using the AGREE II Global Rating Scale. A systematic review process for new literature was performed, recommendations were organized, and there was complete information to inform decision making. However, conflict of interest statements were documented for each member contributing to the guideline and a large majority of the members' document personal remuneration from pharmaceutical companies within the last two years.[2]

New Formulations or Indications:
Actemra (tocilizumab) (May 2017): A new indication was approved for the treatment of adult patients with giant cell arteritis (GCA) for the subcutaneous injection formulation.[7] This approval was based on a randomized, double-blind, multicenter study in which patients with active GCA were randomized to either tocilizumab 162 mg every week or every other week in combination with a 26 week prednisone taper, or two different placebo groups (pre-specified prednisone-taper regimen over 26 weeks and 52 weeks).[77] Enrolled patients were 50 years of age or older with active GCA within 6 weeks before baseline.[77] The proportion of patients achieving the primary efficacy endpoint of sustained remission from week 12 through week 52 was 56% (n=56), 53% (n=26), 14% (n=7), and 18% (n=9), respectively ($p<0.001$ for comparisons of either active treatment with placebo).[77]

Orencia (abatacept) (June 2017): A new indication was approved for the treatment of active psoriatic arthritis in adults.[11] This approval was based on two randomized, double-blind, placebo-controlled studies (n=594) in adult patients with active psoriatic arthritis despite prior DMARD treatment.[78,79] Prior TNF-inhibitor treatment was noted for 37% and 61% of patients in trial 1 and trial 2, respectively.[78,79] The primary efficacy endpoint for both trials was the proportion of patients achieving an ACR20 response at week 24.[78,79] In the first trial (n=170), which was a dose-ranging study, patients received IV study drug at days 1, 15,

29, and every 28 days after for 24 weeks.[79] Patients were randomized to placebo, abatacept 3 mg/kg, abatacept 10 mg/kg (weight range-based dosing: 500 mg for patients weighing less than 60 kg, 750 mg for patients weighing 60 to 100 kg, and 1000 mg for patients weighing greater than 100 kg), or two doses of abatacept 30 mg/kg followed by weight range-based dosing of 10 mg/kg for 24 weeks.[79] In the second trial (n=424), patients were randomized to either weekly SC placebo or abatacept 125 mg without a loading dose for 24 weeks, followed by open-label abatacept 125 mg SC weekly.[78] A higher proportion of patients achieved an ACR20 response at week 24 in both the abatacept 10 mg/kg IV (trial 1) and abatacept 125 mg SC (trial 2) groups compared to placebo (47.5% vs. 19.0%, respectively, p=0.006 vs. placebo in trial 1; 39.4% vs. 22.3%, respectively, p<0.001 vs. placebo in trial 2).[78,79]

Actemra (tocilizumab) (August 2017): A new indication was approved for the IV treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and pediatric patients 2 years of age and older.[7] The efficacy for this indication was assessed in a retrospective analysis of pooled outcome data from clinical trials of CAR T-cell therapies for hematological malignancies.[7] A total of 45 patients treated with tocilizumab 8 mg/kg (12 mg/kg for patients <30 kg) with or without additional high-dose corticosteroids for severe or life-threatening CRS.[7] 31 patients (n=69%; 95% CI 53%-82%) had a response defined as CRS resolved within 14 days of first dose of tocilizumab, no more than 2 doses needed, and no drugs other than tocilizumab or corticosteroids used for treatment.[7] A second independent cohort study of 15 patients confirmed achievement of resolution within 14 days.[7]

Enbrel (etanercept) (September 2017): A new 50 mg/mL Enbrel Mini prefilled cartridge formulation was approved for use with the AutoTouch reusable autoinjector only.[13]

Simponi Aria (intravenous golimumab) (October 2017): Two new indications were approved for the treatment of adult patients with active psoriatic arthritis and adults patients with active ankylosing spondylitis.[10]

- The efficacy for psoriatic arthritis was assessed in a multicenter, randomized, double-blind, placebo-controlled trial (n=480) of adult patients with active psoriatic arthritis despite NSAID or DMARD therapy who were biologic-naïve.[80] Patients were randomized to golimumab 2 mg/kg or placebo IV infusions at weeks 0, 4, 12, and 20.[80] Patients randomized to placebo then received golimumab at week 24, 28 and every 8 weeks after through week 52 while patients randomized to golimumab continued to receive golimumab at week 28 and every 8 weeks after through week 52.[10] A greater proportion of patients achieved the primary efficacy endpoint of an ACR20 response at week 14 in the golimumab group compared to the placebo group (75.1% vs. 21.8%; p<0.001).[80]
- The efficacy for ankylosing spondylitis was assessed in a multicenter, randomized, double-blind, placebo-controlled phase 3 trial (n=208) of adult patients with active ankylosing spondylitis and inadequate response or intolerance to NSAIDs.[81] Patients were randomized to golimumab 2 mg/kg or placebo IV infusions at weeks 0, 4, and 12.[81] Patients randomized to placebo then received golimumab at weeks 16, 20, and every 8 weeks after through week 52 while patients randomized to golimumab continued golimumab at week 20 and every 8 weeks through week 52.[81] A greater proportion of patients achieved the primary efficacy endpoint of an Assessment in Ankylosing Spondylitis (ASAS) 20 response at week 16 in the golimumab group compared to the placebo group (73.3% vs. 26.2%; p<0.001).[81]

Stelara (ustekinumab) (October 2017): An extended indication was approved for moderate to severe plaque psoriasis to include treatment of adolescent patients ages 12-17 years who are candidates for phototherapy or systemic therapy.[8] This approval was based on a multicenter, randomized, double-blind, placebo-controlled phase 3 study of adolescent patients age 12-17 years (n=110) randomized to either placebo or weight-based ustekinumab with a minimum BSA involvement of 10%, PASI score $\geq$12, and a PGA score $\geq$3 whose disease was inadequately controlled by topical therapy.[82] Standard weight-based dosing for ustekinumab was 0.75 mg/kg for patients less than or equal to 60 kg, 45 mg for patients greater than 60 kg and less than or equal to 100 kg, and 90 kg for

patients over 100 kg.[82] A greater proportion of standard weight-based ustekinumab-treated patients compared to placebo-treated patients achieved a PGA score of cleared or minimal (69.4% vs. 5.4%; p<0.001), PASI 75 (80.6% vs. 10.8%; p<0.001), and PASI 90 (61.6% vs. 5.4%; p<0.001) at week 12.[82]

Taltz (ixekizumab) (December 2017): A new indication was approved for the treatment of adults with active psoriatic arthritis.[9] The efficacy for this indication was assessed in 2 randomized, double-blind, placebo-controlled studies in adults with active psoriatic arthritis despite NSAID, corticosteroid, or DMARD treatment.[9] In one trial, only biologic-naïve patients (n=417) were included and 57.9% of the patients in the ixekizumab 80 mg every 4 weeks (Q4W) group achieved the primary efficacy endpoint of an ACR20 response at week 24 compared to 30.2% of placebo-treated patients ($p \leq 0.001$).[83] In the second trial, patients were TNF-alpha inhibitor experienced (n=363) and 53% of the patients in the ixekizumab 80 mg Q4W achieved an ACR20 response at week 24 compared to 20% of placebo-treated patients (p<0.0001).[84]

Xeljanz (tofacitinib) (December 2017): A new indication was approved for the treatment of adult patients with active psoriatic arthritis who have had an inadequate response or intolerance to methotrexate or other DMARDs.[12] The efficacy for this indication was assessed in two multicenter, randomized, double-blind, placebo-controlled trials in adults with active psoriatic arthritis (n=816).[12] The first study randomized patients who had inadequate response with a DMARD to either tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, adalimumab 40 mg SC every 2 weeks, placebo with a switch to tofacitinib 5 mg twice daily at 3 months, or placebo with a switch to tofacitinib 10 mg twice daily at 3 months.[85] The second study randomized patients who had an inadequate response with at least one TNF inhibitor to either tofacitinib 5 mg twice daily, tofacitinib 10 mg twice daily, placebo with a switch to tofacitinib 5 mg twice daily at 3 months, or placebo with a switch to tofacitinib 10 mg twice daily at 3 months.[86] The primary endpoints in both trials were the proportion of patients with an ACR20 response and change from baseline in HAQ-DI at month 3.[85,86] In the first trial of patients with a prior inadequate response to a DMARD, a higher proportion of patients treated with tofacitinib 5 mg twice daily (50%) and 10 mg twice daily (61%) achieved an ACR20 response at month 3 compared to placebo (33%; p=0.01 for comparison of 5 mg dose with placebo; p<0.001 for comparison of 10 mg dose with placebo).[85] For the co-primary endpoint of least squares mean change from baseline in HAQ-DI at month 3, patients treated with tofacitinib 5 mg twice daily and 10 mg twice daily demonstrated greater improvement (-0.35 and -0.40, respectively), compared to placebo (-0.18; p=0.006 for comparison of 5 mg dose with placebo; p<0.001 for comparison of 10 mg dose with placebo).[85] In the second trial of patients with a previous inadequate response to at least one TNF inhibitor, a higher proportion of patients treated with tofacitinib 5 mg twice daily (50%) and 10 mg twice daily (47%) achieved an ACR20 response at month 3 compared to placebo (24%; p<0.001 for both doses compared to placebo).[86] For the co-primary endpoint of least squares mean change from baseline in HAQ-DI at month 3, patients treated with tofacitinib 5 mg twice daily and 10 mg twice daily demonstrated greater improvement (-0.39 and -0.35, respectively), compared to placebo (-0.14; p<0.001 for both doses compared to placebo).[86]

New FDA Safety Alerts:
Otezla (apremilast) (June 2017): A new subsection under the Warnings and Precautions in the prescribing information was added regarding post-marketing reports of severe diarrhea, nausea, and vomiting.[87] Most of the events occurred within the first few weeks of treatment and some patients were hospitalized.[87] Dose reduction or suspension should be considered if severe diarrhea, nausea, or vomiting develops.[87]

Taltz (ixekizumab) (July 2017): An update to the hypersensitivity warning in the prescribing information was added documenting anaphylaxis, including cases leading to hospitalization, has been reported in post-marketing use.[88]

Tysabri (natalizumab) (August 2017): An addition to the warnings documented the higher risk of acute retinal necrosis (ARN) caused by herpes viruses in patients being administered Tysabri.[89] Patients with eye symptoms such as decreased visual acuity, redness, or eye pain should be referred for retinal screening for ARN.[89]

Xeljanz and Xeljanz XR (tofacitinib citrate) (August 2017): An addition to the malignancy and lymphoproliferative disorders warning in the prescribing information documented that other malignancies observed in clinical studies and post-marketing settings include, but are not limited to, lung cancer, breast cancer, melanoma, prostate cancer, and pancreatic cancer.[90]

Remicade (infliximab) (October 2017): Two new subsections were added to the Warnings and Precautions in the prescribing information.[91] The first regards cervical cancer based on a population-based retrospective cohort study using Swedish registries.[91] The data found a 2- to 3-fold increase in the incidence of invasive cervical cancer in women with RA treated with infliximab compared to biologic-naïve patients or the general population.[91] Periodic screening is recommended.[91] The second subsection, "Cardiovascular and Cerebrovascular Reactions During and After Infusion" documents serious cerebrovascular accidents, myocardial ischemia/infarction (some fatal), hypotension, and arrhythmias have been reported during and within 24 hours of infliximab infusion.[91] It is recommended to monitor patients during infusion and discontinue if serious reaction occurs.[91] Further management of reactions should be dictated by signs and symptoms.[91]

Xeljanz and Xeljanz XR (tofacitinib) (December 2017): An addition to the boxed warning was added to include herpes zoster to the list of reported infections.[12] Additionally, information regarding 3 malignancies in patients treated with tofacitinib in the clinical trials for active psoriatic arthritis.[12]

Randomized Controlled Trials:
A total of 252 citations were manually reviewed from the initial literature search. After further review, all 252 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), outcome studied (eg, non-clinical), or published prior to dates of interest.

NEW DRUG EVALUATION: Sarilumab (Kevzara®)

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

Clinical Efficacy:
The approval of sarilumab was based on two randomized, double-blind, placebo-controlled multicenter trials that assessed the safety and efficacy of the drug (the MOBILITY Part B and TARGET studies).[19,20,92] One active comparator study, MONARCH, was published since the approval of sarilumab and several other unpublished studies were also reviewed by the FDA.[18,93]

The MOBILITY Part B study was a randomized, multicenter, double-blind, placebo-controlled phase 3 study comparing sarilumab and placebo over 52 weeks.[19] This study followed MOBILITY Part A which was a dose-ranging phase 2 study.[19] MOBILITY Part B had two cohorts.[19] The first cohort was an extension of a previous phase 2 dose-ranging study used only for the safety analysis.[19] The second cohort included patients randomized after identification of the optimal dose and data from this population was used both for safety and efficacy analyses.[19] The patients in the efficacy cohort (Cohort 2) were randomized to sarilumab 150 mg every 2 weeks, sarilumab 200 mg every 2 weeks, or placebo, in combination with weekly MTX.[19] Patients enrolled in the study had a mean age of 50 years, mean duration of RA for 9 years, and a mean HAQ-DI score of 1.6 (indicating moderate to severe functional disability).[19] Most subjects (80.7%) had no prior biologic DMARD exposure.[19] Three primary efficacy endpoints were investigated: the proportion of patients achieving an ACR20 at week 24, change from physical function baseline to week 16 as assessed by HAQ-DI, and change from baseline to week 52 in the modified Sharp/van der Heijde (SHS) score which assesses radiographic progression of structural damage.[19] A change of around 5 units or more in the SHS score is considered clinically significant.[27] A significant benefit in each of these primary efficacy endpoints was seen with both doses of sarilumab in combination with MTX compared to placebo in combination with MTX.[19] An ACR20 response was seen in 58.0% and 66.4% of patients within the sarilumab 150 mg and 200 mg groups, respectively, compared to 22.4% in the placebo group (150 mg vs. placebo: ARR 35.6%, NNT 3; 200 mg vs. placebo: ARR 44.0%, NNT 3; $p<0.0001$ for both doses of sarilumab vs. placebo).[19] Changes from baseline in HAQ-DI at week 16 for the sarilumab 150 mg, sarilumab 200 mg, and placebo groups were -0.53 $\pm$0.03, -0.55 $\pm$0.03, and -0.29 $\pm$0.03, respectively ($p<0.0001$ for both doses of sarilumab vs. placebo) which are clinically significant differences.[19] Changes from baseline in the SHS at week 52 were statistically but not clinically significant at 0.90 $\pm$4.66, 0.25 $\pm$4.61, and 2.78 $\pm$7.73, respectively, for sarilumab 150 mg, sarilumab 200 mg, and placebo ($p<0.0001$ for both doses of sarilumab vs. placebo).[19] Overall, this manufacturer-funded study was graded as poor quality with significant limitations from unclear methods of blinding for the primary endpoint and high overall attrition (38.5%).[19] Since approximately 80% of patients included in the study were biologic-naive, applicability to patients who have previously tried and failed other biologics is limited.

The TARGET study was a multicenter, randomized, double-blind, placebo-controlled, phase 3 study in which patients were randomized to sarilumab 150 mg, sarilumab 200 mg, or placebo every 2 weeks in combination with background oral DMARD therapy for 24 weeks.[20] Patients enrolled in the study had a mean age of 52 years, mean duration of RA for 28 years, and mean HAQ-DI of 1.77.[20] Approximately 77% of patients had prior exposure to one anti-TNF agent and 23% had prior exposure to more than one anti-TNF agent.[20] The two primary efficacy endpoints studied were the proportion of patients with an ACR20 at week 24 and change from baseline to week 12 in physical function assessed by HAQ-DI.[20] A statistically significant response in ACR20 at week 24 was seen for the sarilumab 150 mg group (55.8% vs. 33.7%; ARR 22.1%; NNT 5; $p<0.0001$) and the sarilumab 200 mg group (60.9% vs. 33.7%; ARR 27.2%; NNT 4; $p<0.0001$) versus placebo.[20] A statistically significant improvement was also seen in change in HAQ-DI score from baseline to week 12 for both the sarilumab 150 mg group (-0.46 $\pm$0.04;

p<0.001) and 200 mg group (-0.47 ±0.04; p<0.001) versus placebo (-0.26 ±0.04), though these results may not be clinically significant.[20] Overall, this manufacturer-funded study was graded as fair quality with adequate randomization, double-dummy blinding, but high overall attrition.

The MONARCH study was a multicenter, randomized, active-controlled, double-blind, double-dummy, phase 3 superiority trial in which patients were randomized to sarilumab 200 mg or adalimumab 40 mg every 2 weeks for 24 weeks.[18] This study was not published at the time of the FDA review and was only highlighted in their report.[93] Patients enrolled in the study were a mean age of 52 years with a mean duration of RA for 7 years, and a mean HAQ-DI of 1.6.[18] Patients included were inappropriate candidates for continued MTX therapy due to intolerance or inadequate response, and patients with prior biologic use were excluded.[18] The primary efficacy endpoint was change from baseline in DAS28-ESR (which evaluates DAS28 with the erythrocyte sedimentation rate as opposed to the C reactive protein in DAS28-CRP) at week 24, in which a statistically significant benefit was seen with sarilumab compared to adalimumab (-3.28 vs. -2.20; difference: -1.08; 95% CI -1.36 to -0.79; p<0.0001).[18] A statistically significant difference was also seen in the secondary endpoints of ACR20 at week 24 (71.7% vs. 58.4%; ARR 13.3%; NNT 8; p=0.0074), ACR50 at week 24 (45.7% vs. 29.7%; ARR 16.0%; NNT 7; p=0.0017), and ACR70 at week 24 (23.4% vs. 11.9%; ARR 11.5%; NNT 9; p=0.0036) for sarilumab versus adalimumab.[18] A statistically significant difference was also found in mean change in HAQ-DI score from baseline to week 24 for sarilumab compared to adalimumab (-0.61 vs. -0.43; 95% CI -0.31 to -0.06; p=0.0037).[18] There is insufficient comparative evidence for RA radiographic progression for sarilumab and adalimumab as this was not studied in the trial.[18] Overall, this was a good quality manufacturer-funded trial with adequate allocation concealment, double-dummy blinding, and low attrition.

Other studies reviewed to support efficacy of sarilumab in the FDA clinical review include MOBILITY Part A, SARIL-RA-ASCERTAIN, SARIL-RA-ONE, SARIL-RA-COMPARE, SARIL-RA-EASY, ACT11575, and SARIL-RA-EXTEND.[93] The phase 2 MOBILITY Part A study showed numerically higher proportion of responders who achieved ACR20 at 12 weeks with sarilumab 150 mg and 200 mg every 2 weeks versus placebo (66.7% and 65.4% vs. 46.2%; p=0.0426 and 0.0363, respectively).[93] A significantly higher proportion of ACR50 responders was also seen for the sarilumab 200 mg every 2 weeks group compared to placebo (40.4% vs. 15.4%; p<0.01).[93] SARIL-RA-ASCERTAIN was an active comparator study of sarilumab and tocilizumab, the only other approved IL-6 receptor blocking agent.[93] Exploratory efficacy endpoints found generally similar efficacy although they were not powered to make comparative efficacy assessments.[93] SARIL-RA-ONE, SARIL-RA-COMPARE, SARIL-RA-EASY, ACT11575, and SARIL-RA-EXTEND were excluded from this review due to early study discontinuation and lack of efficacy analyses, a focus on usability or immunogenicity, or wrong comparator (no control).

Clinical Safety:
The FDA safety analysis of sarilumab included a total of 7875 patients treated with sarilumab in combination with a DMARD, 264 patients treated with sarilumab monotherapy, and 1240 patients treated with placebo in combination with a DMARD.[93] Most of the FDA clinical review safety analysis focused on the phase 3 placebo-controlled population in the pre-rescue period.[93] This group included 579 patients treated with sarilumab 150 mg every 2 weeks plus a DMARD, 582 patients treated with sarilumab 200 mg every 2 weeks plus a DMARD, and 579 patients treated with placebo plus a DMARD from the MOBILITY Part B and TARGET studies.[93]

In the phase 3 placebo-controlled population, there were more serious adverse events (SAEs) in the sarilumab arms compared to placebo (2.1% in placebo vs. 3.3% in sarilumab 150 mg every 2 weeks and 5.8% in sarilumab 200 mg every 2 weeks).[93] The most common SAE were infections and infestations (0.7% vs. 1.0% vs. 1.0%).[93] There were also more SAE rates of neutropenia in the sarilumab 150 mg (1/579; 0.2%) and 200 mg (4/582; 0.7%) arms compared to placebo (0/579; 0%).[93] Adverse events leading to discontinuation for this population was also higher in the sarilumab 150 mg and 200 mg groups (6.4% and 7.6%, respectively)

compared to placebo (3.1%).[93] A summary of the common treatment-emergent adverse events (TEAEs) is in **Table 4.** The TEAEs are consistent with the expected effects of IL-6 inhibition in the RA population.[93] Statistical differences between groups were not reported.[93]

Table 4. Treatment-Emergent Adverse Events (≥0.5% Higher Incidence in Subjects in ≥1 of the Sarilumab Groups) in the Phase 3 Placebo-Controlled Population.[93]

	Placebo + DMARD	Sarilumab 150 mg every 2 weeks + DMARD	Sarilumab 200 mg every 2 weeks + DMARD
Neutropenia	1/579 (0.2%)	40/579 (6.9%)	59/582 (10.1%)
Increased alanine aminotransferase	10/579 (1.7%)	27/579 (4.7%)	28/582 (4.8%)
Injection site erythema	5/579 (0.9%)	26/579 (4.5%)	23/582 (4.0%)
Upper respiratory tract infection	14/579 (2.4%)	21/579 (3.6%)	20/582 (3.4%)
Urinary tract infection	11/579 (1.9%)	18/579 (3.1%)	17/582 (2.9%)
Nasopharyngitis	14/579 (2.4%)	18/579 (3.1%)	14/582 (2.4%)
Hypertension	8/579 (1.4%)	7/579 (1.2%)	13/582 (2.2%)
Leukopenia	0/579 (0%)	5/579 (0.9%)	13/582 (2.2%)
Bronchitis	9/579 (1.6%)	5/579 (0.9%)	12/582 (2.1%)
Sinusitis	5/579 (0.9%)	6/579 (1.0%)	12/582 (2.1%)
Injection site pruritus	1/579 (0.2%)	13/579 (2.2%)	11/582 (1.9%)
Hypertriglyceridemia	3/579 (0.5%)	16/579 (2.8%)	8/582 (1.4%)

The common TEAEs for placebo, sarilumab 150 mg, and sarilumab 200 mg were similar in the entire double-blind population as well: infections and infestations were the most common (28.6%, 34.2%, and 35.2%, respectively); neutropenia (0.5%, 9.8%, and 14.2%, respectively), upper respiratory infections (4.8%, 6.4%, and 7.1%, respectively), and increased alanine aminotransferase (2.6%, 6.7%, and 6.8%, respectively) were also common.[93] Of note, neutropenia appeared to be dose-dependent.[93] Overall, there were a total of 26 deaths from the safety analysis.[93] This rate does not exceed that of the general RA population and the majority of causes (i.e., infection, cardiovascular event, or malignancy) are consistent with that of the general RA population.[93]

The MONARCH study's comparative safety data between adalimumab 40 mg every 2 weeks and sarilumab 200 mg every 2 weeks was not included in the main FDA safety analysis. In this study, the proportion of patients with any adverse event were similar between adalimumab (63.6%) and sarilumab (64.1%).[18] The number of SAEs (6.5% vs. 4.9%), adverse events leading to treatment discontinuation (7.1% vs. 6.0%), infections (27.7% vs. 28.8%), and serious infections (1.1% vs. 1.1%) were similar for adalimumab and sarilumab, respecitvely.[18] However, risk of neutropenia was higher in the sarilumab group (13.6%) compared to the adalimumab group (0.5%).[18] Injection site reactions were also more common in sarilumab-treated patients (9.2%) compared to adalimumab-treated patients (4.3%).[18] The study was not powered to detect differences in adverse events.[18]

Similar to other biologic treatments for RA, labeling for sarilumab includes a boxed warning for risk of serious infections.[92,93] In the phase 3 placebo-controlled population, the incidence rates for infections (17.3% vs. 21.1% vs. 22.3%) and serious infections (0.7% vs. 1.0% vs. 1.0%) were lower with placebo compared to

sarilumab 150 mg and sarilumab 200 mg, respectively.[93] Opportunistic infections were similar with placebo and sarilumab 150 mg but higher with sarilumab 200 mg (0.3% vs. 0.3% vs. 0.7%, respectively).[93]

Labeling for sarilumab also has warnings for neutropenia, thrombocytopenia, elevated liver enzymes, lipid abnormalities, gastrointestinal perforation, hypersensitivity, and avoiding use with live vaccines.[92] These warning labels are similar to tocilizumab, another IL-6 antagonist treatment.[94]

Look-alike / Sound-alike Error Risk Potential: None identified.

Table 5. Pharmacology and Pharmacokinetic Properties of Sarilumab.[92]

Parameter	
Mechanism of Action	Binds to soluble and membrane-bound IL-6 receptors to inhibit IL-6-mediated signaling
Oral Bioavailability	N/A – administered via subcutaneous injection
Distribution and Protein Binding	Apparent volume of distribution of 7.3 L at steady state
Elimination	Not via renal or hepatic pathways; eliminated by parallel linear, non-saturable proteolytic and non-linear saturable target-mediated elimination pathways
Half-Life	Concentration dependent. 200 mg q2w: up to 10 days; 150 mg q2w: up to 8 days
Metabolism	Has not been characterized; expected to be degraded into small peptides and amino acids via catabolic pathways

Abbreviations: IL-6 = interleukin-6; L= liter; N/A = not applicable; q2w = every two weeks

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:
1) Symptomatic improvement (ACR20/50/70, DAS28)
2) Functional status (HAQ-DI)
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoints:
1) ACR20 at week 24
2) Change from baseline in HAQ-DI at weeks 12 and 16
3) Change from baseline in SHS at week 52
4) Change from baseline in DAS28-ESR at week 24

Table 6. Comparative Evidence Table for Sarilumab.

Ref./Study Design	Drug Regimens Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
1. Genovese MC, et al.[19]	Cohort 1 (Safety outcomes) 1. Sarilumab 150 mg q2w	Demographics: • Mean age: 50 yr • 82% Female • 86% White • Mean duration of RA: 9 yr	Efficacy Analysis Group (Cohort 2):	Primary Endpoints: ACR20 at week 24 1. 232/400 (58.0%) 2. 265/399 (66.4%) 3. 133/398 (33.4%)	35.6%/3 44.0%/3	Serious AEs 1. 38 (8.8%) 2. 48 (11.3%) 3. 23 (5.4%)	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Randomization was performed centrally and patients were randomized 1:1:1 for cohort 2 (those randomized after dose selection). Allocation

MOBILITY Part B (Phase 3) MC, DB, PC, RCT	2. Sarilumab 200 mg q2w 3. Placebo <u>Cohort 2 (Efficacy and safety outcomes)</u> 1. Sarilumab 150 mg q2w + weekly MTX 2. Sarilumab 200 mg q2w + weekly MTX 3. Placebo + weekly MTX 52 weeks Randomized 1:1:1	• Mean MTX dosage: 15.4 mg/week • Prior biologic DMARD exposure: 20.2% • Concomitant corticosteroids: 64.9% • Mean SHS: 49.7 • Mean HAQ DI: 1.6 <u>Key Inclusion Criteria</u>: • Age 18-75 years • Active RA ≥3 months despite tx with MTX for ≥12 weeks at a stable dosage at ≥6 weeks prior to screening • ≥1 documented bone erosion OR positive for anti-CCP antibodies OR seropositive for rheumatoid factor on screening lab tests at baseline <u>Key Exclusion Criteria</u>: • Uncontrolled concomitant diseases • Significant extra-articular manifestations of RA • Functional class IV RA (indicating severe disease) • Other inflammatory joint diseases • Current/recurrent infections • Prior nonresponse to a biologic DMARD	<u>ITT</u>: Total: 1197 1. 400 2. 399 3. 398 <u>Attrition</u>: Total: 461 (38.5%) 1. 130 (32.5%) 2. 129 (32.4%) 3. 202 (50.8%) <u>Safety Analysis Group (Cohorts 1 & 2)</u> Total: 1282 1. 431 2. 424 3. 427	p<0.0001 for both strengths of sarilumab + MTX vs. placebo + MTX (RR & CI NR) Change from baseline in HAQ DI at week 16 (<u>+</u> SEM) 1. -0.53 <u>+</u> 0.03 2. -0.55 <u>+</u> 0.03 3. -0.29 <u>+</u> 0.03 p<0.0001 for both strengths of sarilumab + MTX vs. placebo + MTX (CI NR) Change from baseline in the SHS at week 52 (<u>+</u> SEM) 1. 0.90 <u>+</u> 4.66 2. 0.25 <u>+</u> 4.61 3. 2.78 <u>+</u> 7.73 p<0.0001 for both strengths of sarilumab + MTX vs. placebo + MTX (CI NR) <u>Key Secondary Endpoint</u>: ACR70 maintained x24w 1. 51/400 (12.8%) 2. 59/399 (14.8%) 3. 12/398 (3.0%) p<0.0001 for both strengths of sarilumab + MTX vs. placebo + MTX (RR & CI NR)	 NA NA 9.8%/11 11.8%/9	<u>AEs Leading to DC</u> 1. 54 (12.5%) 2. 59 (13.9%) 3. 20 (4.7%) <u>Infections and Infestations</u> 1. 173 (40.1%) 2. 168 (39.6%) 3. 133 (31.1%) <u>Injection Site Reactions</u> 1. 9% 2. 10.1% 3. 1.2% <u>Neoplasms</u> 1. 4 (0.9%) 2. 3 (0.7%) 3. 1 (0.2%) <u>AEs Leading to Death</u> 1. 2 (0.5%) 2. 1 (0.2%) 3. 2 (0.5) p-values, RR, 95% CI were NR	NA NA NA NA NA	stratified by region and prior use of biologic agents. Baseline characteristics similar among treatment groups. <u>Performance Bias</u>: Unclear. Noted double-blinded but did not specify who was blinded or how. Noted a protocol was approved but did not specify that it was standardized across all sites and followed consistently. Use of subjective outcomes may increase bias. <u>Detection Bias</u>: Unclear. Investigators were blinded to CRP and IL-6 levels. Radiograph readers were blinded to treatment assignment, chronologic order of the radiographs, and patient's clinical status. However, method for blinding primary endpoint of ACR20 assessment not mentioned. <u>Attrition Bias</u>: High. Overall high attrition of 38.5%. Attrition similar between sarilumab groups and significantly higher in placebo group. ITT used for efficacy analysis. Missing data for ACR20 classified as nonresponse giving a conservative estimate of effect. Radiographic progression data were imputed using linear extrapolation for missing or post-rescue therapy data. Data before the rescue therapy period were included as observed <u>Reporting Bias</u>: High. Funded by the manufacturer who had a role in the study design, data collection, data analysis, data interpretation, and writing of the manuscript. Study protocol not available. Not all secondary endpoints reported. Confidence intervals not reported. **Applicability**: <u>Patient</u>: The mean age 50 years. Broad exclusion criteria limits applicability to patients with other uncontrolled comorbid condition(s). ~80% of patients did not have prior exposure to a biologic DMARD, which affects applicability. <u>Intervention</u>: Weekly MTX was given in combination with all treatments, which reflects clinical practice with other biologics.

								Comparator: Placebo appropriate to determine efficacy, though a comparative efficacy study would have provided more information regarding place in therapy. Outcomes: Primary outcomes were an appropriate assessment for the treatment of RA, although ACR50 or ACR70 might be considered more clinically important. Setting: The study was conducted at 199 centers across 36 countries. 18.7% of the patients were from either Austria, Australia, Belgium, Canada, Finland, Germany, Greece, Hungary, New Zealand, Portugal, Spain, or the U.S. Proportion of patients from the US not specified.
2. Fleischmann R, et al.[20] TARGET 3-arm, MC, DB, PC, RCT	1. Sarilumab 150 mg q2w+ background conventional synthetic DMARD(s) 2. Sarilumab 200 mg q2w + background conventional synthetic DMARD(s) 3. Placebo q2w + background conventional synthetic DMARD(s) 24 weeks Randomized 1:1:1	Demographics: • Mean age: 52 yr • 82% Female • 71% White • Mean duration of RA: 12.1 yr • Background MTX: 86% • Background leflunomide: 9% • Background sulfasalazine: 6% • Background hydroxychloroquine: 7% • Prior exposure to 1 anti-TNF agent: 77% • Prior exposure to >1 anti-TNF agent: 23% • Mean HAQ DI: 1.77 • Mean DAS28-CRP: 6.2 Key Inclusion Criteria: • Age ≥18 years • Active RA ≥6 months • Inadequate response or intolerance to ≥1 anti-TNF therapy • Continuous tx with background conventional synthetic DMARD(s)	ITT: Total: 546 1. 181 2. 184 3. 181 Attrition: Total: 187 (34%) 1. 56 (31%) 2. 51 (28%) 3. 80 (44%)	Primary Endpoints: ACR20 at week 24 1. 101/181 (55.8%) 2. 112/184 (60.9%) 3. 61/181 (33.7%) p<0.0001 for both strengths of sarilumab + csDMARD(s) vs. placebo + csDMARD(s) (RR & CI NR) Change from baseline in HAQ DI at week 12 (± SEM) 1. -0.46 ± 0.04 2. -0.47 ± 0.04 3. -0.26 ± 0.04 p<0.001 for both strengths of sarilumab + csDMARD(s) vs. placebo + csDMARD(s) (CI NR) Secondary Endpoints: Mean adjusted change in DAS28-CRP (± SEM) 1. -2.4 ± 0.11 2. -2.8 ± 0.11 3. -1.4 ± 0.12 p<0.0001 for both strengths of sarilumab + csDMARD(s) vs. placebo + csDMARD(s) (CI NR)	22.1%/5 27.2%/4 NA NA	Serious AEs 1. 6 (3.3%) 2. 10 (5.4%) 3. 6 (3.3%) AEs leading to DC 1. 14 (7.7%) 2. 17 (9.2%) 3. 8 (4.4%) AEs leading to death 1. 0 (0%) 2. 0 (0%) 3. 1 (0.6%) Infections 1. 40 (22.1%) 2. 56 (30.4%) 3. 48 (26.5%) Injection-site reactions 1. 7.2% 2. 8.2% 3. 1.1% Malignancies 1. 1 2. 1	NA NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Patients randomized centrally and allocated 1:1:1. Baseline characteristics similar between groups. Patients stratified by number of previous anti-TNF agents. Performance Bias: Unclear. Double-blind but not specified which groups blinded. Double-dummy using matching placebo subcutaneous injections. Protocol was approved by ethics committees/institutional review boards. Use of subjective outcomes increases risk of bias. Detection Bias: Low. Investigators blinded and assessors had no access to patient data. Attrition Bias: High. ITT utilized for efficacy and safety analyses. High total attrition (34%) but lower attrition with sarilumab than placebo. Differential attrition >10% for sarilumab vs. placebo with placebo having greater attrition. LOCF applied to impute missing ACR20 data and HAQ-DI data. Reporting Bias: Low. All primary outcomes reported. Documented end point in predefined hierarchy of secondary endpoints. Study was funded by the manufacturer. Confidence intervals not reported **Applicability:**

		Key Exclusion Criteria: • Uncontrolled concomitant disease • Significant extra-articular manifestations of RA • Functional class IV RA • Other inflammatory diseases • Current/recurrent infections • Receiving prednisone (or equivalent) >10 mg/day		ACR50 at week 24: 1. 67/181 (37.0%) 2. 75/184 (40.8%) 3. 33/181 (18.2%) p<0.0001 for both strengths of sarilumab + csDMARD(s) vs. placebo + csDMARD(s) (RR & CI NR) ACR70 at week 24: 1. 36/181 (19.9%) 2. 30/184 (16.3%) 3. 13/181 (7.2%) p<0.001 for #1 and p<0.01 for #2 vs. placebo + csDMARD(s) (RR & CI NR)	18.8%/6 22.6%/5 12.7%/8 9.1%/11	3. 1 p-values, RR, 95% CI were NR		Patient: Broad exclusion criteria limits applicability to patients with uncontrolled concomitant disease and class IV RA. Intervention: Subcutaneous injections were self-administered or administered by a caregiver. Comparator: A comparative efficacy comparison would have been more meaningful than placebo. Outcomes: Primary outcome was an appropriate assessment for the treatment of rheumatoid arthritis. The short study duration prevents ability to report long-term outcomes data. Setting: The study was conducted at 155 study centers across 27 countries including the U.S.
3. Burmester GR, et al.[18] MONARCH MC, active-controlled, DB, DD, phase 3 superiority RCT	1. Sarilumab 200 mg q2w plus placebo q2w 2. Adalimumab 40 mg q2w plus placebo 24 weeks	Demographics: • Mean age: 52 years • 83.2% Female • 90.8% White • Mean duration of RA: 7 yr • Use of 1 prior csDMARD: 46.4% • Concomitant oral corticosteroids: 54.8% • Mean HAQ-DI: 1.6 • Mean DAS28-CRP: 6.0 Key Inclusion Criteria: • Active RA ≥3 months • Intolerant or inappropriate candidate for continued MTX or MTX inadequate responders Key Exclusion Criteria: • Prior biological disease-modifying antirheumatic drugs (bDMARD) experience	ITT: Total: 369 1. 184 2. 185 Attrition: Total: 45 (12.2%) 1. 19 (10.3%) 2. 26 (15.7%)	Primary Endpoint: Change from baseline in DAS28-ESR at week 24 1. -3.28 2. -2.20 Difference: -1.08 95% CI (-1.36 to -0.79) P<0.0001 Secondary Endpoint: DAS28-ESR remission (<2.6) at week 24 1. 49 (26.6%) 2. 13 (7.0%) OR 4.88 95% CI (2.54 – 9.39) P<0.0001 ACR20 at week 24 1. 132 (71.7%) 2. 108 (58.4%) P=0.0074 (RR & CI NR) ACR50 at week 24 1. 84 (45.7%) 2. 55 (29.7%)	NA 19.6%/6 13.3%/8 16.0%/7	Serious AEs 1. 9 (4.9%) 2. 12 (6.5%) AEs leading to DC 1. 11 (6.0%) 2. 13 (7.1%) Infections 1. 53 (28.8%) 2. 51 (27.7%) Serious infections 1. 2 (1.1%) 2. 2 (1.1%) Neutropenia 1. 25 (13.5) 2. 1 (0.5%) Injection site reactions 1. 17 (9.2%) 2. 8 (4.3%) Deaths 1. 1 (0.5%)* 2. 0 (0%)	NA NA NA NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: Low. Centrally randomized using an interactive voice response system. Baseline characteristics similar between groups. Performance Bias: Low. Double-dummy blinding was used. A protocol was used. Use of subjective outcomes increases risk of bias. Detection Bias: Low. Investigators did not have access to randomization information. Attrition Bias: Low. Low total and differential attrition. ITT was used for efficacy analysis. Patients who discontinued treatment were considered nonresponders. Reporting Bias: Low. Study protocol was approved by ethics committees/institutional review boards. Primary and secondary endpoints were reported per hierarchy. The study was funded by the manufacturer. **Applicability**: Patient: Patients with prior bDMARD experience were excluded, limiting the applicability to bDMARD retreatment. Intervention: Sarilumab dosing appropriate. Comparator: Adalimumab dosing appropriate. Outcomes: Primary outcome was an appropriate assessment for RA.

				P=0.0017 (RR & CI NR) ACR70 at week 24 1. 43 (23.4%) 2. 22 (11.9%) P=0.0036 (RR & CI NR) HAQ-DI LS mean change from baseline at week 24 1. -0.61 2. -0.43 Difference: -0.18 95% CI (-0.31 to -0.06) P=0.0037	11.5%/9 NA	*Acute cardiac failure secondary to aortic dissection and papillary muscle rupture		Setting: Conducted at 86 study centers in Europe, Israel, Russia, South Africa, South America, South Korea, and the USA.

Abbreviations [alphabetical order]: ACR20 = American College of Rheumatology 20% Improvement Criteria; ACR50 = American College of Rheumatology 50% Improvement Criteria; ACR70 = American College of Rheumatology 70% Improvement Criteria; AE = adverse event; ARR = absolute risk reduction; bDMARD = biologic disease-modifying antirheumatic drug; CCP = cyclic citrullinated peptide; CI = confidence interval; CRP = C-reactive protein; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; DAS28-CRP = Disease Activity Score in 28 joints using the C-reactive protein level; DAS28-ESR = 28-joint disease activity score using erythrocyte sedimentation rate; DB = double-blinded; DC = discontinuation; DD = double-dummy; DMARD = disease-modifying anti-rheumatic drug; HAQ-DI = Health Assessment Questionnaire disability index; IL-6 = interleukin-6; ITT = intention to treat; LOCF = last observation carried forward; LS = least squares; MC = multicenter; mITT = modified intention to treat; MTX = methotrexate; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; OR = odds ratio; PC = placebo-controlled; PP = per protocol; q2w = every 2 weeks; RA = rheumatoid arthritis; RCT = randomized controlled trial; RR = relative risk; SEM = standard error of the mean; SHS = Sharp/van der Heijde score; TNF = tumor necrosis factor; tx = treatment; yr = year.

NEW DRUG EVALUATION: Guselkumab (Tremfya®)

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

Clinical Efficacy:

Guselkumab, an interleukin (IL)-23 inhibitor, is indicated for treatment of adults with moderate to severe PsO who are candidates for systemic therapy or phototherapy. Two phase 3 trials (VOYGAGE 1 and VOYAGE 2) provide efficacy and safety data for guselkumab in PsO compared to placebo or adalimumab.

In VOYAGE 1, guselkumab was compared to placebo for 16 weeks or adalimumab for 48 weeks in 837 patients with moderate to severe PsO.[21] Patients were randomized in a 2:1:2 ratio to guselkumab 100 mg administered at weeks 0, 4 and 12 and then every 8 weeks; placebo administered at weeks 0, 4, and 12 followed by guselkumab 100 mg at weeks 16 and 20 and every 8 weeks thereafter; or adalimumab 80 mg at week 1 followed by 40 mg every 2 weeks. Co-primary endpoints were the proportion of patients achieving an IGA score of cleared/minimal disease (IGA 0/1) and 90% or greater improvement in PASI score from baseline (PASI 90) at week 16. Secondary endpoints included the proportion of patients who achieved IGA 0/1, PASI 75, and PASI 90 scores at week 16, 24 and 48 in the guselkumab treated group compared to those who received adalimumab. At week 16, the co-primary endpoints of IGA score 0/1 and PASI 90 were achieved by more guselkumab-treated patients compared to placebo patients (85.1% vs. 6.9%; ARR = 78.2%; NNT = 2 and 73.3% vs. 2.9%; ARR = 70.4%; NNT = 2 respectively; p<0.001 for each).[21] At week 16, more guselkumab-treated patients achieved IGA 0/1, PASI 90, and PASI 75 than adalimumab- treated patients (85.1% vs. 65.9%; ARR = 19.2%; NNT =6: 73.3% vs. 49.7%; ARR = 23.6%; NNT = 5: 91.2% vs. 73.1%; ARR = 18.1%; NNT = 6 respectively; p<0.001 for each outcome). A[21] At week 24, IGA score 0/1, and PASI 90 were achieved by significantly more guselkumab-treated patients compared to adalimumab-treated patients (84.2% vs. 61.7% and 80.2% vs. 53.0%, respectively; p<0.001 for each).[21] At week 48, IGA score 0/1, and PASI 90 were achieved by significantly more guselkumab-treated patients than adalimumab-treated patients (80.5% vs. 55.4%, and 76.3% vs. 47.9%, respectively; p<0.001 for each outcome).[21]

VOYAGE 2 consisted of a placebo-controlled phase (weeks 0-16), active comparator-controlled phase (weeks 0-28), and placebo-controlled, randomized withdrawal and retreatment phase (weeks 28-48) in 992 subjects.[22] At baseline patients were randomized 2:1:1 to guselkumab (n=496), placebo (n= 248), or adalimumab (n=248) for the first 28 weeks of the trial.[22] During the subsequent withdrawal/retreatment phase patients were re-randomized to either guselkumab or placebo in the same dosing strategy used for VOYAGE 1. The inclusion and exclusion criteria were similar in both trials. To evaluate maintenance and durability of response, at week 28 subjects with PASI 90 response to guselkumab (n=219) were re-randomized to either continue guselkumab or change to placebo treatment.[22] In addition, patients who were adalimumab non-responders (n=220) were switched to guselkumab or placebo at week 28.[22]

In the VOYAGE 2 trial, the co-primary endpoints of an IGA score 0/1 and PASI 90 were achieved by more guselkumab-treated patients compared to placebo-treated patients at week 16 (84.1% vs. 8.5%; ARR =75.6%; NNT = 2 and 70.0% vs. 2.4%; ARR = 67.6%; NNT = 2 respectively; p<0.001 for both).[22] In addition, more guselkumab-treated patients achieved IGA 0/1, PASI 90 and PASI 75 than adalimumab-treated patients at week 16 (84.1% vs. 67.7%, 70.0% vs. 46.8%, and 86.3% vs. 68.5%, respectively; p<0.001 for each).[22] Similar differences were sustained for another 8 weeks to week 24 (83.5% vs. 64.9% for IGA 0/1; 75.2% vs. 54.8% for PASI 90; and 89.1% vs. 71.0% for PASI 75; p<0.001 for each outcome).[22]

During the re-randomized withdrawal and retreatment period (week 28-48), PASI 90 response was better maintained by the guselkumab week 28 responders who continued guselkumab (maintenance group) compared to those who were re-randomized to placebo (withdrawal group).[22] Through week 48, 88.6% of patients in the maintenance group sustained a PASI 90 response versus 36.8% of those in the withdrawal group (p< 0.001).[22] Guselkumab-treated patients

maintained response whereas psoriasis slowly recurred in patients receiving placebo. Of adalimumab non-responders who switched to guselkumab, 66.1% achieved PASI 90 at week 48.[22] VOYAGE 2 provides data to support the need for continuing therapy with guselkumab to maintain a level of response over 48 weeks and successful transition from adalimumab to guselkumab.[22]

Trial Limitations:
Most of the patients (75%) enrolled in the guselkumab trials had moderate PsO at baseline and a higher percentage of males were enrolled in study. The duration of the VOYAGE 1 trial limited safety assessment to 48 weeks, although open label extension continued to week 160. In VOYAGE 2 the comparison of guselkumab with adalimumab was limited to 24 weeks. Approximately 75% of the VOYAGE trials were conducted outside of the U.S., which limits the applicability of the trial results to U.S. patients.

Comparative Efficacy:
Another Phase 3 trial sponsored by the manufacturer evaluated the efficacy and safety of guselkumab in patients with moderate-to-severe plaque psoriasis who had an inadequate response to 2 doses of open label ustekinumab at weeks 0 and 4.[95] At week 16, patients (n=268) with an inadequate response to ustekinumab (IGA ≥ 2) were randomized (double-blind) to guselkumab 100 mg or to continue ustekinumab; 585 of 871 patients (67%) with IGA 0/1 at week 16 continued open-label ustekinumab.[95] The primary end point was the number of visits at which randomized patients achieved IGA 0/1 and at least a two-grade improvement (from week 16) from week 28 to week 40.[95] The visit interval from week 28 to week 40 included a total of 4 visits; therefore, the possible number of visits for the primary endpoint ranged from 0 to 4. The FDA stated to the manufacturer in advice letters that using the number of visits as a combination of success and duration makes the interpretation of study findings difficult.[96] In their advice letters, the FDA recommended comparing the response rates at a specific time point and comparing the duration of effect for patients who achieved success with treatment.[96] The authors of this trial reported the mean number of visits at which patients achieved IGA 0/1 and at least a two-grade improvement was greater in the guselkumab group compared to the randomized ustekinumab group (1.5 vs. 0.7; P < 0.001, 95% CI not reported).[95] After week 16, 64% of patients in the guselkumab group and 56% in the ustekinumab group had at least one adverse event; infections were the most frequent type of adverse event.[95] Overall, 6.7% (n = 9) of patients in the guselkumab group had at least one serious adverse effect compared with 4.5% (n = 6) for the ustekinumab group.[95] Based on the small number of randomized patients, primary endpoint of limited value, and open label ustekinumab arms, this trial was rated as poor quality and not included in the comparative evidence table.

Clinical Safety:
In VOYAGE 1 through week 16, the proportions of patients with at least one adverse event were comparable across treatment groups (49.4% placebo, 51.7% guselkumab, 51.1% adalimumab).[21] The most commonly reported adverse effects were nasopharyngitis and upper respiratory tract infections. SAEs were reported at similar rates across all 3 treatment arms: 1.7% for placebo, 2.4% for guselkumab, and 1.8% for adalimumab.[21] Through week 48, the proportion of patients with more than one adverse effect were similar in the guselkumab and adalimumab groups (73.9% vs. 74.5%, respectively).[21] SAEs were also reported at a similar rate: 4.9% for the guselkumab group and 4.5% for the adalimumab group.[21] Through week 48, injection site reactions occurred in 2.2% of guselkumab-treated patients and in 9.0% of adalimumab-treated patients.[21] Most injection site reactions were mild. Study discontinuation rates over 48 weeks due to adverse effects with guselkumab were 2.7% compared to 3.6% with adalimumab.[21]

In VOYAGE 2 during the placebo-controlled period (weeks 0-16), at least one adverse effect occurred in 44.8%, 47.6%, and 48.4% of patients in the placebo, guselkumab, and adalimumab groups, respectively.[22] The most commonly reported adverse effects were nasopharyngitis, headache, and upper respiratory tract

infection. SAEs occurred in 1.2%, 1.6%, and 2.4% of patients in the placebo, guselkumab, and adalimumab groups, respectively.[22] Injection-site reactions occurred in 6.9% of adalimumab treated patients compared to 2.6% of guselkumab-treated patients.[22]

Upper respiratory infections, headache and injection site reactions were the most frequent adverse effects observed with guselkumab during clinical trials.[23] Pooled data from VOYAGE 1 and VOYAGE 2 did not demonstrate an increased risk of suicidal ideation or adverse cardiovascular events with guselkumab.[23] A summary of the adverse reactions observed through week 16 in the VOYAGE 1 and 2 trials is presented in **Table 7.**

Table 7: Adverse Reactions Occurring in ≥1% of Subjects through Week 16 in VOYAGE 1 and VOYAGE 2[23]

Adverse Effect	**Guselkumab N=823 n (%)**	**Adalimumab N=196 n (%)**	**Placebo N=422 n (%)**
Upper respiratory infections	118 (14.3)	21 (10.7)	54 (12.8)
Headache	38 (4.6)	2 (1.0)	14 (3.3)
Injection site reactions	37 (4.5)	15 (7.7)	12 (2.8)
Arthralgia	22 (2.7)	4 (2.0)	9 (2.1)
Diarrhea	13 (1.6)	3 (1.5)	4 (0.9)
Gastroenteritis	11 (1.3)	4 (2.0)	4 (0.9)
Tinea infections	9 (1.1)	0	0
Herpes simplex infection	9 (1.1)	0	2 (0.5)

Look-alike / Sound-alike Error Risk Potential: No issues identified.

Table 8. Pharmacology and Pharmacokinetic Properties of Guselkumab

Parameter	
Mechanism of Action	IL-23 inhibition
Distribution	Volume of distribution = 13.5 liters
Elimination	0.516 liters/day
Half-Life	15-18 days
Metabolism	Not characterized

Abbreviations: IL = interleukin

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Symptomatic improvement (PASI 75)
2) Remission
3) Quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:

1)Proportion of patients achieving co-primary endpoint of IGA 0/1 or PASI 90 at week 16 compared to placebo

Table 9. Comparative Evidence Table for Guselkumab

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Blauvelt et al.[21] (VOYAGE 1) Phase 3, DB, MC, RCT 48 weeks N=837	1. Guselkumab 100 mg SC at weeks 0, 4 and 12 and then every 8 weeks through week 48 2. Placebo injections at weeks 0, 4, and 12 followed by guselkumab 100 mg SC at weeks 16 and 20, and every 8 weeks through week 48 3. Adalimumab 80 mg at week 0, 40 mg at week 1, 40 mg every 2 weeks through week 47	Demographics: -Mean age: 44 y -Male: 74% -White: 82% Duration of Psoriasis: 17 years -Median baseline PASI score: 19 -Baseline IGA score = 3 (moderate): 75% Key Inclusion Criteria: ≥18 years with moderate to severe PsO defined as: IGA score ≥3, PASI score ≥12, and ≥10% BSA involvement ≥ 6 mos. Key Exclusion Criteria: -Uncontrolled medical condition -Patients with gutatte, erythrodermic, or pustular psoriasis -Malignancy -History of active TB -Other TNF therapy within 3 months -IL-12/23, IL-17, or IL-23 therapy within 6 months -MTX or phototherapy within 4 weeks	ITT: 1. 329 2. 174 3. 333 PP: 1.301 2.162 3.282 Attrition: 1. 28 (8.5%) 2. 12 (6.9%) 3.52 (15.6%)	Primary Endpoint: Achieved IGA 0/1 or PASI 90 at week 16: IGA 0/1: 1. 280 (85.1%) 2. 12 (6.9%) p < 0.001 (RR and CI NR) PASI 90: 1. 241 (73.3%) 2. 5 (2.9%) p < 0.001 (RR and CI NR) Secondary Endpoints: Achieved PASI 75 at week 16: 1. 300 (91.2%) p < 0.001 vs. 2 (RR and CI NR) 2. 10 (5.7%) 3. 244 (73.1%) p < 0.001 vs. 2 (RR and CI NR) Achieved IGA score 0/1 at week 24 (guselkumab vs. adalimumab) 1. 277 (84.2%) 3. 206 (61.7%) p < 0.001 (RR and CI NR) Achieved PASI 90 at week 24 (guselkumab vs. adalimumab): 1. 264 (80.2%) 3. 177(53%) p < 0.001 (RR and CI NR) Achieved IGA score 0/1 at week 48 (guselkumab vs. adalimumab)	78%/2 70%/2 85%/2 18%/6 23%/5 27%/4	AE through week 16 1. 170 (51.7%) 2. 86 (49.4%) 3. 170 (51.1%) SAE through week 16 1. 8 (2.4%) 2. 3 (1.7%) 3. 6 (1.8%) Discontinued study due to AE through week 16 1. 1.4 (1.2%) 2. 2 (1.1%) 3. 3 (.0.9%)	NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Randomized using IVRS in 2:1:2 ratio. Baseline characteristics balanced between groups. Performance Bias: LOW. Matching placebo used to maintain blinding. Detection Bias: LOW: PASI and IGA are validated instruments to assess PsO. Attrition Bias: UNCLEAR. Higher attrition rate in adalimumab arm vs guselkumab vs placebo. Patients who discontinued study agents or started a protocol-prohibited psoriasis treatment were considered non-responders. Reporting Bias: UNCLEAR. 95% confidence intervals not provided. Protocol available. Supported by Janssen. **Applicability**: Patient: 75% of patients had moderate PsO at baseline, higher percentage of males enrolled in study Intervention: Guselkumab dosing appropriate and is approved by the FDA. Comparator: Placebo and active comparator (adalimumab) used to assess safety and efficacy of guselkumab Outcomes: Validated outcomes: IGA and PASI. Duration of trial may have limited safety assessment to 48 weeks, although OL extension continued to week 160. Setting: 101 clinical sites in 10 countries: Canada (n=11); US (n=27); Hungary (n=6); Poland (n=7); Russia (n=12); Germany (n=14); Spain (n=5); Australia (n=7); Korea (n=6); Taiwan (n=6).

				1. 265 (80.5%) 3. 185 (55.4%) p < 0.001 (RR and CI NR) Achieved PASI 90 at week 48 (guselkumab vs. adalimumab) 1. 251 (76.3%) 3. 160 (47.9%) p < 0.001 (RR and CI NR)	26%/4 28%/4			
2. Reich et al[22] (VOYAGE 2) MC, RCT, DB 48 weeks N=992	1. Guselkumab 100 mg SC at weeks 0, 4, 12 and 20 2. Placebo at week 0, 4, and 12 then guselkumab at week 16 and 20 3.Adalimumab 80mg SC at week 0, 40mg week 1 and then every 2 weeks through week 23 Withdrawal and retreatment period (weeks 28-48) -PASI 90 non-responders continued guselkumab 100 mg SC every 8 weeks. -PASI 90 responders received placebo until loss of ≥50% PASI improvement. Then re-treated with guselkumab 100 mg SC every 8 weeks OR placebo 1.Guselkumab 100 mg SC starting week	Demographics: -Mean age: 43.5 y -Male: 70% -Average duration of psoriasis: 17.8 y -Median baseline PASI score: 19 Baseline IGA score = 3 (moderate): 78% Key Inclusion Criteria: See VOYAGE 1 Key Exclusion Criteria: See VOYAGE 1	Week 0-28 ITT: 1. 496 2. 248 3. 248 PP: 1.470 2.212 3.228 Attrition: 1.26 (5%) 2.21 (8%) 3.20 (8%)	Primary Endpoint: Achieved IGA 0/1 and PASI 90 response at week 16: IGA 0/1 1. 417(84.1%) 2. 21 (8.5%) p < 0.001 (RR and CI NR) PASI 90 1. 347 (70%) 2. 6 (2.4%) p < 0.001 (RR and CI NR) Secondary Endpoints: Proportion of subjects who achieved PASI 75 at week 16: 1. 428 (86.3%) p < 0.001 vs 2 (RR and CI NR) 2. 20 (8.1%) 3. 170 (68.5%) p < 0.001 vs 2 (RR and CI NR) Achieved IGA score 0/1 at week 24 (guselkumab vs. adalimumab) 1. 414 (83.5%) 3. 161 (64.9%) p < 0.001 (RR and CI NR) Achieved PASI 90 at week 24 (guselkumab vs. adalimumab)	75%/2 68%/2 78%/2 19%/6 19%/6	AE: 1. 235 (47.6%) 2. 111 (44.8%) 3. 120 (48.4%) SAE: 1. 8 (1.6%) 2. 3 (1.2%) 3. 6 (2.4%) Discontinued study due to AE: 1. 7 (1.4%) 2. 2 (0.8%) 3. 4 (1.6%) Infections: 1. 106 (21.5%) 2. 46 (18.5%) 3. 58 (23.4%)	NA NA NA NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. Subjects randomized 2:1:1 ratio using permuted block method via IVRS. Baseline demographics comparable amongst groups. Performance Bias: LOW. Matching placebo used to maintain blinding to active treatment arms. Detection Bias: UNCLEAR. Not described Attrition Bias: LOW. Attrition rates similar between arms. Reporting Bias: UNCLEAR. No 95% confidence intervals provided for results. Protocol available. Supported by Janssen. **Applicability**: Patient: Reasonable patient group identified through inclusion/exclusion criteria Intervention: Guselkumab dosing appropriate Comparator: Placebo and active comparator (adalimumab) used to assess efficacy of drug Outcomes Validated outcomes: IGA and PASI Setting: 115 clinical sites in 9 countries: Canada (n=10); Czech (n=7); US (n=31); Poland (n=18); Russia (n=11); Germany (n=10); Spain (n=9); Australia (n=6); Korea (n=13)

	28 followed by 100mg SC 4 weeks later then every 8 weeks through week 48 2.Placebo			1. 373 (75.2%) 3. 136 (54.8%) p < 0.001 (RR and CI NR)	20%/5			

Abbreviations [alphabetical order]: AE = Adverse Effects; ARR = absolute risk reduction; CI = confidence interval; DB= Double Blind; IGA = Investigator's Global Assessment; IL = interleukin; ITT = intention to treat; IVRS = Interactive Voice Response System; MC = Multi-Center; MTX = methotrexate; N = number of subjects; NA = not applicable; NR=Not Reported; NNH = number needed to harm; NNT = number needed to treat; OL = open label; PASI = Psoriasis Area Severity Index; RR=Relative Risk; SAE = Serious Adverse Effects; SC= Subcutaneous; TB = tuberculosis; PP = per protocol YO=Years Old

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Appendix 1: Current Preferred Drug List

Generic	Brand	Formulation	Route	PDL
ETANERCEPT	ENBREL	VIAL	SUB-Q	Y
ETANERCEPT	ENBREL	SYRINGE	SUB-Q	Y
ETANERCEPT	ENBREL SURECLICK	PEN INJCTR	SUB-Q	Y
ETANERCEPT	ENBREL	SYRINGE	SUB-Q	Y
ADALIMUMAB	HUMIRA	SYRINGEKIT	SUB-Q	Y
ADALIMUMAB	HUMIRA PEDIATRIC CROHN'S	SYRINGEKIT	SUB-Q	Y
ADALIMUMAB	HUMIRA PEN	PEN IJ KIT	SUB-Q	Y
ADALIMUMAB	HUMIRA PEN CROHN-UC-HS STARTER	PEN IJ KIT	SUB-Q	Y
ADALIMUMAB	HUMIRA PEN PSORIASIS-UVEITIS	PEN IJ KIT	SUB-Q	Y
ADALIMUMAB	HUMIRA	SYRINGEKIT	SUB-Q	Y
INFLIXIMAB	REMICADE	VIAL	INTRAVEN	N
CERTOLIZUMAB PEGOL	CIMZIA	KIT	SUB-Q	N
CERTOLIZUMAB PEGOL	CIMZIA	SYRINGEKIT	SUB-Q	N
INFLIXIMAB-DYYB	INFLECTRA	VIAL	INTRAVEN	N
INFLIXIMAB-ABDA	RENFLEXIS	VIAL	INTRAVEN	N
VEDOLIZUMAB	ENTYVIO	VIAL	INTRAVEN	N
SECUKINUMAB	COSENTYX (2 SYRINGES)	SYRINGE	SUB-Q	N
SECUKINUMAB	COSENTYX SYRINGE	SYRINGE	SUB-Q	N
SECUKINUMAB	COSENTYX PEN	PEN INJCTR	SUB-Q	N
SECUKINUMAB	COSENTYX PEN (2 PENS)	PEN INJCTR	SUB-Q	N
IXEKIZUMAB	TALTZ AUTOINJECTOR	AUTO INJCT	SUB-Q	N
IXEKIZUMAB	TALTZ AUTOINJECTOR (2 PACK)	AUTO INJCT	SUB-Q	N
IXEKIZUMAB	TALTZ AUTOINJECTOR (3 PACK)	AUTO INJCT	SUB-Q	N
IXEKIZUMAB	TALTZ SYRINGE	SYRINGE	SUB-Q	N
BRODALUMAB	SILIQ	SYRINGE	SUB-Q	N
GUSELKUMAB	TREMFYA	SYRINGE	SUB-Q	N
GOLIMUMAB	SIMPONI	PEN INJCTR	SUB-Q	N
GOLIMUMAB	SIMPONI	SYRINGE	SUB-Q	N
GOLIMUMAB	SIMPONI ARIA	VIAL	INTRAVEN	N
ANAKINRA	KINERET	SYRINGE	SUB-Q	N
ABATACEPT/MALTOSE	ORENCIA	VIAL	INTRAVEN	N
ABATACEPT	ORENCIA	SYRINGE	SUB-Q	N
ABATACEPT	ORENCIA CLICKJECT	AUTO INJCT	SUB-Q	N

CANAKINUMAB/PF	ILARIS	VIAL	SUB-Q	N
APREMILAST	OTEZLA	TABLET	ORAL	N
APREMILAST	OTEZLA	TAB DS PK	ORAL	N
USTEKINUMAB	STELARA	SYRINGE	SUB-Q	N
USTEKINUMAB	STELARA	VIAL	INTRAVEN	N
TOCILIZUMAB	ACTEMRA	VIAL	INTRAVEN	N
TOCILIZUMAB	ACTEMRA	SYRINGE	SUB-Q	N
SARILUMAB	KEVZARA	SYRINGE	SUB-Q	N
RITUXIMAB	RITUXAN	VIAL	INTRAVEN	N
TOFACITINIB CITRATE	XELJANZ	TABLET	ORAL	N
TOFACITINIB CITRATE	XELJANZ XR	TAB ER 24H	ORAL	N
NATALIZUMAB	TYSABRI	VIAL	INTRAVEN	N

Appendix 2: Medline Search Strategy on 10/30/2017

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

1 exp abatacept/ 2730
2 exp Adalimumab/ 4382
3 anakinra.mp. 1481
4 apremilast.mp. 332
5 belimumab.mp. 539
6 brodalumab.mp. 160
7 canakinumab.mp. 436
8 exp Certolizumab Pegol/ 494
9 exp Etanercept/ 5510
10 golimumab.mp 904
11 guselkumab.mp. 50
12 exp Infliximab/ 9326
13 ixekizumab.mp. 214
14 exp Natalizumab/ 1356
15 exp Rituximab/ 12191
16 sarilumab.mp. 42
17 secukinumab.mp. 447
18 tocilizumab.mp. 2284
19 tofacitinib.mp. 768
20 exp Ustekinumab/ 643
21 vedolizumab.mp. 412
22 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 37230
23 exp Arthritis, Rheumatoid/ 111774
24 exp Spondylitis, Ankylosing/ 14540
25 exp Crohn Disease/ 37296
26 exp Arthritis, Juvenile/ 10372
27 exp Psoriasis/ 37269
28 exp Arthritis, Psoriatic/ 5496
29 exp Colitis, Ulcerative/ 32987
30 23 or 24 or 25 or 26 or 27 or 28 or 29 224465
32 22 and 31 14620
33 limit 32 to (English language and humans and yr="2017-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 meta-analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)) 252

Appendix 3: Prescribing Information Highlights for Sarilumab and Guselkumab

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use KEVZARA® safely and effectively. See full prescribing information for KEVZARA.

KEVZARA® (sarilumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

WARNING: RISK OF SERIOUS INFECTIONS

See full prescribing information for complete boxed warning.

- **Serious infections leading to hospitalization or death including bacterial, viral, invasive fungal, and other opportunistic infections have occurred in patients receiving KEVZARA. (5.1)**
- **If a serious infection develops, interrupt KEVZARA until the infection is controlled. (5.1)**
- **Cases of tuberculosis (TB) have been reported. Prior to starting KEVZARA, test for latent TB; if positive, start treatment for TB. (5.1)**
- **Closely monitor patients for signs and symptoms of infection during treatment with KEVZARA. (5.1)**

INDICATIONS AND USAGE

KEVZARA® is an interleukin-6 (IL-6) receptor antagonist indicated for treatment of adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response or intolerance to one or more disease-modifying antirheumatic drugs (DMARDs). (1)

DOSAGE AND ADMINISTRATION

- KEVZARA may be used as monotherapy or in combination with methotrexate (MTX) or other conventional DMARDs. (2.1)
- The recommended dosage of KEVZARA is 200 mg once every two weeks, administered as a subcutaneous injection. (2.1)

General Considerations for Administration

- KEVZARA initiation is not recommended in patients with ANC less than 2000/mm^3, platelets less than 150,000/mm^3 or liver transaminases above 1.5 times ULN. (2.2)

Dosage Modifications

- Modify dosage to manage neutropenia, thrombocytopenia, and/or elevated liver transaminases. (2.1, 2.4)

DOSAGE FORMS AND STRENGTHS

Injection: 150 mg/1.14 mL or 200 mg/1.14 mL solution in a single-dose pre-filled syringe (3)

CONTRAINDICATIONS

KEVZARA is contraindicated in patients with known hypersensitivity to sarilumab or any of the inactive ingredients. (4)

WARNINGS AND PRECAUTIONS

- Serious Infections: Avoid KEVZARA use during an active infection. (5.1)
- Neutropenia, Thrombocytopenia, Elevated Liver Enzymes, Lipid Abnormalities: Monitor laboratory parameters. (5.2)
- Gastrointestinal (GI) Perforation: Risk may be increased with concurrent diverticulitis or concomitant use of NSAIDs or corticosteroids. Promptly evaluate acute abdominal signs or symptoms. (5.3)
- Hypersensitivity reactions. (5.5)
- Live vaccines: Avoid use with KEVZARA due to the risk of infection. Follow vaccination guidelines. (5.7, 7.3)

ADVERSE REACTIONS

Most common adverse reactions (incidence at least 3%) are neutropenia, increased ALT, injection site erythema, upper respiratory infections and urinary tract infections. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact sanofi-aventis at 1-800-633-1610 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

USE IN SPECIFIC POPULATIONS

- Lactation: Discontinue drug or nursing taking into consideration importance of drug to mother. (8.2)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide

Revised: 05/2017

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use TREMFYA safely and effectively. See full prescribing information for TREMFYA.

TREMFYA® (guselkumab) injection, for subcutaneous use

Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------

TREMFYA is an interleukin-23 blocker indicated for the treatment of adult patients with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy. (1)

----------DOSAGE AND ADMINISTRATION----------

100 mg administered by subcutaneous injection at Week 0, Week 4 and every 8 weeks thereafter. (2.1)

----------DOSAGE FORMS AND STRENGTHS----------

Injection: 100 mg/mL in a single-dose prefilled syringe. (3)

----------CONTRAINDICATIONS----------

None (4)

TREMFYA® (guselkumab)

----------WARNINGS AND PRECAUTIONS----------

- Infections: TREMFYA may increase the risk of infection. Instruct patients to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a serious infection develops, discontinue TREMFYA until the infection resolves. (5.1)
- Tuberculosis (TB): Evaluate for TB prior to initiating treatment with TREMFYA. (5.2)

----------ADVERSE REACTIONS----------

Most common (≥1%) adverse reactions associated with TREMFYA include upper respiratory infections, headache, injection site reactions, arthralgia, diarrhea, gastroenteritis, tinea infections, and herpes simplex infections. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Janssen Biotech, Inc. at 1-800-JANSSEN (1-800-526-7736) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------

Avoid use of live vaccines in patients treated with TREMFYA. (7.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 10/2017

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 for autoimmune diseases

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. Approved Indications for Biologic Immunosuppressants.

Drug Name	Ankylosing Spondylitis	Crohn's Disease	Juvenile Idiopathic Arthritis	Plaque Psoriasis	Psoriatic Arthritis	Rheumatoid Arthritis	Ulcerative Colitis	Other
Abatacept (ORENCIA)			≥2 yo		≥18 yo	≥18 yo		
Adalimumab (HUMIRA) and biosimilars	≥18 yo	≥6 yo (Humira) ≥18 yo (biosimilars)	≥2 yo(Humira) ≥4 yo (biosimilars)	≥18 yo	≥18 yo	≥18 yo	≥18 yo	Uveitis (non-infectious) ≥18 yo (Humira)
Anakinra (KINERET)						≥18 yo		NOMID
Apremilast (OTEZLA)				≥18 yo	≥18 yo			
Broadalumab (SILIQ)				≥18 yo				
Canakinumab (ILARIS)			≥2 yo					FCAS ≥4 yo MWS ≥4 yo TRAPS ≥ 4yo HIDS≥ 4 yo MKD≥ 4 yo FMF≥ 4 yo

Certolizumab (CIMZIA)	≥18 yo	≥18 yo			≥18 yo	≥18 yo		
Etanercept (ENBREL) and biosimilars	≥18 yo		≥2 yo	≥4 yo (Enbrel) ≥18 yo (biosimilars)	≥18 yo	≥18 yo		
Golimumab (SIMPONI and SIMPONI ARIA)	≥18 yo				≥18 yo	≥18 yo	≥18 yo (Simponi)	
Guselkumab (Tremfya)				≥18 yo				
Infliximab (REMICADE) and biosimilars	≥18 yo	≥6 yo		≥18 yo	≥18 yo	≥18 yo	≥6 yo (Remicade) ≥18 yo (biosimilars)	
Ixekizumab (TALTZ)				≥18 yo	>18 yo			
~~Natalizumab (TYSABRI)~~		~~>18 yo~~						~~MS >18 yo~~
Rituximab (RITUXAN)						≥18 yo		CLL ≥18 yo NHL ≥18 yo GPA ≥18 yo
Sarilumab (KEVZARA)						>18 yo		
Secukinumab (COSENTYX)	≥18 yo			≥18 yo	≥18 yo			
Tocilizumab (ACTEMRA)			≥2 yo			≥18 yo		CRS >2 yo GCA >18 yo
Tofacitinib (XELJANZ)					>18 yo	≥18 yo		
Ustekinumab (STELARA)		≥ 18 yo		≥12 yo	≥18 yo			
Vedolizumab (ENTYVIO)		≥18 yo					≥18 yo	

Abbreviations: CLL = Chronic Lymphocytic Leukemia; CRS = Cytokine Release Syndrome; FCAS = Familial Cold Autoinflammatory Syndrome; FMF = Familial Mediterranean Fever; GCA = Giant Cell Arteritis; GPA = Granulomatosis with Polyangiitis (Wegener's Granulomatosis); HIDS: Hyperimmunoglobulin D Syndrome; MKD = Mevalonate Kinase Deficiency; ~~MS = Multiple Sclerosis;~~ MWS = Muckle-Wells Syndrome; NHL = Non-Hodgkin's Lymphoma; NOMID = Neonatal Onset Multi-Systemic Inflammatory Disease; TRAPS = Tumor Necrosis Factor Receptor Associated Periodic
Syndrome; yo = years old.

Approval Criteria	
1. What diagnosis is being treated?	Record ICD-10 code.

Approval Criteria		
2. Is the diagnosis funded by OHP?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by the OHP.
3. Is this a request for continuation of therapy?	**Yes**: Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for a non-preferred product and will the prescriber consider a change to a preferred product? Message: • Preferred products are reviewed for comparative effectiveness and safety by the Oregon Pharmacy and Therapeutics Committee.	**Yes:** Inform prescriber of preferred alternatives.	**No:** Go to #5
5. Has the patient been screened for latent or active tuberculosis and if positive, started tuberculosis treatment?	**Yes:** Go to #6	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
6. Is the diagnosis Juvenile Idiopathic Arthritis, non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia, Non-infectious Posterior Uveitis, or one of the following syndromes: • Familial Cold Autoinflammatory Syndrome • Muckel-Wells Syndrome • Neonatal Onset Multi-Systemic Inflammatory Disease • Tumor Necrosis Factor Receptor Associated Periodic Syndrome • Hyperimmunoglobulin D Syndrome • Mevalonate Kinase Deficiency • Familial Mediterranean Fever • Giant Cell Arteritis • Cytokine Release Syndrome AND Is 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
7. Is the diagnosis ankylosing spondylitis and the request for a drug FDA-approved for this condition as defined in Table 1?	**Yes:** Go to #8	**No:** Go to #9
8. Has the patient failed to respond to adalimumab or etanercept after a trial of at least 3 months?	**Yes:** Approve for up to 6 months. Document therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.

Approval Criteria		
9. Is the diagnosis plaque psoriasis 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 #10	**No**: Go to #12
10. 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 #11	**No:** Pass to RPh. Deny; not funded by the OHP.
11. 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; and • One biologic agent: either adalimumab or etanercept for at least 3 months?	**Yes**: Approve for up to 6 months. Document each therapy with dates.	**No:** Pass to RPh. Deny; medical appropriateness.
12. Is the diagnosis rheumatoid arthritis or psoriatic arthritis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #13	**No:** Go to #16

Approval Criteria		
13. Has the patient failed to respond to at least one of the following medications: • Methotrexate, leflunomide, sulfasalazine or hydroxychloroquine for ≥ 6 months; or • Have a documented intolerance or contraindication to disease-modifying antirheumatic drugs (DMARDs)? AND • Had treatment failure with at least one biologic agent: adalimumab or etanercept for at least 3 months?	**Yes:** Go to #14 Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
14. Is the request for tofacitinib?	**Yes:** Go to #15	**No:** Approve for up to 6 months.
15. Is the patient currently on other biologic therapy or on a potent immunosuppressant like azathioprine, tacrolimus or cyclosporine? Note: Tofacitinib may be used concurrently with methotrexate or other oral DMARD drugs.	**Yes:** Pass to RPh. Deny; medical appropriateness.	**No:** Approve for up to 6 months.
16. Is the diagnosis Crohn's disease or ulcerative colitis and the request for a drug FDA-approved for these conditions as defined in Table 1?	**Yes:** Go to #17	**No:** Go to #18

Approval Criteria		
17. 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? • AND • For Crohn's Disease patients only: has the patient tried and failed a 3 month trial of adalimumab?	**Yes:** Approve for up to 12 months. Document each therapy with dates. If applicable, document intolerance or contraindication(s).	**No:** Pass to RPh. Deny; medical appropriateness.
18. 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
19. Is the diagnosis Granulomatosis with Polyangiitis and the requested drug rituximab for *maintenance* of remission?	**Yes:** Go to #20	**No:** Pass to RPh. Deny; medical appropriateness.
20. 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.

Renewal Criteria		
1. Has the patient's condition improved as assessed by the prescribing physician and physician attests to patient's improvement.	**Yes:** Approve for 6 months. Document baseline assessment and physician attestation received.	**No:** Pass to RPh; Deny; medical appropriateness.

P&T/DUR Review: *1/18 (DM; JP); 7/17; 11/16; 9/16; 3/16; 7/15; 9/14; 8/12*
Implementation: *TBD; 9/1/17; 1/1/17; 9/27/14; 2/21/13*

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Class Review with New Drug Evaluations: Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors

Date of Review: January 2018
Generic Name: valbenazine
Generic Name: deutetrabenazine
Generic Name: tetrabenazine

End Date of Literature Search: November 7, 2017
Brand Name (Manufacturer): Ingrezza ® (Neurocrine Biosciences Inc.)
Brand Name (Manufacturer): Austedo® (Auspex Pharmaceuticals Inc.)
Brand Name (Manufacturer): Xenazine® (Valeant Pharmaceuticals Inc.)
Dossier Received: Yes - Ingrezza®; Yes - Austedo®; Yes – Xenazine®

Purpose for Class Review:
To define place in therapy for vesicular monoamine transporter 2 (VMAT2) inhibitors recently approved by the United States (U.S.) Food and Drug Administration (FDA) for the treatment of adults with tardive dyskinesia (TD) or Huntington chorea (HC) as a result of Huntington's Disease (HD).

Research Questions:
1. Do VMAT2 inhibitors differ in efficacy when use to treat patients with TD or HC? How do VMAT2 inhibitors differ in efficacy or effectiveness from other pharmacological therapies used to manage TD or HC?
2. Do VMAT2 inhibitors differ in adverse events or tolerability when used for the treatment patients with TD and HC? How do VMAT inhibitors differ in safety or harms from other pharmacological therapies used to manage TD or HC?
3. Are there subgroups of patients with TD or HC based on demographic characteristics (i.e., age, gender, ethnicity, comorbidities, disease duration or severity) in which one VMAT2 inhibitor may be associated with reduced effectiveness or greater harm than the other VMAT2 inhibitor or other pharmacological therapies used to manage these conditions?

Conclusions:
Efficacy
- This review identified 2 new VMAT2 inhibitors, valbenazine and deutetrabenazine, 2 clinical practice guidelines (published prior to the approval of valbenazine and deutetrabenazine)[1,2], 3 systematic reviews[3–5] and 4 randomized controlled trials[6–9]. Prior to the approval of valbenazine and deutetrabenazine, the only VMAT2 inhibitor available was tetrabenazine which is approved for the use in patients with HC and used off-label for TD. Newer VMAT2 inhibitors are indicated for TD and HC symptom management. **Table 1** lists commonly used outcomes in studies of TD and HD. Recommendations included in this review come from small, short-term studies that are primarily funded by industry. The overall quality of evidence available for consideration is considered low. There is insufficient evidence on subgroup comparisons.

Table 1. Outcome Assessment Measurements for Tardive Dyskinesia and Chorea Symptoms

Outcome	Description	Minimal Clinically Significant Change	Clinical Relevance
Tardive Dyskinesia			
Abnormal Involuntary Movement Scale **(AIMS)**	Validated 12-item scale with a total score ranging from 0-28. Higher scores indicate increased severity of TD symptoms. Amplitude and quality of movement are evaluated using a numeric severity scale ranging from zero (no abnormalities) to four (severe movements).	Not defined	Interpretation of scores has not been well-established and may lack sensitivity due to limited range and non-specificity for movement frequency.
Huntington's Disease			
Unified Huntington's Disease Rating Scale Total Motor Score **(UHDRS-TMS)***	Scoring ranges from 0-106 points with higher scores indicating greater disability.	Not defined	Limited evidence suggests a 1-point increase, in patients in the early stages of HD, correlates with an approximately 10% loss of the likelihood of being able to work, manage finances, drive and supervise children.
Unified Huntington's Disease Rating Scale– total chorea movement subscore **(UHDRS-TCS)***	Subscore is based on frequency and severity of chorea in 7 areas of the body on a scale of 0-28, with a higher number indicating worse disease.	Not defined	Most studies show a difference of 2-4 points which represents a 7-14% change.
Tardive Dyskinesia and Huntington's Disease			
Patients' Global Impression of Change (**PGIC)** score	PGIC measures patients' perspective on overall improvement in movement dysfunction. This is a 1-7 point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse".	Not defined	Patients' perception of symptom improvement is critical in justifying use of therapy.
Clinical Global Impression of Change **(CGIC)**	CGIC is a clinician perspective of the severity of the patient's symptoms using a 1-7 point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse".	Not defined	Limitations to this analysis is reliance on provider recall to determine symptom improvement.
Clinical Global Impression – Tardive Dyskinesia **(CGI-TD)**	CGI-TD is a modified version of the CGIC utilizing the same Likert scale with a focus on tardive dyskinesia symptoms.	Not defined	Limitations to this analysis is reliance on provider recall to determine symptom improvement.
Abbreviations: TD = tardive dyskinesia			

* This scoring system was designed by the Huntington Study Group which also conducted the study of deutetrabenazine for the treatment of HD.

- There is insufficient direct comparative evidence between VMAT2 inhibitors or other active treatments for TD and HD for efficacy outcomes. There is insufficient evidence for the use of VMAT2 inhibitors for treatment of dyskinesia associated with other conditions in adults (e.g., Parkinson's disease and Tourette syndrome). There is insufficient evidence to evaluate long-term efficacy or safety of VMAT2 inhibitors and long-term data in larger populations are needed to determine the significance of harms observed in short-term phase 3 trials.

Tardive Dyskinesia

- There is low quality evidence based on one phase 3, 6-week randomized, placebo-controlled trial that valbenazine is associated with statistical improvement in the AIMS score to reduce involuntary movements in patients with TD.[6] In patients with schizophrenia, schizoaffective disorder, or mood disorder with a history of antipsychotic use, adjusted mean improvement in AIMS score was -1.9 points (95% CI, -3.0 to -0.7; p=0.002 vs. placebo) with valbenazine 40 mg daily and -3.2 points (95% CI, -4.2 to -2.0; p<0.001 vs. placebo) with valbenazine 80 mg daily, and -0.1 points with placebo.[6] A post-hoc subgroup analysis found patients not using antipsychotic medications may have responded better than those on antipsychotic therapy.
- There is low quality evidence that the number of patients who reported overall improvement in their symptoms, defined as "improved" or "very much improved" by the PGIC, were lower with valbenazine 40 mg and valbenazine 80 mg compared to placebo (31.7%, 24.3% and 42.0%, respectively).[6] The inferior efficacy of valbenazine versus placebo raises important concerns of the benefit versus risk of valbenazine.[10]
- There is low quality evidence that deutetrabenazine decreases AIMS scores in adult patients with TD based on evidence from two 12-week, randomized controlled trials.[8,9] The first trial found deutetrabenazine 24 mg decreased AIMS scores by a mean of -1.8 points versus placebo (95% CI, -3.0 to -0.63; P=0.003) and deutetrabenazine 36 mg decreased AIMS scores by a mean of -1.9 points versus placebo (95%; -3.09 to -0.79; p=0.001).[9] The number of patients with at least a 50% improvement in AIMS score was higher in patients treated with deutetrabenazine 24 mg (absolute risk reduction [ARR] 23%/Number-needed-to-treat [NNT] 5 over 12 weeks) and 36 mg (ARR 24%/NNT 5 over 12 weeks) compared to placebo.[9] The second study found deutetrabenazine (mean dose 38.8 mg) decreased AIMS score by -3.0 points versus -1.6 points in patients treated with placebo (mean difference [MD] -1.4; 95% CI, -2.6 to -0.2; P=0.019).[8]
- Similar to valbenazine, there is low quality evidence that PGIC scores were not improved by deutetrabenazine compared to placebo in patients with TD based on evidence from two studies.[8,9]
- Evidence for the use of tetrabenazine comes from a Class III study (non-randomized, controlled study) that demonstrated a 54.2% reduction in AIMS scores compared to placebo (p<0.001) and a 60.4% reduction in patient AIMS self-rating score (p<0.001). Institute for Clinical and Economic Review (ICER) report considers evidence insufficient to make a recommendation for tetrabenazine for the treatment of TD symptoms.[4]
- The Institute for Clinical and Economic Review (ICER) found the evidence for the use of valbenazine and tetrabenazine in TD to be "promising but inconclusive" and "current prices are far out of alignment with the benefits measured in clinical trials".[4]

Huntington Chorea

- There is low quality evidence from one 12-week study that deutetrabenazine (mean dose 40 mg) improved UHDRS-TCS by -4.4 points from baseline compared to -1.9 points for placebo (MD -2.5; 95% CI, -3.7 to -1.3; p <0.001) in patients with mild to moderate functional impairment secondary to HD.[7] This difference is unlikely to be clinically meaningful.
- There is low quality evidence from one study in patients with HD that treatment success based on PGIC scores, defined as a response of "much" or "very much" improved, was higher with deutetrabenazine (mean dose of 40 mg) compared to placebo (deutetrabenazine 51% versus placebo 20%; ARR 31%; NNT 4 over 12 weeks).[7]

- There is low quality evidence, based on one study of 84 patients, that tetrabenazine 100mg improves UHDRS-TCS when compared to placebo (MD -3.5 points; 95% CI, -5.2 to -1.9; p<0.0001).[5] One small study of short duration limits strong conclusions of meaningful clinical improvement.

Safety

- Patients with an uncontrolled depression or at high risk of suicide were excluded from deutetrabenazine and tetrabenazine trials because of increased risk of depression and suicidality associated with their use. [11,12] FDA has issued black box warnings for deutetrabenazine and tetrabenazine against the use of these treatments in patients with a history of depression or prior suicide attempts. Valbenazine does not carry this warning; however, patients with any unstable psychiatric condition were excluded so the impact of its use in this population is unknown.
- All VMAT2 inhibitors may increase the QT interval.[11-13] Use of VMAT2 inhibitors should be avoided in patients with congenital long QT syndromes or with arrhythmias associated with prolonged QT interval. This risk may increase when VMAT2 inhibitors are used in general clinical practice and there is increased potential to be used concomitantly with other drugs (e.g., antipsychotics) that increase the QT interval.
- Common adverse effects for VMAT2 inhibitors is somnolence and dry mouth. Akathisia occurred in 3.3% of patients on valbenazine versus 1.3% on placebo. Deutetrabenazine was associated with increased incidence of diarrhea. Both deutetrabenazine and tetrabenazine were associated with higher rates of fatigue than placebo.

Recommendations:

- Create a new PDL class for VMAT2 inhibitors.
- Implement prior authorization (PA) criteria for valbenazine, deutetrabenazine and tetrabenazine to ensure appropriate use (see Appendix 3).
- Determine PDL status after evaluation of drug prices in the executive session.

Background:

Tardive Dyskinesia

Tardive dyskinesia is a delayed-onset involuntary movement disorder which commonly occurs in patients treated with chronic dopamine receptor blocking agents (DRBA). DRBAs are commonly prescribed for a wide range of psychiatric conditions (e.g., second-generation antipsychotics) or certain gastrointestinal disorders (e.g., metoclopramide).[14] While TD typically manifests after 1-2 years of routine exposure to DRBAs, it may occur within months of starting treatment. The yearly rate of TD development in patients treated with DRBAs is approximately 2-5% with a cumulative 5-year incidence of approximately 20% to 25%.[2] It is estimated that 20-50% of patients treated with a DRBA ultimately develop TD.[14,15] Neuroleptic-induced TD is higher in women, especially those middle-aged and elderly, where incidence rates may reach as much as 30% after 1 year of cumulative exposure.[14] TD may persist for years even after discontinuation of the DRBA, and in many cases, may not be reversible.[16] The debilitating effects of TD lead to increased mortality, decreased physical functioning, medication nonadherence, and a lower quality of life.[17]

TD is one of many disorders thought to arise from dopamine receptor blockade, but it is distinct from other movement disorders such as Parkinson's disease, Tourette syndrome, and Huntington's disease.[14] Genetic testing, neuroimaging, and other diagnostic work-ups may be necessary to rule out other causes of dyskinesia.[14] The Diagnostic and Statistical Manual of Mental Disorders definition for DRBA-induced TD requires exposure for a DRBA for at least 3 months (or 1 month in patients $\geq$ 60 years of age), presentation of symptoms within 4 weeks after withdrawal of an oral medication (or within 8 weeks of a depot medication), and persistence of symptoms for 1 month after discontinuation of offending agent.[14] Irregular, repetitive, orofacial movements including lip smacking, jaw clenching, facial grimacing, and tongue protrusions are classic symptoms of TD that range in severity from mild annoyance to impairment of

speech and swallowing.[16] TD patients may commonly experience random jerking movements in their upper extremities, lower extremities, and trunk which may interfere with daily living activities and create challenges for caregivers.[18]

Many explanations circulate regarding the pathophysiological link between DRBA use and TD. Chronic DRBA exposure, notably first generation antipsychotics, may cause upregulation and hypersensitization of post-synaptic dopaminergic (D2) receptors which disrupt normal dopamine recycling, most notably in the nigrostriatal pathway.[19] Early removal of D2 receptor blockade may slowly reverse the dyskinesia, but the cumulative effects of long-term use of DRBAs may result in irreversible TD.[14] Increased dosages of neuroleptic agents have demonstrated temporary improvements of TD symptoms which lends credibility to the dopamine receptor upregulation hypothesis.[19] Other possible explanations under investigation include cholinergic deficit, gamma-aminobutyric acid (GABA) depletion or abnormalities of striatal GABA neurons, neurotoxicity, and oxidative stress.[14,15,19]

There is currently no curative treatment for TD, and limited evidence is available to guide its management.[1] Estimated remission rates for TD vary from as little as 1% up to 62%.[16] TD occurs in roughly one-third of patients treated with first generation antipsychotics as compared to 13% on second generation (atypical) agents.[17,19] Three broad approaches have been used to manage TD including antipsychotic dose reduction, switching antipsychotic drug therapy, or addition of adjunctive agents.[3] Pharmacologic options for adjunctive treatment of TD are limited. Off-label use of tetrabenazine, clonazepam, amantadine, levetiracetam, resveratrol, and even ginkgo biloba have been used for TD symptom management with varying levels of success.[19] Other studies have investigated off-label use of medications for TD treatment, but authors concluded that prudent use and monitoring of atypical antipsychotics is key to management of TD symptoms.[19] For cases of TD resistant to drug therapy, non-systemic options such a deep brain stimulation have been reported to provide some benefit.[19]

The assessment of TD is challenging due to the variability in research criteria and different rating scales.[20] The AIMS is a clinical tool frequently used for early detection and surveillance of TD.[3] The AIMS has 12 items which assess 7 commonly affected anatomical locations with a total score ranging from 0-28. Higher scores indicate increased severity of TD symptoms. Amplitude and quality of movement are evaluated using a numeric severity scale ranging from 0 (no abnormalities) to 4 (severe movements).[3] The full assessment tool also contains an overall judgement of 3 abnormal movements also rated on a scale from 0-4, and 2 yes/no items concerning problems with teeth and dentures.[13] The AIMS can be completed in less than 10 minutes, and evaluation is suggested at least every 6 months for those on typical antipsychotics.[3] However, there is not a well-established guideline for interpretation of AIMS scores, and there is criticism that it lacks sensitivity due to its limited range and non-specificity for movement frequency.[3] Each section of the AIMS may be totaled, but overall scores are generally not reported. There is no MCID established and evidence has not demonstrated that improvement in AIMs score translates into improved function or quality of life for patients.[10]

Huntington's Disease

Huntington's disease results from a gene abnormality of an exon 1 CAG (cytosine-adenine-guanine [amino acid sequence]) trinucleotide expansion in the huntingtin (HTT) gene. Huntington Disease is a progressive, hereditary neurodegenerative disease that results in involuntary movements, cognitive dysfunction and psychiatric symptoms. Early stages of HD is often characterized by deficiencies in voluntary motor function while mid stages are associated with more of an impact on motor coordination and function.[21] Optimization of quality of life is the focus of HD treatment through symptom management since there is no cure or disease-modifying therapies. The estimated incidence if HD is 5 in 100,000 people in the US.[22]

Prior to the approval to deutetrabenazine, the only treatment approved for chorea symptoms associated with HD was tetrabenazine. The use of tetrabenazine is limited by variable CYP2D6 metabolism that often results in a 3-times daily dosing frequency.[11] Tolerability is also an issue with tetrabenazine with common

adverse effects such as sedation, fatigue, akathisia, anxiety and nausea. Olanzapine, risperidone, aripiprazole, clozapine, haloperidol and fluphenazine have also been used as off-label treatment options for patients with HC.[2]

The severity of HC and functional impact is measured by the Unified Huntington's Disease Rating Scale Total Motor Score (UHDRS-TMS) and is the main endpoint used in many trials. The UHDRS-TMS motor scale uses 106 questions to measure chorea, parkinsonism, dystonia, eye movements, and other signs. There are 31 items that are graded 0 (not affected) to 4 (most severely affected).[2] There is limited evidence that a 1-point increase in the UHDRS-TMS, in patients in the early stages of HD, correlates with an approximately 10% loss of the likelihood of being able to work, manage finances, drive and supervise children. In studies of patients with a diagnosis of HD, the mean annual change in patients UHDRS-TMS was 3.8 points. AAN guidelines define the change in subscores of less than 1-point decrease in UHDRS as unimportant, 1 to less than 2-point decrease as modestly important, 2 to less than 3-point decrease as moderately important and more than a 3-point decrease as very important.[2]

The UHDRS total chorea score (UHDRS-TCS) is a subscore which rates facial, bucco-oral-lingual, trunk and extremity chorea. Standardized assessment of chorea based on the UHDRS-TCS subscore is determined by frequency and severity of chorea in 7 areas of the body by a scale of 0-28, with a higher number indicating worse disease.[2] This subscoring portion represents 23% of the overall UHDRS-TMS and is recommended for determining the impact of chorea symptoms over using the UHDRS-TMS.[21] The clinically important change for this endpoint has not been determined.

Symptom Assessment Used for Both Tardive Dyskinesia and Huntington's Disease
The PGIC is used to determine the patients' perspective on overall improvement in movement dysfunction. This is a 1-7 point Likert scale with a score of 1 representing "very much improved" and a score of 7 suggesting "very much worse". The CGIC is a clinician perspective of the severity of the patient's symptoms utilizing the same scale as the PGIC.[4] Limitations to the CGIC is the reliance on provider recall of patient symptoms. The CGI-TD score is used to rate the overall change in tardive dyskinesia symptoms on a scale from 1 ("very much improved") to 7 ("very much worse"). Since there are no curative treatments for TD or HD, outcomes related to improvement in symptoms are very important and should be a major consideration in treatment selection. The SF-36 quality of life assessment is also used with a higher score indicating an improved quality of life.

The FDA recently approved valbenazine, a selective, reversible VMAT2 inhibitor, for the treatment of adults with TD.[12,13] Deutetrabenazine, a VMAT2 inhibitor initially approved for HC, also recently received FDA approval for TD treatment. A third agent, tetrabenazine was approved in 2008 for use to treat symptoms of HC and has been used off-label for severe TD; however, mixed efficacy and numerous safety concerns has limited its widespread use.[11] This document examines the efficacy and safety for the use of VMAT2 inhibitors in TD and HC.

A summary of relevant drug information is available in **Appendix 1**, which includes pharmacology and pharmacokinetic characteristics of these drugs, contraindications, warnings and precautions, including any Black Boxed Warnings and Risk Evaluation Mitigation Strategies.

Table 2. VMAT2 Inhibitors Indications and Dosing

Drug Name (Manufacturer)	Indication(s)	Strength/Route	Dose and Frequency
Valbenazine[13] (Neurocrine Biosciences, Inc.)	Tardive dyskinesia in adults	40 mg and 80 mg capsules	Initiate dose at 40 mg daily and increase to 80 mg daily after one week

Deutetrabenazine[12] (Teva Pharmaceuticals USA, Inc.)	Chorea associated with Huntington's disease and tardive dyskinesia in adults	6 mg, 9 mg and 12 mg tablets	Huntington's disease: initiate at 6 mg/day and increase by 6 mg per day to recommended dose of 6-48 mg/day Tardive dyskinesia: initiate at 12 mg/day and increase by 6 mg per day to a recommended dose of 6-48 mg/day Doses of 12 mg or more should be given in 2 divided doses
Tetrabenazine[11] (Prestwick Pharmaceuticals)	Chorea associated with Huntington's disease in adults	12.5 mg and 25 mg tablets	Initiate dose at 12.5 mg and titrate as needed to up to 100 mg daily. Doses above 50 mg daily should be divided into 3 times daily regimen

Utilization data:
While utilization for VMAT2 inhibitors is low the annual costs are estimated to be around $75,000 or more per patient per year. There are Oregon Health Plan (OHP) fee-for-service (FFS) claims for tetrabenazine.

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 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), the Cochrane Collaboration, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, BMJ Clinical Evidence, Institute for Clinical and Economic Review (ICER) and the Canadian Agency for Drugs and Technologies2 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:

Tardive Dyskinesia
The National Institute of Health and Care Excellence (NICE): Interventions for Treating or Preventing Antipsychotic-induced Tardive Dyskinesia
A 2017 systematic review and meta-analysis was performed by NICE to assess the efficacy and safety of interventions to treat TD in adults.[3] Randomized trials and observational studies of adults taking a stable dose of antipsychotic drugs for 3 months or more were included. The search ended prior to the approval of valbenazine and deutetrabenazine. One hundred twelve studies were identified but most trials had a high overall risk of bias. Studies were small with 8-170 participants, with the exception of some vitamin E studies which enrolled up to 264 patients.[3] Interventions studied to manage TD symptoms included dose adjustment of antipsychotics, switching antipsychotics and addition of pharmacotherapy to antipsychotics.

Evidence from two small studies of very low quality found reduction of the antipsychotic dose did not result in clinically important improvement relative to continuing the antipsychotic (risk ratio [RR] 0.42; 95% CI, 0.17 to 1.04; p=0.06).[3] Two studies evaluated the effect of switching antipsychotics on TD symptoms

but the results could not be combined. The first study found switching to risperidone resulted in fewer patients with no clinically important improvement in TD symptoms compared to antipsychotic withdrawal (RR of 0.45; 95% CI, 0.23 to 0.89; p=0.02; ARR 38%/NNT 3). Low quality evidence from a second study in 45 patients found no difference in clinically important improvement in TD symptoms when switching to quetiapine versus haloperidol (RR of 0.80; 95% CI, 0.52 to 1.22; p=0.30).[3] Evidence from observational studies found no clear evidence of improvement in TD symptoms with antipsychotic discontinuation versus dose modification based on very low quality evidence. Two studies that evaluated the effect of benzodiazepines on TD symptoms provided very low-quality evidence of no benefit (RR 1.12; 95% CI, 0.6 to 2.09). Vitamin E was evaluated in 6 studies with similar results of no benefit (RR 0.95; 95% CI, 0.89 to 1.01) based on low quality evidence. Another low-quality study (n=42) found improvement in TD symptoms with use of buspirone, added to antipsychotic treatment, (RR 0.53; 95% CI, 0.33 to 0.84; p=0.007; ARR 42%/NNT 3). A study of very low quality could not find a difference at 18 weeks between haloperidol and tetrabenazine in the number of patients with no improvement in TD symptoms (RR 1.07; 95% CI, 0.51 to 2.23; p=0.35).[3] Another small study found less patients on clonazepam had no clinically important improvement in TD symptoms compared to phenobarbital (40% vs. 91%, respectively).

To summarize, the only two strategies found to decrease TD symptoms were switching to risperidone (versus antipsychotic withdrawal) and adding buspirone adjunctively to the antipsychotic. All other comparisons were not clinically or numerically significant.

Institute for Clinical and Economic Review (ICER): Effectiveness and Value of Vesicular Monoamine Transport 2 Inhibitors for Tardive Dyskinesia
A 2017 review on the role of VMAT2 inhibitors in TD was produced by ICER.[4] The focus of the review was on valbenazine, deutetrabenazine and tetrabenazine use in adults with TD. Key intermediate outcomes were AIMS, CGIC and PGIC. Eleven studies of at least 10 patients were included. Thirteen references of conference abstracts/posters were also included.[4] Evidence identified for valbenazine and deutetrabenazine were found to be of fair to high quality studies. Evidence for tetrabenazine was determined to be of poor quality and therefore these studies were not considered in qualitative or quantitative assessments of VMAT2 inhibitors.

ICER rated both valbenazine and deutetrabenazine for the treatment of TD as "promising but inconclusive" based on improvement in AIMS scores compared to placebo but lack consistent improvement in CGIC and PGIC scores.[4] ICER concluded that clinician and patient impressions of symptom improvement is of critical importance since the drugs were approved for this indication. ICER was also concerned with lack of long-term safety data that could reveal additional adverse events with both treatments. Deutetrabenazine carries a FDA boxed warning for depression and suicidality. Evidence for use of tetrabenazine for the treatment TD symptoms suggest a possible benefit but was rated as insufficient.[4] Clinical trial safety data of tetrabenazine found tolerability issues from somnolence, insomnia, and depression.

Huntington's Disease
Cochrane Collaboration – Therapeutic Interventions for Symptomatic Treatment in Huntington's Disease
The pharmacological treatment options for the treatment of HD was reviewed.[5] Evidence for deutetrabenazine and valbenazine was not available as they were approved after the publication date. Randomized, double-blind, placebo-controlled studies with at least 10 patients met inclusion criteria. Twenty-two studies were identified. Mean patient age was 48 years with a mean disease duration of 6.3 years. Only one trial (n=84) for VMAT2 inhibitors was identified, which compared tetrabenazine to placebo. Patients with a confirmatory diagnosis or a compatible family history of HD were included.

The study found tetrabenazine 100 mg daily lowered the UHDRS-TCS score by 5.0 points compared to a decrease of 1.5 points for placebo (MD 3.5 points; 95% CI, -5.2 to -1.9; p<0.0001).[5] Tetrabenazine resulted in a statistically significant difference in change in CGIC score versus placebo (3.0 points vs. 3.7 points, respectively; MD 0.7 points; CI not reported; p<0.007); however, the clinical significance of a 0.7 point change is unlikely to be impactful to the patient. The

exploratory functional endpoints of UHDRS Functional Checklist and the 17-item Hamilton Depression scale were statistically worse with tetrabenazine compared to placebo. Five (9.2%) of patients in the tetrabenazine group discontinued treatment due to adverse events compared to none in the placebo group.[5]

Other treatments have been studied for the reduction of symptoms with HD. Use of riluzole is limited by an excess of hepatic toxicity when used at the effective dose of 200 mg daily. A study of riluzole 100 mg daily showed lack of efficacy. Two small trials studied amantadine for symptoms of chorea with HD. Pooled analysis found no difference between amantadine and placebo (MD -0.25; 95% CI, -0.93 to 0.43; p=0.10); however, a higher number of patients reported subjective improvement in symptoms and quality of life with the use of amantadine.[5]

Therapies studied which demonstrated no measurable effect on chorea symptoms of HD were: cannabidiol, clozapine, creatine, ethtyl-eicosapentaenoic acid, fluoxetine, ketamine, L-acetyl carnitine, minocycline, piracetam, remacemide, sulpiride, tiapride, trans-dihydrolisuride and unsaturated fatty acids.[5]

Guidelines:

American Academy of Neurology (AAN): Treatment of Tardive Syndromes

A clinical practice guideline on the management of tardive syndromes was published in 2013 by the AAN.[1] Evidence was systematically reviewed and graded using a modified GRADE process for evidence synthesis. One of the guideline authors had substantial ties to industry. Treatments included in the guideline were anticholinergics, benzodiazepines, beta-blockers, calcium channel blockers, GABAergic compounds, neuroleptic medications, non-neuroleptic medications that affect the dopamine and noradrenaline systems, vitamin B6 and vitamin E. Each study was graded on quality of evidence, from Class I (randomized clinical trial) to Class IV (consensus/expert opinion). Evidence was given an overall evidence rating ranging from A (established efficacy) to U (data inadequate or conflicting).

There was insufficient evidence to support treatment of TD symptoms by withdrawing the DRBA (Level U).[1] Evidence was conflicting whether switching from typical antipsychotics to atypical antipsychotics reduced TD symptoms (Level U). There was insufficient evidence to support treatment of TD with acetazolamide and thiamine (Level U). Amantadine may be an option for the short-term treatment of TD (Level C). However, neuroleptics may cause TD and mask symptoms and are not recommended to treat symptoms of TD (Level U).[1] Caution should be taken if risperidone or olanzapine are used to treat symptoms of TD. The use of tetrabenazine may be considered for the treatment of TD symptoms based on evidence from two Class III studies (Level C). Clonazepam may be effective for short-term (approximately 3 months) treatment of TD and should be considered (Level B).

There was insufficient data to recommend reserpine, alpha-methyldopa, levetiracetam or anticholinergics for TD (Level U).[1] There was insufficient evidence to support use of thiopropazate, molindone, sulpiride, fluperlapine, flupenthixol, bromocriptine, nifedipine, buspirone, botulinum toxin or baclofen for treatment of TD symptoms (Level U). Galantamine is likely ineffective for the treatment of TD symptoms and is not recommended (Level C). There was insufficient evidence to determine if discontinuing biperiden is effective in treating symptoms of TD (Level U).

American Academy of Neurology (AAN): Pharmacologic Treatment of Chorea in Huntington Disease

The AAN published a treatment guideline of the management of chorea in patients with HD in 2012.[2] Each study was systematically reviewed and graded using a modified GRADE process for evidence synthesis. Evidence was given an overall evidence rating ranging from A (established efficacy) to U (data inadequate or conflicting). AAN guidelines are funded by the academy and authors of this guideline had received grants from industry. Dopamine-modifying drugs, glutamatergic-modifying drugs, energy metabolites, donepezil, coenzyme Q10, minocycline, and nabilone were included. Guidelines were developed before the approval of valbenazine and deutetrabenazine so guidance on these treatments are not available.

AAN guidelines recommend tetrabenazine up to 100 mg daily for patients needing treatment for HC based on level B evidence.[2] Two studies, graded as Class I and Class II, were used as evidence to support the recommendation. A 12-week RCT comparing tetrabenazine to placebo (n=84) found a UHDRS total maximal chorea score decrease of -5.0 points compared to -1.5 points in the placebo group (p=0.0001). CGIC scores also improved with tetrabenazine by an adjusted effect size of -0.7 units (95% CI, -1.3 to -0.2) compared to placebo. A 10% change in symptoms in unlikely to be clinically significant .PGIC scores were not reported. A second study was a tetrabenazine withdrawal study which found that patients in the early discontinuation group had a 5.3-point increase in UHDRS chorea score compared to patients continuing therapy.[2] Reviewers felt that tetrabenazine was likely effective in decreasing chorea symptoms but should be used cautiously as it can worsen depression and Parkinsonian symptoms often present in HD.

Amantadine 300-400 mg daily and riluzole 200 mg daily were also recommended based on Level B evidence. Short-term use of nabilone can also be considered (Level C).

Randomized Controlled Trials:
A total of 41 citations were manually reviewed from the initial literature search. After further review, 37 citations were excluded because of wrong study design (e.g., observational) or outcome studied (e.g., non-clinical). The remaining 4 trials are summarized in the new drug evaluation tables below.

VALBENAZINE NEW DRUG EVALUATION:

Clinical Efficacy:
The efficacy of valbenazine in the treatment of TD was established primarily on the basis of one 6-week randomized, parallel-group, fixed-dose, placebo-controlled study (see **Table 2**).[6] Valbenazine 40 mg daily (n=76) and valbenazine 80 mg daily (n=70) were compared to placebo (n=79) in medically stable patients with moderate to severe TD from various centers in the US (59 sites), Canada (2 sites), and Puerto Rico (2 sites).[6] A majority of patients were diagnosed with schizophrenia or schizoaffective disorder (66.1%) or mood disorder (33.9%) and had a DSM diagnosis of DRBA-induced TD for at least 3 months. Seventeen percent of patients were taking first-generation antipsychotic (FGA) and 77% were taking a second-generation antipsychotic (SGA). The mean baseline AIMS dyskinesia score was 10 and patients had an average 7-year history of TD. Patients with severe psychiatric disease, as indicated by a Positive and Negative Syndrome Scale (PANSS) score of 70 or more or a score of at least 50 on the Brief Psychiatric Rating Scale (BPRS), or significant unstable comorbidities were excluded. Specifically, patients with any other movement disorder more prominent than TD, such as parkinsonism, akathisia or truncal dystonia, were not included. The primary endpoint was a mean change in the AIMS dyskinesia score for items 1-7 on AIMS (range 0-28) from baseline to week 6.[6] Global severity (questions 8-10) and problems with teeth or dentures (questions 11-12) were not assessed. The key secondary endpoint was the change in the 7-point CGI-TD score (range 1-7) from baseline to week 6.[6] PGIC was also a secondary endpoint with scores of 1 (very much improved) or 2 (much improved) classified as PGIC "responders".

The mean total AIMS dyskinesia score was reduced by 1.9 points in the 40 mg group and 3.2 points in the 80 mg valbenazine group, which were statistically significant differences versus the 0.1-point reduction with placebo.[6] However, these differences are unlikely to be meaningful, especially in patients with less severe TD symptoms. A reduction in AIMS dyskinesia score of greater than 50% at 6 weeks from baseline occurred in 23.8% of patients on valbenazine 40 mg (p= 0.02 vs. placebo, NNT = 7) and 40% of patients on valbenazine 80 mg (p<0.001 vs. placebo, NNT = 4).[6] No statistically significant difference was found in CGIC scores between the valbenazine arms and placebo at week 6. The number of treatment responders, as assessed by the PGIC, in the valbenazine 40 mg group was 31.7%, versus 24.3% in the valbenazine 80 mg group and 42.0% for the placebo group. [10] Patients on placebo experienced a statistically greater impression of improvement than patients on valbenazine 80 mg per day.[10]

There insufficient evidence to support the assertion that a statistically significant reduction in AIMS dyskinesia score is associated with clinical relevance because there is no established MCID. Additionally, PGIC scores were lower with valbenazine than with placebo which suggest that patients felt their symptoms were improved less than placebo with treatment. It is also unknown if valbenazine had different effects within the 3 types of psychiatric disorders represented in the study. In addition, not all patients were on an antipsychotic, and there was evidence to suggest that patients not on an antipsychotic may have responded better than patients on antipsychotic therapy.[6] Patients with severe depression or suicidal ideation were excluded from the study so the effects of valbenazine in this population is unknown. The trial's extensive exclusion criteria limit the applicability of the data to healthy, stable psychiatric patients with few to no comorbidities. The effect of valbenazine in complex patients, prescribed multiple high-dose antipsychotics or patients with other types of DRBA-induced TD is unknown. It was unclear why patients were not assessed using the global judgement portion of the AIMS tool. Given the short study duration, unestablished MCID for the AIMS tool, and lack of clinician-reported and patient-reported impression of improvement, the clinical value and long-term effectiveness of valbenazine is unclear.

Clinical Safety:

In KINECT 3, 5.3% of patients in the placebo group and 6% of patients in the valbenazine group prematurely discontinued their medication due to an adverse event.[6] Serious adverse events were reported more frequently in the valbenazine group than placebo (6.6% vs. 3.9%, respectively). However, the specific types of adverse events leading to early discontinuation of treatment or types of serious adverse events were not reported in the study. The most common adverse effects for valbenazine versus placebo were somnolence (5.3% vs. 3.9%, respectively), dry mouth (3.3% vs. 1.3%, respectively), and akathisia (3.3% vs. 1.3%, respectively). [13] Pooled safety data from 3 controlled studies (n=445) reported that somnolence was present in 11% of valbenazine subjects versus 4% for placebo which was higher than what was found in KINECT 3.[6] The short study duration limits the ability to draw conclusions on the safety of valbenazine.

The FDA safety analysis noted QT prolongation with valbenazine which prompted addition of this warning to the labeling.[6] Due to potential increases in serum concentrations of valbenazine's active metabolite ([+]-α-dihydrotetrabenazine), labeling also includes recommendations to avoid concomitant use with monoamine oxidase inhibitors (MAOI) and strong CYP3A4 inducers and to reduce valbenazine dose with co-administration of strong CYP3A4 and CYP2D6 inhibitors.[14] Valbenazine is not recommended for patients with severe renal impairment.[13]

Comparative Clinical Efficacy:

Clinically Relevant Endpoints:

1) Functional improvement
2) Symptom improvement
3) Health-related quality of life
5) Serious adverse events
6) Study withdrawal due to an adverse event

Primary Study Endpoint:

1) AIMS dyskinesia total (change from baseline)

Table 3. Valbenazine Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/ NNH	Risk of Bias/ Applicability
Hauser et al.[6,10,13] DB, PC, Phase 3, RCT	1. valbenazine 40 mg daily 2. valbenazine 80 mg daily 3. Placebo 6 weeks	Demographics: -Mean age: 56 years -Age ≥65 years: 16% -Male: 54% -White: 56% -Black: 38% -Mean AIMS dyskinesia score (items 1-7): 1. 9.8 2. 10.4 3. 9.9 -Schizophrenia/ schizoaffective: 66% -Mood disorder: 34% -APD: 85.5% -SGA: 77% -Antidepressant: 66.5% Key Inclusion Criteria: -Age: 18-85 -Diagnosis of schizophrenia or schizoaffective disorder or mood disorder per DSM-IV criteria for ≥ 3 mo. -DSM diagnosis of DRBA-induced TD for ≥ 3 mo. -Moderate to severe TD per external centralized AIMS video rating score -Maintenance meds at a stable dose for ≥30 days before screening Key Exclusion Criteria: -NCYP3A4 inducers, dopamine agonists, MAOIs -PANSS total score ≥70 or CDSS total score ≥10 -Unstable mental conditions -h/o suicidal ideation -h/o prolonged QT	ITT: 1. 70 2. 79 3. 76 PP: 1. 52 2. 61 3. 66 Attrition: 1. 17% 2. 11% 3. 9%	Primary Endpoint: Change total AIMS score at Week 6: 1. -1.9 2. -3.2 3. -0.1 1. VBZ 40 mg vs. PBO -1.8 (95% CI, -3.0 to -0.7) p= 0.0021 2. VBZ 80 mg vs. PBO -3.1 (95% CI, -4.2 to -2.0) p <0.0001 Secondary Endpoints: % w/ ≥50% decrease in AIMS score: 1. 24% 2. 40% 3. 9% 1. VBZ 40 mg vs. PBO 15% (95% CI NR; p= 0.02) 2. VBZ 80 mg vs. PBO 40% (95% CI NR; p<0.001) LS Mean CGI-TD at Week 6: 1. 2.9; p=NS vs. PBO 2. 2.9; p=NS vs. PBO 3. 3.2 PGIC Treatment Responders 1. 31.7% 2. 24.3% 3. 42.0%	NA NA 15%/7 31%/4 NS NS	SAE 1. 5.6% 2. 7.6% 3. 3.9% DC due to AE: 1. 5.6% 2. 6.3% 3. 5.3% TEAEs: Somnolence 1. 5.6% 2. 5.1% 3. 3.9% Akathisia 1. 4.2% 2. 2.5% 3. 1.3% Dry mouth 1. 6.9% 2. 0% 3. 1.3% p-values NR	NA	**Risk of Bias (low/high/unclear)**: Selection Bias: LOW. IWRS used to randomly assign participants. Use of APDs differed between groups. Ultra-rapid and poor CYP2D6 metabolizers also differed but implications of these differences are unclear. Performance Bias: LOW. Participants, investigators, study site personnel, central AIMS video raters, and the study sponsor blind to treatment assignment. Detection Bias: LOW. AIMS examination video reviewed/scored by blinded experts via central AIMS video. Video rater pairs provided consensus scoring. Attrition Bias: UNCLEAR. Attrition higher in treatment groups (14% vs. 9%). Not a true ITT as analysis excluded some randomized patients. Analyses conducted in the per-protocol population considered supportive. Reporting Bias: UNCLEAR. Study funded by drug sponsor. Of 9 authors, 4 directly employed by drug sponsor and 4 others served as consultants and/or received honoraria from sponsor. Sponsor provided support for writing and editorial assistance of the manuscript. Three authors have equity in drug sponsor. Critical review of manuscript drafts provided by full-time employee of drug sponsor. **Applicability**: Patient: Narrow inclusion criteria limits applicability to patients with schizophrenia, schizoaffective disorder, or mood disorder w/ DRBA-induced TD; study excluded high-risk or medically unstable, violent or suicidal patients; concomitant psychiatric medications likely representative of target population but highly variable. Intervention: VBZ doses used approved by FDA. Comparator: PBO appropriate to assess efficacy. Outcomes: AIMS test score change from baseline, but MCID is unclear; AIMS score results highly subjective and not linear; PGIC and CGIC more clinically relevant outcomes but these did not support efficacy of VBZ. Setting: 63 centers in North America (59 in the United States, two in Canada, and two in Puerto Rico).

Abbreviations: AIMS = Abnormal involuntary movement scale; ARR = absolute risk reduction; APD = antipsychotic drug; CDSS = Calgary Depression Scale for Schizophrenia; CFB = change from baseline; CGIC = Clinical Global Impression of Change; CI = confidence interval; DRBA = dopamine receptor blocking agents; ITT = intention to treat; IWRS = Interactive web response system; LS = least squares; MADRS = Montgomery-Asberg Depression Rating Scale; MAOIs = monoamine oxidase inhibitors; mITT = modified intention to treat; mo = months; N = number of subjects; NA = not applicable; NMS = neuroleptic malignant syndrome; NNH = number needed to harm; NNT = number needed to treat; NR = not reported; NS = not significant; PP = per protocol; Positive and Negative Syndrome Scale = PANSS; SAS = Simpson-Angus Scale; TD = tardive dyskinesia; VBZ = valbenazine; VMAT2 = vesicular monoamine transporter 2; YMRS = Young Mania Rating Scale

DEUTETRABENAZINE NEW DRUG EVALUATION:

Clinical Efficacy:

Deutetrabenazine is a VMAT2 inhibitor approved for chorea associated with HD and TD in adult patients.[12] Deutetrabenazine is a chemically modified form of tetrabenazine that has a longer half-life and lower peak concentrations levels. Deutetrabenazine has been studied in one trial for HD and two trials for TD (**Table 4**). Deutetrabenazine received an orphan drug designation for Tourette syndrome in the pediatric population.[12]

Huntington Chorea

Approval for the use in HC was based on a randomized, placebo-controlled, double-blind, multicenter study in 90 patients with HD.[7] Deutetrabenazine was compared to placebo over 12 weeks. Inclusion criteria included a baseline UHDRS total maximal chorea score of 8 or higher (range 0-28 with lower scores indicating less chorea) and a UHDRS total functional capacity score of 5 or higher which correlates to mild to moderate functional impairment. Patients had a HD diagnosis for approximately 15 years. The mean patient age was 54 years and 56% were male. Mean UHDRS- TCS was 12.7 at baseline. Exclusion criteria included the following: uncontrolled depression as measured by a Hospital Anxiety and Depression Scale (HADS) score of 11 or more, history of significant suicidal thoughts or behavior, prolonged QT interval, hepatic or renal impairment, Unified Parkinson Disease Rating Scale (UPDRS) speech item with scores of 3 or higher, and patients with score of 11 or higher on the Swallowing Disturbance Questionnaire.[7] Patients taking antipsychotics and dopamine agonists were also excluded. The primary endpoint was change in UHDRS-TCS from baseline (average of values from the screening period and day 0 visits) to maintenance therapy (the average of values between Week 9 and Week 12). Studies have used a change of 2.7 points in UHDRS-TCS to indicate a clinically relevant treatment difference, but this only represents a 10% change. MCID for UHDRS-TCS has not been established. Secondary endpoints of interest were the PGIC and CGIC. The PGIC and CGIC were defined as treatment success if patient response was “much” or “very much” improved at week 12.

TCS decreased by -4.4 points the deutetrabenazine group versus -1.9 points in the placebo group (MD -2.5; 95% CI, -3.7 to -1.3; P<0.001) at 12 weeks.[7] Treatment success based on PGIC was achieved in 23 patients (51%) treated with deutetrabenazine compared to 9 patients (20%) on placebo at 12 weeks (MD 31%; 95% CI, 12.4 to – 49.8%; NNT 4). Nineteen patients (42%) in the deutetrabenazine group experienced treatment success at Week 12, based on the CGIC scale, compared to 6 patients (13%) in the placebo group (MD 29%; 95% CI, 11.4 to 46.4%; p=0.02; NNT 4). Patient satisfaction scores improved 0.7 points with deutetrabenazine compared to -3.6 points with placebo (p=0.03) based on the SF-36 validated patient satisfaction tool. After washout at week 13, total maximum chorea scores returned to baseline values.

Study limitations included extensive exclusion criteria limiting the applicability, especially in patients taking antipsychotics. The patients in this trial had worse motor symptoms at baseline compared to evidence for tetrabenazine, which make efficacy comparisons difficult.[5] Secondary endpoints had wide confidence intervals which suggest that no treatment difference could still exist between deutetrabenazine and placebo. This is particularly important because these endpoints evaluate the patient’s perception of improvement, which is an important factor for therapies designed for symptom management.[12]Depression,

stigma and suicide rates are high in patients with HD. The study was not designed or powered to assess CGIC and PGIC so it is difficult to determine the effect of deutetrabenazine on these endpoints in such a small, short-term study.

Tardive Dyskinesia

The 2 multi-center, parallel design, placebo-controlled, double-blind, 12-week studies used to assess deutetrabenazine in management of TD symptoms were similar.[8,9] Both studies enrolled adult patients ages 18-80 years with an AIMS score (on items 1-7) of at least 6 and stable psychiatric illness with use of DRBA for at least 3 months (or age of 60 years or older with use of DRBA for at least one month). The primary endpoint was change in AIMS score from baseline. Secondary endpoints were the number of patients experiencing treatment success based on AIMS score improvement of at least 50%, CGIC "responders" (CGIC score of "much" or "very much" improved), and PGIC "responders" (PGIC score of "much" or "very much" improved). Patient satisfaction was measured by the modified Craniocervial Dystonia Questionnaire (mCDQ-24) in one of the studies.

The ARM-TD study was a phase 2/3 study evaluating the efficacy of deutetrabenazine compared to placebo in patients with TD.[9] The deutetrabenazine dose was titrated over 6 weeks as needed to control symptoms up to a maximum dose of 48 mg per day divided twice daily (or up to 36 mg/day in patients on strong CYP2D6 inhibitors). At the end of the titration period the mean total daily dose was 38.8 mg. Deutetrabenazine decreased AIMS scores by -3.0 points compared to -1.6 points for placebo (MD -1.4; 95% CI, -2.6 to -0.2; p= 0.019). A treatment difference of 5% is unlikely to be a clinically meaningful improvement in TD symptoms for patients. Treatment success as measured by the CGIC was 48.2% in the deutetrabenazine group compared to 40.4% in the placebo group (p-value not significant). PGIC treatment success was 42.9% in the deutetrabenazine group compared to 29.8% in the placebo group (p-value not significant). The difference in patient satisfaction, measured by the mCDQ-24, was not significantly different between deutetrabenazine and placebo, -11.1 and -8.3, respectively.

The AIM-TD study was a phase 3 study that evaluated 3 doses of deutetrabenazine (12, 24 and 36 mg/day) compared to placebo for the treatment of TD in adult patients (doses were divided twice daily).[8] The mean change in AIMS score from baseline was -3.3 in the deutetrabenazine 36 mg group, -3.2 in the deutetrabenazine 24 mg group, -2.1 in the deutetrabenazine group and -1.4 in the placebo group at week 12. The proportion of the patients who achieved at least a 50% improvement in the AIMS score was 33% for deutetrabenazine 36 mg, 35% for deutetrabenazine 24 mg, 13% for deutetrabenazine 12 mg and 12% for placebo. The differences from placebo was 21% (NNT 5; p=0.007) for deutetrabenazine 36 mg and 23% (NNT 4; p=0.005) for deutetrabenazine 24 mg. CGIC treatment success occurred in 44% of deutetrabenazine 36 mg patients (ARR 18/NNT 6; p=0.059), 49% of deutetrabenazine 24 mg patients (ARR 23%/NNT 4; p=0.014), 28% deutetrabenazine 12 mg patients (not-significant compared to placebo) and 26% of placebo patients. PGIC treatment success rates were not statistically significantly different between deutetrabenazine and placebo for all comparisons.

The results of both studies of deutetrabenazine use in patients with TD were most applicable to patients with schizophrenia taking a DRBA with moderate TD symptoms. Risk of bias in both studies was low and they were considered fair quality. A 5% improvement in TD symptoms is unlikely to be meaningful to patients, as demonstrated by a lack of a clinically meaningful change in the patients' perception of symptoms as measured by PGIC. Patients taking deutetrabenazine did not have a higher quality of life, as measured by mCDQ-24, compared to those taking placebo.[8] The FDA sites twice a day dosing of deutetrabenazine as the only clear advantage of it over tetrabenazine. Small sample sizes and short duration of treatment for an indication which is often chronic prevents strong conclusions of efficacy.

Other studies that did not meet our inclusion criteria were the following: an indirect tolerability study between deutetrabenazine and tetrabenazine in patients with HD[23], a long-term safety study of deutetrabenazine in patients with severe TD [24] and an ongoing, open-label, single arm study of converting tetrabenazine to deutetrabenazine[25].

Clinical Safety:
The most common adverse events seen in more than 8% of patients randomized to deutetrabenazine and more than placebo where somnolence, diarrhea, dry mouth and fatigue. Severe adverse reactions occurred in 2.2% of patients in each group. Discontinuations due to adverse events occurred in one patient in each group. The risk of depression and suicidal ideation where similar in both groups. Deutetrabenazine carries a FDA Boxed Warning for its ability to increase the risk of depression and suicide in patients with HD and should be used cautiously in patients with a history of depression. In studies of deutetrabenazine there were no safety signals for worsening depression or suicidality; however, due to the small, short-term nature of approval studies the increased risk could not be ruled out.

The effect of deutetrabenazine on QT prolongation may be clinically relevant in patients who are poor CYP2D6 metabolizers or taking strong CYP2D6 inhibitors.[22] Deutetrabenazine is closely related to tetrabenazine which has been shown to prolong the corrected QT interval by approximately 8 seconds. Metabolism of deutetrabenazine is primarily due to CYP2D6. Deutetrabenazine dosage reduction may be required if administered with strong CYP2D6 inhibitors.[21]

Comparative Clinical Efficacy:

Clinically Meaningful Endpoints:
1) Functional improvement
2) Symptom improvement
3) Health-related quality of life
4) Serious adverse events
5) Study withdrawal due to an adverse event

Primary Study Endpoint:
1) Total maximal chorea score change in HD
2) AIMS score change from baseline in TD

Table 4. Deutetrabenazine Comparative Evidence Table.

Ref./ Study Design	Drug Regimens/ Duration	Patient Population	N	Efficacy Endpoints	ARR/NNT	Safety Outcomes	ARR/NNH	Risk of Bias/ Applicability
1. Huntington Study Group[7] RCT, DB, DD, PC, PG, MC, Phase 3	1. DBZ* 2. PBO * Dose titrated over 8 weeks with a maintenance dose given for 4 weeks. Initiated at 6 mg/day and increased weekly by 6 mg/day till chorea was controlled, patient experienced adverse events or the maximum dose of 48 mg/day achieved. 12 weeks	Demographics: Mean Age: 54 y Male: 56% White: 83% Mean UHDRS functional capacity: 9.5 Mean UHDRS total maximal chorea score: 12.7 Key Inclusion Criteria: - HD verified by motor examination features and an expanded HTT CAG repeat sequence (≥36) - UHDRS total maximum chorea score of 8 or higher - UHDRS total functional capacity score of 5 or higher Key Exclusion Criteria: - Untreated psychiatric illness -prolonged QT interval, left bundle-branch block - hepatic or renal impairment - Use of antipsychotics,	ITT: DBZ: 45 PBO: 45 PP: DBZ: 44 PBO: 43 Attrition: DBZ: 2.3% PBO: 4.5%	Primary Endpoint: Total maximal chorea score change from baseline: DBZ: -4.4 PBO: -1.9 MD -2.5 (95% CI, -3.7 to -1.3) p<0.001 Secondary Endpoints: Treatment success determined by PGIC: DBZ: 23 (51%) PBO: 9 (20%) MD 31.1 (95% CI, 12.4 to –49.8) P = 0.002 Treatment success determined by CGIC: DBZ: 19 (42%) PBO: 6 (13%) MD 28.9 (95% CI, 11.4 to –46.4) P = 0.002 Patient satisfaction determined by mean SF-36: DBZ: 0.7 PBO: -3.6 MD: 4.3 (95% CI, 0.4 to 8.3) p = 0.03	NA 31%/4 29%/4 NA	Somnolence: DBZ: 5 (11.1%) PBO: 2 (4.4%) p-value NR Dry mouth: DBZ: 4 (8.9%) PBO: 3 (6.7%) p-value NR Diarrhea: DBZ: 4 (8.9%) PBO: 0 p-value NR Depression or agitated depression: DBZ: 2 (4.4%) PBO: 3 (6.7%) p-value NR D/C due to AE: DBZ: 1 (2%) PBO: 1 (2%) SAE: DBZ: 1 (2.2%) PBO: 1 (2.2%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Computerized randomization algorithm via an interactive web-based randomization system randomized patients in a 1:1 ratio. Patients were stratified by prior exposure to tetrabenazine. Performance Bias: (low) Patients, site personnel, and study personnel were blinded to treatment. Adherence was accessed via pill count. Pills were identical in each group. Detection Bias: (unclear) Blinding of accessors was not described. Attrition Bias: (low) Attrition rates were low in both groups. Results were analyzed using ITT and LOCF for missing data. Reporting Bias: (low) Outcomes were reported as specified. Trial was funded by Auspex Pharmaceuticals. **Applicability**: Patient: Baseline functional scores suggest mild to moderate impairment. Intervention: Mean dose was 39.7 mg end of treatment period and 34.8 mg for patients with impaired CYP2D6 function (poor metabolizers or taking strong CYP2D6 inhibiting medications). The maximum deutetrabenazine dose is 48 mg/day suggesting study doses are appropriate. Comparator: Placebo comparison appropriate to establish efficacy where no standard of therapy exists. Outcomes: No minimal clinically important difference is available for total maximal chorea score but this a standardized measure for patients with HD, as well as the other secondary endpoints. Setting: Thirty-four sites in the United States and Canada.

		MAOIs, metoclopramide - Drugs known to prolong the QT interval						
2. Anderson, et al[9] (AIM-TD) MC, PG, PC, DB, Phase 3	1. DBZ 12 mg (D12)* 2. DBZ 24 mg (D24)* 3. DBZ 36 mg (D36)* 4. PBO 12 weeks *DBZ started at 12 mg/day divided twice daily and titrated by 6 mg/day till the randomized dose was achieved. Maintenance period was 8 weeks.	Demographics: Mean Age: 56 years Male: 45% TD duration: 5.6 y Baseline AIMS score (items 1-7): 8.4 Key Inclusion Criteria: - 18-80 years - ≥3 months of TD - AIMS score of ≥6 - DRBA use for ≥3 months - stable psychiatric illness - Use of antipsychotic for ≥30 days Key Exclusion Criteria: - Untreated psychiatric illness or neurological illness besides TD - Serious or unstable medical condition - Other treatment for TD - Hepatic or renal impairment	mITT: D12: 60 D24: 49 D36: 55 PBO: 58 PP: D12: 60 D24: 49 D36: 55 PBO: 58 Attrition: D12: 11% D24: 12% D36: 13% PBO: 9%	Primary Endpoint: LS Mean AIMS Change from Baseline: D12: -2.1 D24: -3.2 D36: -3.3 PBO: -1.4 D12 vs. PBO: MD -0.7 (95% CI, -1.84 to 0.42; p=0.217) D24 vs. PBO: MD -1.8 (95% CI, -3.0 to -0.63; p=0.003) D36 vs. PBO: MD -1.9 (95%; -3.09 to -0.79; p=0.001) Secondary Endpoints: ≥ 50% AIMS Improvement: D12: 8 (13%) D24: 17 (35%) D36: 18 (33%) PBO: 7 (12%) D12 vs. PBO: NR D24 vs. PBO: OR 3.96 (95% CI, 1.46 to 10.72; p=0.005) D36 vs. PBO: OR 3.80 (95% CI, 1.40 to 10.36; p=0.007) CGIC Responders: D12: 17 (28%) D24: 24 (49%) D36: 24 (44%) PBO: 15 (26%) D12 vs. P: OR NR; p=0.734	 NS NA NA 23%/5 24%/5 NS	Somnolence: D12: 0 (0%) D24: 1 (1.4%) D36: 3 (4.1%) PBO: 3 (4.1%) p-value NR Headache: D12: 5 (6.8%) D24: 2 (2.7%) D36: 5 (6.8%) PBO: 4 (5.6%) p-value NR Diarrhea: D12: 1 (1.4%) D24: 3 (4.1%) D36: 5 (6.8%) PBO: 2 (2.8%) p-value NR SAEs: D12: 2 (3%) D24: 6 (8%) D36: 4 (5%) PBO: 4 (6%) D/C due to AES: D12: 4 (5%) D24: 2 (3%) D36: 3 (4%) PBO: 2 (3%)	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias: (low) Patients randomized centrally 1:1:1:1 via interactive response technology. Performance Bias: (low) Patients, investigators and site personnel were masked to treatment assignment. Detection Bias: (low) Central raters that were blinded to treatment assignment assigned ratings. Full statistical analyses not reported. Attrition Bias: (low) Attrition was low and similar between groups. Reporting Bias: (low) Outcomes reported as pre-specified. Study was funded by manufacturer. **Applicability**: Patient: Sixty percent or patients had a schizophrenic diagnosis, 17% a bipolar diagnosis and 19% a depression diagnosis. Improvement in primary outcome was irrespective of DRBA; however, a greater improvement was seen in patients not taking DRBAs. Intervention: Doses of deutetrabenazine were consistent with other studies. Comparator: Placebo comparison appropriate. Outcomes: No minimal clinically important difference is available for AIMS score; however, AIMS score is a common surrogate endpoint used in TD studies. Setting: Seventy-five study sites in the US and Europe.

				D24 vs. PBO: OR 2.71 (95% CI, 1.21 to 6.05; p=0.014) D36 vs. PBO: OR 2.11 (95% CI, 0.96 to 4.65; p=0.059) PGIC Responders: D12: 14 (23%) D24: 22 (45%) D36: 22 (40%) PBO: 18 (31%) D12 vs. PBO: OR 0.69 (95% CI, 0.30 to 1.56; p=0.372) D24 vs. PBO: OR 1.82 (95% CI, 0.83 to 3.99; p=0.134) D36 vs. PBO: OR 1.51 (95% CI, 0.69 to 3.29; p=0.296)	23%/5 NS NS NS NS			
3. Fernandez, et al[8] (ARM-TD) MC, PG, PC, DB, Phase II/ III	1. DBZ* 2. PBO 12 weeks *See Huntington Study Group for dosing	Demographics: Mean Age: 55 years Male: 56% TD duration: 6.2 years Baseline AIMS score: 9.6 Key Inclusion Criteria: - See Anderson, et al. Key Exclusion Criteria: See Anderson, et al.	mITT: DBA: 58 PBO: 59 PP: DBZ: 52 PBO: 52 Attrition: DBZ: 10% PBO: 12%	Primary Endpoint: LS Mean AIMS Change from Baseline: DBZ: -3.0 PBO: -1.6 MD -1.4 (95% CI, -2.6 to -0.2) p=0.019 Secondary Endpoints: CGIC Responder: DBZ: 48.2% PBO: 40.4% p- value reported as NS PGIC Responders: DBZ: 43% PBO: 30% p- value reported as NS Patient satisfaction as measured by mCDQ-24: DBZ: -11.1 PBO: -8.3 p- value reported as NS	NA NS NS NS	Somnolence: DBZ: 13.8% PBO: 10.2% p-value NR Headache: DBZ: 5.2% PBO: 10.2% p-value NR Diarrhea: DBZ: 5.2% PBO: 5.1% p-value NR SAEs: DBZ: 3 (5.2%) PBO: 5 (8.5%) p-value NR D/C due to AEs: DBZ: 1 (1.7%) PBO: 2 (3.4%) p-value NR	NA for all	**Risk of Bias (low/high/unclear)**: Selection Bias (low) central randomization by an Interactive Technology Response System in a 1:1 ratio stratified by prior use of DRBA. Performance Bias: (low) Video assessment of TD was done by 2 investigators blinded to treatment assignment. Detection Bias: (low) Central raters that were blinded to treatment assignment assigned ratings. Attrition Bias: (low) Attrition was low for both groups and similar between deutetrabenazine and placebo. Reporting Bias: (low) Outcomes were reported as stated. The study was funded by the manufacturer. **Applicability**: Patient: 68% patients had a schizophrenia, 23% a bipolar disorder, and 26% a depression. The mean age older than most Medicaid patients. 80% patients also on DRBA. Intervention: See Anderson, et al Comparator: See Anderson, et al Outcomes: See Anderson, et al Setting: 46 sites in US and Europe.

Abbreviations: AE = adverse events; ARR = absolute risk reduction; CAG = cytosine-adenine-guanine; CI = confidence interval; CGIC = Clinical Global Impression of Change; DB = double-blind; DD = double-dummy; DBZ = deutetrabenazine; DRBA = dopamine receptor blocking agent; HADS = Hospital Anxiety and Depression Scale; HTT = huntingtin gene; ITT = intention to treat; LOCF = last observation carried forward; MAOI = monoamine oxidase inhibitors; mCDQ-24 = modified Craniocervical Dystonia Questionnaire; MD = mean difference; mITT = modified intention to treat; MOI = monoamine oxidase inhibitors; N = number of subjects; NA = not applicable; NNH = number needed to harm; NNT = number needed to treat; PBO = placebo; PGIC = Patient Global Impression of Change; PP = per protocol; SAE = serious adverse events; TD = tardive dyskinesia; UHDRS = Unified Huntington's Disease Rating Scale; UPDRS = Unified Parkinson Disease Rating Scale.

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

INGREZZA® (valbenazine) capsules, for oral use
Initial U.S. Approval: 2017

----------INDICATIONS AND USAGE----------
INGREZZA is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of adults with tardive dyskinesia. (1)

----------DOSAGE AND ADMINISTRATION----------
- The initial dose is 40 mg once daily. After one week, increase the dose to the recommended dose of 80 mg once daily. (2.1)
- Can be taken with or without food. (2.1)
- The recommended dose for patients with moderate or severe hepatic impairment is 40 mg once daily. (2.2)
- Consider dose reduction based on tolerability in known CYP2D6 poor metabolizers. (2.2)

----------DOSAGE FORMS AND STRENGTHS----------
Capsules: 40 mg and 80 mg. (3)

----------CONTRAINDICATIONS----------
None. (4)

----------WARNINGS AND PRECAUTIONS----------
- Somnolence: May impair patient's ability to drive or operate hazardous machinery. (5.1)
- QT Prolongation: May cause an increase in QT interval. Avoid use in patients with congenital long QT syndrome or with arrhythmias associated with a prolonged QT interval. (5.2)

----------ADVERSE REACTIONS----------
Most common adverse reaction (≥5% and twice the rate of placebo): somnolence. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Neurocrine Biosciences, Inc. at 877-641-3461 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS----------
Dose adjustments due to drug interactions (2.3, 7):

Factors	**Dose Adjustments for INGREZZA**
Use of MAOIs with INGREZZA	Avoid concomitant use with MAOIs.
Use of strong CYP3A4 inducers with INGREZZA	Concomitant use is not recommended.
Use of strong CYP3A4 inhibitors with INGREZZA	Reduce dose to 40 mg.
Use of strong CYP2D6 inhibitors with INGREZZA	Consider dose reduction based on tolerability.

----------USE IN SPECIFIC POPULATIONS----------
- Pregnancy: May cause fetal harm. (8.1)
- Lactation: Advise not to breastfeed. (8.2)
- Renal Impairment: No dosage adjustment is necessary for patients with mild to moderate renal impairment. Use is not recommended in patients with severe renal impairment. (8.8)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: 10/2017

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

AUSTEDO™ (deutetrabenazine) tablets, for oral use
Initial U.S. Approval: 2017

WARNING: DEPRESSION AND SUICIDALITY
See full prescribing information for complete boxed warning.

- Increases the risk of depression and suicidal thoughts and behavior (suicidality) in patients with Huntington's disease (5.2)
- Balance risks of depression and suicidality with the clinical need for treatment of chorea when considering the use of AUSTEDO (5.2)
- Monitor patients for the emergence or worsening of depression, suicidality, or unusual changes in behavior (5.2)
- Inform patients, caregivers and families of the risk of depression and suicidality and instruct to report behaviors of concern promptly to the treating physician (5.2)
- Exercise caution when treating patients with a history of depression or prior suicide attempts or ideation (5.2)
- AUSTEDO is contraindicated in patients who are suicidal, and in patients with untreated or inadequately treated depression (4, 5.2)

INDICATIONS AND USAGE

AUSTEDO is a vesicular monoamine transporter 2 (VMAT2) inhibitor indicated for the treatment of chorea associated with Huntington's disease (1)

DOSAGE AND ADMINISTRATION

- The starting dose is 6 mg once daily. Titrate up at weekly intervals by 6 mg per day to a tolerated dose that reduces chorea, up to a maximum recommended daily dosage of 48 mg (24 mg twice daily) (2.1)
- Administer total daily dosages of 12 mg or above in two divided doses (2.1)
- Administer with food (2.1)
- Swallow tablets whole; do not chew, crush, or break (2.1)
- If switching patients from tetrabenazine, discontinue tetrabenazine and initiate AUSTEDO the following day. See full prescribing information for recommended conversion table (2.2)
- Maximum recommended dosage of AUSTEDO in poor CYP2D6 metabolizers is 36 mg per day (i.e., 18 mg twice daily) (2.4, 8.7)

DOSAGE FORMS AND STRENGTHS

Tablets: 6 mg, 9 mg, and 12 mg (3)

CONTRAINDICATIONS

- Suicidal, or untreated/inadequately treated depression (4, 5.2)
- Hepatic impairment (4, 8.6, 12.3)
- Taking MAOIs, reserpine, or tetrabenazine (XENAZINE®) (4, 7.2, 7.3, 7.7)

WARNINGS AND PRECAUTIONS

- Neuroleptic Malignant Syndrome (NMS): Discontinue if this occurs (5.3, 7.4)
- Akathisia, agitation, restlessness, and parkinsonism: Reduce dose or discontinue if this occurs (5.4, 5.5)
- Sedation/somnolence: May impair the patient's ability to drive or operate complex machinery (5.6)

ADVERSE REACTIONS

Most common adverse reactions (>8% of AUSTEDO-treated patients and greater than placebo) were: somnolence, diarrhea, dry mouth, and fatigue (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Teva Pharmaceuticals at 1-888-483-8279 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

- Concomitant use of strong CYP2D6 inhibitors: Maximum recommended dose of AUSTEDO is 36 mg per day (18 mg twice daily) (2.3, 7.1)
- Alcohol or other sedating drugs: May have additive sedation and somnolence (7.5)

USE IN SPECIFIC POPULATIONS

Pregnancy: Based on animal data, may cause fetal harm (8.1)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 4/2017

Appendix 2: Medline Search Strategy

Database(s): **Ovid MEDLINE(R)** 1946 to November Week 1 2017

Search Strategy:

#	Searches	Results
1	deutetrabenazine.mp.	12
2	valbenazine.mp.	18
3	tetrabenazine.mp. or Tetrabenazine/	1495
4	limit 3 to (english language and humans)	619
5	limit 4 to (clinical trial, phase iii or clinical trial, phase iv or guideline or meta analysis or practice guideline or randomized controlled trial or systematic reviews)	41

Vesicular Monoamine Transporter 2 (VMAT2) Inhibitors

Goal(s):
- Promote safe use of VMAT2 inhibitors in adult patients.
- Promote use that is consistent with medical evidence and product labeling.

Length of Authorization:
- Initial: Up to 2 months
- Renewal: Up to 12 months

Requires PA:
All VMAT2 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. What diagnosis is being treated?	Record ICD10 code. Go to #2	
2. Is the treatment for an OHP-funded condition?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; not funded by OHP
3. Is the request for continuation of vesicular monoamine transporter 2 (VMAT2) inhibitor therapy previously approved by FFS criteria (patient has completed 2-month trial)?	**Yes:** Go to **Renewal Criteria**	**No:** Go to #4
4. Is the request for tetrabenazine or deutetrabenazine in a patient 18 and older with a diagnosis of chorea as a result of Huntington's disease?	**Yes:** Go to #5	**No:** Go to #7

Approval Criteria		
5. Does the patient have a baseline total maximal chorea score of 8 or higher?	**Yes:** Go to #6 Document baseline score: _____	**No:** Pass to RPh. Deny; medical appropriateness
6. Has it been determined that the patient does not have uncontrolled depression or at risk of violent or suicidal behavior?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
7. Is the request for deutetrabenazine in a patient 18 and older with a diagnosis of moderate to severe tardive dyskinesia?	**Yes:** Go to #8 Document baseline modified AIMS* score: _____	**No:** Go to #9
8. Has it been determined that the patient does not have uncontrolled depression or at risk of violent or suicidal behavior?	**Yes:** Go to #10	**No:** Pass to RPh. Deny; medical appropriateness
9. Is the request for valbenazine in a patient 18 and older with a diagnosis of moderate to severe tardive dyskinesia?	**Yes:** Go to #10 Document baseline modified AIMS* score: _____	**No:** Pass to RPh. Deny; medical appropriateness
10. Is there documentation that the patient has been diagnosed with Schizophrenia, Schizoaffective Disorder, or a Mood Disorder?	**Yes:** Go to #11	**No:** Pass to RPh. Deny; medical appropriateness
11. Is the medication being prescribed by, or in consultation with, a neurologist or psychiatrist?	**Yes:** Go to #12	**No:** Pass to RPh. Deny; medical appropriateness

Approval Criteria		
12. Has the patient recently been evaluated and determined to not be at risk for a prolonged QT interval?	**Yes:** Approve for 2 months. Documented evidence of benefit required for renewal consideration (see renewal criteria).	**No:** Pass to RPh. Deny; medical appropriateness

* The dyskinesia score for the modified Abnormal Involuntary Movement Scale (AIMS) for numbers 1-7

P&T/DUR Review: 11/2017
Implementation: TBD

Renewal Criteria		
1. Is the request for a renewal of valbenazine or deutetrabenazine in a patient with tardive dyskinesia?	**Yes:** Go to #2	**No:** Go to #3
2. Has the patient been taking the requested VMAT2 inhibitor for >2 months and has there been documented evidence of improvement by a reduction in AIMS dyskinesia score (items 1-7) by at least 50%?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
3. Is the request for tetrabenazine or deutetrabenazine in a patient with chorea as a result of Huntington's disease?	**Yes:** Go to #4	**No:** Pass to RPh. Deny; medical appropriateness
4. Has the patient been taking the requested VMAT2 inhibitor for >2 months and has there been documented evidence of improvement in total maximal chorea score of at least 2 points from baseline?	**Yes:** Go to #5	**No:** Pass to RPh. Deny; medical appropriateness
5. Has it been determined that the mental status of the patient is stable and there is no indication of uncontrolled depression or risk of violent or suicidal behavior?	**Yes:** Approve for 12 months	**No:** Pass to RPh. Deny; medical appropriateness

P&T/DUR Review: 11/2017 (KS)
Implementation: TBD

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: Oral Antipsychotics

Date of Review: January 2018

Date of Last Review: May 2016
End Date of Literature Search: 10/27/2017

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

Purpose for Class Update:
Evidence for the comparative effectiveness of first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs) was last reviewed by the Oregon Pharmacy & Therapeutic Committee (P&T) in May 2016. Comparative effectiveness of parenteral antipsychotic products were reviewed in September 2017. This review examines recently published comparative evidence of oral first and second generation antipsychotics. In addition, data regarding new expanded indications and one new formulation are summarized.

Research Questions:
1. Is there new comparative evidence of meaningful difference in efficacy or effectiveness outcomes (including symptom improvement, quality of life, response to treatment, social or functional status) for schizophrenia, bipolar mania or major depressive disorders (MDD) between oral antipsychotic agents (first- or second-generation) or compared to parenteral antipsychotic agents (first- or second-generation)?
2. Is there new comparative evidence of meaningful difference in harms between oral antipsychotic agents (first- or second-generation) or compared to parenteral antipsychotic agents?
3. Is there new comparative evidence of meaningful difference in effectiveness or harms in certain subpopulations based on demographic characteristics (age, gender, or comorbidities), treatment history (treatment naive or treatment resistant), or concomitant medications?

Conclusions:
<u>Schizophrenia</u>
- No single SGA was superior to other SGAs for multiple clinically relevant outcomes. In general, clozapine, olanzapine, and risperidone oral did achieve superiority for more efficacy outcomes than other SGAs. Quetiapine and ziprasidone were not superior to any other SGAs for any outcomes.[1]
    - There was low quality evidence of no difference in social or functional status between risperidone, olanzapine, quetiapine, perphenazine, and ziprasidone at 18 months.[1]
    - There was no difference in quality of life at 12 months between olanzapine and risperidone (moderate strength of evidence), ziprasidone (moderate strength of evidence), or quetiapine (low strength of evidence).[1]

- There was low quality evidence that response to treatment was statistically more common with olanzapine (odds ratio [OR] 1.71, 95% confidence interval [CI] 1.11 to 2.68) and risperidone (OR 1.41, 95% CI 1.01 to 2.00) compared to quetiapine.[1] The absolute difference in response rate for individual treatment groups varied depending on the study from 20 to 80%.[1] Other comparisons failed to achieve statistically significant differences.[1]
- There was low quality evidence of statistically greater symptom improvement with clozapine versus other SGAs, with olanzapine and risperidone versus other SGAs and with paliperidone compared to lurasidone and iloperidone. Patients with treatment-resistant schizophrenia had greater improvement when treated with olanzapine compared to quetiapine (standardized mean difference [SMD] -0.29, 95% CI -0.56 to -0.13; small effect size corresponding to an average of -6.08 points on the Positive and Negative Syndrome Scale [PANSS]).[1] Overall differences between treatments were small and may not represent a clinically meaningful change in symptoms between treatment groups. The average improvement in symptoms was generally less than the estimated minimally important difference (11.5 points on the PANSS scale). There was no statistical difference in symptom improvement for other comparisons (low quality of evidence).[1]
- There was low quality evidence of no difference in all-cause mortality between SGAs.[1]
- There was low quality evidence that treatment with clozapine significantly reduced suicide attempts or hospitalizations to prevent suicide (hazard ratio [HR] 0.76, 95% CI 0.58 to 0.97) and symptoms of suicidality (HR 0.78, 95% CI 0.61 to 0.99) compared to olanzapine in patients at high risk for suicide.[1] It is unclear whether these differences are due to treatment itself or a result of the frequent monitoring required with clozapine.
- No difference was observed in the proportion of patients reporting overall adverse effects between SGAs.[1] For most studies the proportion of patients with adverse effects was greater than 60%.[1] A network meta-analysis of 90 head-to-head RCTs provides low quality evidence that treatment with risperidone LAI, olanzapine, aripiprazole, cariprazine and iloperidone had fewer withdrawals due to adverse effects compared to other SGAs.[1]
- Evidence regarding other outcomes (including relapse rate, overall treatment discontinuation, cardiovascular outcomes, diabetes and ketoacidosis and sexual function) was inconsistent between studies and insufficient to draw definitive conclusions between treatment groups.[1]

- Overall, olanzapine, risperidone, ziprasidone, and aripiprazole were comparable to haloperidol or perphenazine regarding improvements in quality of life (low quality evidence) or symptom improvement (low to moderate strength of evidence), but had fewer overall adverse effects and withdrawals due to adverse events.[1]
- There was no difference in withdrawals due to adverse effects upon comparison of haloperidol and clozapine or quetiapine (low quality evidence) and there was insufficient evidence for other comparisons.[1]
- There was insufficient evidence for comparisons of newer SGAs including brexpiprazole, cariprazine, iloperidone or lurasidone for the treatment of schizophrenia.

<u>Bipolar Disorder</u>

- There was no difference in efficacy outcomes (including remission rates, mania symptoms or treatment discontinuation) between olanzapine monotherapy and divalproex or valproate for acute mania in adults with bipolar I (low quality evidence from 4 RCTs [n=867]).[2] There was low quality evidence from a single study (n=488) which reported greater response rate with asenapine compared to olanzapine but no difference in remission rate between therapies.[2] There was insufficient evidence for all other antipsychotic drug comparisons (as monotherapy or in combination with mood stabilizers) for treatment of acute mania.
- One study noted that clinically important weight gain of at least 7% was more common in patients treated with olanzapine, though statistical significance of weight gain was not documented in all studies.[2] Overall, evidence was limited by a lack of direct comparative evidence and there was insufficient comparative evidence to determine differences in safety outcomes or adverse events for patients with bipolar disorder.

<u>Other Diagnoses</u>

- New evidence for the treatment of other conditions including borderline personality disorder and aggression is limited, and there is insufficient new evidence for treatment of other mental health conditions.

Children and Young Adults

- Overall there is insufficient direct comparative evidence for FGAs or SGAs for children or adolescents with bipolar disorder, autism spectrum disorder, ADHD or other conduct disorders, depression, eating disorders, or tic disorders.
- For treatment of schizophrenia in children or adolescents, there was low quality evidence of no difference in symptom improvement, response rate, or global impressions of severity between risperidone and olanzapine.[3] There was insufficient evidence for comparisons of other agents for the treatment of schizophrenia.[3]
- There was insufficient direct comparative evidence evaluating harms or adverse effects of antipsychotics in children or young adults. Upon indirect comparison between agents, pediatric patients treated with clozapine and olanzapine had on average more weight gain (2-5 kg over 6 to 12 weeks) than other antipsychotics (low quality evidence).[3] Upon indirect comparison between classes, there was moderate strength of evidence that SGAs are likely associated with more weight gain (mean difference [MD] 2.62 kg; 95% CI 4.35 to 0.86) and increase in BMI (MD 1.57 kg/m^2; 95% CI 2.49 to 0.53) compared to FGAs.[3] There was low quality evidence that use of SGAs was associated with fewer extrapyramidal symptoms compared to FGAs (relative risk [RR] 2.59; 95% CI 1.00 to 7.00) and low quality evidence of no difference in sedation between groups.[3]
- Subgroup analyses demonstrated no difference in efficacy or harms based on age, sex, or prior treatment history. Duration of treatment did have a slight effect on weight gain for children and young adults, with longer treatment durations associated with larger increases in weight over time (0.04 kg/week; 95% CI 0.014 to 0.071).[3]

Recommendations:

- No changes to the PDL are recommended for oral antipsychotics based on efficacy or safety data. There is a lack of evidence to recommend any new safety edits for the antipsychotic medications.
- Evaluate comparative costs in executive session.

Previous Conclusions (May 2016):

- 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 Maintena (aripiprazole) preferred and make chlorpromazine voluntary non-preferred (no PA required).

Background:

Antipsychotic medications are typically categorized as FGAs and SGAs. **Appendix 1** lists the oral FGAs and SGAs which are currently available. Antipsychotic medications are indicated for a variety of conditions including schizophrenia and schizoaffective disorder, bipolar disorder (acute and maintenance treatment), adjunct treatment for depression, autism, and Tourette's syndrome.[4] They are often used off-label for other mental health conditions including borderline personality disorder, agitation, aggression and nausea or vomiting.[4]

Schizophrenia is characterized by presence of delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior and negative symptoms. Diagnosis based on the Diagnostic and Statistical Manual of Mental Health Disorders (DSM-5) criteria requires presence of at least 2 of these symptoms (one must be either delusions, hallucinations or disorganized speech) for longer than 6 months. Symptoms are commonly categorized as positive symptoms (delusions and hallucinations) or negative symptoms (blunted affect, alogia, asociality, anhedonia, and avolition).[5] Onset of schizophrenia occurs most commonly in early adulthood and can have a significant impact on quality of life. Approximately 20% of patients remain relapse-free after a first psychotic episode.[1] However, the majority of patients experience relapse or continued symptoms which can decrease quality of life and create social or occupational difficulties. Factors associated with worse prognosis and disease course include presence of negative symptoms, longer duration of untreated psychosis, and slow or early disease onset at less than 18 years of age.[6] Schizophrenia has been associated with increased risk of mortality, and is often also associated with increased cannabis use, substance abuse, and higher rates of depression.[6] Treatment indicated for schizophrenia includes both FGAs and SGAs. First-generation antipsychotics are generally associated with higher incidence of extrapyramidal side effects whereas second-generation antipsychotics may have increased risk for long-term cardiovascular adverse effects.[1] Non-pharmacological therapy including psychological counseling, skills training, psychoeducation, or cognitive therapy is also often combined with pharmacological therapy.[6] Initial medication selection is often dependent on effectiveness and risks for adverse effects.

Bipolar disorder is characterized by episodes of mania and episodes of depression or hypomania and is estimated to occur in approximately 2% of the world population.[2,7] Initial diagnosis is most common in patients less than 25 years of age.[7] It is classified as bipolar I disorder (characterized by at least one manic episode) or bipolar II disorder (primarily characterized by history of depressive and hypomanic episodes).[7] It can be further classified as rapid cycling with at least 4 episodes of mania, hypomania or depression per year, mania with mixed features, or mania with psychotic features (including hallucinations or delusions).[7] Frequently bipolar disorder is associated with other mental health conditions including anxiety disorder, ADHD and substance use disorders.[7] First-line treatment for bipolar disorder is medication therapy including antipsychotics or mood stabilizers such as lithium, divalproex, or lamotrigine.[7] Goals of treatment include resolution of acute symptoms and long-term prevention of recurrent mania or depressive episodes.[2] Typically, if acute symptoms do not resolve with treatment, the patient is switched to an alternative medication or an additional medication is added.[7] Other treatments include electroconvulsive therapy (ECT), psychoeducational therapy, cognitive behavioral therapy and social therapy. The American Psychiatric Association and the National Institute for Health and Clinical Excellence (NICE) recommends ECT as an option for patients with life-threatening suicidality, psychosis or refusal to eat.[7] ECT may also be considered with severe or treatment-resistant bipolar depression and as a first-line option for pregnant women with severe depression.[7]

Symptom improvement and disease severity for schizophrenia can be evaluated using a variety of rating scales. The Clinical Global Impression Scale (CGI) evaluates disease severity and improvement using a 7 point analogue scale with lower scores indicating less severe symptoms and a change of 1 point corresponding to a minimum clinically important difference.[2,5] The Positive and Negative Syndrome Scale (PANSS) evaluates 30 items in schizophrenic patients each scored on a 7 point scale with lower scores indicating less severe symptoms. This scale can also be sub-divided to assess general psychopathology, positive symptoms, or negative symptoms. Typically response to treatment is defined as greater than 20% improvement in the PANSS score though this definition can vary among trials.[1,8] Negative symptoms of schizophrenia may also be assessed using the Scale for Assessment of Negative Symptoms (SANS) score which assesses negative symptoms including alogia, affective blunting, avolition-apathy, anhedonia-asociality, and attention impairment. Each item is assessed on a 0-5

point scale with higher scores indicating more severe symptoms. The Brief Psychiatric Rating Scale (BPRS) assesses schizophrenia symptom severity via assessment of 16-18 items (each assessed on a 7-point scale with a total score of 0 to 126). Similarly, quality of life and functional improvement may be assessed using a variety of metrics. The Global Assessment Scale of Functioning (GAF) scale is commonly used for patients with schizophrenia and assesses functional improvement on a 0 to 100 scale. Clinically important improvements in function have been correlated to changes of at least 10 points.[1]

For patients with bipolar disorder, symptom improvement is commonly evaluated using the 11-item Young Mania Rating Scale (YMRS). Using this scale, changes of at least 6 points have been correlated with clinically significant improvements.[2,9] Symptom improvement and severity for patients with bipolar disorder may also be evaluated using the CGI scale (range 1-7 with a minimum clinically important difference of 1 point).[2,5]

In the Oregon Health Plan, antipsychotic medications are exempt from traditional preferred drug list (PDL) and PA requirements. However, clinical PA criteria which address safety concerns or medically inappropriate use may be implemented. Currently, safety edits are implemented for low dose quetiapine to prevent off-label use and for pimavanserin to promote safe use in patients with Parkinson's disease psychosis. The majority of antipsychotic use is for SGAs. Each quarter, approximately 25,000 patients receive a prescription for a SGA and 1700 patients have claims for a FGA. This review will assess new evidence for the use of oral antipsychotics.

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 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), the Cochrane Collaboration, 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 evidence-based clinical practice 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:

Schizophrenia

An AHRQ report examining the effectiveness of first or second generation antipsychotic medications for the treatment of adults with schizophrenia was published in 2017.[1] First generation antipsychotics included in the review were fluphenazine, haloperidol, and perphenazine. Second-generation antipsychotics included aripiprazole, asenapine, brexpiprazole, cariprazine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, and ziprasidone. Comparisons were made between first and second generation antipsychotics and for the following clinical outcomes: functional outcomes (i.e. social or occupational), quality of life, remission rate, mortality, self-harm, symptom improvement, overall adverse effects, and withdrawals due to adverse effects. Re-hospitalization was not assessed as a clinical outcome due to important differences in rationale or indication for re-hospitalization and definition of re-hospitalization between studies. Trials and systematic reviews were included if they had a minimum duration of 12 weeks, were conducted in an outpatient setting, and had fair to good methodological quality.[1] Trials not applicable to a US population, trials reporting only placebo comparisons, trials including only comparisons to older antipsychotic drugs and trials reporting only intermediate outcomes were excluded. Overall, one systematic review (n=47,189) and 24 RCTs

(n=6,672) were included which compared differences between second generation antipsychotics.[1] One systematic review (n=118,503) and 5 RCTs (n=1,055) were included which compared first generation to second generation antipsychotics.[1] The majority of patients included in these trials were 25 to 50 years of age with moderate to severe disease and most included studies were 6 to 12 weeks in duration.[1] In trials assessing first-episode schizophrenia, the mean age was 26 years. Few studies assessed long-term outcomes up to 1 to 2 years.[1] There was little evidence which assessed newer second-generation antipsychotics including brexpiprazole, cariprazine, iloperidone or lurasidone.

- SGA comparisons: No single SGA was superior to other SGAs for multiple clinically relevant outcomes. In general, clozapine, olanzapine, risperidone oral and LAI did achieve superiority for more efficacy outcomes than other SGAs. Quetiapine and ziprasidone were not superior to any other SGAs for any outcomes.[1]
    - There was low quality evidence of no difference in social or functional status (as assessed by the Global Assessment of Functioning [GAF] scale) between risperidone, olanzapine, quetiapine, perphenazine, and ziprasidone at 18 months based on a single large RCT.[1] The GAF scale assesses functional improvement on a 0 to 100 scale and clinically important improvements in functions have been correlated to changes of at least 10 points.[1] There was insufficient evidence to assess differences in employment or residential status between SGAs due to few trials which report these outcomes and limitations in the quality of evidence.[1]
    - Similarly, there was no difference in quality of life at 12 months between olanzapine and risperidone (moderate strength of evidence), ziprasidone (moderate strength of evidence), or quetiapine (low strength of evidence).[1] There was no difference in quality of life between oral risperidone (oral or LAI) and quetiapine or ziprasidone at 12 months (low strength of evidence).[1] For other comparisons of SGAs, there was insufficient data or quality of evidence to draw any meaningful conclusions regarding quality of life.
    - There was low quality evidence that response to treatment was statistically more common with olanzapine (odds ratio [OR] 1.71, 95% CI 1.11 to 2.68) and risperidone (OR 1.41, 95% CI 1.01 to 2.00) than quetiapine based on a network meta-analysis of 46 head-to-head RCTs.[1] The absolute response rate for individual treatment groups varied depending on the study from 20 to 80%.[1] Other comparisons demonstrated no difference in treatment response.[1] The definition of response varied among trials, but was most commonly defined as greater than 20% improvement in the PANSS.[1] Other definitions included improvement of more than 20% on BPRS with either CGI-S score of less than or equal to 3 or BPRS less than 35; 30%, 40%, and 50% improvements in PANSS or BPRS; or a score of less than or equal to 3 on all PANSS items and less than 3 on the CGI-S.[1] Results were based on a network meta-analysis of trials and should be interpreted with caution as results represent indirect comparisons between treatments.[1] In addition, the analysis included limited evidence for the newer SGAs including injectable paliperidone, lurasidone, iloperidone, brexpiprazole, and cariprazine).[1] Remission, defined as complete resolution of symptoms, was rarely reported and there was insufficient evidence to assess treatment differences.
    - There was low quality evidence of no difference in all-cause mortality between SGAs.[1] Mortality rates ranged from 0 to 1.17% at 4 to 24 months. Evidence included large retrospective cohort studies assessing all-cause mortality (n=48,595) or cardiovascular mortality (n=55,582) and 6 RCTs comparing asenapine with olanzapine, quetiapine with risperidone, and paliperidone LAI with risperidone LAI.[1] There was limited evidence in specific populations including elderly patients with dementia-related psychosis or patients with specific diagnosis of schizophrenia due to lack of reported data in these populations and poor quality evidence.
    - There was low quality evidence that treatment with clozapine significantly reduced suicide attempts or hospitalization to prevent suicide (HR 0.76, 95% CI 0.58 to 0.97) and symptoms of suicidality (based on the Clinical Global Impression of Severity-Suicidality scale; HR 0.78, 95% CI 0.61 to 0.99) compared to olanzapine in patients at high risk for suicide.[1] Evidence was based on a single good-quality RCT of 980 patients at high risk of suicide which reported a significantly reduced 2-year event rate with clozapine treatment (NNT 12).[1] Similar trends were observed in observational studies with lower risk of suicidal symptoms associated with clozapine treatment compared to other SGAs.[1] However, it is unclear

whether symptom improvement is a result of the treatment itself or if it may be due in part to more frequent check-ins and follow-up required with clozapine treatment. There is insufficient evidence to assess risk between other SGAs.

- Evidence for symptom improvement relied on 3 large network meta-analyses.[1] These analyses assessed symptom improvement using a standardized mean difference based on pooled analyses of various symptom rating scales including the PANSS and BPRS. The PANSS scale ranges from 30 to 180 possible points with changes of 11.5 points suggested as a minimally clinically important differences for patients with severe disease.[1] Treatment with clozapine resulted in a statistically greater improvement in core illness symptoms compared to other SGAs (SMD of -0.32 to -0.55 associated with a small to medium effect size; low quality evidence).[1] Olanzapine and risperidone had greater improvement in core illness symptoms compared to other SGAs (SMD -0.13 to -0.26; small effect size) and paliperidone had greater improvement compared to lurasidone and iloperidone (SMD -0.17; small effect size; low quality evidence).[1] Patients with treatment-resistant schizophrenia had greater improvement when treated with olanzapine compared to quetiapine (SMD -0.29, 95% CI -0.56 to -0.13; low quality evidence; small effect size corresponding to an average of -6.08 points on the PANSS).[1] Overall differences between treatments were small and may not represent clinically meaningful changes in symptoms between treatment groups. There was no statistical difference in symptom improvement with other agents including clozapine, risperidone, olanzapine, quetiapine, and ziprasidone (low quality of evidence).[1]
- No difference was observed in the proportion of patients reporting overall adverse effects between SGAs.[1] For most studies, the proportion of patients with adverse effects was greater than 60%.[1] A network meta-analysis of 90 head-to-head RCTs provides low quality evidence that treatment with risperidone LAI, olanzapine, aripiprazole, cariprazine and iloperidone had fewer withdrawals due to adverse effects compared to other SGAs.[1] Specifically, risperidone LAI had fewer withdrawals compared clozapine (OR 0.27, 95% CI 0.10 to 0.71); lurasidone (OR 0.39, 95% CI 0.18 to 0.84); quetiapine extended release (ER) (OR 0.43, 95% CI 0.22 to 0.81); risperidone (OR 0.50, 95% CI 0.25 to 0.99); and ziprasidone (OR 0.40, 95% CI 0.20 to 0.82).[1] Olanzapine had a fewer withdrawals compared to clozapine (OR 0.39, 95% CI 0.19 to 0.79); lurasidone (OR 0.57, 95% CI 0.34 to 0.94); quetiapine (OR 0.62, 95% CI 0.44 to 0.87); risperidone (OR 0.72, 95% CI 0.55 to 0.96); and ziprasidone (OR 0.58, 95% CI 0.41 to 0.82).[1] Aripiprazole had lower risk of withdrawals than ziprasidone (OR 0.64, 95% CI 0.44 to 0.94) and clozapine (OR 0.43, 95% CI 0.21 to 0.88).[1] Cariprazine (OR 0.40, 95% CI 0.17 to 0.95) and iloperidone (OR 0.34, 95% CI 0.13 to 0.91) had fewer withdrawals due to adverse effects than clozapine.[1] There was no difference in withdrawals due to adverse effects when comparing other SGAs, though results for the newer SGAs should be interpreted with caution as less data for these agents is available.[1]
- Evidence regarding other outcomes (including relapse rate, overall treatment discontinuation, cardiovascular outcomes, diabetes, ketoacidosis and sexual function) was inconsistent between studies and insufficient to draw definitive conclusions between treatment groups.[1] Similarly, there was limited evidence regarding incidence of tardive dyskinesia. A single observational study suggests an increased risk with risperidone compared with olanzapine (OR 1.70, 95% CI 1.35 to 2.14), but absolute difference in risk was small (3% vs. 1-2%).[1] In addition, severity and incidence of extrapyramidal adverse effects were similar between treatments, though evidence for comparisons between medications was often limited to single studies and use of anticholinergic medications did differ for some comparisons.[1]
- One systematic review evaluated the proportion of patients with a clinically significant weight gain of at least 7%.[1] Greater differences in risk were observed with olanzapine compared to ziprasidone (RR 5.76), asenapine (RR 2.59), aripiprazole (RR 2.31), quetiapine (RR 1.82) and risperidone (RR 1.81) over 3.7 to 24 months.[1] Similarly, olanzapine had a higher risk of metabolic syndrome compared to risperidone (OR 1.60, 95% CI 1.10 to 2.21, I2=0% at 6 weeks to 3 months) and aripiprazole (OR 2.50, 95% CI 1.32 to 4.76; I2=0% at 3.5 to 12 months).[1]

- FGA versus SGA: Overall, olanzapine, risperidone, ziprasidone, and aripiprazole were comparable to haloperidol regarding improvements in quality of life or symptom improvement, but had fewer overall adverse effects and withdrawals due to adverse events.[1]

- Few trials reported improvements in functional status, and evidence was insufficient to evaluate differences between treatment groups. Similarly, there was insufficient evidence to assess difference in mortality or rates of suicide/self-harm between FGAs and SGAs due to lack of reported outcome data.
- Evidence evaluating differences in quality of life between treatment groups was limited. There was low quality evidence of no difference in quality of life between ziprasidone and haloperidol.[1] Evidence was limited by inconsistencies in treatment effects between trials. Similarly, there was no difference between haloperidol and olanzapine (moderate quality evidence) or between perphenazine and olanzapine, quetiapine, risperidone, or ziprasidone (low strength of evidence).[1] There was insufficient evidence to determine differences in quality of life for other comparisons.[1]
- Olanzapine had a statistically greater response rate compared to haloperidol (RR 0.86, 95% CI 0.78 to 0.96) based on low strength evidence from a systematic review of 14 RCTs (n=4,099).[1] Similarly, remission rates were greater with olanzapine than haloperidol (RR 0.64, 95% CI 0.45 to 0.94) based on low quality evidence from 3 RCTs.[1] There was no difference in response rates when comparing haloperidol versus aripiprazole, quetiapine, risperidone, and ziprasidone (moderate strength of evidence for haloperidol vs risperidone; low strength of evidence for all other comparisons).[1] There was no difference in remission rates between haloperidol and risperidone (low strength of evidence) and insufficient evidence for other comparisons.[1] Analyses were limited by moderate to high heterogeneity between studies (I2=29% to 83%).[1]
- Overall, there was no clinically meaningful differences in symptom improvement for core symptoms of schizophrenia upon comparison of FGAs to SGAs.[1] There was a statistically significant differences in symptom improvement with olanzapine compared to haloperidol (MD 2.31 points on the PANSS, 95% CI 0.44 to 4.18) and risperidone versus haloperidol (MD 3.24 points, 95% CI 1.62 to 4.86) based on moderate strength of evidence from an analysis 15 and 21 RCTs, respectively.[1] The clinical significance of these differences is unclear as the minimum clinically important difference for the PANSS scale is suggested to be 11.5 points.[1] Comparisons of other FGAs to other SGAs failed to demonstrate any statistically significant differences (low strength of evidence). [1]
- Negative symptoms (as assessed by the SANS score) were more improved with olanzapine than haloperidol (MD 2.56, 95% CI 0.94 to 4.18; moderate strength of evidence).[1] Similarly, improvement in negative symptoms was better with aripiprazole (MD 0.80, 95% CI 0.14 to 1.46), olanzapine (MD 1.06, 95% CI 0.46 to 1.67), and risperidone (MD 0.80, 95% CI 0.14 to 1.46) compared to haloperidol (as assessed using the negative symptoms subscale of the PANSS scale; low strength of evidence).[1] There were no differences for improvement of negative symptoms upon comparison of other FGAs and SGAs (low quality of evidence).[1]
- There was moderate strength of evidence that overall rates of adverse effects were lower with aripiprazole (RR 1.11; 95 % CI 1.06 to 1.17), risperidone (RR 1.20, 95% CI 1.01 to 1.42), and ziprasidone (RR 1.13, 95% CI 1.03 to 1.23) compared to haloperidol.[1] Similarly, withdrawals due to adverse events were higher with haloperidol compared to aripiprazole (RR 1.25, 95% CI 1.07 to 1.47), olanzapine (RR 1.89; 95% CI 1.57 to 2.27), risperidone (RR 1.32; 95% CI 1.09 to 1.60), and ziprasidone (RR 1.68, 95% CI 1.26 to 2.23; moderate quality evidence).[1] There was no difference in withdrawals due to adverse effect upon comparison of haloperidol and clozapine or quetiapine (low quality evidence) and evidence for other comparisons was insufficient to draw meaningful conclusions.[1]

- Subgroup analyses: Overall results for treatment response and withdrawals due to adverse effects were similar to the general population when analyzed based on study duration, dose, treatment-resistant population, or patients with first-episode psychosis.[1] Slight differences were reported for the following outcomes and subgroups though the quality of evidence is of low quality.[1]
  - In analysis of patients with treatment resistance, patients treated with olanzapine had a slight benefit in core illness and negative symptom improvement compared to other SGAs though response rate and treatment discontinuations were not significantly different between groups.[1] Clozapine also had fewer treatment discontinuations due to lack of efficacy in treatment-resistant patients.[1]

- In patients with first episode psychosis, there was no difference in response rates, remission, or core illness symptom measures when stratified by age, sex, study duration, or blinding of studies.[1] Evidence was based on a systematic review of 17 RCTs.[1] Evidence for treatment discontinuation was limited with conflicting results from five studies.
- There was no difference between olanzapine and risperidone in treatment discontinuation, quality of life, symptom improvement when stratified by age or sex. Upon comparison of clozapine to olanzapine, more women had symptom improvement compared to men (using the CGI or EQ-5D visual analog scale).[1] In addition, women and younger patients (<40 years of age) had a higher risk of new onset diabetes than older or male patients when treated with olanzapine or risperidone compared to FGAs.[1] The exact rate of new onset diabetes remains unclear.[1]

A 2017 Cochrane review examined the safety and efficacy of antipsychotic combination treatments to antipsychotic monotherapy for patients with schizophrenia and schizoaffective disorders.[5] Of the 62 studies included in the review (n=4833), 31 studies compared combination treatment with clozapine to clozapine monotherapy.[5] Most trials had moderate to high risk of bias due to unclear allocation concealment, randomization and blinding methods. In addition, the majority of trials examined treatment durations of less than 12 weeks and only 7 studies examined long-term treatment for greater than 26 weeks.[5] Most trials included populations who had previously failed monotherapy antipsychotics and approximately half of the studies included patients admitted to a facility.[5] Outcomes assessed included clinical response to treatment, relapse, early study discontinuation, hospital admission, change in hospital status, serious adverse events or adverse events requiring treatment discontinuation, and quality of life. For all outcomes, with the exception for early study discontinuation, evidence was assessed as either insufficient or very low quality limiting the ability to draw meaningful conclusions.[5] There was low quality evidence that the number of patients who discontinued treatment was similar with combination antipsychotic treatment and monotherapy antipsychotic use (RR 0.90, 95% CI 0.76 to 1.07, n=3137).[5] Data were limited by high risk or bias in included studies, high heterogeneity, lack of reported outcomes of interest, and short trial duration.

A rapid response report was published in 2016 from CADTH examining a similar topic, the use of combination second-generation antipsychotics for adolescents and adults with schizophrenia.[10] The report included 4 systematic reviews, 8 RCTs, and 2 evidence-based guidelines.[10] Symptom improvement with use of aripiprazole in addition to clozapine compared to clozapine monotherapy was mixed and was overall of insufficient quality to draw meaningful conclusions regarding efficacy. A systematic review of 4 RCTs (n=327) demonstrated no statistical difference in psychotic symptoms between groups, though qualitative synthesis from 6 RCTs (n=130) demonstrates addition of aripiprazole to clozapine may improve psychotic symptoms (especially negative symptoms).[10] In a systematic review of 5 RCTs (n=225), symptom improvement was not significantly different upon clozapine augmentation with risperidone compared to clozapine monotherapy.[10] Similarly, in a single RCT (n=106) comparing clozapine augmentation with either haloperidol or aripiprazole, there was no difference in symptom improvement.[10] However, trials overall were not powered to detect differences in efficacy between groups. There was limited evidence for other comparisons or outcomes due to small populations included in trials, limited duration of studies (<3 months), and lack of reported randomization or blinding methods.[10] Also there was a wide range of inclusion criteria for studies and most comparisons (with the exception of clozapine regimens) had results from only one study, increasing heterogeneity and limiting ability to pool results across trials. Guidelines included in the review recommend a 10-week trial of combination antipsychotic regimens only for patients who previously failed a dose-optimized clozapine regimen.[10]

A 2017 Cochrane review examined efficacy and safety of combination antipsychotic treatment with clozapine for patients with treatment-resistant schizophrenia.[11] Three trials were identified which evaluated antipsychotics including aripiprazole versus haloperidol (n=105), risperidone versus ziprasidone (n=24), and ziprasidone versus quetiapine (n=63) when used in combination with clozapine.[11] Due to high heterogeneity between studies, results could not be combined in a meta-analysis.[11] For most outcomes, evidence was graded as very low quality, limiting confidence in the treatment effect.[11] There was no difference in mental state, clinically significant response, clinically significant symptom improvement, or treatment discontinuation upon comparison of aripiprazole to haloperidol or risperidone to ziprasidone (very low to low quality evidence).[11] There was low quality evidence from a single RCT that more

patients treated with the combination of ziprasidone plus clozapine had a 50% reduction in PANSS score (RR 0.54, 95% CI 0.35 to 0.81) and global severity as assessed by CGI-Score (MD -0.70, 95% CI -1.18 to -0.22) compared to combination treatment with clozapine and quetiapine.[11] A similar systematic review was published in 2016 examining antipsychotic efficacy, acceptability and tolerability in for patients with treatment-resistant schizophrenia.[8] Authors conducted a network meta-analysis of 40 RCTs (n=5172) which examined improvement in symptoms, response to treatment, and treatment discontinuation with various antipsychotic medications.[8] Outcomes examined included overall change in symptoms, improvement in positive or negative symptoms, treatment response, and treatment discontinuation. Though some comparisons demonstrated statistically significant differences between groups, differences were small and not consistent across outcomes.[8] The analysis also had several important limitations with approximately 30% of participants discontinued study treatment and 45% of RCTs with evidence of selective reporting.[8] In addition, few studies reported methods of randomization or allocation concealment.[8] Due to these significant limitations in the evidence, authors concluded that evidence was insufficient to determine differences between agents.[8]

A 2016 Cochrane review evaluated efficacy of chlorpromazine versus second generation antipsychotics for schizophrenia.[12] The review included 71 studies which compared chlorpromazine to olanzapine (n=12), risperidone (n=14), or quetiapine (n=45).[12] Thirty-three additional publications were identified which compared chlorpromazine to other second-generation antipsychotics, the data from which have yet to be published.[12] The majority of included studies were conducted in non-US populations (primarily China) limiting applicability to OHP patients, and participants included both inpatient and outpatient settings.[12] Overall, the majority of included studies were of short duration (<8 weeks) and few included studies examined long-term outcomes beyond 6 months.[12] In addition, few studies adequately described randomization, allocation concealment, or blinding methodology increasing risk of bias. Outcomes examined included changes in global or specific symptoms, adverse events, quality of life, and treatment discontinuation. For the majority of outcomes and comparisons, there was insufficient evidence to determine differences between treatment groups.[12] There was low quality evidence based on results from 3 studies (n=204) that a greater proportion of patients treated with olanzapine had in clinical response to treatment at 6 to 12 weeks compared to treatment with chlorpromazine (RR 2.34, 95% CI 1.37 to 3.99).[12] There was no difference in clinical response between chlorpromazine and quetiapine based on results from 28 RCTs (n=3241, RR 0.93, 95% CI 0.81 to 1.06; moderate quality evidence).[12] There was insufficient quality evidence to evaluate outcomes for chlorpromazine compared to risperidone. Upon comparison of chlorpromazine and quetiapine (n=644), more patients treated with chlorpromazine reported extrapyramidal adverse effects (RR 8.03, 95% CI 4.78 to 13.51; low quality evidence).[12] However, there was no difference between chlorpromazine and quetiapine in patients who discontinued the study treatment (n=1223; RR 1.04, 95% CI 0.77 to 1.41; moderate quality evidence).[12]

A 2016 Cochrane review examined efficacy of oral fluphenazine compared to second generation antipsychotics for patients with schizophrenia.[13] Three relevant RCTs were included in the review comparing fluphenazine with risperidone, quetiapine and olanzapine.[13] The included RCTs had limited population including 25 to 60 patients in each study and was of poor methodological quality.[13] Overall, evidence was insufficient to determine differences in clinical efficacy or safety between the agents.[13]

A systematic review conducted in 2017 examined the impact of clozapine on hospital utilization and readmission for patients with psychosis.[14] The review included data from 3 RCTs and 34 observational studies.[14] Primary outcomes for the review were hospital use for any reason and the number of bed days after initiation of clozapine compared to hospital utilization before initiation of the medication. Comparator medications included both first and second-generation antipsychotics. Outcomes were reported using multiple time points ranging from 28 to 364 weeks.[14] There were fewer patients hospitalized over the duration of the study upon comparison of clozapine to other antipsychotics (RR 0.75, 95% CI 0.67 to 0.83, P<0.001, 13 studies, n=29,559).[14] Similar trends were noted upon comparison to individual agents including risperidone (RR 0.74, 95% CI 0.60 to 0.93, P=0.009, 12 studies, n=8634), quetiapine (RR 0.60, 95% CI 0.45 to 0.79, P=0.0003, 4 studies, n=2686), and olanzapine (RR 0.82, 95% CI 0.69 to 0.97, P=0.02, 8 studies, n=14,617).[14] Similar results were observed in upon subgroup analysis when stratified by duration of treatment (greater than or less than 1 year), diagnosis (patients with treatment-resistant schizophrenia), and reason for

hospitalization (psychiatric illness vs. no reason stated).[14]Comparison of clozapine to haloperidol or to depot treatment with any antipsychotic failed to achieve statistically different results in the proportion of patients hospitalized.[14] Analysis comparing depot injections is limited as evidence regarding use of SGA depot formulations was lacking. Two controlled observational studies compared hospitalization bed days to other antipsychotics (n=162).[14] Clozapine treatment resulted in fewer bed days after treatment compared to control medications (MD -34.41 days, 95% CI -68.22 to -0.60 days, P=0.046).[14] Similar results were observed in uncontrolled studies with an average of 52.86 fewer days after treatment initiation (95% CI -79.86 days to -25.86 days, P<0.001, n = 2917).[14] Subgroup analyses demonstrated that duration of treatment had a significant impact upon hospitalization days. Patients given clozapine for less than 1 year had an average of 24.0 fewer days (95% CI -32.4 days to -15.7 days, P<0.001) compared to patients with treatment durations longer than 1 year (MD -84.23 days, 95% CI -133.08 days to -35.37 days, P=0.001).[14] There was no difference observed in time to hospitalization (n=5 studies).[14] Though results assessing efficacy of clozapine are significant, this analysis has several important limitations. First, the majority of trials had moderate risk of bias and data from this analysis is limited by the lack of good quality RCTs available.[14] Patients prescribed clozapine were also significantly younger by an average 1.33 years and had earlier disease onset (1.92 years) compared to patients prescribed other antipsychotics.[14] In addition, reasons for hospitalization varied between studies with substantial inter-study heterogeneity. Finally, the majority of studies included in the analysis were published before 2005 which limits applicability in today's healthcare setting and limits comparative evidence for newer antipsychotics.

Bipolar Disorder

At the time of this review, a 2017 draft AHRQ report was available which examines the effectiveness of drugs for the treatment of adults with bipolar disorder.[2] Drugs included in the review included second-generation antipsychotics (aripiprazole, asenapine, cariprazine, lurasidone, olanzapine, olanzapine/fluoxetine, quetiapine, risperidone, and ziprasidone), anticonvulsants (carbamazepine, divalproex, and lamotrigine), chlorpromazine, and lithium.[2] RCTs and prospective cohort studies were included if they had a minimum duration of 3 weeks for acute mania, 3 months for depression, and 6 months for maintenance treatments.[2] Trials included both inpatient and outpatient populations for mania and mixed episodes and outpatient populations for depression or maintenance treatment. Studies were excluded if more than 50% of participants were lost to follow-up.[2] Overall, 111 publications including 67 drug studies for acute mania, 6 studies for depression, and 30 studies for maintenance drug treatment were included in the review.[2] The majority of studies for acute mania were focused on adults with bipolar I.[2] Studies assessing improvement in depression included only adults with bipolar II, and approximately 60% of studies assessing maintenance treatment enrolled adults with bipolar I.[2] The majority of included studies were placebo-controlled comparisons and will only be discussed briefly here. Only a few studies included direct comparisons between different drug treatments. Most treatment comparisons (including antipsychotics as monotherapy and in combination with mood stabilizers) had evidence from a single study, and only 3 comparisons involving antipsychotic medications had 4 or more studies which contributed evidence.[2] The following clinical outcomes were evaluated: functional outcomes (i.e. social or occupational, change in disability status), quality of life, reduction of episodes, remission rate, reduced hospitalization, remission of concomitant substance use disorder, self-harm, symptom severity, treatment response, adverse effects (including metabolic syndrome, glucose dysregulation, weight gain), and withdrawals due to adverse effects and treatment adherence.[2]

- There is low quality evidence that FDA-approved antipsychotics (except aripiprazole) improve acute mania symptoms in the short term (at 3 weeks) compared to placebo.[2] Evidence for aripiprazole compared to placebo was of insufficient quality primarily due to high risk of bias and lack of precision.[2] The average improvement of manic symptoms was generally less than the estimated minimally important difference (6 points on the YMRS scale or 1 point on the CGI scale). However, differences were large enough that it is reasonably likely some patients had benefit from treatment.[2]
    - Asenapine versus placebo (3 studies): YMRS mean difference 4.37 (95% CI 1.27 to 7.47) and CGI mean difference 0.5 (95% CI 0.29 to 0.71)[2]
    - Cariprazine versus placebo (3 studies): response rate OR 2.14 (95% CI 1.08 to 4.23) and remission rate OR 1.95 (95% CI 1.45 to 2.63), YMRS mean difference 5.38 (95% CI 1.84 to 8.92) and CGI-BP-S mean difference 0.54 (95% CI 0.35 to 0.73)[2]
    - Olanzapine versus placebo (5 studies): response rate OR 1.99 (95% CI 1.29 to 3.08), remission rate OR 1.75 (95% CI 1.19 to 2.58), YMRS mean difference 4.9 (95% CI 2.34 to 7.45), CGI was not significantly different between groups[2]

- Quetiapine versus placebo (4 studies): response rates OR 2.07 (95% CI 1.39 to 3.09), YMRS mean difference 4.92 (95% CI 0.31 to 9.53), CGI mean difference 0.54 (95% CI 0.35 to 0.74)[2]
- Risperidone versus placebo (2 studies): data not pooled but findings favor risperidone and were consistent across studies with greater improvement with risperidone compared to placebo for response rate, manic symptom improvement (YMRS), and CGI.[2]
- Ziprasidone versus placebo (2 studies): data not pooled but findings favor ziprasidone and were consistent across studies with greater improvement with ziprasidone compared to placebo for response rate, manic symptom improvement (YMRS), and CGI.[2]
- There was insufficient evidence comparing haloperidol and aripiprazole for improvement of mania symptoms.[2]
- Though not FDA-approved for bipolar disorder, there was low strength of evidence from 2 RCTs that paliperidone improved manic symptoms compared to placebo with a YMRS mean difference of 3.4 (p=0.025).[2]

- Direct comparisons for treatment of acute mania were limited. There was no difference in efficacy outcomes (including remission rates, mania symptoms or treatment discontinuation) between olanzapine monotherapy and divalproex or valproate for acute mania in adults with bipolar I (low quality evidence from 4 RCTs [n=867]).[2] One study noted that clinically important weight gain of at least 7% was more common in patients treated with olanzapine, though statistical significance weight gain was not documented in all studies.[2] There was low quality evidence from a single study (n=488) which reported greater response rate with asenapine compared to olanzapine but no difference in remission rate between therapies.[2]
- There was insufficient evidence for all other antipsychotic drug comparisons (as monotherapy or in combination with mood stabilizers) for treatment of acute mania.[2] Similarly, there was insufficient evidence for any treatment and all outcomes for bipolar depression or maintenance treatment.[2] Data was limited by reliance on single studies for specific comparisons, low study quality, high attrition rates, short treatment duration, and small population sizes.[2]

A 2016 CADTH rapid response report examined aripiprazole use as monotherapy or adjunct therapy in combination with lithium or divalproex.[15] A single systematic review (n=2505) and 3 evidence-based guidelines provided clinical evidence for the report. Relevant comparators included haloperidol, lithium and valproic acid.[15] Outcomes included response rate, treatment discontinuation and adverse effects. Overall, response rate with greater than 50% improvement in symptom score, symptom improvement, and treatment discontinuation were similar between aripiprazole and other traditional treatments for bipolar disorder including lithium, divalproex, and haloperidol.[15] Comparisons to individual agents were not evaluated and there was high heterogeneity among analyses.[15] Guidelines included in this review list aripiprazole as one of many possible first line pharmacological treatments for acute mania or maintenance treatment in patients with bipolar disorder and recent mania or mixed episodes, but it is not recommended for acute bipolar depression.[15]

Another rapid response report published by CADTH in 2016 found no published literature regarding the use of combination second-generation antipsychotics for adults or adolescents with bipolar disorder.[16]

<u>Antipsychotic Treatment for Pediatric and Young Adult Patients</u>

An AHRQ report published in 2016 examined efficacy and safety of FGA and SGA use in children and young adults (less than 25 years of age).[3] The report included 135 studies which primarily compared antipsychotic use to placebo.[3] Direct comparative evidence (which will be the focus of this summary) was generally of insufficient or low quality particularly for clinical outcomes. Results were analyzed by class and for individual agents. When grouped by class, there was low quality evidence of no difference between FGAs and SGAs for improvement of negative symptoms, positive symptoms, response rate, and global impression of illness severity for patients with schizophrenia or related psychosis.[3] For the comparison of olanzapine and risperidone, there was no difference in symptom improvement, response rate, or global impressions of severity (low quality evidence based on 6 studies).[3] There was insufficient evidence for comparisons of other agents for the treatment of schizophrenia.[3] There were no studies identified which examined direct comparative efficacy or safety of

either FGAs or SGAs in patients with bipolar disorder, autism spectrum disorder, ADHD or other conduct disorders, depression, eating disorders, or tic disorders.[3] Similarly, there was insufficient evidence regarding efficacy or safety of SGAs in patients with obsessive-compulsive disorder.[3] Due to the lack of head to head data, a network meta-analysis was conducted to compare differences in body mass index and weight gain between agents. Data fromthis analysis should be interpreted with caution due to the indirect nature of the results. Overall, ziprasidone may have less weight gain compared to other FGAs or SGAs.[3] Patients treated with clozapine and olanzapine had on average more weight gain (2-5 kg over 6-12 weeks) than other antipsychotics (low quality evidence).[3] Evidence was strongest for comparisons of olanzapine versus risperidone or quetiapine (greater weight gain and change in BMI with olanzapine) and for quetiapine versus risperidone (no difference in BMI or clinically significant weight gain).[3] Upon comparison between classes, there was moderate strength of evidence that SGAs are likely associated with more weight gain (MD 2.62 kg; 95% CI 4.35 to 0.86) and increase in BMI (MD 1.57 kg/m^2; 95% CI 2.49 to 0.53) compared to FGAs.[3] There was low quality evidence that use of SGAs was associated with fewer extrapyramidal symptoms compared to FGAs (RR 2.59; 95% CI 1.00 to 7.00) and low quality evidence of no difference in sedation between groups.[3] Regarding long-term serious adverse events, there was moderate quality evidence of no difference in mortality upon comparison of SGAs and placebo.[3] There was low quality evidence based on a large retrospective cohort study that use of SGAs for over 1 year increases risk of diabetes compared to patients not treated with antipsychotics (HR 2.89, 95% CI 1.64 to 5.10; 25.3 vs. 7.8 cases per 10,000 person-years follow-up).[3] Subgroup analyses demonstrated no difference in efficacy or harms based on age, sex, or prior treatment history. Duration of treatment did have a slight effect on weight gain, with longer treatment durations associated with larger increases in weight over time (0.04 kg/week; 95% CI 0.014 to 0.071).[3] Overall, these analyses were limited by the populations enrolled in the included studies. Few trials enrolled young adults or children less than 8 years of age and many excluded patients with mild symptom severity or patients with comorbidities. In addition, the majority of studies were of short duration (<6 months) which limits estimates of long-term efficacy and adverse effects.

In May 2017, an AHRQ report was published which examined medical treatment for children with autism spectrum disorder.[17] The report included 11 RCTs and one retrospective cohort which examined use of aripiprazole, risperidone, and haloperidol in children 2 to 12 years of age with autism spectrum disorder.[17] Studies were excluded if the population had less than 10 participants for an RCT or 20 participants for observational studies.[17] Of the studies included, 7 had low risk of bias and 5 had moderate risk of bias.[17] Only 4 of these studies included direct comparative evidence between agents. Data from these studies had significant limitations in that there was limited evidence for long-term outcomes (>6 months) and few studies address similar interventions or outcomes.[17] Upon comparison of aripiprazole to risperidone in 3 small studies, there was no difference in challenging behavior or general improvement between groups at 8 weeks, 24 weeks, or up to 1-2 years (low quality evidence).[17] A single small RCT demonstrated significant symptom improvement with risperidone compared to haloperidol.[17] However, due to the limited population and moderate risk of bias, evidence was insufficient to form meaningful conclusions.[17] The most common adverse effects associated with treatment included weight gain, increased appetite, and drowsiness. All antipsychotic treatments were associated with increased weight gain over time, but differences were not statistically different between groups.[17]

CADTH published a rapid response report in 2016 examining antipsychotic use in pediatric patients (<18 years of age).[18] Evidence was limited to systematic reviews (n=9) and evidence based guidelines (n=3) which provide evidence regarding the efficacy and safety of antipsychotics.[18] Overall, direct comparative evidence was limited. Two systematic reviews including patients with Tourette's syndrome or tic disorders provided evidence of no difference in symptom severity upon comparison of aripiprazole and haloperidol or risperidone.[18] For children with psychosis or schizophrenia, available evidence from 2 systematic reviews demonstrated no difference in efficacy between individual antipsychotic agents or between FGAs and SGAs.[18] There was no comparative evidence for efficacy and safety of antipsychotics in children with other conditions including disruptive behavior disorders or autism spectrum disorders.[18] Evidence regarding adverse events was mixed. The most common adverse events associated with treatment were weight gain, drowsiness, increased appetite, and extrapyramidal adverse effects.[18] In patients with schizophrenia, increased weight gain was observed with olanzapine compared to risperidone (MD 6.1 ± 3.6 kg vs. 3.6 ± 4 kg, p-value not reported), but there was no difference upon comparison of clozapine and olanzapine.[18] Other trials report no difference in adverse effects between

agents, though the ability to detect differences between groups was limited by small population sizes, large heterogeneity, and poor quality of trials included in these systematic reviews.[18]

Other Conditions

In 2017, CADTH published a rapid response report assessing available evidence of aripiprazole treatment for borderline personality disorder.[19] First-line treatment for borderline personality disorder is psychotherapy though pharmacotherapy (including off-label use of antipsychotics, antidepressants and mood stabilizers) may be used as adjunct treatment.[19] Only 2 RCTs (one with direct comparative evidence to olanzapine and one with only placebo comparisons) were included in the review, and evidence was insufficient to assess efficacy, safety, or generalizability to a broader population. Data were limited by small population size (n=76), lack of reported randomization or blinding methods, and inadequate reporting of baseline population characteristics or concomitant medications use.[19]

A Cochrane review published in 2016 attempted to evaluate evidence for haloperidol as a treatment for long-term or persistent aggression in patients with psychosis.[20] Only one low-quality RCT (n=110) with high risk of bias was identified which compared haloperidol to olanzapine or clozapine.[20] There was low quality evidence of no difference in discontinuation rate between treatment groups.[20] Data for other outcomes including treatment efficacy was limited by unclear randomization, allocation concealment or blinding methodology, high attrition rate, and high risk of reporting bias.[20]

New Guidelines:

Guidelines from the Department of Veterans Affairs and Department of Defense were updated in 2016 for the management of major depressive disorder.[21] Recommended first-line pharmacological treatments for mild to moderate major depressive disorder include SSRIs (except fluvoxamine), SNRIs, mirtazapine, or bupropion (strong recommendation).[21] Treatment selection is recommended based on patient preference, safety and adverse effect profile, history of prior treatment response, family history of response to a medication, concurrent comorbidities or medications, cost and provider training.[21] In patients with only partial response or no response to initial treatment, treatment should be switched to another treatment or augmented with another medication or psychotherapy. Similarly, for patients with severe depression, combination psychotherapy and pharmacotherapy is recommended (strong recommendation).[21] Medication augmentation strategies include addition of bupropion, buspirone, lithium, liothyronine, or SGAs to first-line pharmacotherapy.[21] Due to the significant potential of adverse effects with SGAs, they are recommended only when other strategies have failed.[21] Recommendation was based on 2 systematic reviews demonstrating aripiprazole, olanzapine, quetiapine, and risperidone improved remission rates compared to placebo.[21] However, there was fair quality evidence that adverse effects including akathisia were statistically more common with aripiprazole, and sedation were more common with olanzapine and quetiapine.[21] Aripiprazole, olanzapine, quetiapine and risperidone were also more commonly associated with weight gain compared to placebo (fair quality evidence).[21]

The Department of Veterans Affairs and Department of Defense also updated guidelines for the management of post-traumatic stress disorder (PTSD) in 2017.[21] Briefly, second-generation antipsychotics are not recommended as monotherapy or as augmentation therapy for the treatment of PTSD due to a lack of evidence regarding efficacy in this population and known adverse effects associated with treatment (weak recommendation).[21]

In 2016, the American Psychiatric Association updated guideline recommendations for the use of antipsychotics in patients with dementia.[22] Most recommendations focus on use of antipsychotics in the nonemergency setting. Overall, evidence was based on low to moderate quality evidence and few recommendations were made for specific antipsychotic regimens. In general, frequent assessment (at least monthly) and evaluation of risks and benefits of treatment is recommended.[22] In addition, nonemergency antipsychotics should be used for treatment of agitation or psychosis only when symptoms are severe,

dangerous, or cause significant distress for the patient (strong recommendation; moderate quality evidence).[22] The minimum effective dose should be used, and discontinuation of the medication is recommended if no significant response is observed after a trial of 4 weeks (strong recommendation; moderate quality evidence).[22] In patients with an adequate treatment response, an attempt to taper the medication should be made within 4 months unless symptoms reoccur upon treatment discontinuation (strong recommendation based on low quality evidence).[22] Haloperidol is not recommended as a first-line nonemergency medication in patients with dementia and without delirium (strong recommendation; moderate quality evidence).[22] In addition, long-acting injectable antipsychotic medications are not recommended unless used for patients with concomitant chronic psychotic disorders (strong recommendation; moderate quality evidence).[22]

Guidelines from the American Society of Clinical Oncology were updated in 2017 to include olanzapine as a recommended option for prevention of chemotherapy-induced nausea and vomiting in patients with high-emetic-risk chemotherapy regimens (strong recommendation based on high quality evidence).[23] Olanzapine is recommended as prophylaxis in combination with a neurokinin 1 receptor antagonist (eg, aprepitant, fosaprepitant, or rolapitant), a serotonin receptor antagonist (eg, ondansetron, palonosetron, or granisetron) and dexamethasone.[23] The recommendation is primarily based on one phase 3 RCT in which olanzapine was added to standard antiemetic prophylaxis. The proportion of patients without symptoms of nausea at 24 hours and 120 hours was significantly greater in those prescribed olanzapine compared to the standard of care (74% vs. 45% of patients at 24 hours and 37% vs. 22% at 120 hours following chemotherapy).[23] Similarly, for patients who were not prescribed prophylactic olanzapine, it is recommended as an option for breakthrough nausea and vomiting in addition to the standard antiemetic regimen (moderate strength recommendation based on intermediate quality evidence).[23]

New Formulations or Indications:
In May 2016, Fanapt® (iloperidone) received an expanded indication for maintenance treatment of schizophrenia. It had previously been indicated only for short-term treatment. In addition, Saphris® (asenapine) was approved for pediatric patients 10 to 17 years with bipolar I disorder, and Latuda® (lurasidone) received approval from the FDA for treatment of schizophrenia in adolescents aged 13 to 17 years.

In November 2017, the FDA approved Abilify Mycite®, a new formulation of aripiprazole oral tablets with a sensor.[24] This formulation is a drug-device combination product with an ingestible event marker sensor which is intended to track whether the tablet is consumed.[24] Approval was based on prior efficacy and safety analysis of aripiprazole tablets. Abilify Mycite is indicated for treatment of adults with schizophrenia, adjunct treatment of adults with MDD, and acute or maintenance treatment of bipolar I disorder (as monotherapy or in combination with lithium or valproate).[24] The sensor embedded in the tablet activates upon contact with gastric fluid and sends a signal to a Mycite® Patch which is worn by the patient.[24] This patch then transmits the data to a smartphone app for the patient and/or web-based portal for healthcare providers. Labeling specifies that improved compliance with this formulation has not been established, and that tracking drug ingestion in “real-time” or during an emergency is not recommended because detection of sensors may be delayed or not occur.[24]

New FDA Safety Alerts:
In 2017, the FDA updated warnings for all SGAs and haloperidol to include risk for falls. Labeling specifies that antipsychotics have been associated with somnolence, postural hypotension, and motor or sensory instability which may lead to falls. A complete fall risk assessment is advised upon initiation of these medications and intermittently for patients on long-term therapy.[25]

In February 2017, the FDA updated clozapine labeling to include warnings for severe and life-threatening hepatotoxicity. Reports of hepatotoxicity occurred in post-marketing studies of clozapine and the exact incidence or frequency of hepatotoxicity is unclear. Monitoring is recommended for signs and symptoms of hepatotoxicity including fatigue, nausea, jaundice, and hepatic encephalopathy.[25]

In October 2016, olanzapine labeling was updated to include a warning for drug reaction with eosinophilia and systemic symptoms. Discontinuation of treatment is recommended if symptoms are observed.[25]

Labeling for aripiprazole was updated in 2016 to include warnings for pathological gambling and other compulsive behaviors. Compulsive urges, particularly for gambling, have been reported in post-marketing experience. Dose reduction or treatment discontinuation should be considered if symptoms are present.[25]

Randomized Controlled Trials:
A total of 344 citations were manually reviewed from the initial literature search. After further review, 340 citations were excluded because of wrong study design (eg, observational), comparator (eg, no control or placebo-controlled), or outcome studied (eg, non-clinical or exploratory). Only trials reporting new comparative evidence were considered for inclusion, and trials which offered no new additional information from sources already in the review were excluded. The remaining 4 trials are summarized in the table below. Full abstracts are included in **Appendix 2**.

Table 1. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results
Mohamed S, et al.[26] AC, single-blind, MC, PG, RCT N=1522 Duration: 36 weeks	1. Switch to bupropion 150-400 mg daily 2. Add bupropion 150-400 mg daily 3. Add aripiprazole 5-15 mg daily Doses titrated based on tolerability and treatment effect	Veterans with MDD unresponsive to at least one antidepressant	Remission at 12 weeks defined as a score of ≤5 on the 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated (QIDS-C16) score	1. 114/511 (22.3%) 2. 136/506 (26.9%) 3. 146/505 (28.9%) 1 vs. 3: ARR: 6.6%; RR 1.30 (95% CI 1.05-1.60); *p*= 0.02 1 vs. 2 and 2 vs. 3 were not significant
Cheon E, et al.[27] AC, MC, OL, PG, RCT N=103	1. Addition of aripiprazole 2.5 to 20 mg daily (mean 2.99 mg/day) 2. Addition of bupropion 150 to 300 mg daily (mean 199 mg/day)	MDD unresponsive to SSRI treatment of at least 4 weeks	Mean change in the Montgomery Asberg Depression Rating Scale total score from baseline to 6 weeks	1. -13.77 (SD 8.59) 2. -9.45 (SD 9.45) Difference between groups was not significant

Duration: 6 weeks				
Nierenberg A, et al.[28] MC, PG, Single-blind RCT N=482 Duration: 6 months	1. Lithium (mean dose 1007 mg) 2. Quetiapine (mean dose 345 mg) Medication titrated to maximum tolerated dose. Treatment given in combination with adjunctive personalized treatment which could include any medication except SGAs or lithium.	Bipolar I or II disorder	Clinical Global Impressions-Efficacy Index (range -3 [no benefit, significant harms] to +3 [significant benefit, no harm]) Necessary clinical adjustments (defined as the number of changes necessary in adjunctive treatment due to new, persistent or worsened symptoms or adverse effects)	Clinical Global Impressions-Efficacy Index 1. 1.58 (95% CI 1.32 to 1.84) 2. 1.52 (95% CI 1.26 to 1.78) MD 0.06 (95% CI -0.16 to 0.29); p=0.59 Average number of necessary clinical adjustments per month 1. 0.8 (SD 0.8) per month 2. 0.9 (SD 1.0) per month P=0.15
Lamberti M, et al.[29] OL, RCT N=44 Duration: 24 weeks	1. Risperidone 0.25 to 3 mg daily 2. Aripiprazole 1.25 to 15 mg daily Dose titrated based on clinical response	Italian patients with autism spectrum disorder and ADHD	Change in ADHD-rating scale (18 questions evaluating symptom improvement) or CGI-I (range 1-7) rating scales from baseline	ADHD-RS at 24 weeks 1. 19.1 (SD 3) 2. 26.7 (SD 7.8) P=0.842 CGI-I at 24 weeks 1. 2.7 (SD 0.7) 2. 3.0 (SD 1.2) P=0.356

Abbreviations: AC = active comparator; ADHD = attention-deficit/hyperactivity disorder; FGA = first generation antipsychotic; MC = multicenter; MD = mean difference; MDD = major depressive disorder; OL = open label; PG = parallel-group; RCT = randomized clinical trial; RR = relative risk; SD = standard deviation; SGA = second generation antipsychotic

References:

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Appendix 1: Current Preferred Drug List

ROUTE	FORM	BRAND	GENERIC	PDL	CARVEOUT
FIRST GENERATION ORAL ANTIPSYCHOTICS					
ORAL	ELIXIR	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	ORAL CONC	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	TABLET	FLUPHENAZINE HCL	FLUPHENAZINE HCL	Y	Y
ORAL	TABLET	HALOPERIDOL	HALOPERIDOL	Y	Y
ORAL	ORAL CONC	HALOPERIDOL LACTATE	HALOPERIDOL LACTATE	Y	Y
ORAL	CAPSULE	LOXAPINE	LOXAPINE SUCCINATE	Y	Y
ORAL	TABLET	PERPHENAZINE	PERPHENAZINE	Y	Y
ORAL	TABLET	THIORIDAZINE HCL	THIORIDAZINE HCL	Y	Y
ORAL	CAPSULE	THIOTHIXENE	THIOTHIXENE	Y	Y
ORAL	TABLET	TRIFLUOPERAZINE HCL	TRIFLUOPERAZINE HCL	Y	Y
ORAL	TABLET	CHLORPROMAZINE HCL	CHLORPROMAZINE HCL	V	Y
ORAL	TABLET	ORAP	PIMOZIDE	V	Y
ORAL	TABLET	PIMOZIDE	PIMOZIDE	V	Y
SECOND GENERATION ORAL ANTIPSYCHOTICS					
SUBLINGUAL	TAB SUBL	SAPHRIS	ASENAPINE MALEATE	Y	Y
ORAL	TABLET	CLOZAPINE	CLOZAPINE	Y	Y
ORAL	TABLET	LATUDA	LURASIDONE HCL	Y	Y
ORAL	TABLET	OLANZAPINE	OLANZAPINE	Y	Y
ORAL	TABLET	ZYPREXA	OLANZAPINE	Y	Y
ORAL	TABLET	QUETIAPINE FUMARATE	QUETIAPINE FUMARATE	Y	Y
ORAL	TABLET	SEROQUEL	QUETIAPINE FUMARATE	Y	Y
ORAL	SOLUTION	RISPERDAL	RISPERIDONE	Y	Y
ORAL	SOLUTION	RISPERIDONE	RISPERIDONE	Y	Y
ORAL	TABLET	RISPERDAL	RISPERIDONE	Y	Y
ORAL	TABLET	RISPERIDONE	RISPERIDONE	Y	Y
ORAL	SOLUTION	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	TAB RAPDIS	ARIPIPRAZOLE ODT	ARIPIPRAZOLE	V	Y
ORAL	TABLET	ABILIFY	ARIPIPRAZOLE	V	Y
ORAL	TABLET	ARIPIPRAZOLE	ARIPIPRAZOLE	V	Y
ORAL	TABLET	REXULTI	BREXPIPRAZOLE	V	Y
ORAL	CAP DS PK	VRAYLAR	CARIPRAZINE HCL	V	Y
ORAL	CAPSULE	VRAYLAR	CARIPRAZINE HCL	V	Y
ORAL	ORAL SUSP	VERSACLOZ	CLOZAPINE	V	Y
ORAL	TAB RAPDIS	CLOZAPINE ODT	CLOZAPINE	V	Y

ORAL	TAB RAPDIS	FAZACLO	CLOZAPINE	V	Y
ORAL	TABLET	FANAPT	ILOPEIDONE	V	Y
ORAL	TAB RAPDIS	OLANZAPINE ODT	OLANZAPINE	V	Y
ORAL	TAB RAPDIS	ZYPREXA ZYDIS	OLANZAPINE	V	Y
ORAL	TAB ER 24	INVEGA	PALIPERIDONE	V	Y
ORAL	TAB ER 24	PALIPERIDONE ER	PALIPERIDONE	V	Y
ORAL	TABLET	NUPLAZID	PIMAVANSERIN TARTRATE	V	Y
ORAL	TAB ER 24H	QUETIAPINE FUMARATE ER	QUETIAPINE FUMARATE	V	Y
ORAL	TAB ER 24H	SEROQUEL XR	QUETIAPINE FUMARATE	V	Y
ORAL	TAB RAPDIS	RISPERDAL M-TAB	RISPERIDONE	V	Y
ORAL	TAB RAPDIS	RISPERIDONE ODT	RISPERIDONE	V	Y
ORAL	CAPSULE	GEODON	ZIPRASIDONE HCL	V	Y
ORAL	CAPSULE	ZIPRASIDONE HCL	ZIPRASIDONE HCL	V	Y

Appendix 2: Abstracts of Comparative Clinical Trials

1. Cheon E-J, Lee K-H, Park Y-W, et al. Comparison of the Efficacy and Safety of Aripiprazole Versus Bupropion Augmentation in Patients With Major Depressive Disorder Unresponsive to Selective Serotonin Reuptake Inhibitors: A Randomized, Prospective, Open-Label Study. *Journal of clinical psychopharmacology.* 2017;37(2):193-199.

   PURPOSE: The purpose of this study was to compare the efficacy and safety of aripiprazole versus bupropion augmentation in patients with major depressive disorder (MDD) unresponsive to selective serotonin reuptake inhibitors (SSRIs)., METHODS: This is the first randomized, prospective, open-label, direct comparison study between aripiprazole and bupropion augmentation. Participants had at least moderately severe depressive symptoms after 4 weeks or more of SSRI treatment. A total of 103 patients were randomized to either aripiprazole (n = 56) or bupropion (n = 47) augmentation for 6 weeks. Concomitant use of psychotropic agents was prohibited. Montgomery Asberg Depression Rating Scale, 17-item Hamilton Depression Rating scale, Iowa Fatigue Scale, Drug-Induced Extrapyramidal Symptoms Scale, Psychotropic-Related Sexual Dysfunction Questionnaire scores were obtained at baseline and after 1, 2, 4, and 6 weeks of treatment., RESULTS: Overall, both treatments significantly improved depressive symptoms without causing serious adverse events. There were no significant differences in the Montgomery Asberg Depression Rating Scale, 17-item Hamilton Depression Rating scale, and Iowa Fatigue Scale scores, and response rates. However, significant differences in remission rates between the 2 groups were evident at week 6 (55.4% vs 34.0%, respectively; P = 0.031), favoring aripiprazole over bupropion. There were no significant differences in adverse sexual events, extrapyramidal symptoms, or akathisia between the 2 groups. CONCLUSIONS: The present study suggests that aripiprazole augmentation is at least comparable to bupropion augmentation in combination with SSRI in terms of efficacy and tolerability in patients with MDD. Both aripiprazole and bupropion could help reduce sexual dysfunction and fatigue in patients with MDD. Aripiprazole and bupropion may offer effective and safe augmentation strategies in patients with MDD who are unresponsive to SSRIs. Double-blinded trials are warranted to confirm the present findings.

2. Lamberti M, Siracusano R, Italiano D, et al. Head-to-Head Comparison of Aripiprazole and Risperidone in the Treatment of ADHD Symptoms in Children with Autistic Spectrum Disorder and ADHD: A Pilot, Open-Label, Randomized Controlled Study. *Paediatric drugs.* 2016;18(4):319-329.

   BACKGROUND: Autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) are frequently overlapping neurodevelopmental disorders. Individuals in whom the disorders are comorbid show more severe impairment because of deficits in the processing of social situations, adaptive functioning, and executive control than individuals with either disorder alone., OBJECTIVE: This open-label pilot study aimed to evaluate and compare the efficacy and tolerability of risperidone and aripiprazole for treating ADHD symptoms in patients with both ASD and ADHD over the course of 24 weeks of treatment., METHODS: Patients (n = 44) were randomly assigned to start treatment with risperidone (22 patients) or aripiprazole (22 patients). Children were evaluated before starting treatment (T0), and after 12 weeks (T1) and 24 weeks (T2) of treatment. At each visit, specific psychiatric clinical scales were administered to assess the efficacy of the two drugs. RESULTS: The mean age was 8.4 +/- 2.9 years in the aripiprazole group and 7.8 +/- 2.3 years in the risperidone group. A total of 37 children (29 boys and 8 girls) completed the study (18 in the aripiprazole group and 19 in the risperidone group). Aripiprazole and risperidone appeared to have similar benefits in terms of efficacy and tolerability, although there were slight differences between the two drugs. Both groups showed a significant improvement in ADHD symptoms after 24 weeks of treatment (ADHD Rating Scale, Conners Parent Rating Scale-Hyperactivity, and Clinical Global Improvement-Severity Scale). No significant difference between the two drugs on any parameters at 24 weeks were found. Prolactin levels were decreased in the aripiprazole group. Both drugs were well tolerated, with no serious adverse events detected. CONCLUSIONS: Our study confirms the efficacy of both aripiprazole and risperidone in ameliorating ADHD symptoms of children also presenting with ASD.

3. Mohamed S, Johnson GR, Chen P, et al. Effect of Antidepressant Switching vs Augmentation on Remission Among Patients With Major Depressive Disorder Unresponsive to Antidepressant Treatment: The VAST-D Randomized Clinical Trial. *Jama.* 2017;318(2):132-145.

   Importance: Less than one-third of patients with major depressive disorder (MDD) achieve remission with their first antidepressant., Objective: To determine the relative effectiveness and safety of 3 common alternate treatments for MDD., Design, Setting, and Participants: From December 2012 to May 2015, 1522 patients at 35

US Veterans Health Administration medical centers who were diagnosed with nonpsychotic MDD, unresponsive to at least 1 antidepressant course meeting minimal standards for treatment dose and duration, participated in the study. Patients were randomly assigned (1:1:1) to 1 of 3 treatments and evaluated for up to 36 weeks., Interventions: Switch to a different antidepressant, bupropion (switch group, n=511); augment current treatment with bupropion (augment-bupropion group, n=506); or augment with an atypical antipsychotic, aripiprazole (augment-aripiprazole group, n=505) for 12 weeks (acute treatment phase) and up to 36 weeks for longer-term follow-up (continuation phase)., Main Outcomes and Measures: The primary outcome was remission during the acute treatment phase (16-item Quick Inventory of Depressive Symptomatology-Clinician Rated [QIDS-C16] score <=5 at 2 consecutive visits). Secondary outcomes included response (>=50% reduction in QIDS-C16 score or improvement on the Clinical Global Impression Improvement scale), relapse, and adverse effects. Results: Among 1522 randomized patients (mean age, 54.4 years; men, 1296 [85.2%]), 1137 (74.7%) completed the acute treatment phase. Remission rates at 12 weeks were 22.3% (n=114) for the switch group, 26.9% (n=136) for the augment-bupropion group, and 28.9% (n=146) for the augment-aripiprazole group. The augment-aripiprazole group exceeded the switch group in remission (relative risk [RR], 1.30 [95% CI, 1.05-1.60]; P=.02), but other remission comparisons were not significant. Response was greater for the augment-aripiprazole group (74.3%) than for either the switch group (62.4%; RR, 1.19 [95% CI, 1.09-1.29]) or the augment-bupropion group (65.6%; RR, 1.13 [95% CI, 1.04-1.23]). No significant treatment differences were observed for relapse. Anxiety was more frequent in the 2 bupropion groups (24.3% in the switch group [n=124] vs 16.6% in the augment-aripiprazole group [n=84]; and 22.5% in augment-bupropion group [n=114]). Adverse effects more frequent in the augment-aripiprazole group included somnolence, akathisia, and weight gain. Conclusions and Relevance: Among a predominantly male population with major depressive disorder unresponsive to antidepressant treatment, augmentation with aripiprazole resulted in a statistically significant but only modestly increased likelihood of remission during 12 weeks of treatment compared with switching to bupropion monotherapy. Given the small effect size and adverse effects associated with aripiprazole, further analysis including cost-effectiveness is needed to understand the net utility of this approach.

4. Nierenberg AA, McElroy SL, Friedman ES, et al. Bipolar CHOICE (Clinical Health Outcomes Initiative in Comparative Effectiveness): a pragmatic 6-month trial of lithium versus quetiapine for bipolar disorder. *The Journal of clinical psychiatry.* 2016;77(1):90-99.

BACKGROUND: Bipolar disorder is among the 10 most disabling medical conditions worldwide. While lithium has been used extensively for bipolar disorder since the 1970s, second-generation antipsychotics (SGAs) have supplanted lithium since 1998. To date, no randomized comparative-effectiveness study has compared lithium and any SGA. METHOD: Within the duration of the study (September 2010-September 2013), participants with bipolar I or II disorder (DSM-IV-TR) were randomized for 6 months to receive lithium (n = 240) or quetiapine (n = 242). Lithium and quetiapine were combined with other medications for bipolar disorder consistent with typical clinical practice (adjunctive personalized treatment [APT], excluding any SGA for the lithium + APT group and excluding lithium or any other SGA for the quetiapine + APT group). Coprimary outcome measures included Clinical Global Impressions-Efficacy Index (CGI-EI) and necessary clinical adjustments, which measured number of changes in adjunctive personalized treatment. Secondary measures included a full range of symptoms, cardiovascular risk, functioning, quality of life, suicidal ideation and behavior, and adverse events. RESULTS: Participants improved across all measures, and over 20% had a sustained response. Primary (CGI-EI, P = .59; necessary clinical adjustments, P = .15) and secondary outcome changes were not statistically significantly different between the 2 groups. For participants with greater manic/hypomanic symptoms, CGI-EI changes were significantly more favorable with quetiapine + APT (P = .02). Among those with anxiety, the lithium + APT group had fewer necessary clinical adjustments per month (P = .02). Lithium was better tolerated than quetiapine in terms of the burden of side effects frequency (P = .05), intensity (P = .01), and impairment (P = .01)., CONCLUSIONS: Despite adequate power to detect clinically meaningful differences, we found outcomes with lithium + APT and quetiapine + APT were not significantly different across 6 months of treatment for bipolar disorder.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to October Week 3 2017, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 2013 to Daily Update

1	exp Fluphenazine/	463
2	exp Haloperidol/	7642
3	exp Loxapine/	276
4	exp Perphenazine/	373
5	exp Thioridazine/	620
6	exp Thiothixene/	37
7	exp Trifluoperazine/	889
8	exp Chlorpromazine/	2727
9	exp Pimozide/	443
10	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9/	12619
11	limit 10 to english language/	11856
12	limit 11 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	3121
13	limit 12 to yr="2016 -Current"	158
14	remove duplicates from 13	71

1	exp aripiprazole/ or exp clozapine/ or exp paliperidone palmitate/ or exp quetiapine fumarate/ or exp risperidone/	18070
2	paliperidone.mp.	1521
3	ziprasidone.mp.	2279
4	pimavanserin.mp.	153
5	olanzapine.mp.	10231
6	cariprazine.mp.	171
7	brexpiprazole.mp.	151
8	exp Lurasidone Hydrochloride/	292
9	asenapine.mp.	488
10	iloperidone.mp.	246
11	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10	27310
12	limit 11 to english language	25863
13	limit 12 to (clinical trial, all or clinical trial, phase iii or clinical trial, phase iv or clinical trial or comparative study or controlled clinical trial or meta analysis or multicenter study or pragmatic clinical trial or randomized controlled trial or systematic reviews)	8300
14	limit 13 to yr="2016 -Current"	722

15	limit 14 to humans	633
16	remove duplicates from 15	273

Low Dose Quetiapine

Goal(s):
- To promote and ensure use of quetiapine that is supported by the medical literature.
- To discourage off-label use for insomnia.
- Promote the use of non-pharmacologic alternatives for chronic insomnia.

Initiative:
- Low dose quetiapine (Seroquel® and Seroquel XR®)

Length of Authorization:
- Up to 12 months (criteria-specific)

Requires PA:
- Quetiapine (HSN = 14015) doses <50 mg/day
- Auto PA approvals for :
    - Patients with a claim for a second generation antipsychotic in the last 6 months
    - Patients with prior claims evidence of schizophrenia or bipolar disorder
    - Prescriptions identified as being written by a mental health provider

Covered Alternatives:
- Preferred alternatives listed at www.orpdl.org/drugs/
- Zolpidem is available for short-term use (15 doses/30 days) without PA.

Table 1. Adult (age ≥18 years) FDA-approved Indications for Quetiapine

Bipolar Disorder	F3010; F302; F3160-F3164; F3177-3178; F319	
Major Depressive Disorder	F314-315; F322-323; F329; F332-333; F339; F3130	For Seroquel XR® only, Adjunctive therapy with antidepressants for Major Depressive Disorder
Schizophrenia	F205; F209; F2081; F2089	
Bipolar Mania	F3010; F339; F3110-F3113; F312	
Bipolar Depression	F3130	

Table 2. Pediatric FDA-approved indications

Schizophrenia	Adolescents (13-17 years)	
Bipolar Mania	Children and Adolescents (10 to 17 years)	Monotherapy

Approval Criteria		
1. What diagnosis is being treated?	Record ICD10 code. Do not proceed and deny if diagnosis is not listed in Table 1 or Table 2 above (medical appropriateness)	
2. Is the prescription for quetiapine less than 50 mg/day? (verify days' supply is accurate)	**Yes**: Go to #3	**No:** Trouble-shoot claim processing with the pharmacy.
3. Is planned duration of therapy longer than 90 days?	**Yes:** Go to #4	**No:** Approve for titration up to maintenance dose (60 days).
4. Is reason for dose <50 mg/day due to any of the following: • low dose needed due to debilitation from a medical condition or age; • unable to tolerate higher doses; • stable on current dose; or • impaired drug clearance? • any diagnosis in table 1 or 2 above?	**Yes:** Approve for up to 12 months	**No:** Pass to RPh. Deny for medical appropriateness. Note: may approve up to 6 months to allow taper.

P&T/DUR Review: *11/17 (SS) 9/15; 9/10; 5/10*
Implementation: *1/1/18; 10/15; 1/1/11*

Pimavanserin (Nuplazid™) Safety Edit

Goals:

- Promote safe use of pimavanserin in patients with psychosis associated with Parkinson's disease.

Length of Authorization:

- Up to 6 months

Requires PA:

- Pimavanserin

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		
5. What diagnosis is being treated?	Record ICD10 code	
6. Is the treatment for hallucinations and/or delusions associated with Parkinson's disease?	**Yes:** Go to #3	**No:** Pass to RPh. Deny; medical appropriateness
7. Are the symptoms likely related to a change in the patient's anti-Parkinson's medication regimen?	**Yes:** Go to #4 Consider slowly withdrawing medication which may have triggered psychosis.	**No:** Go to #5
8. Has withdrawal or reduction of the triggering medication resolved symptoms?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #5
9. Is the patient on a concomitant first- or second-generation antipsychotic drug?	**Yes:** Pass to RPh; Deny; medical appropriateness	**No:** Go to #6
10. Has the patient been recently evaluated for a prolonged QTc interval?	**Yes:** Approve for up to 6 months	**No:** Pass to RPh; Deny; medical appropriateness

P&T Review: *01/2017 (SS)*
Implementation: *4/1/17*

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Class Update – PCSK9 Inhibitors

Date of Review: January 2018 Date of Last Review: November 2016

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

Research Questions:
1. Is there any new comparative evidence for Proprotein Convertase Subtilisin Kexin type 9 (PCSK9) Inhibitors in reducing cardiovascular (CV) outcomes or mortality in adult patients being treated for the primary or secondary prevention of cardiovascular disease (CVD)?
2. Is there any new comparative evidence for harms of PCSK9 inhibitors in patients being treated for the primary or secondary prevention of CV disease?
3. Are there subpopulations of patients based on demographics (e.g., age, sex, race, and diagnoses) for which one PCSK9 inhibitor is more effective or associated with more harm than other non-statin agents?

Conclusions:
- One high quality systematic review evaluated the effects of PCSK9 inhibitors as a class on lipid parameters and the incidence of CVD.[1]
  - There is moderate quality evidence for a reduction in low-density lipoprotein cholesterol [LDL-C] at 24 weeks with PCSK9 inhibitors compared to placebo (-54%; 95% Confidence Interval [CI] 58.6 to 49.1), compared to ezetimibe (30.2%; 95% CI 34.2 to 26.2) and compared to ezetimibe plus statin (39.2%; 95% CI 56.15 to 22.26).
  - There is moderate quality evidence of a modest reduction in cardiovascular disease [CVD] events with PCSK9 inhibitors compared to placebo (odds ratio [OR] 0.86; 95% CI 0.8 to 0.92; absolute risk reduction [ARR] 0.9%; number needed to treat [NNT] 112) from 6 to 36 months of follow up.
  - Low quality evidence suggests a beneficial effect on cardiovascular [CV] outcomes with PCSK9 inhibitors compared to ezetimibe and statins (OR 0.45; 95% CI 0.27 to 0.75; ARR 1.1%, NNT 91) with significant uncertainty.
  - There was no significant difference in mortality between PCSK9 inhibitors and placebo (OR 1.02; 95% CI 0.91 to 1.14) with follow up of 6 to 36 months.
  - There is low quality evidence of an increase in adverse events with PCSK9 inhibitors compared to placebo (OR 1.08; 95% CI 1.04 to 1.12; absolute risk increase [ARI] 1.5%; number needed to harm [NNH] 67). There was no significant difference in any one individual adverse event (myalgia, influenza, cancer, elevated creatinine) and the effect of PCSK9 inhibitors on the risk of an event was modest, with changes in risk often less than 1%. The increase in adverse events was largely driven by two trials evaluating bococizumab, which was discontinued due to immunogenicity
- There is moderate quality evidence from one large, good quality trial with a median duration of follow-up of 26 months that evolocumab added on to statin therapy reduces non-fatal CV events compared to placebo with a modest magnitude of benefit (9.8% vs. 11.3%, respectively, ARR 1.5%; NNT 67) in those patients with clinically evident CVD at high risk for recurrence.[2]

- There is moderate quality evidence that evolocumab added on to statin therapy does not reduce the risk of mortality (3.2% vs. 3.1%) or CV death (1.8% vs. 1.7%) compared to placebo, respectively, and there was a numerically high risk of both with treatment compared to placebo.[2]
- There is low quality evidence of no difference in serious adverse events, musculoskeletal, or new onset diabetes between evolocumab and placebo.
- There remains conflicting evidence on the risk of neurocognitive adverse events with PCSK9 inhibitors and the overall incidence is low (< 1%). A recent systematic review found no difference in neurocognitive adverse events with PCSK9 inhibitors compared to standard of care (0.8% vs. 0.5%; OR 1.29; 95% CI 0.64 to 2.59) with mild between-study heterogeneity. However, a subgroup analysis using only the two larger outcome trials with longer duration of follow-up did demonstrate a significant increase in neurocognitive adverse events (1% vs. 0.4%; OR 2.81; 95% CI 1.32 to 5.99) with PCSK9 inhibitors compared to standard of care with a wide confidence interval.[3] These events were self-reported with no objective analysis.
- There is insufficient evidence to directly compare the effectiveness or safety of evolocumab and alirocumab.
- There remains insufficient evidence that alirocumab is effective in preventing CV events. Ongoing trials will help evaluate effectiveness once completed.
- There is insufficient evidence evaluating PCSK9 inhibitors on quality of life outcomes.

Recommendations:
- Continue to require prior authorization for approval of evolocumab and alirocumab (**Appendix 4**) to approve for high CV risk patients that have been included in clinical studies.
- No changes to PDL recommended. Evaluate costs in executive session.

Previous Conclusions:
- Moderate quality evidence shows proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are efficacious at reducing low-density lipoprotein cholesterol (LDL-C) levels by over 50% from baseline in patients with familial hypercholesterolemia already on a statin and ezetimibe and in non-familial hypercholesterolemia who cannot achieve adequate LDL-C lowering.
- However, evidence is insufficient at this time to support the use of PCSK9 inhibitors to reduce adverse CV outcomes including all-cause mortality.
- In patients with homozygous familial hypercholesterolemia already on a statin and ezetimibe, there is insufficient evidence to use alirocumab
- There is insufficient evidence that directly compares efficacy and harms between PCSK9 inhibitors.
- Moderate quality evidence from short term trials suggests PCSK9 inhibitors are associated with increased neurocognitive adverse events compared to placebo.[8] The FDA has directed developers of PCSK9 inhibitors to monitor for neurocognitive adverse effects in ongoing clinical trials. A higher frequency of neurocognitive adverse events was observed with both evolocumab (0.9% versus 0.3% for placebo) and alirocumab (1.2% versus 0.5% for placebo
- There is insufficient evidence to differentiate between differences in harms between PCSK9 inhibitors. It is unknown if significantly lowering LDL-C will adversely affect gastrointestinal, metabolic and neurocognitive functions.

Previous Recommendations:
- Designate alirocumab and evolocumab as non-preferred in the "Other Dyslipidemia Drugs" class. Preferred status cannot be made at this time due to limited evidence of long-term CV benefit and harms.
- Restrict use of PCSK9 Inhibitors to the following populations: 1) non-familial hypercholesterolemia unable to achieve at least 50% LCL-C reduction despite high-intensity statin therapy and ezetimibe; 2) familial hypercholesterolemia; or 3) persistent myopathy or myalgia with several adequate trials of statin therapy.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted from November 2016 to November 2017. 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, evidence-based guidelines, and randomized controlled trials (RCTs) evaluating clinical cardiovascular (CV) outcomes. Randomized controlled trials of surrogate outcomes will be emphasized if evidence is lacking or insufficient from those preferred sources.

Background:

The association between hypercholesteremia and CVD is well established. Statins have been the primary treatment option for prevention of CVD and have been shown to decrease CV events and mortality in patients with CVD and patients at high CV risk.

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) Task Force on Practice Guidelines advocate for a substantial shift in strategies to assess and manage elevated cholesterol to reduce CVD.[4] Recommendations were derived from randomized trials, meta-analyses, and observational studies that were considered high quality using National Heart, Lung and Blood Institute (NHLBI) criteria. [4] The previous Adult Treatment Panel (ATP) III guidelines focused on reducing LDL-C and non-high density lipoprotein cholesterol (non-HDL-C) to specific target levels. The updated ACC/AHA guidelines recommend adjusting the intensity of statin therapy to reduce CVD risk in patients most likely to benefit from therapy using a risk estimator.[11] According to the ACC/AHA, non-statin therapies do not provide acceptable CVD risk reduction benefits. [4] For high risk patients including those with atherosclerotic CVD, LDL greater than or equal to 190 mg/dl and diabetics who are statin intolerant or unable to achieve sufficient response to statins, non-statin options such as niacin, fibric acid derivatives, ezetimibe, or omega-3 fatty acids can be considered to further lower LDL-C. [4] However, the benefit of CVD risk reduction with non-statin therapy should be evaluated against the risks of adverse effects and drug-drug interactions. [4] Since the 2013 guidelines, the IMPROVE-IT trial demonstrated a modest CV benefit with ezetimibe add-on therapy. The PCSK9 inhibitors were not part of the ACC/AHA practice guidelines since they were not yet approved in 2013.

PCSK9 promotes the degradation of the LDL receptor, resulting in an increase in plasma LDL. Inhibition of PCSK9 may enhance the lipid-lowering effects of statin due to a statin-induced increase in PCSK9 expression.[1] There are currently two PCSK9 inhibitors available, evolocumab and alirocumab (**Table 1**). A third agent, bococizumab, was removed from the development phase due to significant immune reactions and a decreased efficacy seen over time. These are both monoclonal antibodies that have been studied in challenging populations including those intolerant to statins and those with familial hypercholesterolemia. They have been shown to result in significant additive LDL reduction (>50%) on top of statin therapy in high-risk patients. However, at the time of approval, there was insufficient evidence on their effect on CV outcomes. Data from observational studies and small randomized trials led to a FDA warning regarding the risk of cognitive deficits as a result from considerable lowering of LDL-C.[5]

Table 1: FDA approved indications and dose for available PCSK9 inhibitors

PCSK9 Inhibitor	Dose	FDA approved indications

Evolocumab[6]	140 mg SubQ every 2 weeks
	420 mg SubQ every month
		• To reduce the risk of myocardial infarction, stroke, and coronary revascularization in adults with established CVD
		• As adjunct therapy for adults with primary hyperlipidemia
		  ○ heterozygous familial hypercholesterolemia
		  ○ homozygous familial hypercholesterolemia

Alirocumab[7]	75 mg SubQ every 2 weeks 300 mg SubQ every month	• Adjunct therapy for adults with heterozygous familial hypercholesterolemia • Adjunct therapy for patients with clinical ASCVD requiring additional LDL-C lowering
Abbreviations: ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; LDL-C = low density lipoprotein cholesterol; SubQ = subcutaneously		

Systematic Reviews Including Clinical Outcomes:

1. A systematic review from Cochrane Collaboration evaluated short-term (24 weeks), medium-term (one year), and long term (five years) effects of the PCSK9 inhibitors on lipid parameters and the incidence of CVD.[1] Twenty industry funded RCTs including participants with CVD or at high risk of CV events were included (n=67,237) from a literature search through March 2016, of which 12 included alirocumab and only four included evolocumab. They were analyzed together as a class of medications. Three large RCTs published in March 2017 were also included. Of the study participants, 67,237 (30%) were female, 6984 (11%) did not have CVD, and 2513 had familial hypercholesterolemia (FH) (7%). The primary reason for study exclusion was follow-up time less than 24 weeks. Included studies were all industry funded and about one-third of the trials had unclear risk of bias due to insufficient detail on randomization or allocation concealment. Overall, most trials had a low risk of bias with a few exceptions (open-label OSLER trials).

   There was moderate quality evidence for the PCSK9 inhibitors in percentage change from baseline of LDL-C at 24 weeks compared to placebo (mean difference in percentage change from baseline of 54%; 95% CI 58.6 to 49.1), compared to ezetimibe (mean difference 30.2%; 95% CI 34.2 to 26.23), and compared to ezetimibe and statins (mean difference 39.20%; 95% CI 56.15 to 22.26). At one year, six trials showed similar results in LDL-lowering compared to statins (-52.9%; 95% CI 60 to 45.7). Additionally, there was moderate quality evidence of a reduction in CVD events compared to placebo (OR 0.86; 95% CI 0.8 to 0.92; ARR 0.9%; NNT 112) from 6 to 36 months of follow up. There was a significant reduction in myocardial infarction (MI) (OR 0.77; 95% CI 0.69 to 0.85) and any stroke (OR 0.76; 95% CI 0.65 to 0.89). The absolute rates of MI and stroke were not provided. There was significant heterogeneity between studies. However, the authors concluded that consistency in direction of effect and differences in magnitude were similar enough to provide clinically relevant treatment effect estimates. Results were consistent when analyzed by the following subgroup populations: gender, age, baseline LDL, history of CVD, and history of diabetes. There was no dose-response seen on LDL-C lowering. Very low quality evidence suggests a stronger protective effect on CV risk compared to ezetimibe and statins (OR 0.45; 95% CI 0.27 to 0.75; ARR 1.1%, NNT 91) with significant uncertainty. There was no significant difference in mortality between PCSK9 inhibitors and placebo (OR 1.02; 95% CI 0.91 to 1.14). There was insufficient data on clinical outcomes to evaluate comparisons to ezetimibe, and data on quality of life were unavailable for all studies. Clinical outcome data comes largely from the FOURIER trial and two trials evaluating bococoizumab which was never FDA approved (SPIRE-1 and SPIRE-2). Median follow-up was still less than three years in these large trials, and longer follow up data on efficacy and safety is still needed.

Lastly, low quality evidence shows an increase in adverse events with the PCSK9 inhibitors compared to placebo (OR 1.08; 95% CI 1.04 to 1.12; ARI 1.5%; NNH 67) and compared to ezetimibe and statins (OR 1.18; 95% CI 1.05 to 1.24; ARI 3.7%; NNT 27). There was no significant difference in any one individual adverse event (myalgia, influenza, cancer, elevated creatinine), and the effect of PCSK9 inhibitors on the risk of an event was modest, with changes in risk often less than 1%. The increase in adverse events was largely driven by two trials evaluating bococizumab, which was discontinued due to immunogenicity. There was no significant difference see in neurological events (OR 1.04; 95% CI 0.88 to 1.24), risk of cancer or type 2 diabetes mellitus, but with limited follow-up duration to detect a difference. The authors concluded that over medium term follow up, PCSK9 inhibitors decrease CVD but may increase the risk of adverse events. Evidence of efficacy and safety compared to active treatments was low to very low quality with short follow-up times and few events. Estimated risk differences suggested only a modest change in absolute risk (less than 1%).

2. Another systematic review evaluated RCTs of alirocumab or evolocumab that reported ≥1 health outcome (CV events), lipid outcome, or harms.[8] A total of 17 studies were included from a literature search through September 2015. No studies were found to be poor quality. The results based on study population are as follows:
    a. Heterozygous familial hypercholesterolemia and homozygous familial hypercholesterolemia (HeFH and HoFH): There was low strength evidence that alirocumab resulted in a higher LDL-C reduction compared to placebo (difference in LDL-C change of -8.0% to -57.4%) in HeFH in addition to maximally dosed statin and ezetimibe. No studies were identified with alirocumab in HoFH. There was high strength evidence that evolocumab resulted in a higher LDL-C reduction compared to placebo (difference in LDL-C change of -44.1% to -61.3%) in those with HeFH on a high-intensity statin plus ezetimibe. Lastly, there was low strength evidence that evolocumab achieved a higher LDL-C reduction in those with HoFH on a high intensity statin plus ezetimibe. There was no significant difference in serious adverse events, neurocognitive events, or withdrawals due to adverse events.
    b. Statin-intolerant: There was no evidence for alirocumab in those who were statin intolerant. There was low strength evidence that evolocumab led to a greater reduction in LDL-C than placebo and that the combination of evolocumab plus ezetimibe led to a greater LDL-C reduction than placebo.
    c. High CV risk: Moderate strength evidence suggests that alirocumab resulted in a higher proportion of patients reaching a LCL-C < 70 mg/dl than placebo (RR 1.70; 95% CI 1.46 to 1.95) and that there was no difference in serious adverse events. There was high strength evidence that alirocumab resulted in a higher proportion of patients reaching an LDL-C < 70 mg/dl (RR 9.65; 95% CI 7.7-12.0) and no difference in serious adverse events or discontinuations due to adverse events. There was moderate – and low-strength evidence of no difference in adjudicated CV events between alirocumab and placebo at 52 weeks.

3. A systematic review using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines was conducted to assess long term safety of the PCSK9 inhibitors.[3] Only trials > 6 months in duration were included. A total of 11 studies (n=10656) were included; the majority including patients with unspecific hypercholesterolemia (7 trials). The risk of bias was assessed using the Cochrane tool and all included studies were determined to be low risk of bias. There was no difference in serious adverse events between PCSK9 inhibitors and standard of care (10.3% vs. 11%, respectively; OR 1.00; 95% CI 0.88 to 1.15). There was no difference in musculoskeletal adverse events with the PCSK9 inhibitors and standard of care (14.2% vs. 12.7%; OR 1.01; 95% CI 0.87 to 1.13) with mild between-study heterogeneity. Neurocognitive events, defined as delirium, cognitive and attention disorders, dementia, disturbances in thinking and mental impairment disorders) was reported in 8 studies and there was also no difference between PCSK9 inhibitors and standard of care (0.8% vs. 0.5%; OR 1.29; 95% CI 0.64 to 2.59) with mild between-study heterogeneity and low rates overall. However, a subgroup analysis using only the two larger outcome trials did demonstrate a significant increase in neurocognitive adverse events (1% vs. 0.4%; OR 2.81; 95% CI 1.32 to 5.99) with PCSK9 inhibitors compared to standard of care with a wide confidence interval.[3] These events were self-reported with no objective analysis.

Guidelines:
In 2016, the American College of Cardiology (ACC) published the first expert consensus decision pathway on the role of non-statin therapies for LCL-C lowering in the management of atherosclerotic cardiovascular disease (ASCVD) risk. A focused update was published in 2017 to include new evidence on the efficacy and safety of PCSK9 inhibitors, including data from the FOURIER trial.[9] However, this was an expert consensus document meant to provide guidance for clinicians in areas where evidence may be limited or evolving. Since this process did not involve formal systematic reviews, grading of the evidence, or synthesis of evidence it will not be used to make conclusions or recommendations.

The expert group recommends consideration of a PCSK9 inhibitor or ezetimibe for the following populations: 1) patients without clinical ASCVD and with baseline LDL-C greater than or equal to 190 mg/dl on statin therapy who do not achieve at least 50% LCL-C reduction, 2) patients with clinical ASCVD and baseline LCL-C greater than or equal to 190 mg/dl who do not achieve at least 50% LCL-C reduction on high intensity statin, 3) patients with clinical ASCVD and comorbidities (recent ASCVD, chronic kidney disease, symptomatic heart failure, current daily cigarette smoking, symptomatic peripheral artery disease, etc.) who do not achieve at least 50% LCL-C reduction on maximally tolerated statin therapy, 4) patients with stable clinical ASCVD without comorbidities on maximally tolerated statin AND ezetimibe therapy who do not achieve at least 50% LDL-C reduction.

Safety Updates:
None

New formulations or indications:
On December 1, 2017 FDA approved evolocumab to prevent MI, stroke, and coronary revascularization in adults with established CVD.[6] Approval was based on FDA review of clinical outcome data from the FOURIER Trial (**Table 2**). Evolocuamb is now also approved for primary hyperlipidemia (including heterozygous familial hypercholesterolemia).

Clinical Trials Evaluating CV outcomes:
Evolocumab
The FOURIER trial is the first published trial that evaluated CV clinical outcomes as the primary outcome (**Table 2**).[2] It is a parallel group, double-blind, very large good quality RCT (n=27,654) that included adults with history of clinically evident CVD with LDL-C greater than or equal to 70 mg/dl or non-high density lipoprotein cholesterol (HDL-C) of at least 100 mg/dl with at least one major risk factor (diabetes, smoker, age ≥65 years, recent acute coronary syndrome [ACS]) or two minor risk factors (coronary revascularization, residual coronary artery disease [CAD], metabolic syndrome, LDL-C ≥130 mg/dl). Clinically evident ASCVD was defined as a history of MI, ischemic stroke, or symptomatic peripheral artery disease. Participants were randomized to evolocumab plus moderate- or high-intensity statin background therapy or placebo plus statin background therapy with or without ezetimibe. Patients with heart failure with reduced ejection fraction, uncontrolled hypertension, ventricular tachycardia, homozygous familial hypercholesterolemia (HoFH), or requiring LDL or plasma apheresis, estimated glomerular filtration rate (eGFR) less than 20ml/min, active liver disease, or elevated creatinine kinase (CK) were excluded from the trial. The primary outcome was a CV composite outcome including CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization. There was a low risk of bias overall, but was funded and supported by Amgen.

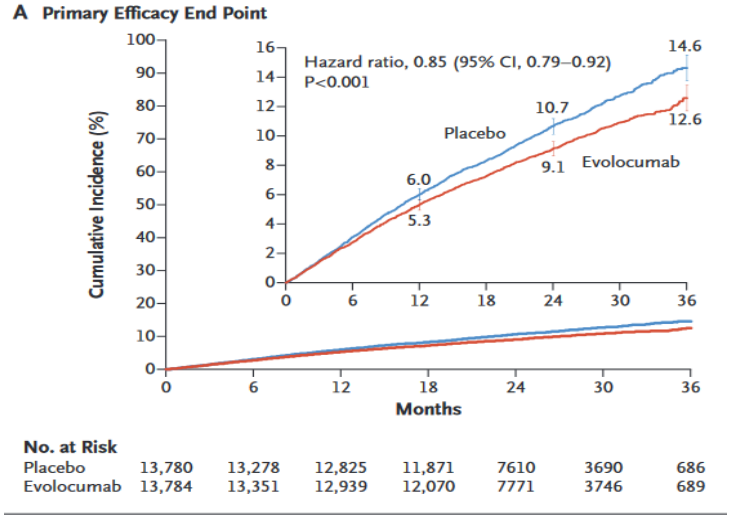
Baseline characteristics were similar between the two groups. The majority of the participants were from Europe (62.9%), and only 16.6% were from North America. Approximately 80% of participants had a history of a MI and 36% had diabetes at baseline. Only around 5% of those in each group were on ezetimibe,

and almost 70% were on high intensity statin. The study population had a relatively well-controlled lipid profile with a median LDL-C of 92 mg/dl and triglycerides of 133 mg/dl. The median duration of follow-up was 26 months.

Consistent with other trials, LDL-C was significantly reduced with evolocumab compared to placebo, with a least-squares mean reduction of 59% compared to placebo (95% CI 55 to 57). At 48 weeks, LDL-C was reduced to less than or equal to 70 mg/dl in 87% of evolocumab-treated patients compared to 18% in the placebo group (ARR 69%; NNT 2). The median LDL-C after 48 weeks of evolocumab was 30 mg/dl. The primary CV composite outcome was significantly reduced with evolocumab compared to placebo (9.8% vs. 11.3%; HR 0.85; 95% CI 0.79 to 0.92; ARR 1.5%; NNT 67) with a modest absolute risk reduction of 1.5%. There was also a significant reduction in the composite of CV death, MI or stroke (5.9% vs. 7.4%; HR 0.80; 95% CI 0.73 to 0.88; ARR 1.5%; NNT 67). The magnitude of risk reduction increased over time beyond the first year (**Figure 1**). There was no significant reduction in individual outcomes including CV death or overall mortality, and there was numerically a higher rate of overall mortality (3.2% vs. 3.1%) and CV death (1.8% vs. 1.7%) in the evolocumab group compared to placebo. The primary composite outcome was largely driven by a difference in non-fatal events (MI, stroke, or coronary revascularization).

Results were consistent across subgroups, including age, sex, baseline atherosclerotic disease and baseline LDL-C. Subgroup analysis based on blood pressure or diabetes was not included. There was no significant difference in the primary CV outcome seen in those participants who were on ezetimibe. However, overall numbers were small in this subgroup and it is difficult to make any conclusive statement from this finding.

Figure 1: Effect on Primary Outcome over TIme[2]



There was no significant difference in the percentage of patients with serious adverse events (24.8% vs. 24.7%) or those withdrawing due to adverse events (1.6% vs. 1.5%), with evolocumab versus placebo, respectively. There was no difference between myalgia, cataract, neurocognitive adverse events, or hemorrhagic stroke. Injection site reactions occurred more frequently in the evolocumab group compared to placebo (2.1% vs. 1.6%). There was no significant difference in new-onset diabetes (HR 1.05; 95% CI 0.94 to 1.17).

Alirocumab

The effect of alirocumab on CV events is being studied in the ODYSSEY OUTCOMES trial and is estimated to be completed in December 2017.[10]

Table 2: Summary of Clinical Trials Evaluating Clinical CV Outcomes

Study	Comparison	Population	Primary Outcome	Results	
FOURIER trial[2] RCT, DB 48 weeks, 26 months follow-up	Evolocumab 140 mg Q2W or 420 mg QMO add on Vs. Placebo injection add on	Adults with history of clinically evidence CVD at high risk for a recurrent event with LDL-C ≥ 70 mg/dl or non-HDL-C ≥ 100 mg/dl (n=27,654)	Major CV events (CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization)	<u>Major CV events</u> Evolocumab: 1,344 (9.8%) Placebo: 1,563 (11.3%) HR 0.85; 95% CI 0.79 to 0.92 ARR 1.5%; NNT 67 <u>CV death, MI or stroke</u> Evolocumab: 816 (5.9%) Placebo: 1013 (7.4%) HR 0.80; 95% CI 0.73 to 0.88 ARR 1.5%; NNT 67	<u>Serious Adverse Events</u> Evolocumab: 3410 (24.8%) Placebo: 3404 (24.7%) <u>Withdrawals due to Adverse Events:</u> Evolocumab: 628 (4.6%) Placebo: 581 (4.2%)

Abbreviations: DB = double-blind; CVD = cardiovascular disease; CV = cardiovascular; LDL-C = low density lipoprotein cholesterol; MI = myocardial infarction; Q2W = every 2 weeks; QMO = every month; RCT = randomized controlled trial.

Additional Randomized Controlled Trials:

A total of 30 citations were manually reviewed from the literature search. After manual review, 24 trials were excluded because of wrong study design (observational), outcome studied, or published prior to dates of interest. The remaining 6 trials are briefly described in the table below. Full abstracts are included in **Appendix 2**.

Table 3. Description of Additional Randomized Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Quality Comments
ODYSSEY COMBO II[11] DB, RCT, PG 104 weeks	Alirocumab 75 mg Q2 weeks titrated up to 150 mg Q2W+ ezetimibe 10 mg daily Vs. Placebo + Ezetimibe 10 mg daily	Participants with hypercholesterolemia, established CVD or CVD risk equivalents (e.g. chronic kidney disease), and on a maximally tolerated dose of statin	Change from baseline in LDL-C	<u>Change from baseline in LDL-C over 2 years:</u> Alirocumab: 49% Placebo: 17% LS mean difference -32%; 95% CI -38 to -26 P<0.0001 <u>Discontinuations due to AE:</u> Alirocumab: 36(7.5%) Placebo: 13 (5.4%)	Low risk of bias Funded by Sanofi and Regeneron Not powered for analysis of CV events

	Both add-on to statins	(n=720)			
ODYSSEY OPTIONS II[12] DB, PC, PG, RCT 24 weeks	Alirocumab 75 mg Q2W titrated up to 150 mg Q2W add-on Vs. Ezetimibe 10 mg add-on Vs. Additional 10-20 mg rosuvastatin	History of CVD and LDL-C levels ≥ 70 mg/dl, or CVD risk factors and LDL-C ≥ 100 mg/dl receiving rosuvastatin 10 or 20 mg/day (n=305)	Change from baseline in LDL-C at week 24	<u>Change from baseline in LDL-C at week 24:</u> Alirocumab: 50.6% Ezetimibe: 14.4% Double-dose rosuvastatin: 16.4% P<0.0001 favoring alirocumab versus all other comparisons	Low risk of bias Funded by Sanofi and Regeneron
ODYSSEY HIGH FH[13] DB, PG, RCT 78 weeks	Alirocumab 150 mg Q2 weeks vs. placebo Both add-on to statin and possible other lipid lowering therapies	HeFH on maximally tolerated dose of statin with LDL-C ≥ 160 mg/dl	Change from baseline in LCL-C at week 24	<u>Change from baseline in LDL-C at week 24:</u> Alirocumab: -45.7% Placebo: -6.6% Difference of -39.1%; p<0.0001	Low risk of bias Funded by Sanofi and Regeneron
EBBINGHAUSE[5] Subgroup analysis of FOURIER Trial	Evolocumab 140 mg Q2W or 420 QMo + statin Vs. Placebo + statin therapy	ASCVD and LDL ≥70 mg/dl on moderate- or high-intensity statin Patients with dementia or cognitive dysfunction at baseline were excluded	Mean change from baseline in spatial working memory (SWM) index of executive function	<u>Mean change in SWM:</u> Evolocumab: -0.21 Placebo: -0.29 P<0.001 for noninferiority P=0.85 for superiority <u>Cognitive adverse events:</u> Evolocumab: 11 (1.9%) Placebo: 8 (1.3%) P=NS	Short follow up to detect differences in cognitive function High risk patients for cognitive impairment excluded Tool used is validated but not used in clinical practice Funded by Amgen
ODYSSEY DM-INSULIN[14] RCT, DB, PC, PG 24 weeks	Alirocumab titrated up to 150 mg Q2W Vs. Placebo	Insulin treated T2D or T1D and established ASCVD or at least one CV risk factor with LDL ≥ 70 mg/dl on maximally tolerated statin therapy	Change from baseline in LCL-C at week 24	<u>Change from baseline in LCL-C at week 24</u> Alirocumab: -48.2% Placebo: +0.8% Difference -49% (p<0.0001)	Extensive exclusion criteria Funded by Sanofi and Regeneron

GLAGOV[15] DB, RCT, PC 76 weeks	Evolocumab 420 mg QMO Vs. Placebo Plus statin	Participants with angiographic coronary disease (n=968)	Nominal change in percent atheroma volume (PAV) from baseline	<u>Change in PAV from baseline</u> Evolocumab: -0.95% Placebo: +0.05% Difference -1.0%; 95% CI -1.8% to -0.64%; p<0.01	Unknown clinical significance of measured outcome Funded by Amgen
Ray et al.[16] Pooled analysis of 10 ODYSSEY trials	Alirocumab 75/150 mg Q 2 weeks Vs. Control On background statin	Participants with ASCVD or high CV Risk (3182 taking alirocumab, 1174 taking placebo, 618 taking ezetimibe).	Relationship between LDL and MACE	For every 39 mg/dL lower achieved LDL-C, the risk of MACE appeared to be 24% lower (adjusted hazard ratio, 0.76; 95% CI, 0.63–0.91; P=0.0025)	Post-hoc analyses

Abbreviations: AE = adverse events; ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; DB = double blind; CI = confidence interval; CV = cardiovascular; HDL-C = high density lipoprotein cholesterol; HEFH = heterozygous familial hypercholesterolemia; LDL-C = low density lipoprotein cholesterol; MC = multi-centered; mg = milligram; MACE = major adverse cardiovascular events; MI = myocardial infarction; PC = placebo controlled; PG = parallel group; Q2W = every 2 weeks; QMO = every month; RCT = randomized controlled trial; T1D = type 1 diabetes; T2D = type 2 diabetes.

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12. Farnier M, Jones P, Severance R, et al. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: The ODYSSEY OPTIONS II randomized trial. *Atherosclerosis.*244:138-146.
13. Ginsberg HN, Rader DJ, Raal FJ, et al. Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia and LDL-C of 160 mg/dl or Higher. *Cardiovascular Drugs & Therapy.*30(5):473-483.
14. Leiter LA, Cariou B, Muller-Wieland D, et al. Efficacy and safety of alirocumab in insulin-treated individuals with type 1 or type 2 diabetes and high cardiovascular risk: The ODYSSEY DM-INSULIN randomized trial. *Diabetes, obesity & metabolism.* 2017;19(12):1781-1792.
15. Nicholls SJ, Puri R, Anderson T, et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. *JAMA.*316(22):2373-2384.
16. Ray KK, Ginsberg HN, Davidson MH, et al. Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab With Control. *Circulation.*134(24):1931-1943.

Appendix 1: Current Status of PDL Class.

PCSK9 Inhibitors

ROUTE	FORMULATION	BRAND	GENERIC	PDL
SQ	PEN INJCTR	PRALUENT PEN	ALIROCUMAB	N
SQ	WEAR INJCT	REPATHA PUSHTRONEX	EVOLOCUMAB	N
SQ	PEN INJCTR	REPATHA SURECLICK	EVOLOCUMAB	N
SQ	SYRINGE	REPATHA SYRINGE	EVOLOCUMAB	N

Appendix 2: Abstracts of RCTs

1. El Shahawy M, Cannon CP, Blom DJ, et al. Efficacy and Safety of Alirocumab Versus Ezetimibe Over 2 Years (from ODYSSEY COMBO II). Am J Cardiol. 2017 Sep 15;120(6):931-939. doi: 10.1016/j.amjcard.2017.06.023. Epub 2017 Jun 28.

Abstract
The proprotein convertase subtilisin/kexin type 9 inhibitor alirocumab has been shown to substantially reduce low-density lipoprotein cholesterol (LDL-C). Demonstrating whether efficacy and safety are maintained over a long duration of exposure is vital for clinical decision-making. The COMBO II trial compared the efficacy and safety of alirocumab versus ezetimibe over 2 years. A prespecified first analysis was reported at 52 weeks. Here we report the final end-of-study data (on-treatment) and evaluate post hoc the safety profile with longer versus shorter duration of alirocumab exposure. Patients (n = 720) on maximally tolerated statin dose were treated with alirocumab (75/150 mg every 2 weeks) or ezetimibe (10 mg/day). Overall mean adherence for both treatment groups during the first and second year was >97%. At 2 years, LDL-C was reduced by 49% (alirocumab) versus 17% (ezetimibe; p <0.0001), and LDL-C <70 mg/dl was achieved by 73% of alirocumab-treated versus 40% of ezetimibe-treated patients. Overall safety was similar in both treatment groups at 2 years and during the first versus the second year. Local injection-site reactions were reported by 2.5% (alirocumab) versus 0.8% (ezetimibe) during the first year, and 0.2% versus 0.5% during the second year, indicating early occurrence during prolonged alirocumab exposure. Two consecutive calculated LDL-C values <25 mg/dl were observed in 28% of alirocumab-treated patients (vs 0.4% with ezetimibe). Persistent anti-drug antibody responses were observed in 1.3% (6 of 454) of alirocumab-treated versus 0.4% (1 of 231) of ezetimibe-treated patients. Neutralizing antibodies (that inhibit binding in vitro) were observed in 1.5% (7 of 454) of alirocumab-treated patients (0 with ezetimibe), mostly at isolated time points. Alirocumab sustained substantial LDL-C reductions and was well tolerated up to 2 years in the COMBO II trial.

2. Farnier M, Jones P, Severance R, Averna M, Steinhagen-Thiessen E. Efficacy and safety of adding alirocumab to rosuvastatin versus adding ezetimibe or doubling the rosuvastatin dose in high cardiovascular-risk patients: The ODYSSEY OPTIONS II randomized trial. Atherosclerosis. 2016 Jan;244:138-46. doi: 10.1016/j.atherosclerosis.2015.11.010. Epub 2015 Nov 14.

OBJECTIVE:
To compare lipid-lowering efficacy of adding alirocumab to rosuvastatin versus other treatment strategies (NCT01730053).
METHODS:
Patients receiving baseline rosuvastatin regimens (10 or 20 mg) were randomized to: add-on alirocumab 75 mg every-2-weeks (Q2W) (1-mL subcutaneous injection via pre-filled pen); add-on ezetimibe 10 mg/day; or double-dose rosuvastatin. Patients had cardiovascular disease (CVD) and low-density lipoprotein cholesterol (LDL-C) ≥70 mg/dL (1.8 mmol/L) or CVD risk factors and LDL-C ≥100 mg/dL (2.6 mmol/L). In the alirocumab group, dose was blindly increased at Week 12 to 150 mg Q2W (also 1-mL volume) in patients not achieving their LDL-C target. Primary endpoint was percent change in calculated LDL-C from baseline to 24 weeks (intent-to-treat).
RESULTS:
305 patients were randomized. In the baseline rosuvastatin 10 mg group, significantly greater LDL-C reductions were observed with add-on alirocumab (-50.6%) versus ezetimibe (-14.4%; p < 0.0001) and double-dose rosuvastatin (-16.3%; p < 0.0001). In the baseline rosuvastatin 20 mg group, LDL-C reduction with add-on

alirocumab was -36.3% compared with -11.0% with ezetimibe and -15.9% with double-dose rosuvastatin (p = 0.0136 and 0.0453, respectively; pre-specified threshold for significance p < 0.0125). Overall, ~80% alirocumab patients were maintained on 75 mg Q2W. Of alirocumab-treated patients, 84.9% and 66.7% in the baseline rosuvastatin 10 and 20 mg groups, respectively, achieved risk-based LDL-C targets. Treatment-emergent adverse events occurred in 56.3% of alirocumab patients versus 53.5% ezetimibe and 67.3% double-dose rosuvastatin (pooled data).
CONCLUSIONS:
The addition of alirocumab to rosuvastatin provided incremental LDL-C lowering versus adding ezetimibe or doubling the rosuvastatin dose.

3. Ginsberg HN, Rader DJ, Raal FJ, Guyton JR, et al. Efficacy and Safety of Alirocumab in Patients with Heterozygous Familial Hypercholesterolemia and LDL-C of 160 mg/dl or Higher. Cardiovasc Drugs Ther. 2016 Oct;30(5):473-483.

PURPOSE:
Even with statins and other lipid-lowering therapy (LLT), many patients with heterozygous familial hypercholesterolemia (heFH) continue to have elevated low-density lipoprotein cholesterol (LDL-C) levels. ODYSSEY HIGH FH (NCT01617655) assessed the efficacy and safety of alirocumab, a proprotein convertase subtilisin/kexin type 9 monoclonal antibody, versus placebo in patients with heFH and LDL-C ≥ 160 mg/dl despite maximally tolerated statin ± other LLT.
METHODS:
Patients were randomized to subcutaneous alirocumab 150 mg or placebo every 2 weeks (Q2W) for 78 weeks. The primary endpoint was percent change in LDL-C from baseline to week 24.
RESULTS:
Mean baseline LDL-C levels were 196.3 mg/dl in the alirocumab (n = 71) and 201.0 mg/dl in the placebo groups (n = 35). Significant mean (standard error [SE]) reductions in LDL-C from baseline to week 24 were observed with alirocumab (-45.7 [3.5] %) versus placebo (-6.6 [4.9] %), a difference of -39.1 (6.0) % (P < 0.0001). Absolute mean (SE) LDL-C levels were reduced from baseline by 90.8 (6.7) mg/dl with alirocumab at week 24, with reductions maintained to week 78. Treatment-emergent adverse events were generally comparable between groups. Injection-site reactions were more frequent in the alirocumab group (8.3 %) versus placebo (5.7 %); most were mild in severity and did not result in study medication discontinuation.
CONCLUSIONS:
In patients with heFH and very high LDL-C baseline levels despite maximally tolerated statin ± other LLT, alirocumab 150 mg Q2W demonstrated significant reductions in LDL-C levels with 41 % of patients achieving predefined LDL-C goals. Alirocumab was generally well tolerated.

4. Giugliano RP1, Mach F, Zavitz K, Kurtz C, Im K, et al. Cognitive Function in a Randomized Trial of Evolocumab. N Engl J Med. 2017 Aug 17;377(7):633-643. doi: 10.1056/NEJMoa1701131.

Abstract
Background Findings from clinical trials of proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors have led to concern that these drugs or the low levels of low-density lipoprotein (LDL) cholesterol that result from their use are associated with cognitive deficits. Methods In a subgroup of patients from a randomized, placebo-controlled trial of evolocumab added to statin therapy, we prospectively assessed cognitive function using the Cambridge Neuropsychological Test Automated Battery. The primary end point was the score on the spatial working memory strategy index of executive function (scores

range from 4 to 28, with lower scores indicating a more efficient use of strategy and planning). Secondary end points were the scores for working memory (scores range from 0 to 279, with lower scores indicating fewer errors), episodic memory (scores range from 0 to 70, with lower scores indicating fewer errors), and psychomotor speed (scores range from 100 to 5100 msec, with faster times representing better performance). Assessments of cognitive function were performed at baseline, week 24, yearly, and at the end of the trial. The primary analysis was a noninferiority comparison of the mean change from baseline in the score on the spatial working memory strategy index of executive function between the patients who received evolocumab and those who received placebo; the noninferiority margin was set at 20% of the standard deviation of the score in the placebo group. Results A total of 1204 patients were followed for a median of 19 months; the mean (±SD) change from baseline over time in the raw score for the spatial working memory strategy index of executive function (primary end point) was -0.21±2.62 in the evolocumab group and -0.29±2.81 in the placebo group (P<0.001 for noninferiority; P=0.85 for superiority). There were no significant between-group differences in the secondary end points of scores for working memory (change in raw score, -0.52 in the evolocumab group and -0.93 in the placebo group), episodic memory (change in raw score, -1.53 and -1.53, respectively), or psychomotor speed (change in raw score, 5.2 msec and 0.9 msec, respectively). In an exploratory analysis, there were no associations between LDL cholesterol levels and cognitive changes. Conclusions In a randomized trial involving patients who received either evolocumab or placebo in addition to statin therapy, no significant between-group difference in cognitive function was observed over a median of 19 months

5. Leiter LA, Cariou B, Müller-Wieland D, et al.and safety of alirocumab in insulin-treated individuals with type 1 or type 2 diabetes and high cardiovascular risk: The ODYSSEY DM-INSULIN randomized trial. Diabetes Obes Metab. 2017 Dec;19(12):1781-1792. doi: 10.1111/dom.13114. Epub 2017 Oct 10.

AIMS:
To investigate the efficacy and safety of alirocumab in participants with type 2 (T2D) or type 1 diabetes (T1D) treated with insulin who have elevated LDL cholesterol levels despite maximally tolerated statin therapy.
METHODS:
Participants at high cardiovascular risk with T2D (n = 441) or T1D (n = 76) and LDL cholesterol levels ≥1.8 mmol/L (≥70 mg/dL) were randomized 2:1 to alirocumab:placebo administered subcutaneously every 2 weeks, for 24 weeks' double-blind treatment. Alirocumab-treated participants received 75 mg every 2 weeks, with blinded dose increase to 150 mg every 2 weeks at week 12 if week 8 LDL cholesterol levels were ≥1.8 mmol/L. Primary endpoints were percentage change in calculated LDL cholesterol from baseline to week 24, and safety assessments.
RESULTS:
Alirocumab reduced LDL cholesterol from baseline to week 24 by a mean ± standard error of 49.0% ± 2.7% and 47.8% ± 6.5% vs placebo (both P < .0001) in participants with T2D and T1D, respectively. Significant reductions were observed in non-HDL cholesterol (P < .0001), apolipoprotein B (P < .0001) and lipoprotein (a) (P ≤ .0039). At week 24, 76.4% and 70.2% of the alirocumab group achieved LDL cholesterol <1.8 mmol/L in the T2D and T1D populations (P < .0001), respectively. Glycated haemoglobin and fasting plasma glucose levels remained stable for the study duration. Treatment-emergent adverse events were observed in 64.5% of alirocumab- vs 64.1% of placebo-treated individuals (overall population).
CONCLUSIONS:
Alirocumab produced significant LDL cholesterol reductions in participants with insulin-treated diabetes regardless of diabetes type, and was generally well tolerated. Concomitant administration of alirocumab and insulin did not raise any safety concerns

6. Nicholls SJ, Puri R, Anderson T, Ballantyne CM, et al. Effect of Evolocumab on Progression of Coronary Disease in Statin-Treated Patients: The GLAGOV Randomized Clinical Trial. JAMA. 2016 Dec 13;316(22):2373-2384. doi: 10.1001/jama.2016.16951.

IMPORTANCE:
Reducing levels of low-density lipoprotein cholesterol (LDL-C) with intensive statin therapy reduces progression of coronary atherosclerosis in proportion to achieved LDL-C levels. Proprotein convertase subtilisin kexin type 9 (PCSK9) inhibitors produce incremental LDL-C lowering in statin-treated patients; however, the effects of these drugs on coronary atherosclerosis have not been evaluated.
OBJECTIVE:
To determine the effects of PCSK9 inhibition with evolocumab on progression of coronary atherosclerosis in statin-treated patients.
DESIGN, SETTING, AND PARTICIPANTS:
The GLAGOV multicenter, double-blind, placebo-controlled, randomized clinical trial (enrollment May 3, 2013, to January 12, 2015) conducted at 197 academic and community hospitals in North America, Europe, South America, Asia, Australia, and South Africa and enrolling 968 patients presenting for coronary angiography.
INTERVENTIONS:
Participants with angiographic coronary disease were randomized to receive monthly evolocumab (420 mg) (n = 484) or placebo (n = 484) via subcutaneous injection for 76 weeks, in addition to statins.
MAIN OUTCOMES AND MEASURES:
The primary efficacy measure was the nominal change in percent atheroma volume (PAV) from baseline to week 78, measured by serial intravascular ultrasonography (IVUS) imaging. Secondary efficacy measures were nominal change in normalized total atheroma volume (TAV) and percentage of patients demonstrating plaque regression. Safety and tolerability were also evaluated.
RESULTS:
Among the 968 treated patients (mean age, 59.8 years [SD, 9.2]; 269 [27.8%] women; mean LDL-C level, 92.5 mg/dL [SD, 27.2]), 846 had evaluable imaging at follow-up. Compared with placebo, the evolocumab group achieved lower mean, time-weighted LDL-C levels (93.0 vs 36.6 mg/dL; difference, -56.5 mg/dL [95% CI, -59.7 to -53.4]; P < .001). The primary efficacy parameter, PAV, increased 0.05% with placebo and decreased 0.95% with evolocumab (difference, -1.0% [95% CI, -1.8% to -0.64%]; P < .001). The secondary efficacy parameter, normalized TAV, decreased 0.9 mm3 with placebo and 5.8 mm3 with evolocumab (difference, -4.9 mm3 [95% CI, -7.3 to -2.5]; P < .001). Evolocumab induced plaque regression in a greater percentage of patients than placebo (64.3% vs 47.3%; difference, 17.0% [95% CI, 10.4% to 23.6%]; P < .001 for PAV and 61.5% vs 48.9%; difference, 12.5% [95% CI, 5.9% to 19.2%]; P < .001 for TAV).
CONCLUSIONS AND RELEVANCE:
Among patients with angiographic coronary disease treated with statins, addition of evolocumab, compared with placebo, resulted in a greater decrease in PAV after 76 weeks of treatment. Further studies are needed to assess the effects of PCSK9 inhibition on clinical outcomes.

7. Ray KK, Ginsberg HN, Davidson MH, et al. Reductions in Atherogenic Lipids and Major Cardiovascular Events: A Pooled Analysis of 10 ODYSSEY Trials Comparing Alirocumab with Control. *Circulation*. 2016 Dec 13;134(24):1931-1943. Epub 2016 Oct 24.

BACKGROUND:
A continuous relationship between reductions in low-density lipoprotein cholesterol (LDL-C) and major adverse cardiovascular events (MACE) has been observed in statin and ezetimibe outcomes trials down to achieved levels of 54 mg/dL. However, it is uncertain whether this relationship extends to LDL-C levels <50

mg/dL. We assessed the relationship between additional LDL-C, non-high-density lipoprotein cholesterol, and apolipoprotein B100 reductions and MACE among patients within the ODYSSEY trials that compared alirocumab with controls (placebo/ezetimibe), mainly as add-on therapy to maximally tolerated statin.
METHODS:
Data were pooled from 10 double-blind trials (6699 patient-years of follow-up). Randomization was to alirocumab 75/150 mg every 2 weeks or control for 24 to 104 weeks, added to background statin therapy in 8 trials. This analysis included 4974 patients (3182 taking alirocumab, 1174 taking placebo, 618 taking ezetimibe). In a post hoc analysis, the relationship between average on-treatment lipid levels and percent reductions in lipids from baseline were correlated with MACE (coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or unstable angina requiring hospitalization) in multivariable analyses.
RESULTS:
Overall, 33.1% of the pooled cohort achieved average LDL-C <50 mg/dL (44.7%-52.6% allocated to alirocumab, 6.5% allocated to ezetimibe, and 0% allocated to placebo). In total, 104 patients experienced MACE (median time to event, 36 weeks). For every 39 mg/dL lower achieved LDL-C, the risk of MACE appeared to be 24% lower (adjusted hazard ratio, 0.76; 95% confidence interval, 0.63-0.91; P=0.0025). Percent reductions in LDL-C from baseline were inversely correlated with MACE rates (hazard ratio, 0.71; 95% confidence interval, 0.57-0.89 per additional 50% reduction from baseline; P=0.003). Strengths of association materially similar to those described for LDL-C were observed with achieved non-high-density lipoprotein cholesterol and apolipoprotein B100 levels or percentage reductions.
CONCLUSIONS:
In a post hoc analysis from 10 ODYSSEY trials, greater percentage reductions in LDL-C and lower on-treatment LDL-C were associated with a lower incidence of MACE, including very low levels of LDL-C (<50 mg/dL). These findings require further validation in the ongoing prospective ODYSSEY OUTCOMES trial.

Appendix 3: Medline Search Strategy

Ovid MEDLINE(R) without Revisions 1996 to November week 4, 2017

1 evolocumab223
2 alirocumab.mp 272
3 PCSK9 inhibitors.mp 290
4 1 or 2 or 3
5 Stroke/ or Cardiovascular Diseases/ or Coronary Disease/ or Myocardial Infarction/ or Coronary Artery Disease/ 545407

6 4 and 5 and 7
limit 14 to (humans 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 meta analysis or practice guideline or pragmatic clinical trial or randomized controlled trial or systematic reviews) and last 3 years)30

PCSK9 Inhibitors

Goal:

- Restrict use of PCSK9 inhibitors to populations in which the drugs have demonstrated efficacy.

Length of Authorization:

- Up to 12 months

Requires PA:

- All PCSK9 inhibitors

Covered Alternatives:

- Preferred alternatives listed at www.orpdl.org/drugs/

Approval Criteria		
1. Is this a request for renewal of a previously approved prior authorization?	Yes: Go to Renewal Criteria	No: Go to #2
2. What diagnosis is being treated?	Record ICD10 code; go to #3	

Approval Criteria		
3. Does the patient have clinical atherosclerotic cardiovascular disease, defined as documented history of ≥1 of the following: • Myocardial infarction • Unstable angina • Coronary revascularization procedure (PCI or CABG) • Diagnosis of clinically significant coronary heart disease by coronary angiography, stress test using treadmill, stress echocardiography or nuclear imaging Or a coronary heart disease (CHD) risk-equivalent, defined as documented history of ≥1 of the following: • Peripheral arterial disease • Ischemic stroke of atherothrombotic origin • Chronic kidney disease (CrCl 30-60 mL/min) • Diabetes mellitus PLUS ≥2 additional risk factors: ○ Hypertension; ankle-brachial index ≤0.90; micro- or macro-albuminuria; retinopathy; or family history of early coronary heart disease?	Yes: Go to #4	No: Go to #8

Approval Criteria		
4. Has the patient taken a daily high-intensity statin (see table below) and ezetimibe 10 mg daily for at least 12 months with <50% LDL-C reduction? Prescriber to submit chart documentation of: 1) Doses and dates initiated of statin and ezetimibe; 2) Baseline LDL-C (untreated); 3) Recent LDL-C (within last 12 weeks).	Yes: Confirm documentation; go to #5 1. Statin: Dose: Date Initiated: 2. Ezetimibe 10 mg daily Date Initiated: Baseline LDL-C _____ mg/dL Date:_____ Recent LDL-C _____ mg/dL Date:_____	No: Go to #6
5. Is the patient adherent with a high-intensity statin and ezetimibe?	Yes: Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence (both lipid-lowering prescriptions refilled 5 months' supply in last 6 months)	No: Pass to RPh; deny for medical appropriateness
6. Does the patient have a history of rhabdomyolysis caused by a statin; or alternatively, a history of creatinine kinase (CK) levels >10-times upper limit of normal with muscle symptoms determined to be caused by a statin? Note: Prescriber must provide chart documentation of diagnosis or CK levels. A recent LDL-C level (within last 12 weeks) must also be submitted.	Yes: Confirm chart documentation of diagnosis or labs and approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	No: Go to #7

Approval Criteria		
7. Is there chart documentation the patient experienced persistent myalgia or myopathy on 3 separate trials (each trial ≥8 weeks' duration) of moderate- or high-intensity statin (see table below), separated by an adequate washout period of ≥2 weeks? Note: Prescriber must provide chart documentation of myalgia/myopathy from each statin trial and provide chart documentation of recent LDL-C (within last 12 weeks).	Yes: Document statin trials and approve for up to 12 months 1. Statin: Dose: Date Initiated: Date D/C: Cause of D/C: 2. Statin: Dose: Date Initiated: Date D/C: Cause of D/C: 3. Statin: Dose: Date Initiated: Date D/C: Cause of D/C Recent LDL-C _____ mg/dL Date:_____	No: Pass to RPh; deny for medical appropriateness.
~~7.~~8. Does the patient have a diagnosis of homozygous or heterozygous familial hypercholesterolemia and already takes a maximally tolerated statin and/or ezetimibe? Note: Prescriber must provide chart documentation of diagnosis and recent LDL-C (within last 12 weeks).	Yes: Document diagnosis and approve for up to 12 months Recent LDL-C _____ mg/dL Date:_____	No: Pass to RPh; deny for medical appropriateness.

Renewal Criteria		
1. What is the most recent LDL-C (within last 12 weeks)?	Recent LDL-C _____ mg/dL Date:_____ ; go to #2	
2. Is the patient adherent with PCSK9 inhibitor therapy?	Yes: Approve for up to 12 months Note: pharmacy profile may be reviewed to verify >80% adherence (PCSK9 inhibitor prescription refilled 10 months' supply in last 12 months)	No: Pass to RPh; deny for medical appropriateness

High- and Moderate-intensity Statins. Stone NJ, et al. 2013 ACC/AHA Blood Cholesterol Guideline.

High-intensity Statins (≥50% LDL-C Reduction)		**Moderate-intensity Statins** (30 to <50% LDL-C Reduction)	
Atorvastatin 40-80 mg	Rosuvastatin 20-40 mg	Atorvastatin 10-20 mg Fluvastatin 80 mg Lovastatin 40 mg	Pitavastatin 2-4 mg Pravastatin 40-80 mg Simvastatin 20-40 mg Rosuvastatin 5-10 mg

References:
1. NICE Clinical Guideline 181. Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. Available at: guidance.nice.org.uk/cg181. Accessed 18 September 2015.
2. Stone NJ, Robinson JG, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;129(25 Suppl 2):S1-45. doi: 10.1161/01.cir.0000437738.63853.7a.

P&T / DUR Review: *1/18 (MH), 11/16 (DM); 11/15 (AG)*
Implementation: *TBD; 1/1/17*

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Pharmacy Utilization Summary Report: July 2016 - June 2017

Eligibility	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Total Members (FFS & Encounter)	1,018,479	1,005,560	991,736	990,652	980,593	969,749	956,495	953,093	978,100	991,147	991,908	994,823	985,195
FFS Members	145,488	143,283	149,942	155,740	139,906	142,728	144,554	140,575	146,756	144,374	130,857	135,409	143,301
OHP Basic with Medicare	32,597	32,574	32,707	32,844	32,823	32,859	32,850	32,815	33,065	33,156	33,179	33,308	32,898
OHP Basic without Medicare	13,155	13,263	13,490	13,382	12,478	12,602	12,851	12,507	12,526	12,803	12,559	12,546	12,847
ACA	99,736	97,446	103,745	109,514	94,605	97,267	98,853	95,253	101,165	98,415	85,119	89,555	97,556
Encounter Members	872,991	862,277	841,794	834,912	840,687	827,021	811,941	812,518	831,344	846,773	861,051	859,414	841,894
OHP Basic with Medicare	40,186	40,383	40,452	40,531	40,691	40,697	40,501	40,586	40,562	40,614	40,798	40,843	40,570
OHP Basic without Medicare	69,438	68,793	67,857	67,357	67,819	67,277	67,089	67,386	67,328	67,031	67,125	66,631	67,594
ACA	763,367	753,101	733,485	727,024	732,177	719,047	704,351	704,546	723,454	739,128	753,128	751,940	733,729

Gross Cost Figures for Drugs	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	YTD Sum
Total Amount Paid (FFS & Encounter)	$65,695,875	$71,045,169	$67,932,801	$68,305,053	$68,714,085	$69,401,753	$72,775,276	$68,974,502	$76,840,335	$68,821,689	$76,396,599	$75,200,797	$850,103,935
Mental Health Carve-Out Drugs	$7,818,910	$8,456,103	$7,889,079	$7,591,298	$7,800,551	$7,807,415	$8,125,700	$7,711,923	$8,462,436	$7,738,563	$8,401,378	$8,178,437	$95,981,792
OHP Basic with Medicare	$820	$373	$753	$571	$263	$1,066	$1,485	$1,159	$3,134	$954	$912	$37	$11,527
OHP Basic without Medicare	$3,258,374	$3,506,338	$3,345,002	$3,146,213	$3,328,153	$3,324,446	$3,427,491	$3,256,589	$3,538,296	$3,171,738	$3,442,054	$3,334,810	$40,079,505
ACA	$4,499,995	$4,876,500	$4,482,950	$4,387,007	$4,407,208	$4,420,839	$4,633,994	$4,391,280	$4,841,958	$4,494,255	$4,877,395	$4,769,262	$55,082,644
FFS Physical Health Drugs	$3,245,095	$3,778,350	$3,651,811	$3,616,107	$3,468,582	$3,231,382	$3,782,091	$3,457,219	$3,740,927	$3,268,691	$3,492,633	$3,151,258	$41,884,147
OHP Basic with Medicare	$206,008	$305,966	$214,518	$277,259	$295,141	$203,069	$302,332	$289,950	$264,349	$238,202	$242,693	$229,641	$3,069,128
OHP Basic without Medicare	$942,671	$1,121,245	$1,069,465	$1,039,983	$924,524	$880,054	$1,008,992	$927,660	$1,275,721	$1,053,864	$1,121,164	$953,861	$12,319,205
ACA	$2,013,202	$2,245,632	$2,261,235	$2,192,744	$2,148,451	$2,063,764	$2,353,455	$2,131,739	$2,080,046	$1,821,219	$2,001,873	$1,810,238	$25,123,595
FFS Physician Administered Drugs	$1,587,188	$1,632,454	$1,880,000	$1,700,895	$1,704,885	$2,359,990	$2,867,822	$2,718,693	$2,566,488	$1,830,721	$2,832,333	$2,819,792	$26,501,260
OHP Basic with Medicare	$303,285	$341,720	$416,386	$334,626	$319,948	$319,411	$372,932	$362,721	$436,844	$417,814	$419,963	$331,186	$4,376,835
OHP Basic without Medicare	$233,033	$213,973	$400,978	$339,971	$232,377	$208,845	$325,771	$390,043	$391,707	$250,690	$1,244,383	$1,215,063	$5,446,835
ACA	$755,402	$816,605	$818,262	$809,276	$925,521	$1,084,152	$1,708,004	$1,304,553	$1,294,759	$753,789	$865,876	$892,456	$12,028,656
Encounter Physical Health Drugs	$43,926,133	$46,535,689	$44,738,958	$45,134,356	$46,887,911	$46,114,101	$47,276,968	$44,575,689	$50,819,111	$45,744,555	$50,113,614	$49,318,231	$561,185,315
OHP Basic with Medicare	$122,115	$144,249	$133,938	$140,880	$130,960	$116,418	$122,050	$116,407	$121,947	$114,965	$116,185	$109,262	$1,489,377
OHP Basic without Medicare	$11,813,234	$12,960,709	$12,293,476	$12,371,263	$12,811,247	$12,921,889	$13,135,377	$12,453,291	$13,691,968	$12,354,008	$13,530,417	$13,221,665	$153,558,545
ACA	$31,602,017	$32,951,237	$31,837,171	$32,182,953	$33,424,599	$32,525,509	$33,478,420	$31,415,680	$36,379,351	$32,686,958	$35,768,840	$35,309,865	$399,562,602
Encounter Physician Administered Drugs	$9,118,548	$10,642,572	$9,772,953	$10,262,398	$8,852,156	$9,888,866	$10,722,696	$10,510,978	$11,251,374	$10,239,159	$11,556,640	$11,733,079	$124,551,421
OHP Basic with Medicare	$184,152	$258,921	$200,824	$180,667	$196,461	$213,738	$234,350	$221,576	$268,497	$198,767	$254,867	$202,240	$2,615,060
OHP Basic without Medicare	$2,273,968	$2,402,546	$2,098,821	$2,344,744	$2,180,027	$2,565,423	$2,575,473	$2,313,145	$2,186,454	$2,348,429	$2,515,050	$2,305,663	$28,109,741
ACA	$6,006,716	$7,315,541	$7,111,331	$7,299,530	$6,260,861	$6,862,349	$7,719,932	$7,728,968	$8,615,892	$7,522,674	$8,519,781	$9,057,324	$90,020,900

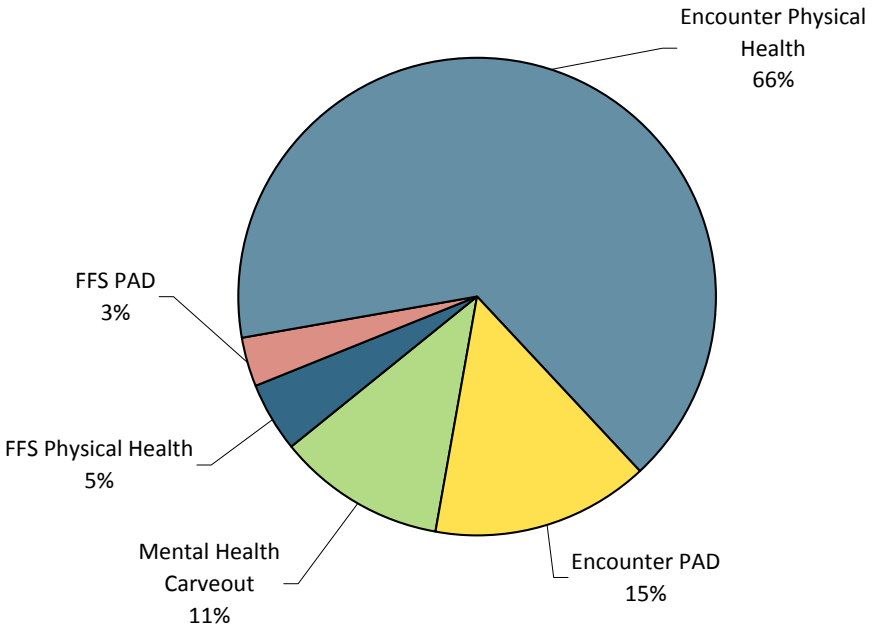
OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

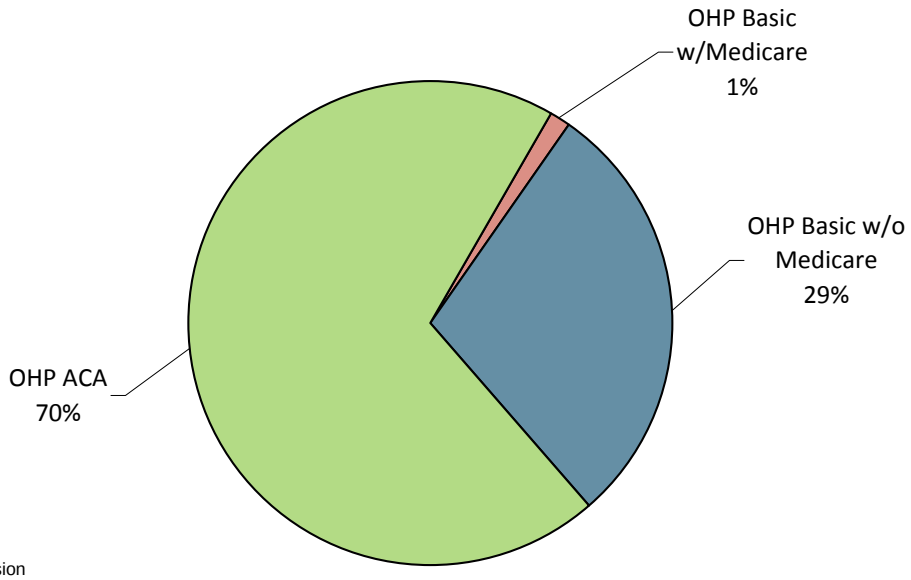
Last Updated: January 17, 2018

Drug Use Research & Management Program
DHS - Health Systems Division
500 Summer Street NE, E35, Salem, OR 97301-1079
Phone 503-947-5220 | **Fax** 503-947-1119

Pharmacy Utilization Summary Report: July 2016 - June 2017

YTD Percent Paid Amounts





OHP = Oregon Health Plan
ACA = Affordable Care Act expansion
PAD = Physician-administered drugs
Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

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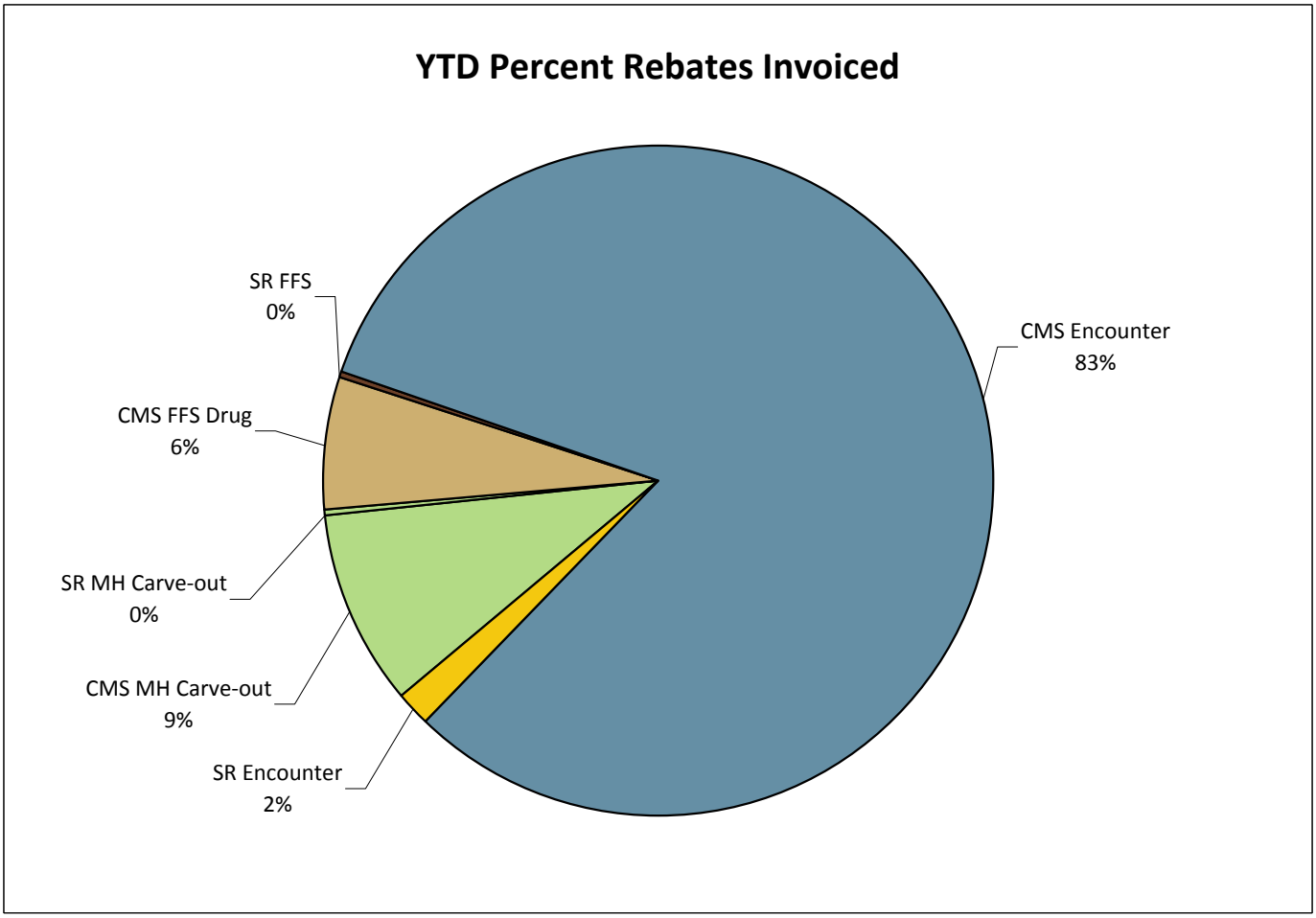
Pharmacy Utilization Summary Report: July 2016 - June 2017

Quarterly Rebates Invoiced	2016-Q3	2016-Q4	2017-Q1	2017-Q2	YTD Sum
Total Rebate Invoiced (FFS & Encounter)	$91,725,712	$100,306,583	$104,745,074	$146,298,846	$443,076,215
CMS MH Carve-out	$10,698,536	$9,516,452	$10,795,124	$10,313,237	$41,323,349
SR MH Carve-out		$512,346	$634,141	$595,005	$1,741,492
CMS FFS Drug	$5,905,328	$6,453,704	$7,981,325	$7,613,573	$27,953,930
SR FFS	$310,068	$275,999	$212,682	$219,390	$1,018,139
CMS Encounter	$73,587,961	$82,100,815	$83,010,368	$124,372,907	$363,072,051
SR Encounter	$1,223,820	$1,447,267	$2,111,433	$3,184,734	$7,967,254

Quaterly Net Drug Costs	2016-Q3	2016-Q4	2017-Q1	2017-Q2	YTD Sum
Estimated Net Drug Costs (FFS & Encounter)	$112,948,133	$106,114,309	$113,845,039	$74,120,239	$407,027,720
Mental Health Carve-Out Drugs	$13,465,556	$13,170,465	$12,870,794	$13,410,136	$52,916,951
FFS Phys Health + PAD	$9,559,503	$9,352,138	$10,939,232	$9,562,465	$39,413,338
Encounter Phys Health + PAD	$89,923,074	$83,591,705	$90,035,014	$51,147,638	$314,697,431



SR = Supplemental Rebate
CMS = Center for Medicaid Services
PAD = Physician-administered drugs
MH = Mental Health

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Pharmacy Utilization Summary Report: July 2016 - June 2017

Gross PMPM Drug Costs (Rebates not Subtracted)	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
PMPM Amount Paid (FFS & Encounter)	$64.50	$70.65	$68.50	$68.95	$70.07	$71.57	$76.09	$72.37	$78.56	$69.44	$77.02	$75.59	$71.94
Mental Health Carve-Out Drugs	$7.68	$8.41	$7.95	$7.66	$7.95	$8.05	$8.50	$8.09	$8.65	$7.81	$8.47	$8.22	$8.12
FFS Physical Health Drugs	$22.30	$26.37	$24.35	$23.22	$24.79	$22.64	$26.16	$24.59	$25.49	$22.64	$26.69	$23.27	$24.38
FFS Physician Administered Drugs	$10.91	$11.39	$12.54	$10.92	$12.19	$16.53	$19.84	$19.34	$17.49	$12.68	$21.64	$20.82	$15.52
Encounter Physical Health Drugs	$50.32	$53.97	$53.15	$54.06	$55.77	$55.76	$58.23	$54.86	$61.13	$54.02	$58.20	$57.39	$55.57
Encounter Physician Administered Drugs	$10.45	$12.34	$11.61	$12.29	$10.53	$11.96	$13.21	$12.94	$13.53	$12.09	$13.42	$13.65	$12.33

Claim Counts	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Total Claim Count (FFS & Encounter)	973,754	1,037,962	995,151	1,009,290	1,006,948	988,262	1,032,861	972,753	1,093,763	1,009,960	1,076,783	1,025,121	1,018,551
Mental Health Carve-Out Drugs	145,016	156,001	146,047	146,342	146,382	144,472	148,825	138,430	156,070	146,682	158,908	152,231	148,784
FFS Physical Health Drugs	64,257	70,184	67,875	68,302	67,922	68,116	71,963	67,820	72,265	63,828	67,192	64,091	67,818
FFS Physician Administered Drugs	15,998	16,413	16,244	16,543	16,445	17,050	24,466	21,538	21,984	16,447	16,276	15,555	17,913
Encounter Physical Health Drugs	651,865	691,801	665,255	673,768	675,626	659,452	683,779	644,385	733,387	679,109	731,636	697,051	682,260
Encounter Physician Administered Drugs	96,618	103,563	99,730	104,335	100,573	99,172	103,828	100,580	110,057	103,894	102,771	96,193	101,776

Gross Amount Paid per Claim (Rebates not Subtracted)	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Average Paid / Claim (FFS & Encounter)	$67.47	$68.45	$68.26	$67.68	$68.24	$70.23	$70.46	$70.91	$70.25	$68.14	$70.95	$73.36	$69.53
Mental Health Carve-Out Drugs	$53.92	$54.21	$54.02	$51.87	$53.29	$54.04	$54.60	$55.71	$54.22	$52.76	$52.87	$53.72	$53.77
FFS Physical Health Drugs	$50.50	$53.83	$53.80	$52.94	$51.07	$47.44	$52.56	$50.98	$51.77	$51.21	$51.98	$49.17	$51.44
FFS Physician Administered Drugs	$99.21	$99.46	$115.74	$102.82	$103.67	$138.42	$117.22	$126.23	$116.74	$111.31	$174.02	$181.28	$123.84
Encounter Physical Health Drugs	$67.39	$67.27	$67.25	$66.99	$69.40	$69.93	$69.14	$69.18	$69.29	$67.36	$68.50	$70.75	$68.54
Encounter Physician Administered Drugs	$94.38	$102.76	$97.99	$98.36	$88.02	$99.71	$103.27	$104.50	$102.23	$98.55	$112.45	$121.97	$102.02

Gross Amount Paid per Claim - Multi Source Drugs (Rebates not Subtracted)	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Multi-Source Drugs: Average Paid / Claim (FFS & Encounter)	$28.18	$27.85	$27.25	$26.84	$27.31	$27.81	$27.27	$27.24	$26.86	$26.16	$26.26	$26.57	$27.13
Mental Health Carve-Out Drugs	$37.55	$37.32	$36.54	$33.83	$33.80	$33.93	$34.24	$34.26	$33.25	$30.97	$30.21	$30.05	$33.83
FFS Physical Health Drugs	$24.27	$24.46	$23.64	$22.38	$23.23	$22.11	$23.85	$23.28	$22.65	$20.87	$21.20	$20.77	$22.73
Encounter Physical Health Drugs	$26.39	$25.96	$25.47	$25.70	$26.24	$27.00	$26.04	$26.09	$25.86	$25.57	$25.83	$26.30	$26.04

Gross Amount Paid per Claim - Single Source Drugs (Rebates not Subtracted)	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Single Source Drugs: Average Paid / Claim (FFS & Encounter)	$636.63	$630.84	$596.43	$588.51	$632.92	$634.05	$636.65	$649.24	$658.51	$655.34	$670.90	$685.66	$639.64
Mental Health Carve-Out Drugs	$728.43	$742.03	$754.62	$762.38	$781.59	$793.10	$800.67	$807.82	$808.01	$837.60	$852.43	$864.59	$794.44
FFS Physical Health Drugs	$423.92	$462.21	$451.14	$445.09	$425.89	$387.38	$421.88	$424.10	$444.00	$458.66	$468.93	$437.29	$437.54
Encounter Physical Health Drugs	$650.20	$638.95	$599.18	$590.10	$641.46	$646.22	$646.46	$659.43	$667.36	$658.64	$673.76	$692.38	$647.01

Multi-Source Drug Use Percentage	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Multi-Source Drug Use Percentage	94.1%	94.0%	93.5%	93.5%	93.7%	93.8%	93.7%	93.8%	93.9%	94.0%	94.0%	94.0%	93.8%
Mental Health Carve-Out Drugs	97.6%	97.6%	97.6%	97.5%	97.4%	97.4%	97.3%	97.2%	97.3%	97.3%	97.2%	97.2%	97.4%
FFS Physical Health Drugs	93.4%	93.3%	92.9%	92.8%	93.1%	93.1%	92.8%	93.1%	93.1%	93.1%	93.1%	93.2%	93.1%
Encounter Physical Health Drugs	93.4%	93.3%	92.7%	92.7%	93.0%	93.1%	93.1%	93.2%	93.2%	93.4%	93.4%	93.3%	93.1%

Preferred Drug Use Percentage	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Avg Monthly
Preferred Drug Use Percentage	85.98%	85.77%	85.54%	85.45%	85.15%	85.11%	86.67%	86.67%	86.64%	86.57%	86.43%	86.30%	86.0%
Mental Health Carve-Out Drugs	75.18%	75.02%	75.01%	76.23%	76.04%	76.02%	75.89%	75.79%	75.67%	75.64%	75.29%	75.09%	75.6%
FFS Physical Health Drugs	95.33%	95.37%	95.19%	95.26%	95.56%	95.45%	95.42%	95.35%	95.33%	95.17%	95.28%	95.25%	95.3%
Encounter Physical Health Drugs	87.42%	87.18%	86.87%	86.48%	86.11%	86.05%	88.09%	88.10%	88.12%	88.14%	88.01%	87.89%	87.4%

Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

Last Updated: January 17, 2018

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Top 40 Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2017

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	LATUDA	Antipsychotics, 2nd Gen	$4,804,682	14.6%	4,408	$1,090	Y
2	INVEGA SUSTENNA	Antipsychotics, Parenteral	$1,919,745	5.8%	1,051	$1,827	V
3	ABILIFY MAINTENA	Antipsychotics, Parenteral	$969,861	2.9%	544	$1,783	Y
4	REXULTI	Antipsychotics, 2nd Gen	$807,316	2.4%	798	$1,012	V
5	FLUOXETINE HCL	Antidepressants	$593,290	1.8%	30,651	$19	Y
6	PALIPERIDONE ER	Antipsychotics, 2nd Gen	$575,297	1.7%	1,510	$381	V
7	ATOMOXETINE HCL	ADHD Drugs	$572,473	1.7%	4,429	$129	Y
8	SAPHRIS	Antipsychotics, 2nd Gen	$516,262	1.6%	829	$623	Y
9	VRAYLAR	Antipsychotics, 2nd Gen	$510,286	1.5%	484	$1,054	V
10	DULOXETINE HCL	Antidepressants	$493,629	1.5%	28,158	$18	V
11	SERTRALINE HCL	Antidepressants	$462,241	1.4%	40,037	$12	Y
12	INVEGA TRINZA	Antipsychotics, Parenteral	$457,814	1.4%	85	$5,386	V
13	VENLAFAXINE HCL ER	Antidepressants	$437,538	1.3%	1,985	$220	V
14	RISPERDAL CONSTA*	Antipsychotics, Parenteral	$434,742	1.3%	501	$868	Y
15	TRAZODONE HCL	Antidepressants	$417,856	1.3%	36,872	$11	
16	BUPROPION XL	Antidepressants	$400,990	1.2%	20,216	$20	V
17	LAMOTRIGINE ER	Antiepileptics (oral & rectal)	$399,222	1.2%	1,717	$233	V
18	MAKENA*	Progestational Agents	$330,257	1.0%	138	$2,393	Y
19	VIIBRYD	Antidepressants	$318,001	1.0%	1,320	$241	V
20	ARIPIPRAZOLE	Antipsychotics, 2nd Gen	$301,425	0.9%	13,566	$22	V
21	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$276,321	0.8%	1,868	$148	
22	TRINTELLIX	Antidepressants	$276,166	0.8%	809	$341	V
23	QUETIAPINE FUMARATE ER*	Antipsychotics, 2nd Gen	$268,551	0.8%	2,845	$94	V
24	AMITRIPTYLINE HCL	Antidepressants	$268,187	0.8%	15,715	$17	Y
25	LAMOTRIGINE	Antiepileptics (oral & rectal)	$257,541	0.8%	21,424	$12	Y
26	ESCITALOPRAM OXALATE	Antidepressants	$248,100	0.8%	21,663	$11	Y
27	BUSPIRONE HCL	STC 07 - Ataractics, Tranquilizers	$244,988	0.7%	15,797	$16	
28	CITALOPRAM HBR	Antidepressants	$234,679	0.7%	24,168	$10	Y
29	ARISTADA	Antipsychotics, Parenteral	$221,329	0.7%	129	$1,716	Y
30	Unclassified Drugs Or Biolog	Physican Administered Drug	$213,573	0.6%	18	$11,865	
31	CHLORPROMAZINE HCL	Antipsychotics, 1st Gen	$203,888	0.6%	629	$324	V
32	HUMIRA PEN*	Biologics for Autoimmune Conditions	$198,353	0.6%	63	$3,148	Y
33	VENLAFAXINE HCL ER	Antidepressants	$194,216	0.6%	14,143	$14	Y
34	QUETIAPINE FUMARATE*	Antipsychotics, 2nd Gen	$186,649	0.6%	14,307	$13	Y
35	LANTUS	Diabetes, Insulins	$181,449	0.5%	541	$335	Y
36	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$167,378	0.5%	48	$3,487	Y
37	FETZIMA	Antidepressants	$163,717	0.5%	449	$365	V
38	CLOZAPINE	Antipsychotics, 2nd Gen	$160,123	0.5%	2,843	$56	Y
39	BUPROPION HCL SR	Antidepressants	$156,407	0.5%	10,560	$15	Y
40	GENVOYA	HIV	$152,409	0.5%	78	$1,954	Y
		Top 40 Aggregate:	**$19,996,950**		**337,396**	**$1,032**	
		All FFS Drugs Totals:	**$33,019,364**		**651,665**	**$445**	

*** Drug requires Prior Authorization**

Notes
- FFS Drug Gross Costs only, rebates not subtracted
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

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Top 40 Physical Health Drugs by Gross Amount Paid (FFS Only) - Fourth Quarter 2017

Rank	Drug	PDL Class	Amount Paid	% Total FFS Costs	Claim Count	Avg Paid per Claim	PDL
1	MAKENA*	Progestational Agents	$330,257	3.0%	138	$2,393	Y
2	Epoetin Alfa, 100 Units Esrd	Physican Administered Drug	$276,321	2.5%	1,868	$148	
3	Unclassified Drugs Or Biolog	Physican Administered Drug	$213,573	2.0%	18	$11,865	
4	HUMIRA PEN*	Biologics for Autoimmune Conditions	$198,353	1.8%	63	$3,148	Y
5	LANTUS	Diabetes, Insulins	$181,449	1.7%	541	$335	Y
6	ENBREL SURECLICK*	Biologics for Autoimmune Conditions	$167,378	1.5%	48	$3,487	Y
7	GENVOYA	HIV	$152,409	1.4%	78	$1,954	Y
8	METHYLPHENIDATE ER*	ADHD Drugs	$152,199	1.4%	1,111	$137	N
9	Infliximab Not Biosimil 10mg	Physican Administered Drug	$149,778	1.4%	89	$1,683	
10	ORKAMBI*	Cystic Fibrosis	$146,452	1.3%	10	$14,645	N
11	ADVATE	Antihemophilia Factors	$140,680	1.3%	10	$14,068	
12	ADVAIR DISKUS	Corticosteroids/LABA Combination, Inhaled	$129,655	1.2%	436	$297	Y
13	TRIUMEQ	HIV	$124,486	1.1%	54	$2,305	Y
14	PROAIR HFA	Beta-Agonists, Inhaled Short-Acting	$122,719	1.1%	2,038	$60	Y
15	Factor Viii Recombinant Nos	Physican Administered Drug	$115,301	1.1%	5	$23,060	
16	VENTOLIN HFA	Beta-Agonists, Inhaled Short-Acting	$105,259	1.0%	1,953	$54	Y
17	NUVARING	STC 63 - Oral Contraceptives	$96,520	0.9%	468	$206	
18	Inj Pembrolizumab	Physican Administered Drug	$94,934	0.9%	25	$3,797	
19	LANTUS SOLOSTAR*	Diabetes, Insulins	$94,640	0.9%	288	$329	Y
20	VYVANSE	ADHD Drugs	$92,650	0.9%	631	$147	Y
21	PULMOZYME	Cystic Fibrosis	$87,117	0.8%	56	$1,556	Y
22	SPIRIVA	Anticholinergics, Inhaled	$86,813	0.8%	259	$335	Y
23	Rituximab Injection	Physican Administered Drug	$86,736	0.8%	57	$1,522	
24	TRUVADA	HIV	$83,110	0.8%	70	$1,187	Y
25	NOVOLOG	Diabetes, Insulins	$82,121	0.8%	255	$322	Y
26	Factor Viii Pegylated Recomb	Physican Administered Drug	$80,367	0.7%	3	$26,789	
27	Drugs Unclassified Injection	Physican Administered Drug	$76,521	0.7%	4,258	$18	
28	SYMBICORT	Corticosteroids/LABA Combination, Inhaled	$74,987	0.7%	314	$239	Y
29	EPCLUSA*	Hepatitis C, Direct-Acting Antivirals	$74,789	0.7%	3	$24,930	Y
30	QVAR	Corticosteroids, Inhaled	$74,010	0.7%	580	$128	Y
31	ZEPATIER*	Hepatitis C, Direct-Acting Antivirals	$72,839	0.7%	4	$18,210	Y
32	Etonogestrel Implant System	Physican Administered Drug	$72,117	0.7%	112	$644	
33	NOVOLOG FLEXPEN	Diabetes, Insulins	$71,716	0.7%	174	$412	Y
34	Aflibercept Injection	Physican Administered Drug	$70,828	0.7%	131	$541	
35	FLOVENT HFA	Corticosteroids, Inhaled	$70,800	0.7%	427	$166	Y
36	ONFI*	Antiepileptics (oral & rectal)	$70,034	0.6%	137	$511	N
37	HUMALOG	Diabetes, Insulins	$69,709	0.6%	249	$280	Y
38	LEVEMIR FLEXTOUCH*	Diabetes, Insulins	$67,997	0.6%	156	$436	Y
39	Mirena, 52 Mg	Physican Administered Drug	$63,835	0.6%	115	$555	
40	Factor Ix Recombinant Nos	Physican Administered Drug	$61,929	0.6%	1	$61,929	
		Top 40 Aggregate:	**$4,583,389**		**17,233**	**$5,621**	
		All FFS Drugs Totals:	**$10,873,248**		**199,875**	**$453**	

*** Drug requires Prior Authorization**

Notes
- FFS Drug Gross Costs only, rebates not subtracted
- PDL Key: Y=Preferred, N=Non-Preferred, V=Voluntary, Blank=Non PDL Class
- Amount Paid on the Claim = 1) Ingredient Cost (lower of [AAAC/FUL/WAC) x Dispense Quantity]) + Dispensing Fee and if Billed Amount is lower use Billed Amount then, 2) – Copay – TPL amount

Last updated: January 17, 2018

ProDUR Report for October through December 2017

High Level Summary by DUR Alert

DUR Alert	Disposition	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts	% Overridden
DA (Drug/Allergy Interaction)	Set alert/Pay claim	19	7	0	12	0.01%	36.84%
DC (Drug/Inferred Disease Interaction)	Set alert/Pay claim	1,622	386	0	1,236	1.43%	23.80%
DD (Drug/Drug Interaction)	Set alert/Pay claim	156	51	0	105	0.13%	32.69%
ER (Early Refill)	Set alert/Deny claim	75,999	15,294	170	60,517	68.60%	20.12%
ID (Ingredient Duplication)	Set alert/Pay claim	22,898	6,379	15	16,488	20.63%	27.86%
LD (Low Dose)	Set alert/Pay claim	717	177	0	533	0.60%	24.69%
LR (Late Refill/Underutilization)	Set alert/Pay claim	5	4	0	1	0.00%	80.00%
MC (Drug/Disease Interaction)	Set alert/Pay claim	895	228	0	666	0.77%	25.47%
MX (Maximum Duration of Therapy)	Set alert/Pay claim	726	188	1	536	0.63%	25.90%
PG (Pregnancy/Drug Interaction)	Set alert/Deny claim	54	24	0	30	0.01%	44.44%
TD (Therapeutic Duplication)	Set alert/Pay claim	7,622	2,441	2	5,166	6.83%	32.03%
	Totals	**110,713**	**25,179**	**188**	**85,290**	**99.66%**	**22.74%**

ProDUR Report for October through December 2017

Top Drugs in Enforced DUR Alerts

DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Remeron (Mirtazapine)	1,252	218	1,034	11,101	11.3%	17.4%
ER	Hydrocodone/APAP	62	19	43	4,233	1.5%	30.6%
ER	Oxycodone	98	35	63	2,402	4.1%	35.7%
ER	Oxycodone/APAP	16	4	12	1,280	1.3%	25.0%
ER	Tramadol	24	5	19	1,106	2.2%	20.8%
ER	Buspirone (Buspar)	2,179	346	1,832	21,668	10.1%	15.9%
ER	Lorazepam	705	165	540	16,119	4.4%	23.4%
ER	Alprazolam	506	103	403	11,661	4.3%	20.4%
ER	Diazepam	284	64	220	6,599	4.3%	22.5%
ER	Lamictal (Lamotrigine)	3,987	851	3,136	33,824	11.8%	21.3%
ER	Abilify (Aripiprazole)	2,096	397	1,698	20,574	10.2%	18.9%
ER	Seroquel (Quetiapine)	2,459	585	1,869	25,162	9.8%	23.8%
ER	Risperdal (Risperidone)	1,120	307	813	13,559	8.3%	27.4%
ER	Wellbutrin (Bupropion)	4,368	784	3,584	46,308	9.4%	17.9%
ER	Zoloft (Sertraline)	5,279	990	4,289	53,633	9.8%	18.8%
ER	Prozac (Fluoxetine)	3,788	621	3,167	41,570	9.1%	16.4%
ER	Celexa (Citalopram)	2,656	426	2,230	31,827	8.3%	16.0%

ProDUR Report for October through December 2017

Top Drugs in Early Refill

DUR Alert	Drug Name	# Overrides	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-14 LTC Leave of Absence
ER	Remeron (Mirtazapine)	218	13	11	33	0	161	0
ER	Hydrocodone/APAP	19	0	0	8	0	11	0
ER	Oxycodone	35	0	1	14	0	20	0
ER	Oxycodone/APAP	4	0	0	3	0	1	0
ER	Tramadol	5	0	0	0	0	5	0
ER	Buspirone (Buspar)	346	11	15	82	0	238	0
ER	Lorazepam	165	5	4	37	1	118	0
ER	Alprazolam	103	5	5	17	0	76	0
ER	Diazepam	64	0	4	15	0	45	0
ER	Lamictal (Lamotrigine)	851	31	37	196	0	587	0
ER	Abilify (Aripiprazole)	397	20	26	83	0	268	0
ER	Seroquel (Quetiapine)	585	14	25	144	0	402	0
ER	Risperdal (Risperidone)	307	2	8	51	0	246	0
ER	Wellbutrin (Bupropion)	784	58	52	93	1	580	0
ER	Zoloft (Sertraline)	990	35	39	313	2	601	0
ER	Prozac (Fluoxetine)	621	32	28	153	2	406	0
ER	Celexa (Citalopram)	426	27	25	77	2	295	0
	Totals =	**5,920**	**253**	**280**	**1,319**	**8**	**4,060**	**0**

ProDUR Report for October through December 2017 (Approx. 1,015,995 Enrolled Recipients)

DUR Alert	Drug Name	# Alerts	# Overrides	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lorazepam	705	165	16,119	4.4%	23.4%
ER	Alprazolam	506	103	11,661	4.3%	20.4%
ER	Diazepam	284	64	6,599	4.3%	22.5%
	4Q2017 Total =	**1,495**	**332**	**34,379**		

ProDUR Report for October through December 2015 (Approx. 1,074,781 Enrolled Recipients)

DUR Alert	Drug Name	# Alerts	# Overrides	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden
ER	Lorazepam	1,731	390	27,267	6.3%	22.5%
ER	Alprazolam	1,247	219	20,641	6.0%	17.6%
ER	Diazepam	685	152	11,988	5.7%	22.19%
	4Q2015 Total =	**3,663**	**761**	**59,896**		

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

Retro-DUR Intervention History by Quarter FFY 2016 - 2017

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Cost Savings	Dose Optimization	Total Claims Identified	50	131	121	86
		Total Faxes Successfully Sent	37	31	23	22
		Prescriptions Changed to Recommended Dose Within 3 Months of Fax Sent	14	14	8	5
		Prescriptions Changed to Alternative Dose Within 3 Months of Fax Sent	6	4	3	2
		Prescriptions Unchanged after 3 Months of Fax Sent	16	11	12	
		Safety Monitoring Profiles Identified	1	2		4
		Cumulative Pharmacy Payment Reduction (12 months) Associated with Faxes Sent	$86,626	$55,262	$7,207	$2,006

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Retro-DUR Intervention History by Quarter FFY 2016 - 2017

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Pediatric Psychotropics	ADHD New Start with Follow Up In First 30 Days	Members Identified	21			
		Profiles Sent	5			
		Responses Received	0			
		Response Rate	0%			
		Information Useful or Will Change Practice	0			
		Patient Not With Office	0			
		Already Scheduled	0			
		Will Not Schedule	0			
		Requested No Future Notifications	0			
	Antipsychotic Metabolic Monitoring	Members Identified	658			
		Profiles Sent	649			
		Members With Response	18			
		Response Rate	3%			
		Newly Scheduled	12			
		Provider Contacted	247			
		Provider Responses	11			
		Provider Agreed with Recommendation	5			
		Patient Not With Office	5			

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Retro-DUR Intervention History by Quarter FFY 2016 - 2017

Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Profile Review	Children under age 12 antipsychotic	RetroDUR_Profiles Reviewed	90	91	92	46
		Estimated Savings				
	Children under age 18 on 3 or more psychotropics	RetroDUR_Profiles Reviewed	8	18	19	8
		Estimated Savings				
	Children under age 18 on any psychotropic	RetroDUR_Profiles Reviewed	92	97	119	47
		Estimated Savings				
	Children under age 6 on any psychotropic	RetroDUR_Profiles Reviewed	14	14	17	13
		Estimated Savings				
	Dose Consolidation Safety Monitoring	RetroDUR_Profiles Reviewed		3	2	1
		Estimated Savings				
	Lock-In	RetroDUR_Profiles Reviewed	51	26	20	10
		RetroDUR_Letters Sent To Providers	3	2	1	
		Provider Responses	0	0	0	
		Provider Agreed / Found Info Useful	0	0	0	
		Locked In	13	2	1	0
		Estimated Savings	$3,446	$512	$153	
	Polypharmacy	RetroDUR_Profiles Reviewed		48	41	12
		RetroDUR_Letters Sent To Providers		1		2
		Provider Responses		0		0
		Provider Agreed / Found Info Useful		0		0
		Estimated Savings				

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Program	Initiative	Metric	Quarter 1 Oct - Dec	Quarter 2 Jan - Mar	Quarter 3 Apr - Jun	Quarter 4 Jul - Sep
Safety Net	ICS/LABA	Disqualified	1	5	21	27
		Disqualified - No Provider Info	1			
		Disqualified - Erroneous denial		5	21	27
		Faxes Sent	5	4	6	2
		Fax Sent - Combination Inhaler	1	3	2	
		Fax Sent - SABA	1		2	
		Fax Sent - Controller	2	1	2	
		No Subsequent Pulmonary Claims	1			2