Oregon State University
College of Pharmacy

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

Oregon Health Authority

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, May 30, 2013 1:00-5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING AGENDA

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to coverage, PDL composition, or 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.

I. CALL TO ORDER
- a. Roll Call & Introductions — B. Origer (Chair)
- b. Conflict of Interest Declaration — R. Citron (OSU)
- c. Approval of Agenda and Minutes — B. Origer (Chair)
- d. Department Update — T. Douglass (DMAP)

II. DUR ACTIVITIES
- a. HCMB Process Discussion — R. Citron (OSU)
  1. Draft Procedure and Timeline
  2. Public Comment
- b. ProDUR Report — R. Holsapple (HP)
- c. RetroDUR Report — T. Williams (OSU)
- d. Quarterly Utilization Reports — R. Citron (OSU)
- e. Oregon State Drug Reviews — K. Sentena (OSU)
  1. *Management of Gout in the Presence of Chronic Kidney Disease*
- f. FDB Drug File Updates* — T. Williams (OSU)
  1. List of Drugs
  2. Public Comment
  3. Discussion of Clinical recommendations to OHA

III. NEW BUSINESS
- a. Makena® (17 alpha-hydroxyprogesterone caproate)* — B. Fouts (OSU)
  1. Drug Use Evaluation
  2. Public Comment
  3. Discussion of Clinical recommendations to OHA
- b. Fycompa® (perampanel)* — B. Liang (OSU)
  1. New Drug Evaluation
  2. Public Comment
  3. Discussion of Clinical recommendations to OHA
- c. Aubagio® (teriflunomide)* — S. Argyres (OSU)
  1. Drug Use Evaluation
  2. Public Comment
  3. Discussion of clinical recommendations to OHA

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

d. Acthar Gel® (repository corticotropin injection)* — M. Herink (OSU)
   1. New Drug Evaluation
   2. Public Comment
   3. Discussion of Clinical recommendations to OHA
e. CF Vitamin Abbreviated Class Review* — M. Herink (OSU)
   1. Class Review
   2. Public Comment
   3. Discussion of clinical recommendations to OHA
e. Juxtapid® (lomitapide)* — M. Herink (OSU)
   1. New Drug Evaluation
   2. Public Comment
   3. Discussion of Clinical recommendations to OHA
f. Kynamro® (mipomersen)* — M. Herink (OSU)
   1. Drug Use Evaluation
   2. Public Comment
   3. Discussion of clinical recommendations to OHA
g. Drug Class Scans* — M. Herink (OSU)
   1. Cough and Cold Products
   2. Topical Antibiotics
   3. Oral Immunosuppresants
   4. Public Comment
   5. Discussion of clinical recommendations to OHA

IV. EXECUTIVE SESSION

V. RECONVENE for PUBLIC RECOMMENDATIONS

VI. ADJOURN

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Oregon Health Authority

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, March 28, 2013 1:00-5:00 PM
Clackamas Community Training Center
29353 SW Town Center Loop East
Wilsonville, OR 97070

MEETING MINUTES

NOTE: Any agenda items discussed by the DUR/P&T Committee may result in changes to coverage, PDL composition, or 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.

Members Present: Cathy Zehrung, RPh; David Pass, MD; Phillip Levine, PhD; Stacy Ramirez, PharmD; William Origer, MD
Members Present by Phone: Joshua Bishop, PharmD; Tracy Klein, FNP; William Nunley, MD
Staff Present: Kathy Ketchum, RPh, MPA:HA; Megan Herink PharmD, BCPS; Richard Holsapple, RPh; Roger Citron, RPh; Ted Williams, PharmD; Trevor Douglass, DC, MPH; Valerie Smith
Staff Present by Phone: Kathy Sentena, PharmD
Audience: Jenny Blackham (Lilly); Diana Dills; Carol Choutka (Natl. MS Society); Jason Parks (ACSCAN); Bruce Dudley; Don Stetcher (Novartis); Mike Whitenak (lilly); Debbie McCalez; Kristina Harmach (BMS); Danielle Sobel (OMA); Barry Benson (Merck); Jim Gardner (PhRMA); Tzeli Triantafillon (VIIV); Jacob Owings (OSU COP); Bob Snediker (J&J); Tim Peterson (OSU COP); Brendon Blustein (OSU COP); Sheila Albeke (OSU COP); Lorren Sandt (Caring Ambassadors); Bill Struyk (J&J); Kim Lanbmeier (Otsuka); Lori Howarth; Deborah Crawford; Trish McDaid O'Neil; Dana Garet; Nancy Jodoin (Otsuka); Annie Ogostalick (Abbvie); Steve Hall; Bob Gustafson (Lundbeck); Bruice Smith (GSK); Paul Barham (NovoNordisk); Bruce Howard (Acorda); Shane Hall (Purdue); Michael Estos (Pfizer); Art Saig (Pfizer); Darren Coffman (HERC); Steve Isaki (Sunovion); John Goddard; Scott Goldfarb; Madalo Malin; Kathy Kirk (OPMC); Caryn McKesin (Western Oregon Advanced Health); Cat Linvingston (HERC)

I. CALL TO ORDER
a. The meeting was called to order at approximately 1pm.
b. Mr. Citron reported there are no new conflicts of interest to declare.
c. The January 31, 3012 meeting minutes were reviewed.

ACTION: Approved as is.

II. DUR ACTIVITIES
a. Mr. Holsapple presented the ProDUR Report.

ACTION: The Committee recommended discontinuing to allow CC-7 "Medically Appropriate" as an override code for early refills.
b. Dr. Williams presented the RetroDUR Report.
c. Mr. Citron presented the Quarterly Utilization Reports.

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

d. Dr. Sentena presented the Oregon State Drug Review *The Future of Newer Obesity Medication.*

III. HERC COVERAGE GUIDANCE

Cat Livingston and Darren Coffman presented HERC coverage guidance on High Cost Marginal Benefit. Public comment was presented by: BJ Cavnor with NW Patient Education Network (written comment); Carol Choutka with the National MS Society; Deborah Crawford with Accorda Therapeutics; Jason Parks with the American Cancer Society; Jim Gardner with Gardner & Gardner Law Firm on behalf of PhRMA (written); and Lorren Sandt with Caring Ambassadors Foundation (written).

ACTION: The Committee recommended forming a Sub-Committee that will review High Cost Marginal Benefit drugs and report back the P&T Committee.

IV. NEW BUSINESS

a. Dr. Williams presented a drug use evaluation on tapentadol recommending it be added to the High Dose Opioid PA Criteria, apply quantity limits consistent with PA Criteria, package insert and table optimization, and not grandfather patients currently receiving tapentadol.

***ACTION:** All in favor.

b. Ms. Ketchum presented a drug use evaluation on Colony Stimulating Factor Use in Patients with Heaptitis C recommending no further action is needed.

***ACTION:** All in favor.

c. Ms. Ketchum presented a drug use evaluation on Intramuscular Antipsychotics recommending OHA continues to allow billing of IM antipsychotics via drug claims, ensure professional claims and drug claims are reimbursed at the same but lowest rate, and consider engaging pharmacists via RetroDUR to evaluate patients for conversion to oral antipsychotics.

***ACTION:** All in favor.

d. Dr. Sentena presented a new drug evaluation on apixaban within the Anticoagulant Abbreviated drug class recommending making apixaban, rivaroxaban and dabigatran non-preferred with PA criteria to ensure appropriate use. Diana Dill with Pfizer presented public comment on apixaban. Steve Hall with Behringer Ingelheim presented public comment on dabigitran. Bob Sneticker with J&J/Janssen presented public comment on Xarelto.

***ACTION:** After Executive Session, all in favor.

e. Dr. Herink presented a new drug evaluation on tofacitinib within the Targeted Immune Modulators drug class recommending no changes be made to previous status of TIMS on the current PDL, but evaluate costs in Executive Session, Update the PA criteria to include the new indication of ulcerative colitis for adalimumab, reserve use of tofacitinib for patients who have tried another standard-of-care medications, and include tofacitinib in current TIMS PA criteria and evaluate comparative costs in Executive Session. Arti Baig with Pfizer presented public comment on tilfacitinib.

***ACTION:** After Executive Session, all in favor.

f. Dr. Herink presented a new drug evaluation on linaclotide recommending using the Exclude List PA criteria for linaclotide since IBS and constipation are below the OHP line of covered diagnoses. No PDL changes needed.

***ACTION:** After Executive Session, all in favor.

g. Dr. Herink presented drug class scans recommending:

1. Topical Analgesics - no further research or review.

***ACTION:** After Executive Session, all in favor.

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2. Topical Steroids – no further research or review and make desonide cream and ointment and alclometasone cream non-preferred, grandfathering current patients using these medications.

***ACTION:** After Executive Session, all in favor.

3. Antifungals - no further research or review and code Oravig® as non-preferred since it is not rebatable.

***ACTION:** After Executive Session, all in favor.

4. Topical Antifungals - no further research or review.

***ACTION:** After Executive Session, all in favor.

V. The meeting was adjourned at approximately 4:30pm.

DRAFT

**Agenda items will be discussed by Committee members for the purpose of making recommendations to the Oregon Health Plan for adoption into Oregon Administrative Rules 410-121-0030 & 410-121-0040 as required by 414.325(9)*

Oregon Health Authority

OREGON HEALTH AUTHORITY
DRUG USE REVIEW/PHARMACY AND THERAPEUTICS COMMITTEE (P&T)

Therapies with High Cost and Marginal Benefit (HCMB) Policy

GOAL:
To collaborate with and assist the Health Evidence Review Committee (HERC) to evaluate available evidence with a transparent process to encourage safe and financially sustainable policies that maximize access to high value medications for patients served by the Oregon Health Plan (OHP).

PROCEDURES:

1. The P&T thoroughly evaluates drugs for evidence for clinical effectiveness and safety as defined by the P&T Operating Procedures for PDL decision-making.
    a. The reviews are made in public with opportunity and consideration of public comment and input.

2. After the clinical review, cost is considered in executive session. After the executive session, recommendations are made with a public vote.

3. The P&T may direct the HCMB to review drugs that exhibit one or more of the following:
    a. Marginal or clinically unimportant benefit, or
    b. Very high cost in which the cost does not justify the benefit, or
    c. Significantly greater cost compared to alternate therapies when both have similar efficacy

4. The HCMB will meet separate from the P&T for a detailed assessment of the cost benefit relationship of the referred drug and bring conclusions back to the P&T.

5. HCMB recommendations include either of the following:
    a. Add drug to the HCMB Table XX located at www._____ to be prioritized on the line that corresponds with the condition being treated listed in OHP ANCILLARY GUIDELINE XXX, THERAPIES WITH MARGINAL BENEFIT OR HIGH COST.
    b. Drug does not meet HCMB criteria. Continue with previous P&T recommendations.

6. The P&T makes final HCMB recommendations in a public vote.

7. The HCMB Table XX is updated biannually (April 1st and October 1st) to coincide with the OHP prioritized list updates.

SUBCOMMITTEE:

1. The HCMB shall meet as directed by the P&T.

2. Members of the subcommittee shall be appointed by the P&T and will include the following:
    a. One P&T member who will serve as chair.
    b. One HERC member
    c. One standing member who is a clinician with expertise in medical evidence evaluation.
    d. One ad-hoc physician member with a specialty relating to the referred drug.
    e. Additional members, not to exceed five in total, as the P&T deems necessary at time of referral.

3. HCMB members shall adhere to P&T conflict of interest policies.

4. The HCMB will follow P&T process for meeting notification and document posting.
    a. All meetings will be held in compliance with Oregon Public Meetings Law.
    b. All official actions will be taken by a public vote.
    c. Written testimony and public testimony will be allowed and provided.
    d. Final documents will be posted 30 days prior to the meeting.

5. The HCMB will review any information they consider creditable, evidence-based and relevant to:
    a. Determine whether the referred drug is of "marginal benefit" or "clinically unimportant benefit" and may consider therapies in addition to drug therapies.
    b. Determine if the referred drug's cost does not justify the benefit and may consider costs and therapies in addition to drug costs.
    c. Determine if the drug is significantly greater cost relative to available alternative therapies of similar benefit.

6. The HCMB will recommend P&T add the referred drug to the HCMB Table XX if it meets one criteria in #5.

ProDUR Report for March 2013- April 2013

High Level Summary by DUR Alert

DUR Alert	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
ER (Early Refill)	35,315	6,869	58	28,381	67.00%
PG (Pregnancy/Drug Interaction)	1,804	1,195	4	604	3.40%
ID (Ingredient Duplication)	8,530	2,437	5	6,068	16.15%
TD (Therapeutic Duplication)	3,748	1,281	3	2,458	7.10%

ProDUR Report for March 2013- April 2013								
Top Drugs in Early Refill- Requirement of Clarification Code began 1/13/2013								
DUR Alert	Drug Name	# Alerts	# Overrides	# Cancellations & Non-Response	# Claims Screened	% Alerts/Total Claims	% Alerts Overridden	[redacted]
ER	[redacted]	491	83	408	3,737	13.1%	16.9%	
		497	97	400	3,535	14.1%	19.5%	15.5%
		254	62	192	4,625	5.5%	24.4%	
		210	33	177	3,951	5.3%	15.7%	[redacted]
		164	72	91	2,128	7.7%	43.9%	
		122	50	72	1,811	6.7%	41.0%	[redacted]
		1,286	224	1,062	17,284	7.4%	17.4%	
		1,018	243	775	12,973	7.8%	23.9%	[redacted]
		980	162	816	11,977	8.2%	16.5%	
		806	150	656	9,637	8.4%	18.6%	12.6%
		551	87	464	7,709	7.1%	15.8%	
		476	78	398	5,968	8.0%	16.4%	3.8%
		589	93	496	5,497	10.7%	15.8%	
		459	80	379	4,800	9.6%	17.4%	10.4%
		1,401	283	1,117	11,856	11.8%	20.2%	
		1,388	287	1,101	10,887	12.7%	20.7%	2.4%
		845	181	663	7,308	11.6%	21.4%	
		828	203	624	6,692	12.4%	24.5%	14.5%
		264	47	217	2,859	9.2%	17.8%	
		156	44	112	1,666	9.4%	28.2%	[redacted]
		289	81	208	1,989	14.5%	28.0%	
		218	65	153	1,626	13.4%	29.8%	6.4%
		1,117	216	901	9,558	11.7%	19.3%	
		1,122	215	906	8,256	13.6%	19.2%	[redacted]
		1,463	306	1,156	10,759	13.6%	20.9%	
		1,412	303	1,107	9,280	15.2%	21.5%	2.6%
		1,261	227	1,033	9,872	12.8%	18.0%	
		1,241	283	958	8,997	13.8%	22.8%	26.7%
		748	150	598	5,774	13.0%	20.1%	
		675	170	505	5,252	12.9%	25.2%	25.6%
		361	70	289	2,925	12.3%	19.4%	
		342	66	276	2,628	13.0%	19.3%	[redacted]
		254	50	203	4,608	5.5%	19.7%	
		237	38	199	3,457	6.9%	16.0%	[redacted]
		513	113	400	4,145	12.4%	22.0%	
		484	95	389	3,663	13.2%	19.6%	[redacted]
		1,305	182	1,123	13,938	9.4%	13.9%	
		1,317	164	1,153	12,654	10.4%	12.5%	[redacted]
		326	78	248	3,543	9.2%	23.9%	
		273	49	224	3,068	8.9%	17.9%	[redacted]
		1,904	317	1,587	17,581	10.8%	16.6%	
		1,768	302	1,466	15,853	11.2%	17.1%	2.6%
		1,581	224	1,356	15,870	10.0%	14.2%	
		1,399	192	1,206	14,486	9.7%	13.7%	[redacted]

	[redacted]	1,524	228	1,296	15,542	9.8%	15.0%	
		1,408	203	1,205	13,739	10.2%	14.4%	[redacted]
		716	116	600	7,080	10.1%	16.2%	
		698	98	600	6,854	10.2%	14.0%	[redacted]
		536	80	456	5,735	9.3%	14.9%	
		452	47	405	5,181	8.7%	10.4%	[redacted]
		2,269	338	1,931	19,378	11.7%	14.9%	
		2,102	329	1,772	17,714	11.9%	15.7%	5.1%
		1,212	139	1,073	11,404	10.6%	11.5%	
		1,075	135	940	10,058	10.7%	12.6%	9.5%
		742	103	639	7,984	9.3%	13.9%	
		623	91	532	7,288	8.5%	14.6%	5.2%
		1,052	143	909	9,894	10.6%	13.6%	
		866	123	743	8,801	9.8%	14.2%	4.5%
		398	50	348	4,075	9.8%	12.6%	
		357	45	312	3,652	9.8%	12.6%	0.3%

ProDUR Report for March 2013- April 2013

Top Drugs in Early Refill- Requirement of Clarification Code began 1/13/2013

DUR Alert	Drug Name	CC-3 Vacation Supply	CC-4 Lost Rx	CC-5 Therapy Change	CC-6 Starter Dose	CC-7 Medically Necessary	CC-13 Emergency	CC-14 LTC Leave of Absence	CC-Other
ER	Remeron (Mirtazapine)-March/April	2	11	20	1	38	0	1	1
	Hydrocodone Bit/APAP-March/April	1	1	17	0	5	0	0	1
	Oxycodone HCl-March/April	2	1	14	1	16	0	0	2
	Lorazepam-March/April	12	7	98	2	75	0	0	2
	Alprazolam-March/April	6	11	54	0	38	0	0	0
	Diazepam-March/April	2	8	20	2	34	0	0	1
	Buspar (Buspirone)-March/April	4	7	28	3	16	0	0	0
	Lamictal (Lamotrigine)-March/April	8	17	120	2	64	0	1	2
	Depakote (Divalproex Sodium)-March/April	0	6	56	1	86	0	1	4
	Clonazepam-March/April	3	1	13	0	17	0	0	2
	Gabapentin-March/April	1	3	29	1	13	0	0	0
	Abilify (Aripiprazole)-March/April	7	12	65	8	85	0	0	1
	Seroquel (Quetiapine)-March/April	6	12	81	2	106	0	1	4
	Risperdal (Risperidone)-March/April	4	8	86	5	121	0	0	1
	Zyprexa (Olanzapine)-March/April	3	12	45	3	54	0	0	0
	Geodon (Ziprasidone)-March/April	0	5	21	0	21	0	0	0
	Albuterol-March/April	1	2	13	1	15	0	0	0
	Lithium Carbonate-March/April	3	1	20	0	32	0	0	0
	Wellbutrin (Bupropion)-March/April	5	13	48	0	51	0	0	4
	Prilosec (Omeprazole)-March/April	0	2	12	0	21	0	1	2
	Zoloft (Sertraline)-March/April	6	12	127	4	96	0	1	1
	Celexa (Citalopram)-March/April	8	11	57	4	74	0	0	1
	Prozac (Fluoxetine)-March/April	9	19	87	2	47	0	0	3
	Lexapro (Escitaloprim)-March/April	6	5	30	2	31	0	0	0
	Paxil (Paroxetine)-March/April	3	6	15	0	16	0	0	0
	Trazodone-March/April	11	15	127	10	120	0	0	2
	Cymbalta (Duloxetine)-March/April	6	9	31	2	51	0	0	1
	Effexor (Venlafaxine)-March/April	6	5	24	0	34	0	0	1
	Amitriptyline-March/April	2	6	54	2	41	0	0	1
	Straterra (Atomoxetine)-March/April	0	2	10	0	15	0	0	0
	TOTALS	**127**	**230**	**1422**	**58**	**1433**	**0**	**6**	**37**

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College of Pharmacy

Retro-DUR Intervention History by Quarter - FFY 2012-2013

Letters Sent

	Profile Review-Based Lettering	Polypharmacy	Duplicate PPIs	Duplicate Statins	Change Form Follow-Up (mult. str.)	Lock-In	Psychotropics in Children	Prescription Change Form Request	Antidepressants	Atypical antipsychotics
Quarter 1 Oct-Dec										
Unique Patients	0	0	0	0	0	0	33	92	92	26
Unique Patients Sent Interventions	0	0	0	0	0	0	0	92	92	26
% Sent	-	-	-	-	-	-	0%	100%	100%	100%
Quarter 2 Jan-Mar										
Unique Patients	0	0	0	0	0	255	0	26	26	5
Unique Patients Sent Interventions	0	0	0	0	0	0	0	26	26	5
% Sent	-	-	-	-	-	0%	-	100%	100%	100%
Quarter 3 Apr-Jun										
Unique Patients	0	0	0	0	0	138	0	0	0	0
Unique Patients Sent Interventions	0	0	0	0	0	0	0	0	0	0
% Sent	-	-	-	-	-	0%	-	-	-	-
Quarter 4 Jul-Sep										
Unique Patients	1	0	0	0	0	41	0	0	0	0
Unique Patients Sent Interventions	0	0	0	0	0	0	0	0	0	0
% Sent	0%	-	-	-	-	0%	-	-	-	-
Year to date summary										
Unique Patients	1	0	0	0	0	434	33	118	118	31
Unique Patients Sent Interventions	0	0	0	0	0	0	0	118	118	31
% Sent	0%	-	-	-	-	0%	0%	100%	100%	100%
ROI per intervention	$51	NA	NA	NA	NA	NA	NA	$49	$220	
Estimated program savings	$0	NA	NA	NA	NA	NA	NA	$5,782	$6,820	

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Retro-DUR Intervention History by Quarter - FFY 2012-2013 Le

	Criteria-based lettering	High Dose Methadone
Quarter 1 Oct-Dec		
All Patients on Drug of Interest		234
Patients Hitting Criteria in Qtr		30
Patients Hitting Criteria / 100 Users		13
Unique Patients		11
Unique Patients Sent Interventions		5
% Sent		45%
Quarter 2 Jan-Mar		
All Patients on Drug of Interest		93
Patients Hitting Criteria in Qtr		16
Patients Hitting Criteria / 100 Users		17
Unique Patients		0
Unique Patients Sent Interventions		0
% Sent		-
Quarter 3 Apr-Jun		
All Patients on Drug of Interest		0
Patients Hitting Criteria in Qtr		0
Patients Hitting Criteria / 100 Users		-
Unique Patients		0
Unique Patients Sent Interventions		0
% Sent		-
Quarter 4 Jul-Sep	**scontinued**	
All Patients on Drug of Interest		0
Patients Hitting Criteria in Qtr		0
Patients Hitting Criteria / 100 Users		-
Unique Patients		0
Unique Patients Sent Interventions		0
% Sent		-
Year to date summary		
Unique Patients		11
Unique Patients Sent Interventions		5
% Sent		45%
ROI per intervention		NA
Estimated program savings		NA

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Retro-DUR Intervention History by Quarter - FFY 2012-2013

Responses Received

	Profile Review-Based Lettering	Polypharmacy	Duplicate PPIs	Duplicate Statins	Change Form Follow-Up (mult. str.)	Lock-In	Psychotropics in Children	**Criteria-based lettering**	LABA Monotherapy	High Dose Methadone
Quarter 1 Oct-Dec										
Unique Prescribers Sent Interventions	0	0	0	0	0	0		0	7	
Responses Received	0	0	0	0	0	0		0	1	
Response Rate	-	-	-	-	-	-		-	20%	
% Agree with message	-	-	-	-	-	-		-	-	
% Consider in future prescribing	-	-	-	-	-	-		-	-	
Quarter 2 Jan-Mar										
Unique Prescribers Sent Interventions	0	0	0	0	0	0		0	0	
Responses Received	0	0	0	0	0	0		0	0	
Response Rate	-	-	-	-	-	-		-	-	
% Agree with message	-	-	-	-	-	-		-	-	
% Consider in future prescribing	-	-	-	-	-	-		-	-	
Quarter 3 Apr-Jun										
Unique Prescribers Sent Interventions	0	0	0	0	0	0		0	0	
Responses Received	0	0	0	0	0	0		0	0	
Response Rate	-	-	-	-	-	-		-	-	
% Agree with message	-	-	-	-	-	-		-	-	
% Consider in future prescribing	-	-	-	-	-	-		-	-	
Quarter 4 Jul-Sep										
Unique Prescribers Sent Interventions	0	0	0	0	0	0		0	0	
Responses Received	0	0	0	0	0	0		0	0	
Response Rate	-	-	-	-	-	-		-	-	
% Agree with message	-	-	-	-	-	-		-	-	
% Consider in future prescribing	-	-	-	-	-	-		-	-	
Year to date summary										
Unique Prescribers Sent Interventions	0	0	0	0	0	0		0	7	
Responses Received	0	0	0	0	0	0		0	1	
Response Rate	-	-	-	-	-	-		-	20%	
% Agree with message	-	-	-	-	-	-		-	-	
% Consider in future prescribing	-	-	-	-	-	-		-	-	

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Oregon State University
College of Pharmacy

OHP FFS Average Cost PMPM Top 40 Drugs (brand name) - First Quarter 2013

previous year quarter is comparator (red = top 75th percentile of growth; yellow = top 50th percentile of growth)

			Cost PMPM			Rx Dispensed PMPM (x100)			Cost/Claim		
Rank	Class Number	Brand Name	2013	2012	%	2013	2012	%	2013	2012	%
1	7	ABILIFY	$3.83	$3.60	6.3%	0.52	0.56	-7.7%	$737	$640	15.1%
2	11	CYMBALTA	$1.83	$1.58	15.5%	0.70	0.71	-2.0%	$262	$222	17.9%
3	71	REMODULIN	$1.42	$1.37	3.3%	0.01	0.01	-17.5%	$27,520	$21,951	25.4%
4	10	METHYLPHENIDATE ER	$1.34	$1.41	-4.9%	0.77	0.84	-8.4%	$174	$167	3.8%
5	33	SYNAGIS	$1.06	$1.85	-42.6%	0.05	0.08	-40.1%	$2,214	$2,314	-4.3%
6	15	PROAIR HFA	$0.76	$0.70	8.0%	1.33	1.30	2.0%	$57	$54	5.9%
7	7	SEROQUEL XR	$0.70	$0.63	9.7%	0.13	0.15	-12.1%	$532	$426	24.8%
8	42	HUMIRA	$0.66	$0.60	10.9%	0.03	0.03	-1.1%	$2,247	$2,004	12.1%
9	58	LANTUS	$0.62	$0.62	0.0%	0.29	0.30	-4.8%	$215	$204	5.1%
10	42	ENBREL	$0.57	$0.39	46.2%	0.03	0.02	33.5%	$2,015	$1,839	9.6%
11	11	INTUNIV	$0.56	$0.40	40.4%	0.25	0.21	18.5%	$219.48	$185.21	18.5%
12	11	STRATTERA	$0.55	$0.61	-10.0%	0.23	0.27	-15.4%	$235.91	$221.67	6.4%
13	33	TRUVADA	$0.53	$0.83	-36.3%	0.05	0.08	-38.8%	$1,110.75	$1,066.76	4.1%
14	51	FLOVENT HFA	$0.51	$0.46	10.4%	0.29	0.29	-1.6%	$174.25	$155.31	12.2%
15	15	ADVAIR DISKUS	$0.50	$0.46	7.6%	0.18	0.18	-3.0%	$279	$252	11.1%
16	99	PULMOZYME	$0.49	$0.49	-0.2%	0.02	0.02	0.5%	$2,597	$2,619	-0.8%
17	33	INCIVEK	$0.48	$0.74	-34.5%	0.00	0.00	-41.7%	$18,435.14	$16,410.35	12.3%
18	23	TOBI	$0.45	$0.47	-4.4%	0.01	0.01	-18.0%	$5,857.52	$5,028.40	16.5%
19	12	DEXTROAMPHETAMINE-AMPHETAMINE	$0.44	$0.55	-19.5%	0.28	0.31	-9.6%	$160.39	$180.12	-11.0%
20	12	VYVANSE	$0.44	$0.41	5.4%	0.24	0.25	-4.5%	$184.68	$167.23	10.4%
21	15	SPIRIVA	$0.43	$0.40	9.1%	0.16	0.16	-0.4%	$276.19	$252.30	9.5%
22	40	OXYCONTIN	$0.40	$0.94	-57.3%	0.08	0.19	-55.5%	$475.43	$495.50	-4.1%
23	7	INVEGA SUSTENNA	$0.38	$0.27	39.1%	0.03	0.02	32.4%	$1,210.07	$1,152.17	5.0%
24	30	REVLIMID	$0.38	$0.24	58.7%	0.00	0.00	39.8%	$9,658.76	$8,504.93	13.6%
25	33	ATRIPLA	$0.38	$0.86	-56.5%	0.02	0.05	-58.0%	$1,754.32	$1,695.45	3.5%
26	48	SABRIL	$0.37	$0.16	130.8%	0.01	0.00	84.2%	$7,316.15	$5,840.15	25.3%
27	58	HUMALOG	$0.37	$0.31	20.5%	0.14	0.12	12.1%	$273.70	$254.53	7.5%
28	40	HYDROCODONE-ACETAMINOPHEN	$0.37	$0.42	-10.4%	2.36	2.93	-19.5%	$15.80	$14.19	11.3%
29	15	COMBIVENT	$0.37	$0.41	-10.7%	0.15	0.18	-15.8%	$244.48	$230.37	6.1%
30	69	CREON	$0.32	$0.29	12.4%	0.03	0.03	9.5%	$1,051.50	$1,026.78	2.4%
31	77	LOVENOX	$0.32	$0.36	-13.2%	0.03	0.03	-17.5%	$1,100.35	$1,050.89	4.7%
32	1	OMEPRAZOLE	$0.31	$0.30	3.4%	1.78	1.69	5.2%	$17.41	$17.72	-1.7%
33	58	NOVOLOG	$0.30	$0.30	1.5%	0.13	0.14	-6.4%	$225.91	$208.52	8.3%
34	7	ZIPRASIDONE HCL	$0.30	$0.16	83.1%	0.15	0.08	96.4%	$194.05	$208.16	-6.8%
35	7	LATUDA	$0.27	$0.14	90.0%	0.05	0.03	62.9%	$559.00	$479.37	16.6%
36	48	VIMPAT	$0.27	$0.22	24.0%	0.04	0.04	8.5%	$606.31	$531.01	14.2%
37	7	INVEGA	$0.26	$0.23	13.9%	0.04	0.04	-4.5%	$690.23	$579.19	19.2%
38	11	MODAFINIL	$0.26			0.03			$922.42		
39	99	AVONEX	$0.25	$0.10	143.0%	0.00	0.00	-17.9%	$9,762.93	$3,297.50	196.1%
40	71	TYVASO	$0.24	$0.13	82.3%	0.00	0.00	85.6%	$12,419.68	$12,644.68	-1.8%
		Aggregate	$55.67	$61.21	-9.1%	100.73	101.16	-0.4%	$67	$78	-14.3%
		75th Percentile			42.1%			28.7%			15.6%
		50th Percentile (Median)			3.4%			-1.4%			2.1%

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OHP FFS Average Cost PMPM Top 30 Drug Class – First Quarter 2013

previous year quarter is comparator (red = top 75th percentile of growth; yellow = top 50th percentile of growth)

			Cost PMPM			Rx Dispensed PMPM (x100)			Cost/Claim		
Rank	Class Number	Class Description	2013	2012	%	2013	2012	%	2013	2012	%
1	7	Ataractics, Tranquilizers	$7.17	$11.15	-35.7%	5.3	6.3	-15.4%	$136	$178	-23.8%
2	11	Psychostimulants, Antidepressants	$4.65	$5.16	-9.9%	9.0	9.5	-4.9%	$51	$53	-3.2%
3	33	Antivirals	$4.37	$6.99	-37.5%	0.6	0.8	-16.9%	$640	$905	-29.2%
4	99	Miscellaneous	$3.28	$2.93	12.0%	1.5	1.4	7.7%	$188	$206	-8.6%
5	48	Anticonvulsants	$3.14	$2.64	19.2%	4.9	5.4	-9.0%	$50	$44	13.5%
6	15	Bronchial Dilators	$3.05	$3.54	-13.8%	3.3	3.5	-6.3%	$92	$101	-8.2%
7	58	Diabetic Therapy	$2.47	$2.42	1.9%	1.9	2.1	-7.1%	$126	$115	9.1%
8	71	Other Hypotensives	$2.32	$2.13	9.2%	2.6	2.8	-8.2%	$85	$72	18.0%
9	10	CNS Stimulants	$2.11	$2.42	-12.6%	1.7	1.9	-11.8%	$125	$126	-1.0%
10	30	Antineoplastic	$1.71	$0.93	83.8%	0.3	0.3	-23.1%	$519	$263	97.3%
11	40	Narcotic Analgesics	$1.69	$2.81	-39.9%	5.6	7.3	-22.5%	$30	$39	-23.2%
12	42	Antiarthritics	$1.65	$1.41	17.2%	2.0	2.2	-8.6%	$82	$64	26.6%
13	51	Gluco Corticoids	$1.31	$1.24	5.6%	1.8	2.0	-8.0%	$72	$63	14.8%
14	64	Other Hormones	$1.29	$0.99	30.4%	0.1	0.1	7.3%	$1,021	$753	35.6%
15	12	Amphetamine Preps	$1.26	$1.41	-10.8%	0.9	1.0	-11.3%	$139	$138	0.5%
16	63	Oral Contraceptives	$1.23	$1.18	4.9%	2.6	2.6	-0.4%	$48	$46	5.2%
17	1	Antacids	$1.04	$1.14	-9.2%	3.5	3.6	-3.2%	$29	$31	-6.2%
18	27	Other Antibiotics	$0.90	$0.47	91.2%	0.7	0.7	-2.3%	$110	$59	87.7%
19	41	Non-narcotic Analgesics	$0.83	$0.82	1.0%	6.3	5.1	23.1%	$13	$16	-20.7%
20	6	Laxatives	$0.79	$0.66	19.8%	6.5	5.3	21.2%	$12	$12	-1.1%
21	87	Electrolytes and Misc Nutr	$0.72	$0.61	17.4%	3.2	2.8	13.1%	$22	$21	4.4%
22	65	Lipotropics	$0.59	$0.64	-7.4%	2.1	1.8	13.7%	$28	$35	-18.6%
23	77	Anticoagulants	$0.55	$0.87	-36.0%	0.5	0.5	-10.1%	$123	$172	-28.6%
24	23	Streptomycins	$0.51	$0.50	2.8%	0.0	0.0	2.7%	$1,545	$1,386	11.4%
25	80	Fat Soluble Vitamins	$0.45	$0.37	22.9%	4.6	3.7	26.6%	$10	$10	-2.9%
26	69	Enzymes	$0.44	$0.38	15.8%	0.1	0.0	18.3%	$873	$891	-2.1%
27	82	Multivitamins	$0.40	$0.34	15.4%	3.8	3.3	13.8%	$10	$10	-0.2%
28	14	Antihistamines	$0.32	$0.30	9.1%	2.8	2.6	8.2%	$12	$12	0.4%
29	22	Penicillin	$0.32	$0.27	16.0%	1.5	1.7	-13.7%	$18	$16	15.0%
30	76	Other Cardiovascular Preps	$0.31	$0.28	8.0%	1.7	1.9	-6.2%	$17	$15	13.5%
		Aggregate	$55.67	$61.21	-9.1%	100.73	101.16	-0.4%	$67	$78	-14.3%
		75th Percentile			29.5%			20.5%			14.3%
		50th Percentile (Median)			4.9%			0.6%			0.0%

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Pharmacy Utilization Summary Report: April 2012 - March 2013

	2012									2013			
	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	JANUARY	FEBRUARY	MARCH	
Eligibility													AVG/YTD
Total Members	618,741	619,071	619,994	618,940	619,527	621,079	619,870	618,962	621,328	621,239	624,167	626,033	620,746
FFS Members	98,227	93,871	95,264	97,124	95,914	103,154	101,337	85,412	80,358	76,316	78,706	79,138	90,402
Standard	5,743	5,631	5,627	5,694	5,626	6,046	6,171	4,095	3,486	2,980	3,134	3,076	4,776
Plus	66,770	62,683	63,941	65,530	64,208	70,631	68,720	54,699	50,213	46,670	48,911	49,171	59,346
Medicare Wrap	25,714	25,557	25,696	25,900	26,080	26,477	26,446	26,618	26,659	26,666	26,661	26,891	26,280
Gross Figures													
Total Cost	$12,933,080	$12,909,929	$11,822,541	$12,111,184	$12,196,994	$10,921,498	$12,138,439	$10,701,517	$10,499,548	$11,455,506	$10,316,820	$10,876,171	$138,883,227
FFS Drugs	$4,303,494	$4,326,964	$3,966,307	$4,002,675	$4,000,231	$3,764,062	$4,227,529	$3,256,201	$3,098,380	$3,550,656	$2,983,249	$3,080,121	$44,559,869
Mental Health Carveout Drugs	$8,629,587	$8,582,964	$7,856,234	$8,108,509	$8,196,763	$7,157,436	$7,910,911	$7,445,316	$7,401,168	$7,904,850	$7,333,571	$7,796,050	$94,323,358
Total Rx	182,966	190,235	178,304	180,179	184,181	172,761	192,095	170,300	167,020	170,933	154,091	162,644	2,105,709
FFS Drugs	80,994	84,688	78,210	79,057	81,158	78,188	87,765	70,784	67,627	69,814	62,904	65,443	906,632
Mental Health Carveout Drugs	101,972	105,547	100,094	101,122	103,023	94,573	104,330	99,516	99,393	101,119	91,187	97,201	1,199,077
Cost/Rx	$70.69	$67.86	$66.31	$67.22	$66.22	$63.22	$63.19	$62.84	$62.86	$67.02	$66.95	$66.87	$65.94
FFS Drugs	$53.13	$51.09	$50.71	$50.63	$49.29	$48.14	$48.17	$46.00	$45.82	$50.86	$47.43	$47.07	$49.03
Mental Health Carveout Drugs	$84.63	$81.32	$78.49	$80.19	$79.56	$75.68	$75.83	$74.82	$74.46	$78.17	$80.42	$80.21	$78.65
Generic	$33.94	$30.75	$28.48	$28.36	$27.45	$25.05	$24.95	$23.67	$22.86	$23.56	$23.74	$23.84	$26.39
Brand	$345.71	$343.71	$349.80	$357.92	$356.92	$350.83	$350.39	$355.44	$354.94	$386.09	$381.88	$379.39	$359.42
PMPM Figures													
Cost PMPM	$57.76	$59.96	$54.31	$54.31	$54.94	$48.01	$54.48	$50.15	$50.47	$59.25	$49.65	$51.37	$53.72
Standard	$151.50	$156.18	$146.71	$143.20	$152.43	$126.19	$136.17	$119.27	$129.53	$163.42	$123.13	$140.80	$140.71
Plus	$58.64	$62.90	$55.47	$55.50	$56.30	$49.01	$56.55	$56.50	$58.67	$68.15	$56.48	$59.41	$57.80
Medicare Wrap	$17.91	$17.18	$16.52	$16.00	$17.11	$15.84	$17.75	$13.38	$13.49	$15.68	$14.76	$12.08	$15.64
FFS Drugs	$43.81	$46.09	$41.63	$41.21	$41.71	$36.49	$41.72	$38.12	$38.56	$46.53	$37.90	$38.92	$41.06
Mental Health Carveout Drugs	$13.95	$13.86	$12.67	$13.10	$13.23	$11.52	$12.76	$12.03	$11.91	$12.72	$11.75	$12.45	$12.66
Rx PMPM	0.99	1.07	0.98	0.98	1.01	0.91	1.03	0.99	1.00	1.08	0.95	0.98	1.00
Standard	2.10	2.22	2.07	2.05	2.19	1.92	2.16	2.04	2.00	2.40	1.98	2.14	2.11
Plus	0.85	0.93	0.84	0.83	0.86	0.77	0.89	0.86	0.87	0.99	0.85	0.88	0.87
Medicare Wrap	0.99	1.05	0.99	1.02	1.03	0.96	1.04	0.99	1.01	0.94	0.86	0.89	0.98
FFS Drugs	0.82	0.90	0.82	0.81	0.85	0.76	0.87	0.83	0.84	0.91	0.80	0.83	0.84
Mental Health Carveout Drugs	0.16	0.17	0.16	0.16	0.17	0.15	0.17	0.16	0.16	0.16	0.15	0.16	0.16
Utilization Percentages													
Generic %	88.2%	88.1%	88.2%	88.2%	88.2%	88.3%	88.3%	88.2%	88.0%	88.0%	87.9%	87.9%	88.1%
FFS Drugs	90.5%	90.6%	90.7%	90.8%	90.8%	90.7%	90.8%	91.1%	91.0%	91.1%	91.3%	91.3%	90.9%
Mental Health Carveout Drugs	86.4%	86.2%	86.3%	86.2%	86.2%	86.3%	86.1%	86.1%	85.9%	85.9%	85.6%	85.6%	86.0%
PDL %	92.2%	92.9%	93.2%	93.2%	94.0%	94.2%	91.7%	91.4%	91.1%	92.4%	92.4%	92.2%	92.6%

PMPM calculated as sum of physical health and mental health carve-outs
Data from DSSURS and DMAP FCHP first of month reports
Dates are service dates
All eligibility groups included except for CAWEM, QS, QB
Drug Cost = Amt Paid +Copay + Other Insurance Paid

Last Updated: April 19, 2013

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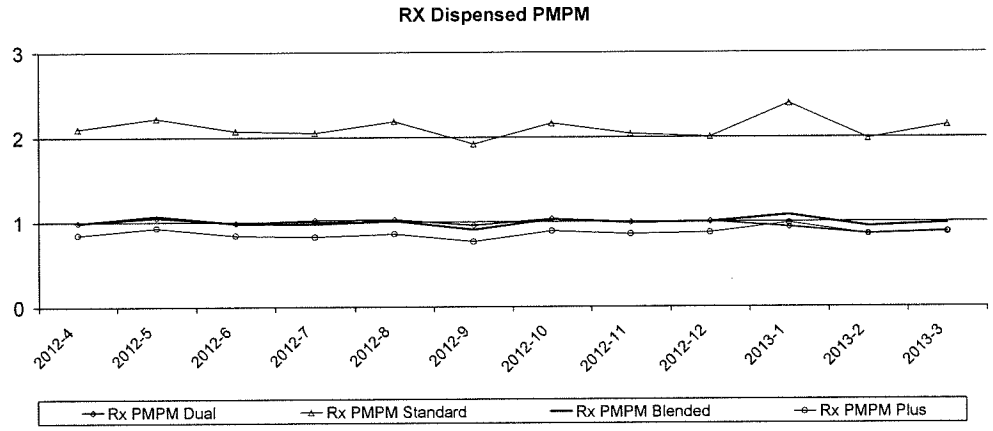
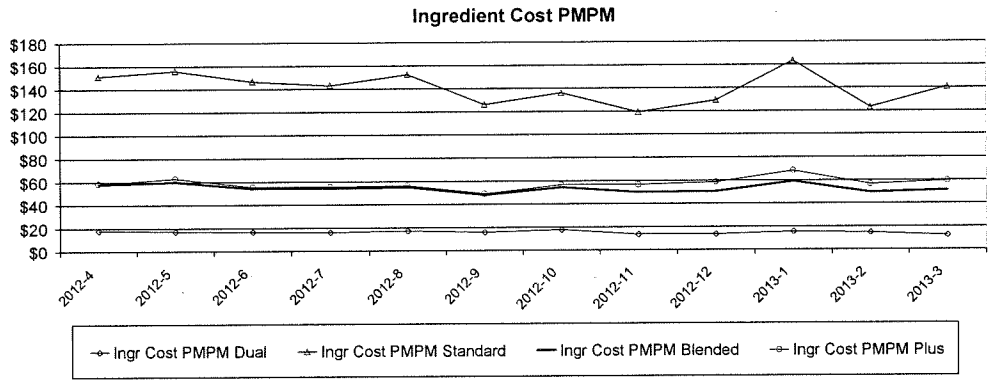
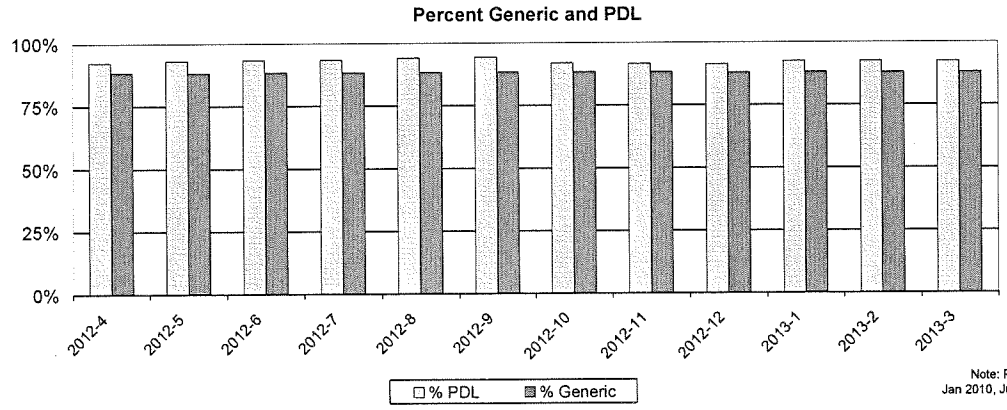
Pharmacy Utilization Summary Report: April 2012 - March 2013







Note: PDL updated
Jan 2010, Jul 2010, Jan 2011

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Management of Gout in the Presence of Chronic Kidney Disease

By Abby Floeter and Andrew Albanese, Pharm.D. Candidates 2013, Megan Herink, Pharm.D., and Harleen Singh, Pharm.D., BCPS, all from Oregon State University College of Pharmacy

Management of acute and chronic gout is challenging in the setting of chronic kidney disease (CKD). Common gout treatments have been associated with severe adverse events in patients with renal dysfunction.[1-5] The recently published guidelines from the American College of Rheumatology (ACR) provide some guidance on the treatment and prevention of gout in CKD .[6,7] However, many of the new recommendations are based on consensus and expert opinion (Level C) and are not evidence based. The purpose of this newsletter is to provide direction on the management of gout in patients with CKD, including pertinent updates from the new guidelines.

Acute Management of Gout

The primary treatment options for acute gout include non-steroidal anti-inflammatory drugs (NSAIDs), colchicine, and corticosteroids. Pharmacologic treatment should begin within 24 hours of onset of an acute gout attack (Level C). The ACR guidelines do not recommend one therapeutic class over another due to lack of robust evidence for any particular drug class. Drug selection should take into account patient comorbidities.[7]

NSAIDs are one of the first-line modalities in the treatment of acute gout.[7] All NSAIDs have similar efficacy when initiated early at appropriate doses.[1,2] The ACR guidelines do not recommend one NSAID over another. However, naproxen (Level A), indomethacin (Level A), and to a lesser extent sulindac (Level B), have the most evidence of efficacy.[7] All NSAIDs can cause acute renal injury and worsen CKD. Other renal side effects of NSAIDS include: acute tubular necrosis, acute interstitial nephritis, proteinuria, and hyperkalemia. Although the guidelines do not provide specific dosing recommendations for NSAIDs in patients with renal impairment, it is suggested to start with low doses.[7] In certain patients who require aggressive inflammatory doses of NSAIDs for acute gouty flares, CKD may pose a challenge. Risks versus benefits should be considered when prescribing NSAIDs in patients with renal impairment. Those at risk of developing NSAID-induced renal insufficiency should be monitored every 2 to 4 weeks for changes in serum creatinine.[3] NSAIDs are generally not recommended in Stage 4 or 5 CKD and should be used with caution or avoided in patients with congestive heart failure, a history of active peptic ulcer disease, hepatic dysfunction, and in patients taking anticoagulants.[7,3]

Oral colchicine is a good option in patients who are unable to tolerate NSAIDs or high doses of corticosteroids, however, there are significant concerns in using colchicine in those with CKD.[8] Colchicine is only recommended if it can be initiated within 36 hours of an acute gout attack (Level of Evidence C).[7] The clearance of colchicine is significantly reduced in CKD, and prolonged use can lead to colchicine-induced axonal neuropathy, neutropenia, and myopathy. The guidelines refer to the FDA-approved product labeling for dose adjustments in patients with CKD and recommend that dose adjustments be individualized. In patients with severe renal impairment (CrCl <30ml/min), the usual acute treatment doses can be given, but dosing should not be repeated more than once every two weeks.[10] In dialysis patients, a one time 0.6 mg dose is recommended, and dosing should not be repeated more than once every two weeks.[10] Dose reduction or drug avoidance should be considered with concomitant use of strong inhibitors of cytochrome P450 3A4 and of P-glycoprotein inhibitors.[7,10] Colchicine should also be used with caution in elderly patients because creatinine levels may appear normal despite significant underlying renal impairment.[3] A recent review found an association between colchicine and rhabomyolysis, acute pancreatitis, and myopathy in patients with CKD.[3]

The guidelines do not specify corticosteroids as an alternative in patients with CKD, however, they are the preferred treatment option for management of acute gout attacks in CKD due to renal concerns with NSAIDs and colchicine. Oral, intramuscular, or intravenous steroids can provide relief for acute gout. The number of joints with active arthritis should be considered when selecting the route of corticosteroid therapy.[7] Prednisone should be initiated at 0.5 mg/kg per day for 5 to 10 days and then stopped (Level A).[7] Alternatively, a dose of 0.5 mg/kg per day can be used for 2 to 5 days, tapered for 7 to 10 days, and then stopped (Level C).[7] Dosing of intraarticular corticosteroids should be based on the size of the joint involved (Level B).[7] Intraarticular corticosteroids may be used in combination with oral corticosteroids, NSAIDs, or colchicine (Level B).[7]

The ACR guidelines recommend combination therapy for severe acute gout attacks and for patients not responding adequately to initial pharmacologic monotherapy (Level C).[7] Potential combinations include: 1) colchicine and an NSAID 2) colchicine and an oral corticosteroid or 3) intraarticular corticosteroid and any other treatment modality.[7] NSAIDs and systemic corticosteroids are not recommended in combination due to increased risk of gastrointestinal (GI) toxicity.[7]

Chronic Management of Gout/Hyperuricemia

Chronic hyperuricemia can trigger acute gouty attacks. Long term prophylaxis with urate lowering therapy (ULT) is indicated to maintain serum uric acid levels below 6mg/dl (ideally 5mg/dl).[6,7,11,12] First-line ULT agents are the xanthine oxidase inhibitors (XOIs) allopurinol and febuxostat, with no preference given to one agent over the other (Level A).[6] Second line alternatives are uricosurics, such as probenecid (Level B).[6]

Traditionally, the starting dose of allopurinol in patients with preserved renal function has been 300 mg/day. However, the ACR guidelines now recommend that starting doses be no greater than 100 mg/day (Level B).[6] In stage 4 or worse CKD, the starting dose should be 50 mg/day (Level B).[6] Initiation of therapy with lower doses can potentially reduce the likelihood of early gout flares after ULT initiation and allopurinol-induced hypersensitivity reactions. It is recommended to gradually titrate up doses every 2 to 5 weeks to reduce serum urate to target levels (Level C).[6] Doses can be increased above 300 mg/day to meet serum urate goals, even in patients with renal impairment as long as appropriate monitoring and patient education is provided.[6] This recommendation is based on evidence that doses of 300 mg/day or lower failed to decrease uric acid levels below 6 mg/dl or 5 mg/dl.[12] The common algorithm used to adjust doses based on renal function is not evidence based and is not recommended in the new guidelines.[6,13]

Allopurinol is well tolerated, however 2% of patients develop a mild rash.[1] In contrast, severe allopurinol hypersensitivity syndrome (AHS) is a rare but serious side effect and is associated with significant mortality (20-25%).[6] AHS includes symptoms of Stevens-Johnson syndrome and toxic epidermal necrolysis, as well as systemic disease features including eosinophilia, vasculitis, rash and end-organ disease.[14,15] Renal impairment and concomitant thiazide diuretic use can increase the risk of AHS. Although no studies have shown an association between allopurinol doses and the development of AHS,[14] it is recommended to initiate allopurinol at low doses and gradually increase the dose to mitigate the risk of AHS.[6] In select patients who are at a higher risk for AHS (e.g., Koreans with stage 3 or worse CKD, and Han Chinese and Thai), consideration should be given to polymerase chain reaction (PCR)-based HLA-B*5801 screening before initiating therapy (Level A).[6] In patients using allopurinol, the ACR guidelines strongly recommend diligent monitoring for hypersensitivity and other side effects such as pruritus, rash, elevated liver function tests (LFTs), and eosinophilia.[6]

Another ULT first-line option for the treatment of chronic gout is febuxostat. In contrast to allopurinol, febuxostat is metabolized by hepatic glucuronidation and oxidation.[16] Renal elimination plays only a small role in febuxostat pharmacokinetics, therefore, it does not require renal dose adjustment in mild to moderate CKD.[16,17,18] Evidence is lacking on the safety of febuxostat in stage 4 CKD or worse, and there is no safety data regarding febuxostat in patients with a history of allopurinol hypersensitivity.[16,19] The usual starting dose of febuxostat is 40 mg/day with a maximum FDA-approved dose of 80 mg/day.[16] The ACR guidelines endorse titrating up to 120 mg/day (used outside USA) in patients with refractory gout despite FDA labeling.[6]

When managing gout on a chronic basis, it is reasonable to substitute one XOI for another in patients who experience intolerable side effects, or if the serum urate goal is not achieved with the current XOI (Level C).[6] The ACR guidelines recommend regular monitoring of serum urate every 2 to 5 weeks during ULT titration and continuing measurements every 6 months once the serum urate target is achieved.[6]

Although the guidelines do not preferentially recommend one XOI over another, febuxostat treatment is significantly more expensive than allopurinol. A one month supply of febuxostat 40 mg/day costs approximately $192 compared to a month supply of allopurinol 300 mg/day costing approximately $24.[20] The National Institute for Health and Clinical Excellence (NICE) recommends that febuxostat be reserved for patients intolerant to allopurinol, due to cost differences.[21]

The uricosuric agent probenecid is considered an alternative first-line ULT option in patients with a contraindication or intolerance to a XOI (Level B).[6] Probenecid is not recommended in patients with a creatinine clearance less than 50 ml/min and shown to be ineffective when GFR is 30 mL/min or less.[3,6] The guidelines suggest other agents with uricosuric effects, such as fenofibrate or losartan, should be utilized (Level B).[6] In disease refractory to XOIs, the addition of an agent with uricosuric effects can be considered (Level B).[6]

Gout Attack Prophylaxis

Prophylaxis against acute flares is advised during the initiation of ULT because rapid lowering of serum urate levels is associated with gout flares. The ACR guidelines recommend prophylaxis with low-dose colchicine (0.6 mg once or twice a day) or low-dose NSAIDs (naproxen 250 mg orally twice daily) as acceptable first-line options, with a higher evidence level for colchicine (Level A).[7] In patients with severe renal impairment (CrCl <30ml/min), the recommended starting dose of colchicine is 0.3 mg/day. For patients on dialysis, the starting dose is 0.3 mg twice a week.[10] In CKD even reduced doses of colchicine can lead to toxicity.

Despite limited data, low-dose (≤ 10 mg daily) prednisone or prednisolone are recommended if first-line agents fail to prevent acute attacks (Level C).[7] The risks associated with prolonged corticosteroid therapy should be considered.[7] The length of therapy is determined by the presence of tophi and the attainment of target serum urate levels. The ACR guidelines recommend continuation of prophylactic therapy for the greater of the following: 6 months duration (Level A), 3 months after achieving target serum urate levels in patients without tophi (Level B) or 6 months after achieving target serum urate levels in patients where there has been resolution of tophi (Level C).[7]

Non-pharmacologic Therapy

The ACR guidelines do not recommend complimentary therapies such as cherry juice, ginger, flaxseed, or charcoal.[7] Topical ice can be used in conjunction with other pharmacological therapies (Level B).[7] Lifestyle and dietary measures such as losing weight, avoiding foods rich in purines, smoking cessation, limiting alcohol consumption, and consuming vegetables are encouraged by the guidelines.[6,7]

Evidence Grades for Recommendations
Level A: Supported by multiple (i.e., ≥1) randomized clinical trials or meta-analyses
Level B: Derived from a single randomized trial, or nonrandomized studies
Level C: Consensus opinion of experts, case studies, or standard-of-care

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Recent Additions to the First DataBank (FDB) Drug File

Following is a list of agents recently added to the FDB drug file which were not subject to previous PA criteria. In accordance with OAR 410-121-0040(5)(b)

> *If the new drug is indicated for a condition below the funding line on the Prioritized List of Health Services, PA shall be required to ensure that the drug is prescribed for a condition funded by OHP*

these medications require a Prior Authorization to ensure use only for funded conditions.

Week of:	Generic	Brand	FDA Approved Indication(s)	ICD9 Code	HERC Funding Line
3/3/2013	CROFELEMER	Fulyzaq®	Diarrhea secondary to HIV treatment	995.20, 995.29	113 Funded
				787.91	n/a, Unfunded
4/26/2013	OSPEMIFENE	OSPHENA®	Dyspareunia	625.0	552 Unfunded

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Oregon Health Authority

New Drug Evaluation: 17 alpha-hydroxyprogesterone caproate

Month/Year of Review: May 2013
Generic Name: 17 alpha-hydroxyprogesterone caproate

End date of literature search: January 1, 2013
Brand Name (Manufacturer): Makena® (Baxter Pharmaceutical Solutions LLC)

FDA Approved Indication: Hydroxyprogesterone caproate is a progestin indicated to reduce the risk of preterm birth in women with a singleton pregnancy who have a history of singleton spontaneous preterm birth.

Research Questions:

- Is 17 alpha-hydroxyprogesterone caproate (17-HP) safe and effective in reducing the risk of recurrent preterm birth?
- Are there efficacy or safety differences in the various formulations of progesterone (e.g. suppositories, intramuscular injection, gel)?
- Are there certain patient subgroups that benefit from the use of 17-HP?

Conclusions:

- Evidence shows that 17-HP is associated with a significant reduction in the rate of recurrent preterm delivery among high risk women, measured by the rate of preterm birth at <37, <35 and <32 weeks. Improvements in these surrogate endpoints did not correlate with an improvement in infant mortality.
- Additional efficacy data is necessary to establish long-term efficacy for clinically meaningful outcomes when using 17-HP for the prevention of preterm birth.
- There is no evidence that shows intramuscular progesterone is safer or more effective than other routes of administration. Limited evidence suggests that vaginal progesterone is more effective than intramuscular progesterone for the prevention of preterm birth and leads to fewer adverse effects. More studies are necessary to determine the optimal route, dose, and duration of progesterone use for preterm birth.
- While the FDA acknowledges that manufactured products provide a greater assurance of safety and effectiveness than compounded products, an FDA-conducted analysis of the compounded product did not identify any major safety problems.

Recommendations:

- Due to limited long term safety and efficacy data, prior authorize 17-HP for appropriate use.
- Limit use of 17-HP in women with a singleton gestation and a prior spontaneous preterm singleton birth between 16 weeks, 0 days and 20 weeks, 6 days of gestation, regardless of transvaginal ultrasound cervical length, to reduce the risk of recurrent spontaneous preterm birth. Treatment should be continued through 36 weeks of gestation or delivery, whichever occurs first. 17-HP should not be used in women with multiple gestations.
- Due to insufficient data to support the compounded product and additional inherent compounding risks, prefer the branded product over the compounded product.

Background:

Preterm birth is defined as delivery earlier than 37 weeks of gestation.[1] The risk of infant morbidity and mortality is inversely proportional to gestational age, as the highest risk is for neonates born prior to 34 weeks, and lowest for those born between 39 and 40 weeks.[2] Infants who are born prematurely have a higher risk of mortality in their first year of life, and those that survive have a higher risk of hospital readmissions and long-term impairment.[3] Approximately 20-30% of preterm deliveries are due to premature rupture of membranes, 20-25% are due to infection and/or inflammation, and 25-30% are spontaneous (unexplained).[1]

A history of preterm birth is the most significant risk factor for a subsequent preterm birth. It is estimated that the risk of recurrence in a woman with a history of preterm birth is about 15%, and this increases to 32% in women who have had two prior preterm births.[3] Short cervical length (<35mm) has also been associated with a risk of preterm birth. There are a number of other risk factors that have been identified (poor nutrition, low prepregnancy weight, socioeconomic status, poor prenatal care, etc.), but are unreliable in predicting preterm labor with accuracy and precision.[1]

Until the approval of 17α-hydroxyprogesterone caproate (17-HP) in 2011, there was no FDA approved product available to reduce the risk of preterm birth, however, 17-HP has been compounded by pharmacists in the past and widely used for this indication.[4,5] Related studies have been conducted since 1975, with a number of small clinical trials showing conflicting results. It wasn't until the National Institute of Health conducted a large clinical trial in 2003 that a manufacturer sought FDA approval of a manufactured form of 17-HP. Compounded formulations of 17-HP are known to be much more affordable.[6] Other formulations of progesterone have also been used to reduce the risk of preterm birth in patients who are at high risk, including intravaginal and oral delivery, but none are approved for this purpose. Clinical head-to-head studies are not available for 17-HP.

In an effort to improve access to this drug, the FDA issued a statement in March 2011, indicating that the agency does not intend to take enforcement action against pharmacies that compound 17-HP based on a valid prescription for an individually identified patient unless the compounded products are unsafe, of substandard quality, or are not being compounded in accordance with appropriate standards.[4] The manufacturer of Makena maintained that compounded products are not as safe or as effective as the manufactured product, and the FDA responded by conducting its own analysis. The FDA later announced, "although the analysis of this limited sample...did not identify any major safety problems, approved drug products, such as Makena, provide a greater assurance of safety and effectiveness than do compounded products." The FDA also said it was applying its "normal enforcement policies" in declining to stop compounding pharmacies from making Makena, and focusing its actions on products that are likely to cause harm.[7]

In April 2013, the Oregon Board of pharmacy discussed the compounding of 17-HP and indicated that because a branded product is commercially available, a pharmacy may not compound 17-HP unles it is compounded pursuant to a prescription for an individual patient and the prescriber has clearly intended for the patient to receive the compounded product. There also must be documentation that the prescriber considered the availability of the manufactuered product and that the compounded medication is necessary for the patient.

The American College of Obstetricians and Gynecologists (ACOG) recently published their recommendations for the prediction and prevention of preterm birth. The recommendations state that women with a singleton gestation and a prior spontaneous preterm singleton birth should be offered progesterone supplementation starting at 16-24 weeks of gestation to reduce the risk of recurrent spontaneous preterm birth. This is a Level A recommendation, based on good and consistent scientific evidence. ACOG does not specify what type of progesterone formulation is preferred.[2]

Clinical Efficacy:

A phase 3 study evaluated the efficacy of 17-HP in reducing preterm delivery in 463 high-risk women. In the double-blind, placebo-controlled, multicenter trial, patients were randomized to receive 17-HP or an inert oil placebo. Women were eligible if they had a history of spontaneous preterm delivery in a previous pregnancy and a current pregnancy between 15 weeks and 20 weeks, 3 days of gestation. Women were enrolled at 16 to 20 weeks of gestation and received weekly injections of 17-HP or placebo until delivery or to 36 weeks of gestation. Analyses were performed on the intent-to-treat principal.[8]

Baseline characteristics between the two groups were similar. Results show that 17-HP significantly reduced the risk of delivery at less than 37 weeks with an incidence of 36.3% in the treatment group versus 54.9% in the placebo group [RR 0.66 (95% CI 0.54-0.811)]. Statistically significant reductions were seen in the 17-HP group for delivery at less than 35 weeks of gestation [20.6% vs. 30.7% for placebo; RR 0.67 (95% CI 0.48-0.93)] and 32 weeks of gestation [11.4% vs. 19.6%; RR 0.58 (95% CI 0.37-0.91)]. Results for fetal death, antepartum or intrapartum were not statistically different [2.0% 17-HP vs. 1.3% placebo; RR 1.50 (95% CI 0.31-7.34)]. There were lower rates of birth weights <2500g, necrotizing enterocolitis, intraventricular hemorrhage, and need for supplemental oxygen in infants whose mothers were treated with 17-HP.[8]

The study is limited in that over 27% of the study participants came from one center, the University of Alabama, raising concern about whether study results can be extrapolated to larger populations. Additionally, for the endpoints of preterm birth rates at <35 and <32 weeks, the magnitude of statistical significance was lower than expected to support approval of a drug based on these findings.[5] Due to the modest clinical benefit noted in the trial, the FDA is requiring a second confirmatory trial, with anticipated completion in 2016.[5]

There are a number of studies that evaluate the efficacy and safety of other formulations of progesterone (suppositories, gel) compared to placebo; some that show benefit[9] and some that do not.[10] There is only one published head-to-head trial that directly compares intramuscular progesterone to a different formulation, specifically, vaginal progesterone gel. In this prospective, randomized, open-label trial, 518 women with a history of preterm birth and a current singleton pregnancy were randomized to 90mg of vaginal progesterone gel daily, or 250mg intramuscular progesterone weekly. The IM progesterone product was Proluton® Depot, manufactured by Bayer Schering Pharma AG, Berlin, Germany.[11]

In this head-to-head trial, patients receiving vaginal progesterone experienced a significantly lower rate of preterm birth at <34 weeks compared to those treated with intramuscular progesterone [16.6% vs 25.7%, p=0.02; OR 0.58(95%CI 0.37-0.89)]. However, patients were not blinded which increases the risk of bias and the study was conducted at a single center in Saudi Arabia, limiting the generalizability of the results.[11]

Clinical Safety:

In the phase 3 trial which led to the FDA approval of 17-HP, there was no significant difference in neonatal deaths [2.6% 17-HP vs. 5.9% placebo; RR 0.44 (95% CI 0.17-1.13)], however the study was not powered to assess this endpoint. Overall, 50% of the women in the study experienced at a least one adverse effect with the most common event being injection site reactions. More women in the progesterone group than placebo group had swelling at the injection site (1.2% vs. 7.8%, P=0.007) or a lump at injection site (5.5% vs. 1.3%, P=0.03).[8]

A follow-up study was conducted to evaluate children who were exposed to 17-HP in utero versus placebo.[12] This study evaluated 278 of the 348 (80%) eligible surviving children of the multicenter, placebo controlled study conducted by Meis et al. In this study the guardian was interviewed about the child's general

heath and children underwent a physical examination and developmental screen using the Ages and Stages Questionnaire. The mean age at follow-up was 48 months. The Ages and Stages Questionnaire showed no differences between the 17-HP and placebo groups (P=0.61). The Preschool Activities Inventory, designed to find gender-specific differences, resulted in a mean score for boys of 67.3 and 66.5 for the placebo and 17-HP groups, respectively (P=0.3). For females the mean scores were 33 and 32 for the 17-HP and placebo groups, respectively (p=0.50). There were no significant differences in the physical characteristics of height, weight, head circumference, or blood pressure. Study participants had growth similar to national averages. Genital abnormalities were found in 2.1% of the study group and 1.2% of the placebo group (P=1.0). Genital abnormalities in the 17-HP group were two males with micropenis, one male with an undescended testicle that had been surgically repaired, and one female with early puberty (3.5 years). In the placebo group one female had pubic hair present. Based on these results, 17-HP appears to be safe for the fetus when administered in the second and third trimesters, however the sample size was smaller than planned there was limited statistical power to detect treatment differences.[12]

In the head-to-head trial comparing vaginal and intramuscular formulations, patients using the intramuscular formulation experienced a higher rate of adverse events than those using the vaginal gel (14.1% vs 7.5%, respectively, P=0.017). The most common adverse events in the intramuscular group were pain and swelling related to the injection site, and headaches. The most common adverse events in the vaginal group were bloating, nausea and vaginal soreness. Infants who had been exposed to intramuscular progesterone in utero also experienced a higher rate of neonatal intensive care unit admissions that those in the vaginal progesterone group (25.7% vs 15.4%, respectively, P=0.006). There were no significant differences in the other safety parameters.

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Neonatal mortality
2) Neonatal morbidity
3) Premature birth rate (the rate of preterm birth prior to 37 weeks is a surrogate endpoint that is likely to predict clinical benefit).[5]

Primary Study Endpoint:

1) Delivery at less than 37 weeks of gestation.

Ref./Study Design	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
Meis et al.8 RCT, DB, PC, MC	1. 17-HP 250 mg weekly (n= 310) 2. Placebo (Pbo) injection weekly (n=153)	Demographics (17-HP, Pbo): • Age: 26.0, 26.5 • Duration of gestation at time of delivery (wk): 30.6, 31.3 • No. of previous preterm deliveries 1.4, 1.6 • Duration of gestation at randomization (wk): 18.4, 18.4 Inclusion Criteria: • History of spontaneous preterm delivery in previous pregnancy • Current pregnancy between 15 weeks and 20 weeks 3 days of gestation Exclusion Criteria: • Multifetal gestation, known fetal anomaly, progesterone or heparin treatment during the current pregnancy • Current or planned cervical cerclage • Hypertension requiring medication • Seizure disorder • Plan to deliver elsewhere	Randomized: 17-HP: 310 Pbo: 153	<u>Delivery before 37 wk of gestation:</u> 17-HP: 36.3% Pbo: 54.9% P-value: <0.001 RR 0.66, 95% CI (0.54-0.81). <u>Delivery before 35 wk of gestation:</u> 17-HP: 20.6% Pbo: 30.7% P-value: 0.02 RR 0.67, 95% CI (0.48-0.93). <u>Delivery before 32 wk of gestation:</u> 17-HP: 11.4% Pbo: 19.6% P-value: 0.02 RR 0.58, 95% CI (0.37-0.91). <u>Fetal death, antepartum or intrapartum:</u> 17-HP 2.0% Pbo: 1.3% RR 1.50, 95% CI (0.31-7.34). <u>Birth weight <2500 g:</u> 17-HP: 27.2% Pbo: 41.1% P-value: 0.003 RR 0.66, 95% CI (0.51-0.87). <u>Neonatal Death:</u> 17-HP: 2.6% Pbo: 5.9% RR 0.44, 95% CI (0.17-1.13).	18.6%/5 10.1%/10 8.2%/12 N/A 13.9%/7 3.3%/30	206 women (50%) had at least one adverse effect. The most common were injection-site reactions (34.2%), swelling (14.1%), itching (11.3%), and bruising (6.7%). More women in the progesterone group than placebo group had swelling at injection site (1.2% vs. 7.8%, p= 0.007) or lump at injection site (5.5% vs. 1.3%, P=0.03).		**Quality Rating: Fair** **Internal Validity:** <u>Selection:</u> Adequate randomization assignment (computer generated algorithm); patients were given test injections; groups similar at baseline. <u>Performance:</u> The women, their caregivers, and research personnel were unaware of study-group assignment. <u>Detection:</u> Unclear if outcome assessors were blinded. <u>Attrition:</u> Data on hospital visit for preterm labor were missing for 1 woman in the placebo group; data on tocolytic therapy were missing for 2 women in the placebo group, and data on corticosteroids for fetal lung maturity were missing for 14 women in the progesterone group and 1 women in the placebo group. **External Validity:** <u>Recruitment:</u> A research nurse approached candidates from the 19 participating centers and explained the study. If candidates met inclusion criteria they were deemed eligible and invited to participate. After trial injections, women who returned one week after were included in the study. <u>Patient Characteristics:</u> Ave age: 26 years; 59% non-Hispanic black women; average body-mass index before pregnancy was 27 (17-HP) and 26 (Pbo); 20% smoked during pregnancy; 6% used alcohol; and 3% reported substance use in each group. <u>Setting:</u> Women returned weekly for injections and received prenatal care at their institutions. Patients came from a single center. <u>Outcomes:</u> After delivery study personnel reviewed all records. Infants were followed until hospital discharge.

[11] Maher et al. R, OL, AC, SS	1. IM progesterone, 250mg once a week 2. Progesterone gel, 90mg applied once daily	Inclusion Criteria: • History of at least 1 mid-trimester preterm birth or cerclage suture inserted in a previous pregnancy, but not the current • Carrying a singleton pregnancy between 14 and 18 weeks gestation Exclusion Criteria: • Fetal anomaly or loss • Advanced cervical dilatation • Membranes bulging into the vagina • History of ruptured membranes • Short cervix or significant funneling • Plans to under go cervical cerclage or who already had cerclage inserted • Major chronic medical disorder • Multiple pregnancy	Randomized IM: 249 Vaginal: 253	<u>Delivery before 34 wk of gestation:</u> IM: 25.7% Vaginal: 16.6% P-value: 0.02 OR 0.58, 95% CI (0.37-0.89).	9.1%/11	Adverse effects: IM: 14.1% Vaginal: 7.5% P-Value: 0.017 OR 2.01, 95% CI (1.12-3.63). The most common adverse effects in the intramuscular group were pain and swelling related to injection site and headache. In the vaginal group the adverse reactions were bloating, nausea and vaginal soreness.	6.6%/15	**Quality Rating: Fair** **Internal Validity:** <u>Selection:</u> Adequate randomization using a computer-generated random list; groups were similar at baseline. <u>Performance:</u> This was an unblinded study using two different routes of administration. <u>Detection:</u> Unclear if outcome assessors were blinded. <u>Attrition:</u> 9 of the original 262 subjects in the vaginal progesterone group were lost to follow-up and 7 of the 256 patients in the intramuscular progesterone were lost to follow-up. **External Validity:** <u>Recruitment:</u> Study was conducted at a single study center that has 8000-9000 deliveries per year. <u>Patient Characteristics:</u> Average age of women was between 27 and 28 years old. Average body mass index was 25 and the average gestational age at randomization was just over 15 weeks. <u>Setting:</u> Patients assigned to IM progesterone received 2 week supply at each visit, with one of the shots administered at each visit. Drug packaging was used to assess compliance. All patients were instructed to undergo periods of bed rest and were educated about the symptoms of preterm birth. This specific drug formulation is not available in the U.S. <u>Outcomes:</u> Returned for visits every 2 weeks. All data for timing of labor onset, along with maternal and neonatal complications were documented.
RCT: randomized controlled trial, DB: double-blind, PC: placebo controlled; MC: multi-centered, OL: open-label, AC: active-comparator, SC: single-center, RR: relative risk, CI: confidence interval, OR: Odds Ratio								

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

PHARMACOKINETICS[13]

Parameter	Result
Peak serum levels	3-7 days
Protein Binding	Extensively binds to plasma proteins including albumin and corticosteroid binding globulins
Excretion	50% recovered in feces, and 30.5% recovered in the urine
Half-Life	7.8 (+/-3.0) days
Metabolism	Phase I and II reactions in hepatocytes

DOSE & AVAILABILITY[13]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
250 mg/ 1mL	Intramuscularly (IM)	Once weekly until week 37 of gestation or delivery, whichever occurs first	250 mg	Not studied	Not studied	Not indicated for use in children	Not intended for use in postmenopausal women	Treatment should begin between 16 weeks, 0 days and 20 weeks, 6 days of gestation.

DRUG SAFETY[13]

Serious (REMS, Black Box Warnings, Contraindications):

Contraindicated in women with a current or history of thrombosis or thromboembolic disorders; hepatic impairment, hepatic tumors or cholestatic jaundice of pregnancy; carcinoma of the breast (known or suspected) or other hormone sensitive cancers; undiagnosed vaginal bleeding unrelated to pregnancy; uncontrolled hypertension; current or history of thrombosis or thromboembolic disorders.

Warnings and Precautions:

Discontinue if arterial thrombosis, DVT, or thromboembolic events occur. May have adverse effects on glucose tolerance. Use in caution in women with diabetes, depression, or diseases exacerbated by fluid retention.

Not for use in women with multiple gestations or other risk factors for preterm birth.

Appendix 2: Suggested PA Criteria

17 alfa-hydroxyprogesterone caproate (Makena®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which hydroxyprogesterone caproate injection has been shown to be effective and safe.

Length of Authorization: Up to 20 weeks

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the client between 16 weeks and 0 days and 36 weeks 6 days gestation with a singleton pregnancy?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Has the patient had a prior history of preterm delivery before 37 weeks gestation (spontaneous preterm singleton birth)?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny (medical appropriateness)
4. Is treatment being initiated at 16 weeks, 0 days and to 20 weeks, 6 days of gestation?	**Yes:** Approve through week 37 of gestation or delivery, whichever occurs first (no more than 20 doses).	**No:** Pass to RPH; Deny (medical appropriateness)

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Oregon Health Authority

New Drug Evaluation:

Month/Year of Review: January 2013
Generic Name: Perampanel
PDL CLASS: Anticonvulsants

End date of literature search: December 2012
Brand Name (Manufacturer): Fycompa™ (Eisai Inc.)
Dossier Received: Pending

FDA Approved Indications: Adjunctive therapy for treatment of partial-onset seizures with or without secondary generalized seizures in patients with epilepsy aged 12 years and older.[1] Perampanel has been studied for the off-label use of parkinson's disease, neuropathic pain, multiple sclerosis, and migraine headache.

Research Questions:

- Is perampanel more effective than other antiepileptic drugs (AEDs)?
- Is perampanel safer than other AEDs?
- Are there subpopulations that will benefit from perampanel in terms of effectiveness or harms compared to other AEDs?

Conclusions:

- There is moderate level of evidence that perampanel as adjunctive therapy is effective in reducing seizure frequency compared to placebo in refractory partial seizures .[2–4]
- There is no data to show perampanel's efficacy in less refractory patients and other seizure types.
- The maximum tolerable dose of perampanel was not explored and defined in clinical trials.
- The black box warning on serious life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats warrant close monitoring and may potentially limit permpanel's role in therapy. As a first in class drug, there remains many unanswered safety concerns.
- There is insufficient evidence comparing perampanel to other currently available AEDs.

Recommendations

- Make perampanel a second line non-preferred oral anticonvulsant to ensure appropriate use; as adjunct treatment when previous treatment with other AEDs has not provided adequate response or has not been tolerated. Due to the lack of comparative effectiveness data that perampanel is more effective or safer than other antiepileptic agents for managing partial-onset seizure.

Background/Current landscape

A seizure represents the clinical expression of abnormal, excessive, synchronous discharges of neurons residing primarily in the cerebral cortex. Epilepsy describes a clinical phenomenon in which a person has recurrent seizures due to a chronic, underlying process The International Classification of Epileptic Seizures is used by most neurologists to classify seizure types. This classification divides seizures into two basic groups based upon clinical and electroencephalographic(EEG) data: partial and generalized.[5] The age-adjusted prevalence of epilepsy in developed countries is 4 to 8 per 1,000 population.[6–8] Overall incidence figures show that partial (focal) seizures (simple and complex) are the most common seizure type in all age groups and account for more than 50 percent of all seizures in children. Complex partial (focal seizures with alterations of awareness or consciousness) are the most common subtype. Generalized seizures are more common in children than in adults, with generalized tonic-clonic, absence, and myoclonic seizures following partial seizures in frequency of occurrence.[8].

The management of patients with epilepsy is focused on three main goals: controlling seizures, avoiding treatment side effects, and maintaining or restoring quality of life. In all people, the goal should be to achieve seizure freedom.[9] The mainstay of treatment is anticonvulsant medication, and the drug of choice depends on an accurate diagnosis of the epileptic syndrome, probably owing to the different pathophysiologic mechanisms in the types of seizure and the specific epileptic syndromes. People with epilepsy usually initiate treatment with one antiepileptic drug at the time of diagnosis, but many will become refractory to this medication at some point. Selecting an effective drug with the least potential for side effects becomes an important decision for providers. Common side effects that lead to withdrawal of drug treatment include drowsiness, dizziness, lethargy, and cognitive slowing. [9] Another important issue involves generic substitution of innovator medications. There remains insufficient comparative evidence to state that one AED is conclusively better than another and few head to head trials exist. [9]

The exact mechanism of perampanel is unknown. Perampanel is a first-in-class, non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system and is implicated in a number of neurological disorders caused by neuronal over excitation.[1] In population studies, exposure to perampanel was lower in patients receiving concomitant enzyme-inducing AEDs (carbamazepine, phenobarbital, phenytoin, oxcarbazepine, primidone). These increase the clearance of parampanel 2-3 fold. The starting dose and recommended titration schedule differs based on if the patient is on concurrent inducers.

Clinical Efficacy and Safety

The efficacy and safety of perampanel in partial-onset seizures, with or without secondary generalization, were evaluated in 3 randomized, double blind, placebo controlled, multicenter trials (study 304, study 305 and study 306)[2–4] in adult and adolescent (aged 12 and older) patients who were not adequately controlled with 1-3 concomitant AEDs., only one of which could be and enzyme-inducing drug antiepileptic drug (EIAED). All trials had an initial 6 – week baseline period, during which patients were required to have more than 5 seizures. Treatment started after 6 weeks of the baseline period, followed by 6 weeks dose titration phase and 13 weeks of maintenance phase. The primary endpoint of the three studies was the percent change in seizure frequency per 28 days during the treatment period compared with baseline period. The responder rate (percentage of patients who experienced at least a 50% reduction in seizure frequency in the maintenance period relative to baseline) was also measured. The mean age in the Phase III trials was 34.9 years. In the studies, 51.3% were treated with 2 AEDs at baseline, and 34.5% with 3 AEDs. The FDA medical reviewer noted no significant differences in concomitant medications and diseases between parampanel and placebo groups, but did not imbalances in specific dose groups; particularly in the 12 mg dose group compared to placebo.[10] The significant exclusion criteria (see evidence table) may limit the generalizability of the data to the general population.

Study 304[2] was a fair quality study that included 388 patients with partial onset seizures who had failed ≥2 AEDs. It was a multiple fixed dose, double blind, multi-center study in which patients were randomized to receive target doses of perampanel of either 8mg or 12mg daily, or placebo. The primary endpoint showed 21%, 26.3% (p =0.0261) and 34.5% (p = 0.0158) achieved a reduction in seizure frequency per 28 days for placebo, perampanel 8mg and perampanel 12mg groups respectively. The 50% responder rates compared t placebo were 37.6% with 8 mg (p=0.0760), 36.1% with 12 mg (p=0.0914) and 26.4% with placebo. This study showed much higher placebo response rate at 21% compared with other studies conducted in Europe, North America, and Austrulia[3], or in central Europe and Asia.[4] The dose-response relationship is also shown in this study.

Study 305[3] was a good quality double blind, multi-center, multi-national study that randomized total of 386 patients on a stable regimen of 1-3 AEDs to placebo, perampanel 8mg, and perampanel 12mg groups. The primary endpoint showed a 9.7%, 30.5% (p =0.0008) and 17.6% (p = 0.0105) reduction in seizure frequency per 28 days for placebo, perampanel 8mg and perampanel 12mg groups respectively. The 50% responder rates compared to placebo were 33.3% with 8 mg (p=0.0018), 33.9% with 12 mg (p<0.001) compared to 14.7% with placebo. The dose-response relationship was not demonstrated in this study. The treatment groups showed much greater treatment related events (69.0% and 77.7% for perampanel 8mg and 12mg groups respectively compared with 47.8% in placebo group).

Unlike the previous studies, patients in study 306[4] were randomized into four treatment groups with total of 706 patients: placebo, perampanel 2mg, 4mg and 8mg groups. The primary endpoint showed 10.7%, 13.6% (p =NS), 23.3% (p = 0.003) and 30.8% (p < 0.001) reduction in seizure frequency per 28 days for placebo, perampanel 2mg, 4mg and 12mg groups respectively.

As noted ealier, EIAEDs reduce the plasma levels of perampanel 2-3 fold, and the trials did not alter the dosing in study patients according to their baseline AEDs. About 60% of patients were taking an EIAED at baseline, and this had a profound effect on treatment response. It is clear that patients receiving EIAEDs had a much lower treatment response than those not taking an EIAED at baseline (In Studies 304 and 305 combined, the median percent difference from placebo at 12 mg was about -19% in patients taking EIAEDs, compared to -33% in non-EIAED patients). There is a clear increase in response between 4 and 8 mg/day (in both EIAED and non-EIAED patients). The dose response between 8 and 12 m/day (in both EIAED and non-EIAED patients) is considerably smaller, though still somewhat evident. Nevertheless the treatment effect is much smaller in patients taking EIAEDs than in non-EIAED patients for any given daily dose.[11] It is evident that the effect on seizure frequency is similar for a given plasma level (regardless if the patient is on an EIAED or not). Unfortunately all studies did not adequately explore the maximum effective dose range in patients taking EIADEs based on plasma drug levels.

In clinical trials, perampanel caused typical adverse reactions referable to the nervous system (e.g., dizziness, ataxia, diplopia), as well as somnolence, and an increased incidence of falls, but few other significant adverse events. However, in a small number of patients,perampanel can cause significant psychiatric/behavioral symptoms. These symptoms include, most importantly, anger, aggression, and hostility, and can result in some cases in homicidal ideation and physical assaults.[11] Other areas of safety concern identified by the FDA medical reviewer included dizziness and coordination, somnolence and fatigue, falls and injuries, and metabolic effects (increases in weight, total cholesterol, and blood pressure). As with effectiveness, the incidence of adverse reactions also dependents upon whether patients were taking EIAEDs or not. Overall, the percentage of patients discontinuing perampanel due to adverse events was higher in the 12 mg group than the 8 mg group and placebo (19.4%, 6.8%, and 6.6% respectively).

Evidence Table:

Relevant Endpoints: 1) All cause Mortality
2) Quality of life
3) Tolerability

Study Endpoints: 1) Partial Seizure frequency change
2) Complex partial seizure requency change
3) Decrease in seizure frequency at least 50% compared to the baseline

Ref./ Study Design[1]	Drug Regimens	Patient Population	N	Duration	Efficacy Results[2] (CI, p-values)	ARR / NNT[3]	Safety Results^ (CI, p-values)	ARR / NNH	Quality Rating[4]; Comments
Study 304[2] Frech JA el.al DB, PC, RCT; MC	F1: perampanel 8mg once daily F2: perampanel 12mg once daily P: placebo	Mean age (P/F1/F2): 35.6/35.8/36.7 Female (P/F1/F2): 55%/51%/48.5% Caucasian (P/F1/F2): 85.1%/86.5%86.6% Seizure frequency (attacks/28days; P/F1/F2): 13.7/14.3/12.0 % of concomitant AEDs at baseline (P/F1/F2): 1 AED: 12.4/19.5/14.2 2 AEDs: 52.9/52.6/61.2 3 AEDs: 34.7/27.8/24.6 Inclusion criteria: ≥12 year of age, on stable dose of 1 2 or 3 AEDs (only 1 inducer) Exclusion criteria: Pregnant, evidence of clinically significant disease, active hepatic disease, active hematological disease, ECG abnormality, psychotic disorder, drug or alcohol dependency, use of vigabatrin	N= 388 P: 121 F1: 133 F2: 134	19 weeks	Primary endpoint Median % change in seizure frequency: F1: -26.3% (p = 0.0261) F2: -34.5% (p = 0.0158) P: -21.0% Secondary endpoint Fifty percent Responder Rates (95% CI): F1: 37.6% (29.4, 45.8; p = 0.0760) F2: 36.1% (27.9, 44.3; p = 0.0914) P: 26.4%% (18.6, 34.3) Percent change in complex partia plus secondary generalized seizures: F1: -33.0% (p = 0.0020) F2: -33.1% (p = 0.0081) P: -17.9%	F1: 5.3%/19 F2: 13.5%/7 F1: 11.2%/9 F2: 9.7%/10 F1: 15.1%/7 F2: 15.2%/7	Any events (P/F1/F2): 82.6%/88.0%/91.8% (CI , p not reported) Tx related events (P/F1/F2 47.9%/74.4/80.6% Discontinuation due to tx (P/F1/F2): 5.0%/6.0%/6.7% Common Tx related events (P/F1/F2): Dizziness: 9.9%/37.6%/38.1% Somnolence: 13.2%/18.0%/17.2% Headache: 13.2%/15.0%/13.4% Fall: 6.6%/9.8%/12.7% Irritability: 5.0%/7.5%/14.2%	NA	Fair Internal Validity Review of Bias: Selection: Low bias; the randomizatio and allocation concealment was clear. Performance: Low bias; blinding of patients and study monitors Attrition: Relatively low attrition at 12% and 14% for placebo and perampanel 8mg groups respectively, much higher at 25% in perampanel 12mg group. ITT analysis. External Validity Review of Bias: Patient characteristics: Majority pts were Caucasian in range of 85.1 - 86.6% among groups. Significant exclusion criteria may limit the generalizability. Setting: The pt's adherence rate was not reported. Treatment groups experienced much higher rate of adverse events, which might compromise the binding. The placebo response rate was high at 21% for primary endpoint. May suggest pt selection or study conduct may have been an issue. Outcomes: The study was designed to show treatment efficacy in patients who are treatment-resistant partial-onset seizures. Its efficacy in less refractory patients and other seizure types is unknown.

Study 305[3] French et. al DB, PC, RCT; MC	F1: perampanel 8mg once daily F2: perampanel 12mg once daily P: placebo	Mean age (P/F1/F2): 34.4/36.7/35.5 Female (P/F1/F2): 47.8%/49.6%/58.7% Caucasian (P/F1/F2): 84.6%/82.9%/82.6% Seizure frequency (attacks/28days; P/F1/F2): 11.8/13.0/13.7 % of concomitant AEDs at baseline (P/F1/F2): 1 AED: 12.5/12.4/7.4 2 AEDs: 47.1/52.7/52.1 3 AEDs: 40.4/34.9/40.5 Key inclusion/exclusion criteria same as study above	N= 386 P: 136 F1: 129 F2: 134	19 weeks	Primary endpoint Median % change in seizure frequency: F1: -30.5% (p = 0.0008) F2: -17.6% (p = 0.0105) P: -9.7% Secondary endpoint Fifty percent Responder Rates (95% CI): F1: 33.3% (p = 0.002) F2: 33.9% (p < 0.001) P: 14.7% Percent change in complex partial plus secondary generalized seizures F1: -32.7% (p <0.001) F2: -21.9% (p = 0.005) P: -8.1%	F1: 20.8/5 F2: 7.9%/13 F1:18.6%/5 F2: 19.2%/5 F1: 24.6%/4 F2: 13.8%/7	Any events (P/F1/F2): 68.4%/86.8%/86.0% (CI , p not reported) Tx related events (P/F1/F2) 47.8%/69.0/77.7% Discontinuation due to tx (P/F1/F2): 4.4%/9.3%/14.0% Common Tx related events (P/F1/F2): Dizziness: 7.4%/32.6%/47.9% Somnolence: 2.9%/12.4%/18.2% Headache: 13.2%/8.5%/13.2% Fatigue: 8.1%/13.2%/16.5% Falls: P: 2.9% F1+F2: 6.0%	NA	Good Internal Validity Review of Bias: Selection: Low bias; the randomizatio and allocation concealment was clear. Performance: Low bias; blinding of patients and study monitors Attrition: Relatively low attrition at 12% and 16% for placebo and perampanel 8mg groups respectively, higher rate at 23% in perampanel 12mg group. ITT analysis. External Validity Review of Bias: Patient characteristics: Majority pts were Caucasian in range of 82.6 – 84.6% among groups. Significant exclusion criteria may limit the generalizability. Setting: The study design is multi-national. Compared with other similar studies conducted in other regions have shown regional differences that can't be explained by the authors. The pt's adherence rate was not reported. Treatment groups experienced much higher rate of adverse events, which might compromise the binding. Outcomes: The study was designed to show treatment efficacy in patients who are treatment-resistant partial-onset seizures. Its efficacy in less refractory patients and other seizure types is unknown.

Study 306[4] Krauss GL et al DB, PC, RCT; MC	F1: perampanel 2mg once daily F2: perampanel 4mg once daily F3: perampanel 8mg once daily P: placebo	Mean age (P/F1/F2/F3): 34.4/33.8/33.6/34.6 Female (P/F1/F2/F3): 48.6%/52.8%/48.8%/5.4 Caucasian (P/F1/F2/F3): 64.3%/66.1%/61.0%/6.6% Seizure frequency (attacks/28days; P/F1/F2/F3): 9.3/10.1/10.0/10.9 % of concomitant AEDs at baseline (P/F1/F2/F3): 1 AED: 15.1/16.7/11.0/16.0 2 AEDs: 48.6/44.4/51.2/48.5 3 AEDs: 36.2/38.9/37.8/35.5 Key inclusion/exclusion criteria same as studies above	N = 706 P: 184 F1: 180 F2: 172 F3: 169	19 weeks	Primary endpoint Median % change in seizure frequency: F1: -13.6% (p = NS) F2: -23.3% (p = 0.003) F3: -30.8 (p <0.001 P: -10.7% Secondary endpoint Fifty percent Responder Rates (95% CI): F1: 20.6% (p = NS) F2: 28.5% (p = 0.013) F3: 34.9% (p < 0.001) P: 17.9% Percent change in complex partial plus secondary generalized seizures F1: -20.5% (p = NS) F2: -31.2% (p = 0.007) F3: -38.7% (p < 0.001) P: -17.6%	F1: NA F2: 12.6%/8 F3:20.2%/5 F1: NA F2: 10.6%/9 F3: 17%/6 F1: NA F2: 13.6%/7 F3: 21.1%/5	Any events (P/F1/F2/F3): 54.6%/61.7%/64.5%/71.6 (CI , p not reported) Tx related events (P/F1/F2/F3): 31.9%/37.2%/44.8%/56.8% Discontinuation due to tx (P/F1/F2/F2): 3.8%/6.7%/2.9%/7.1% Common Tx related events (P/F1/F2/F3): Dizziness: 9.7%/10.0%/16.3%/26.6% Somnolence: 6.5%/12.2%/9.3%/16.0% Headache: 8.6%/8.9%/11.0%/10.7% Fatigue: 2.7%/4.4%/7.6%/5.3%		Good Internal Validity Review of Bias: Selection: Low bias; the randomization and allocation concealment was clear. Performance: Low bias; blinding of patients and study monitors
								NA	Attrition: Low attrition at 10%, 14%, 8% and 14% for placebo, perampanel 2mg, 4mg and 8mg groups respectively. ITT analysis. External Validity Review of Bias: Patient characteristics: Majority pts were Caucasian in range 61.0 -68.6%. Significant exclusion criteria may limit the generalizability. Setting: The study design is multi-national. Compared with other similar studies conducted in other regions have shown regional differences that can't be explained by the authors. The pt's adherence rate was not reported. Outcomes: The study was designed to show treatment efficacy in patients who are treatment-resistant partial-onset seizures. Its efficacy in less refractory patients and other seizure types is unknown.

[1]**Study design abbreviations:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover.
[2]**Results abbreviations:** RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
[3]**NNT/NNH** are reported only for statistically significant results
[4]**Quality Rating:** (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)

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Appendix A: Specific Drug Information

CLINICAL PHARMACOLOGY[1]

Perampanel is a non-competitive antagonist of the ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons. Glutamate is the primary excitatory neurotransmitter in the central nervous system and is implicated in a number of neurological disorders caused by neuronal over excitation. The precise mechanism of action of perampanel antiepileptic effects in humans has not been fully elucidated.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications): Perampanel carries the black box warning on serious life-threatening psychiatric and behavioral adverse reactions including aggression, hostility, irritability, anger, and homicidal ideation and threats. Patient should be monitored for these reactions as well as for changes in mood, behavior, or personality that are not typical for the patient, especially duration the titration period and at higher dose; if these symptoms occur dose should be reduced and treatment should be discontinued immediately if symptoms are severe or are worsening.

Tolerability: At recommended doses, most common adverse reactions (≥ 4% and ≥1% higher than placebo) include dizziness, somnolence, fatigue, irritability, falls, nausea, weight gain, vertigo, ataxia, gait disturbance, and balance disorder.

Pregnancy/Lactation rating: C. There are no adequate well-controlled studies in pregnant women. Perampanel should be used during pregnancy only when the potential benefit to the patient justifies the potential risk to the fetus. To provide information regarding the effects on in *utero* exposure to perampanel, providers are advised to recommend that pregnant patients taking perampanel enroll in the North American Antiepileptic Drug (NAAED) Pregnancy Registry. Enrollment must be done by patients themselves. It is not known whether perampanel is excreted in human milk. Since many drugs are excreted in human milk, caution should be exercised when perampanel is given to a nursing mother.

Look-alike / Sound-alike (LA/SA) Error Risk Potential

LA/SA names are assessed during the PDL selection of drugs. Based on clinical judgment and an evaluation of LA/SA information from four data sources (Lexi-Comp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexi-Comp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for perampanel [generic]	None	None	None	None	propranolol, Tylenol
LA/SA for Fycompa™[brand]	None	None	None	None	Ixempra®, Tycopan®, Liposyn®, Procomp®

ADVERSE REACTIONS (in pooled double-blind trials and reactions ≥ 2% of patients in 12mg group and more frequent than placebo)[1]

Adverse Events	Incidence %(placebo/4mg/8mg/12mg)
Ear and Labyrinth Disorders	
Vertigo	1/4/3/5
Eye Disorders	
Diplopia	1/1/1/3
Blurred vision	1/1/3/4
Gastrointestinal Disorders	
Constipation	2/2/2/3
Nausea	5/3/6/8
Vomiting	3/2/3/4
Infections and Infestations	
Upper respiratory tract infection	3/3/3/4
Injury, Poisoning and Procedural Complications	
Contusion	1/0/2/2
Falls	3/2/5/10
Head/Limb injury	≈2/2/2/5
Skin Laceraton	1/0/2/2
Investigations	
Weight gain	1/4/4/4
Nervous System Disorders	
Asthenia	1/1/2/2
Ataxia/balance disorder/coordination abnormal	4/3/14/17
Dizziness	9/16/32/43
Dysarthria	0/1/3/4
Fatigue, hypersomnia, somnolence	12/18/26/33
Headache	11/11/11/13
Others (hypoaesthesia, memory impairment, paraesthesia)	2/0/2/7
Psychiatric Disorders	
Aggretion/anxiety/anger/irritability	≈6/7/13/22
Others (Confusion, euphoric, altered mood	≈2/2/≈3/6

DOSE & AVAILABILITY:[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
2, 4, 6, 8, 10 and 12mg	Tablets	Oral	Once daily	Can be used in patients with moderate renal impairment with close monitoring. Use in patients with severe renal impairment of patients on hemodialysis is not receommended.	Starting dose of 2mg; max. daily dose of 6mg for patients with mild hepatic impairment and 4mg for in patients with moderate hepatic impairment; use in patients with severe hepatic impairment is not recommended	Pediatric patients above 12 years old can be dosed similar to adults.	Same as adult dose.	None.

PHARMACOKINETICS:[1]

Parameter	Result
Oral Bioavailability	74-80%
Tmax	0.5 to 2.5 hours under fasting condition. Under fed conditions, Tmax was delayed by 2-3 hours compared to that under fasting conditions.
Protein Binding	Approximately 95-96%
Elimination	Approximately 22% of dose is excreted in urine and 48% in feces
Half-Life	About 105 hours.
Metabolism	Extensively metabolized via primary oxidation and sequential glucuronidation in liver.

ALLERGIES/INTERACTIONS:[1]

Drug-Drug: Oral contraceptives, CYP P450 inducers, concurrent use of perampanel with strong CYP3A inducers (such as rifampin, St. John wort) should be voided. Alcohol and other CNS depressants may increase CNS depression.

Food-Drug: Grapefruit juice or grapefruit containing products.

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Oregon Health Authority

New Drug Evaluation: Teriflunomide

Month/Year of Review: May 2013
Generic Name: Teriflunomide
PDL Class: MS Drugs

End date of literature search: December 1, 2012
Brand Name (Manufacturer): Aubagio®
Dossier Received: Yes

FDA Approved Indication:

Teriflunomide (TER) is indicated for the treatment of patients with relapsing forms of multiple sclerosis (MS).[1]

Research Questions:

- Is TER superior to placebo (PLA) for reducing relapses, disability progression, and lesion activity in subjects with relapsing MS?
- How does the efficacy and safety of teriflunomide compare to that of other DMD?
- Are there important unanswered safety questions associated with TER?

Conclusions:

- At this time, the evidence supporting the TER efficacy is low, due to the lack of a sufficient number of adequately controlled phase 3 studies, as well as issues with internal and external validity. The strongest evidence is in affecting relapse rate and evidence is more robust for the TER 14 mg dose than the 7 mg dose
    - The TEMSO trial demonstrated TER 7 mg and 14 mg compared to PLA resulted in significantly reduced rates of relapse (31.2% for TER 7mg and 31.5% for TER 14 mg), active inflammatory lesions (risk reductions were 39.4% and 67.4% for TER 7 mg and 14 mg, respectively, v PLA), and, in the case of TER 14 mg, risk of disability progression as measured by the proportion of patients with sustained disability progression (27.3% for PLA, 21.7% for TER 7 mg (NS), and 20.2% for TER 14 mg, corresponding to a NNT of 14 for TER 14 mg). The Kaplan-Meier estimated percentage of patients without relapse over 108 weeks were 45.6% for PLA, 53.7% for TER 7 mg, and 56.5% for TER 14 mg, corresponding to a NNTs of 12 and 9.[2] For Study 2001, TER 7 mg and 14 mg were superior to placebo in reducing the number of combined unique (CU) active lesions per MRI scan (the primary endpoint) during the 36-week study; however, they were not significantly superior to PLA for ARR and only TER 14 mg was superior to placebo at preventing disability progression (key secondary endpoints).[3] An interim analysis of the TOWER study revealed the percentages of patients without confirmed relapses were 66%, 76.5%, and 77.1% for PLA, TER 7 mg, and TER 14 mg, corresponding to NNTs of 10 and 9 for TER 7 mg and 14 mg, respectively.[4]

- Due to external validity concerns, one is unable to draw conclusions about the efficacy of TER in populations with secondary progressive (SP) and progressive relapsing (PR) MS, non-Caucasian patients, patients with more advanced disability, and populations who may have greater experience with DMDs, such as those in the U.S. In its review, the FDA noted the treatment effect on relapse tended to be greater among those who began with an EDSS score ≤3.5 at baseline and those with known relapsing remitting (RR) multiple sclerosis (MS).
- No head-to-head trials for TER have been published and therefore insufficient evidence to make comparative conclusions. The TENERE study assessed TER compared to interferon beta-1a, however the primary endpoints were not clinically relevant.[5] In the phase 3 TEMSO trial, both TER doses reduced the risk of relapse by about 31%, which is similar to other first-line disease modifying drugs (DMD). However, cross-trial comparisons should be viewed cautiously, as cross-trial comparisons of DMD efficacy have been found to be misleading and potentially contradictory to head-to-head trials.[6]
- There is low quality evidence for TER in reducing the risk of disability progression. However, the ARR and MRI data indicate TER would have a positive effect on disability progression, because the effect of treatment on relapse and the effect of treatment on disability are significantly correlated.[7]
- Some uncertainty surrounds the extent to which TER is safe and TER is clearly unsafe in pregnancy.
- TER comes with numerous safety concerns including hepatotoxicity and teratogencitiy, considerable monitoring, and an accelerated elimination procedure. Providers and patients may find it difficult to comply with these processes. Nevertheless, options for patients who are unable to self-administer injections or who have conditions precluding them from repeated injections have only fingolimod as an oral option. Because of fingolimod's potential to induce life-threatening bradycardia, cardiovascular monitoring is required following first dose and the drug poses a greater risk to cardiovascular patients. Therefore, TER may be an important option for patients unable to take injectables and fingolimod.

Recommendations:

- Prior authorize teriflunomide to limit use to confirmed patients with documentation of prior failed use of an interferon for MS or glatiramer acetate (Appendix 2).
- Documentation of compliance with requisite laboratory evaluation prior to prescribing

Background:

Disease modifying drugs (DMD) and symptomatic therapies are the mainstay for managing MS. The disease has no cure; therefore, the primary goals of disease modifying therapy are to prevent relapses, progression of demyelination, and long-term disability. Long-term disability progresses over many years and each patient's course varies widely. Also, patients recover some or all function over the weeks and months following an acute attack. Therefore, studies of MS treatments are limited by their short duration, their population focus, and assessment tools that inadequately predict disease course.[8-10]

MS is a chronic, progressive, immune-mediated disorder characterized by inflammation of the white and gray matter of the central nervous system and destruction of axonal myelin sheaths, resulting in neurodegeneration and gliotic sclerosis. MS affects about 350,000 people in the US and more than 1 million worldwide. MS occurs 2–2.5 times more frequently in women than in men.[11,12]

MS symptoms typically present between the ages of 18 and 45 and include combinations of the following: fatigue; heat sensitivity; weakness; depression; bladder, bowel, or sexual dysfunction; or impaired vision, sensation, coordination or balance.[11,12]

The subtypes of MS are relapsing remitting (RRMS), secondary progressive (SPMS), progressive relapsing (PRMS), and primary progressive (PPMS). About 85–90% of patients present with RRMS, which is marked by episodes of worsening or new neurological symptoms followed by periods of

inactivity. Most patients with RRMS develop SPMS within 20–40 years. SPMS is characterized by steady neurological decline with few or no clinical relapses. The least common form of MS is PRMS, which is progressive from onset and has acute relapses with progression between relapses. About 10–15% of patients present with PPMS, which is characterized by steady neurologic decline from onset for at least a year without distinct relapses.[11–14]

The goal of MS therapy is to prevent the long-term accumulation of irreversible disability. Relapse rate is the most often used primary efficacy endpoint in phase 3 clinical trials of DMD, while disease progression, as measured by change in EDSS score, and MRI-detected lesion activity have been more often used as a secondary efficacy endpoints. Each of these endpoints has limitations. Because of the uncertainty in the correlation of outcome measures and future function, the evidence from clinical trials using a combination of outcome measures—both clinical and MRI—are considered stronger.[8]

Relapse rate is the preferred primary endpoint because evaluating treatment effect on disability progress would require large patient samples sizes that could be followed for several years. A 2010 pooled analysis of published RCTs in RRMS, with treatment durations of 2 to 3 years, has found a significant correlation between the effect of treatments on relapse and the effect of treatment on disability worsening, as measured by EDSS. However, how relapses impact long-term disability is still unclear.[7]

The EDSS is based on the results of a neurological examination and the patient's ability to walk and is scored from 0, no neurological abnormality, to 10, death from multiple sclerosis. An EDSS score between 4.0 and 6.0 typically would correspond to limited walking ability and to the need for unilateral support for walking.[18–21]

The EDSS's shortcomings include the following: (1) the scale is non-linear, so the clinical importance of a 1.0-point change in EDSS varies with the baseline score; (2) the EDSS emphasizes ambulation and poorly measures cognitive and visual impairment; (3) the ratings, which are based on neurological exam, are subjective and subject to within and between rater variability; (4) the EDSS has reduced sensitivity in the mid and upper ranges of scores. Nevertheless, the EDSS is widely accepted as a measure of clinical progression in clinical trials.[22,23]

In most clinical trials of DMA, disease progression has been defined as a sustained 3- or 6-month increase in EDSS of at least 1.0 point recorded in a period when the patient had no exacerbation.[21] Because the EDSS scores for many patients continue to improve for 3 months after relapse, confirming worsening at 6 months may be a better indicator of long-term accrual of disability than assessments performed at 3 months.[22]

MRI-detected lesion activity is a well-accepted endpoint used in MS clinical trials. Often, MRI serves as a primary outcome in phase 2 studies and a secondary outcome in phase 3 studies. MRI is used to evaluate the inflammatory and degenerative aspects of MS. Treatment effects on MRI-detected lesion activity correlate well with relapse activity but only weakly with accumulated disability.[22]

Two categories of MRI measures are used to monitor MS treatment: those that reflect disease activity (new or enlarged T2 lesions, galodinium-enhancing and new enhancing lesion counts, and enhancing lesion volume) and those that reflect burden of disease and are markers of irreversible tissue loss (T2 lesion load, T1-hypointence lesions, and brain atrophy).[20]

Immunomodulatory agents—interferon (IFN)-β-1a, IFN)-β-1b, glatiramer acetate, natalizumab, and fingolimod—are used to reduce the risk of relapse and slow disease progression, but are unable to stop or reverse disability. Anti-inflammatory drugs, such as glucocorticoids are used for acute attacks.[10]

The limitations of these agents, whether delivery or side effect profile, has fueled the search for oral agents. Interferon and glatiramer acetate are first-line agents delivered by self-injection, with 12% of patients citing injection site reactions as one of many reasons patients discontinue these medications. At 30%, perceived lack of efficacy is the most oft cited reason.[9,10]

The FDA approved fingolimod as the first DMA delivered orally. Although fingolimod was approved as a first-line agent, it has been associated with potentially life-threatening bradycardia and requires 6 hours or more of hourly pulse and blood pressure monitoring in every patient and overnight ECGs in high risk cardiovascular patients. For these reasons, some practitioners believe the interferons and glatiramer acetate should be tried before prescribing fingolimod. Natalizumab, a second-line agent for patients uncontrolled on interferon or glatiramer, has been associated with progressive multifocal leukoencephalopathy.[9,10]

Guidelines from the American Academy of Neurology (AAN), National Institute for Health and Clinical Excellence (NICE), and European Federation of Neurological Societies (EFNS) have not been updated since the introduction of TER and fingolimod.[8,14,24] The following is a table for comparing their use, efficacy, and safety; however, cross-trial comparisons of DMD efficacy have been found to be misleading and potentially contradictory to head-to-head trials.[4,6]

Medication 1st or 2nd line	**Indication**	**Maintenance dose/Route of delivery**	**Efficacy**	**Safety concern**
Avonex (IFNβ-1a) 1st line	↓ exacerbations & slows physical disability in relapsing forms	30 mg qWK IM	32% RRR 37% reduction disability	Decreases blood count, hepatic injury, flu-like symptoms
Rebif (IFNβ-1a) 1st line	↓ exacerbations & slows physical disability in relapsing forms	22 mcg tiw SQ 44 mg tiw SQ	29% RRR 32% RRR	Hepatic injury, flu-like symptoms, injection site reaction
Betaseron (IFNβ-1b) 1st line	↓ exacerbations & delay physical disability in relapsing forms	0.25 mg qOD SQ	30% RRR	Injection site necrosis, flu-like symptoms
Copaxone (glatiramer acetate) 1st line	↓ exacerbations In RRMS and includes patients with CIS	20 mg/1 ml qD SQ	29-75% RRR	Transient chest pain, post-injection reaction, skin necrosis
Tysabri (natalizumab) 2nd line	↓ exacerbations & delays physical disability in relapsing forms of MS	300 mg q4WK IV	61% RRR 33% reduction disability progression	PML, immunosuppression, malignant melanoma, hepatic toxicity
Novantrone (mitoxantrone)	↓ exacerbations & neurological disability in SPMS	12 mg/m^3 q3MO IV	60% RRR	Cumulative cardiotoxicity, AML

2nd line	or worsening RRMS		64% reduction disability progression	
Gilenya (fingolimod) 1st line	↓ exacerbations & delays physical disability in relapsing forms of MS	0.5 mg PO qD	55-58% RRR 29-30% reduction disability	AV conduction delay, ↓ in HR with 1st dose, infections, macular edema, ↓ pulmonary functions, increase ↑ in liver enzymes

Clinical Efficacy:

The FDA approved TER based on one phase 3 clinical trial, called TEMSO, that is published, along with supporting, descriptive evidence from one phase 2 clinical trial, called Study 2001, and an interim analysis of a phase 3 clinical trial, called TOWER, that has not been published.[2-4]

The TEMSO trial demonstrated TER treatment resulted in significantly reduced rates of relapse, active inflammatory lesions, and, in the case of TER 14 mg, risk of disability progression. TEMSO compared TER 7 mg once daily and TER 14 mg once daily to PLA in 1088 patients randomized 1:1:1. The subjects were aged 18 to 55, had EDSS scores ≤5.5 (mean 2.68), were predominantly Caucasian (97%), female (72%), and without DMD treatment in the 2 years before randomization (73%). Most subjects had RRMS (91%) and EDSS scores≤3.5 (77%). The primary endpoint for the 108 week study was annualized relapse rate (ARR) and key secondary endpoints were confirmed disability progression and total lesion volume. Confirmed relapse was defined as the appearance of a new clinical sign or symptom (S/S) or clinical worsening of a previous S/S that had been stable for ≥30 days and persisted for ≥24 hours and an increase of 1 point in each of 2 EDSS functional-system scores or 2 points in 1 EDSS functional-system score or 0.5 points in the EDSS score from the previous clinically stable assessment. Disability progression was defined as a ≥1.0 increase in EDSS score for patients with a baseline EDSS score ≤5.5 and ≥0.5 for those with an EDSS score >5.5 that persisted for ≥12 weeks. The adjusted ARRs were 0.54 (CI: 0.47 to 0.62), 0.37 (CI: 0.32 to 0.43, p=0.01), and 0.37 (0.31 to 0.44, p=0.01) for the PLA, TER 7 mg, and TER 14 mg groups, respectively, corresponding to relative reductions v. PLA of 31.2% for TER 7mg and 31.5% for TER14 mg. The Kaplan-Meier estimated percentages of patients without relapse were 45.6% (CI: 40.2 to 51) for PLA, 53.7% (CI: 48.3 to 59.1, p<0.001) for TER 7 mg, and 56.5% (CI: 51 to 62, p=0.003) for TER 14 mg, corresponding to a NNTs of 12 and 9, respectively, to prevent 1 subject from having a relapse over 108 weeks. The percentages of patients with sustained disability progression were 27.3% (CI: 22.3 to 32.3) for PLA, 21.7% (CI: 17.1 to 26.3, NS) for TER 7 mg, and 20.2% (CI: 15.6 to 24, p=0.03) for TER 14 mg, corresponding to a hazard ratio reduction of 29.8% and an NNT of 14 for TER 14 mg. The changes in total lesion volume from baseline were 2.21±7.00 for PLA, 1.31±6.80 for TER 7 mg, and 0.72±7.59 for TER 14 mg, corresponding to relative risk reductions of 39.4% and 67.4% for TER 7 mg and 14 mg, respectively.[2] Subgroup analyses reported to the FDA revealed patients from the Americas (n=245) experienced no benefit for disability progression: hazard ratio (HR) 1.397 (CI: 0.684 to 2.851) TER 7 mg and 1.114 TER 14 mg (CI: 0.523 to 2.371) v. PLA. However, TEMSO was not powered to examine subgroups.[4]

Key limitations of TEMSO trial included the following:

- The study duration was short compared to the lengthy course of disability progression in MS.
- The patient population was less advanced in their disease state; therefore, one is unable to determine how more advanced patients will respond to TER.
- The study population was predominantly Caucasian; therefore, one is unable to determine how non-Caucasians will respond to TER.
- TER was tested only in patients with relapsing forms of MS, predominantly relapsing remitting; therefore, one is unable to draw conclusions about the efficacy of TER in patients with SPMS and PRMS (for example, subgroup analyses reported to the FDA show the relative risk TER14 mg v. PLA in this patient population is 0.985, p=0.9708. However, the n is only 26.).

- Only sustained disability progression for 12 weeks was reported. FDA analysis to estimate the percentage of patients with 24-week sustained disability progression at week 108 revealed neither TER dose had a statistically significant benefit: 25% risk reduction for TER 7 mg (p=0.1459) and 25.1% risk reduction TER 14 mg (p=0.125).[4]
- Most patients (67–77%) had not been treated with a DMD in the two years prior to randomization, only 22% of patients were from the Americas, and a subgroup analysis of patients from the Americas showed no benefit for disability progression. This casts uncertainty on how the U.S. population initially receiving TER will respond.
- The risk of disability progression was not significantly reduced in the TER 7 mg, suggesting the possibility of a dose response and the weaker efficacy of TER 7mg.

For Study 2001, TER 7 mg once daily and 14 mg once daily were superior to placebo in reducing the number of combined unique (CU) active lesions (T1 plus T2 new and persisting active lesions) per MRI scan (the primary endpoint) during the 36-week study; however, they were not significantly superior to PLA for ARR and only TER 14 mg was superior to placebo at preventing disability progression (key secondary endpoints). Disability progression was defined as an EDSS score increase ≥1.0 in patients with baseline EDSS scores ≤5.5 or a score increase ≥0.5 in patients with baseline EDSS scores ≥5.5. Study 2001, a phase 2 PLA-controlled study of TER efficacy and safety, randomized (1:1:1) 179 patients age 18 to 65 with relapsing forms of MS and EDSS scores of ≤6 (median 2.33). Patients primarily had RRMS (88%) and were predominantly female (67% PLA, 75% 7 mg, 79% TER 14 mg). Racial demographics were not reported. The mean number of CU active lesions was less for the TER groups: 1.04±0.37 for TER 7 mg and 1.06±0.38 for TER 14 mg v. 2.68±0.39 for PLA, resulting in relative reductions of -61.1% and -61.3% for TER 7 mg and TER 14 mg, respectively. However, only the TER 14 mg group had a median change in BOD (T2 lesion volume) from baseline that was significantly different from PLA: -4.1 TER 14 mg, 2.9 TER 7 mg, 5.2 PLA (p<0.02 for TER 14 mg). The TER groups had lower mean ARRs v. PLA, but not significantly: 0.58±0.85 TER 7 mg and 0.55±1.12 TER 14 mg v. 0.81±1.22 (NS). The TER 14 mg group had a larger proportion of subjects who were relapse-free v. PLA, but not significantly: 65% TER 7 mg and 77% TER 14 mg v. 62% for PLA (NS). The proportion of patients with an increase in disability was only significantly lower for the TER14 mg group v. PLA: 7.4% v. 21.3%, p<0.04.[3,4]

Because Study 2001 is a phase 2 trial, its limitations are numerous. Some key limitations include the following: the study size was small and the duration short; the study had imbalanced discontinuation rates; MRI was the primary outcome; no follow-up confirmation of EDSS progression or confirmation of relapse was performed; 6 patients were included who did not meet inclusion criteria; protocol deviations occurred for 30 patients (including the use of corticosteroids prior to MRI in 8 PLA, 7 TER 7 mg, and 10 TER 14 mg patients); the TER groups had a greater percentage of females; several figures were unreported in the published study; inadequate numbers of patients who were non-Caucasian and had SPMS were included in the study; patients with PRMS were not included; and the study did not meet several secondary efficacy measures. According to the FDA Medical Review, Study 2001 "had an inadequate design to be relied on for proving efficacy."

As further evidence of the efficacy of TER, the FDA performed an interim analysis of the TOWER study, a placebo-controlled trial of 1096 subjects randomized 1:1:1 to receive TER 7 mg, TER 14 mg, or PLA once daily. Included were subjects age 18–55 with an EDSS≤5.5 who were ambulatory and had relapsing forms of MS. Most subjects were female (71%), Caucasian (83.5%), and without DMA treatment in the 2 years prior to randomization (67%). Most subjects had RRMS (97%) and EDSS scores ≤3.5 (75%). The primary outcome was confirmed ARR. The median duration of treatment for subjects was 313 days for PLA, 302 for TER 7 mg, and 317.5 for TER 14 mg. About 44% of the three treatment groups received the specified 48 weeks of treatment. The adjusted ARR was 0.531 (CI: 0.444 to 0.634) for PLA, 0.371 (CI: 0.300 to 0.459) for TER 7 mg, and 0.321 (CI: 0.258 to 0.400) for TER 14 mg, corresponding to ARR reductions of 30% for TER 7 mg and 42.7% for TER 14 mg. The percentages of patients without confirmed relapses were 66%, 76.5%, and 77.1% for PLA, TER 7 mg, and TER 14 mg, corresponding to NNTs of 10 and 9 for TER 7 mg and 14 mg, respectively. Subgroup analysis

revealed TER outperformed PLA in all groups except for those previously treated with immunomodulators; however, the FDS noted the study is incomplete and TER was superior to PLA for this group in the TEMSO trial, which was not powered to examine subgroups.[4]

The limitations of the TOWER interim analysis are myriad due to its nature. Based on study population and design, the limitations of the TOWER study at its conclusion would be similar to that of the TEMSO trial.

Clinical Safety:[1]

In PLA-controlled studies of TER in patients with relapsing forms of MS, increased ALT, alopecia, diarrhea, influenza, nausea, and paresthesia were the most frequently reported adverse reactions (ADRs), defined as an ADR with an incidence ≥10% and ≥2% greater than PLA. Alopecia was the most common cause of discontinuation due ADRs: 0.5% and 1.4% of patients on TER 7 mg and 14 mg, respectively, and 0% on PLA). Incidents of peripheral neuropathy (<2% TER v. 0% PLA), acute renal failure (1.2% v. 0%), hyperkalemia (1% v. 0.2%), and hypertension (4% v. 2%) have been reported during TER use.

Hepatotoxicity, hematologic dysfunction, interstitial lung disease, infection, severe skin reactions, and malignancy due to immunosuppression are potential risk factors with TER, as they have been reported with leflunomide, the prodrug of TER. Therefore, TER is contraindicated in those with severe liver impairment, is not recommended in those with severe immune dysfunction, should be avoided in those with unresolved acute or chronic liver disease or infections, and liver function tests (LFTs) should be performed before and after initiating TER. TER has caused birth defects in animals; therefore, the pregnancy category for TER is X and women of childbearing potential should use contraception. TER has been detected in human semen; therefore, men on TER as well as their female partners also should use reliable contraception. In PLA-controlled trials, peripheral neuropathy was reported more frequently in patients taking TER. Clinicians should consider suspending TER and using an accelerate elimination protocol in those who develop infection, symptoms of peripheral neuropathy, or new or worsening pulmonary symptoms. In trials, 1.2% of TER-treated subjects v. 0% of PLA-treated subjects had transient acute renal failure (likely due to TER's ability to cause increased renal uric acid clearance), 1.0% of TER-treated subjects v. 0.2% of PLA-treated subjects developed hyperkalemia, and 4% of patients treated with TER v. 2% on PLA developed hypertension.

TER stays in the body for up to 2 years (8 months average); therefore, an accelerated elimination procedure must be used to rapidly clear the drug from the body when certain patients need to stop the drug. For example, this procedure, involving taking cholestyramine three times daily or charcoal twice daily for 11 days, is recommended in those who are having serious AEs, have become pregnant, are women of childbearing potential, and are men intending to father a child.

Unanswered safety questions include the following:
What are the long-term risks of taking TER? What are the safety concerns for pediatric or geriatric patients? What are the endogenous transporter-based interactions between TER and other drugs? What are the safety concerns for those who are not Caucasian and for those who have more advanced disease? What is the mutagenic potential of TER, as the results of mutagenicity assays were mixed? What are the risks of co-administrating TER with antineoplastic or immunosuppressive therapies used for treating MS has not been evaluated? What are the risks of male-mediated fetal toxicity with TER?

COMPARATIVE CLINICAL EFFICACY[2-4]

Relevant Endpoints:

1) Disability progression
2) Relapse rate
3) Disease activity as measured by MRI
4) Health-related quality of life
5) Serious adverse effects

Primary Study Endpoint:

1) Annualized relapse rate
2) Number of combined CU active lesions/scan

Ref./Study Design[a]	Drug Regimens/ Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. TEMSO O'Connor Sept 24, 2004– March 13, 2008 Phase 3, DB, PC, EDSS- and site- stratified, RT 127 centers 21 countries	1. TER 7 mg QD 2. TER 14 mg QD 3. PLA QD Duration: 108 wks	**Demographics** (PLA, TER 7 mg, TER 14 mg): · Age: 38.4, 37.4, 37.8 · Female (%): 75.8, 69.7, 71.0 · White race (%): 98.3, 97.3, 96.9 · Time from 1st MS symptom (yr): 8.6, 8.8, 8.7 · Relapses (no.) in prior year: 1.4±0.7, 1.4±0.7, 1.3±0.7 in prior 2 yrs: 2.2±1.0, 2.3±1.2, 2.2±1.0 · MS subtype (%) RR: 90.6, 91.0, 92.8 SP: 6.1, 4.6, 3.3 PR: 3.3, 4.4, 3.9 · Use of DMD in previous 2 years (%): 24.8, 27.9, 28.4 · mean EDSS: 2.68±1.34, 2.68±1.34, 2.67±1.24 · Total lesion volume (ml): 19.34, 20.37, 18.08 **Inclusion Criteria:** · age 18 to 55 yrs · RR, SP, or PRMS · EDSS ≤5.5 who are ambulatory · ≥1 relapse in the previous yr or ≥2 relapses in the previous 2 yrs · clinically stable in the 30 d before randomization	Modified ITT: 1. 365 2. 358 3. 363 Attrition: 1. 91 2. 95 3. 104	<u>Adjusted annualized relapse rate:</u> 1. 0.37 (0.32 to 0.43; < 0.001) 2. 0.37 (0.31 to 0.44; <0.001) 3. 0.54 (0.47 to 0.62) *relative reduction v. PLA:* *TER 7 mg: 31.2%* *TER 14 mg: 31.5%* <u>Kaplan Meier estimate of absence of relapse during 108 wk:</u> 1. 53.7% (48.3 to 59.1, 0.01) 2. 56.5% (51 to 62, p=0.003) 3. 45.6% (40.2 to 51) <u>Sustained disability progression (≥12 wk):</u> 1. 21.7% (17.1 to 26.3; NS) 2. 20.2% (15.6 to 24.7; 0.03) 3. 27.3% (22.3 to 32.3)	NA 8.1%/12 10.9%/9 NS 7.1%/14	**Serious AEs** TER 7 mg: 14.1% TER 14 mg: 15.9% PLA: 12.8% **AEs leading to D/C of study drug** TER 7 mg: 9.8% TER 14 mg: 10.9% PLA: 8.1%	1 1.3%/77 3.1%/32 1.7%/59 2.8%/36	Quality Rating: Fair <u>Internal Validity:</u> · High but similar D/C rates in all groups: 29% PLA, 25% TER 7 mg, and 27% TER 14 mg · FDA analysis to estimate the percentage of patients with 24-week sustained disability progression at week 108 revealed neither TER dose had a statistically significant benefit: 25% risk reduction for TER 7 mg (p=0.1459) and 25.1% risk reduction TER 14 mg (p=0.125).) · Mean EDSS score on low end of scale: 2.68 <u>External Validity:</u> · Patients predominantly female, Caucasian, and RRM subtype. Most patients had not taken DMD in previous 2 years. · Patients ambulatory and 77% of patients with EDSS scores <3.5 (% from FDA analysis)

		Exclusion Criteria: · relapses in the 60 days before randomization · systemic diseases · abnormal CBC · pregnant or planned to conceive during the trial · prior or concomitant use of immunosuppressants · prior use of natalizumab, interferons or cytokines in last 4 mo, glatiramer acetate or investigational drugs in preceding 6 mo · liver function impairment or persistent LFT elevations · moderate to severe renal impairment		*hazard ratio reduction v. PLA:* *TER 7 mg 23.7%* *TER 14 mg 29.8%* <u>Total lesion volume (change from baseline):</u> 1. 1.31±6.8 mL (p=0.03) 2. 0.72±7.59 mL (p<0.001) 3. PLA: 2.21±7 mL *relative reduction v. PLA:* *TER 7 mg: 39.4%* *TER 14 mg: 67.4%*				Analysis: · Unable to draw conclusions about the efficacy and safety of TER in more advanced patients. · Unable to draw conclusions about efficacy and safety of TER in non-Caucasian and in patients with SP/PRMS due to inadequate numbers. · The study may not reflect the U.S. MS patient population, who may have more experience with DMDs. · Treatment effect is modest particularly for TER 7 mg. NNTs to prevent relapse over 2 years are 12 and 9 for TER 7 mg and 14 mg, respectively, and to prevent sustained disability progression were NS and 14, respectively. · While TER 14 mg appears to be more effective than 7 mg, there is a greater chance of serious AE on TER 14 mg.
2. Study 2001 O'Connor Phase 2 "proof of concept" study April 2001 to March 2003 DB, PC, RT, EDSS- and site-stratified 16 centers, 2 countries	1. TER 7 mg QD 2. TER 14 mg QD 3. PLA QD (double dose given the 1st wk) Duration: 36 wks	**Demographics** (PLA, TER 7 mg, TER 14 mg): · Age: 39.2, 40.1, 40.1 · Female (%): 67, 75, 79 · Caucasian (%)*: 96.7, 91.8, 91.2 · Time since diagnosis (yr) 4.4±5.7 6.0±5.6 5.4±6.2 · Disease duration (yr) 8.6±7.9 10.3±8.1 8.5±7.1 · Relapses (no., range): in previous yr 1 (0-3), 1 (0-4), 1 (0-3) in previous 3 yrs 3 (1-9), 2 (2-5), 3 (2-6) · MS subtype (%): RR 86.9, ,88.5, 87.7 SP 13.1, 11.5, 12.3 · median EDSS score*: 2.5, 2.5, 2.0 · MRI assessments	ITT: 1. 61 2. 57 3. 61 Attrition: 1. 2 2. 11 3. 4	**Primary outcome:** No. of combined CU active lesions/scan Median 1. 0.2 2. 0.3 3. 0.5 Mean (± SE) 1. 1.04±0.37 2. 1.06±0.38 3. 2.68±0.39 *mean difference v. PLA:* *TER 7 mg:–1.64 (CI –2.69 to –0.59,*	NA NA NA	**Overall AEs** (at least one adverse event) TER 7 mg: 100% TER 14 mg:100 % PLA: 100% **Serious AEs** (elevated liver enzymes, hepatic dysfunction, neutropenia, rhabdomyolysis, trigeminal neuralgia) TER 7 mg: 8.2% TER 14 mg: 12.3%	NA NA NA 0.8/125	Quality Rating: Poor *Figures marked with * were obtained from the FDA Medical Review, as they were not reported in the published study Internal Validity: · Because this is a phase 2 study, there are insufficient patient numbers and study duration and MRI is the primary endpoint · Use of disease-modifying therapy in prior 2 years not reported. However, article states distribution

		· patients w CU active lesions (%): 62.3, 47.5, 61.4 · mean CU active lesions/scan: 2.16±0.63, 1.3±0.60, 2.48±0.62 · mean T2 lesion volume, mm^3: 9119, 10338, 8475 **Inclusion Criteria:** (see protocol) · MS · age 18 to 65 yrs · EDSS ≤6 · 2 relapses in prior 3 yrs and 1 clinical relapse during prior yr · willing to use contraception during and for 24 mos after study drug use · MRI w abnormalities consistent w MS **Exclusion Criteria:** · prior treatment w interferon, γ-globulin, glatiramer acetate, or other noncorticosteroid in the 4 mos before the trial		*p<0.03)* *TER 14 mg: –1.62* *(CI –2.68 to –0.56, p<0.01)* *relative reduction v. PLA* *TER 7 mg: –61.6%* *TER 14 mg: –61.3%* **Secondary outcomes:** Median change in BOD (T2 lesion volume) from baseline (%) at 18 weeks 1. –0.1[NS] 2. –3.8 [NS] 3. 1.1 at 36 weeks 1. 2.9 [NS] 2. –4.1 (p<0.02) 3. 5.2 Mean annualized relapse rate: 1. 0.58±0.85 [NS] 2. 0.55±1.12 [NS] 3. 0.88±1.22 % relapse-free patients 1. 65%* 2. 77% [NS] 3. 62% % patients with increased EDSS score from baseline to endpoint 1. 28.8% 2. 7.4% (p<0.04) 3. 21.3%	NA NA NA NA NS NS NS 13.9/7	PLA: 11.5% AEs leading to D/C of study drug TER 7 mg: 4.9% TER 14 mg: 14% PLA: 6.6%	NA 7.4/14	of previous meds for MS and concomitant meds given during trial were similar across groups. · FIS score not reported · Median EDSS was 2.33.* · No follow-up confirmation of EDSS progression · Relapse confirmation not performed. · 6 patients were included who did not meet inclusion criteria · protocol deviations occurred for 30 patients, including the use of corticosteroids prior to MRI in 8 PLA, 7 TER 7 mg, and 10 TER 14 mg patients · the TER groups had a greater % of females External validity: · Median EDSS was 2.33. · Changes in relapse rates were not significant over 36 weeks for TER v PLA · Change in burden of disease not significant at 36 weeks for TER 7 mg v PLA · Compared to PLA, more than twice as many patients on TER 14 mg dropped out of the study. · PRMS patients not included in study Analysis: Because this is a phase 2 study, it is inadequately designed for proving efficacy of TER and can only serve as descriptive evidence. ·TER was not significantly

								superior to PLA in preventing relapse. TER 7 mg was significantly superior to PLA in preventing disability; however, TER 14 mg was (NNT 7). TER 7 mg also was not significantly superior to PLA in reducing BOD.
3. TOWER (FDA interim analysis) August 26, 2008–February 28, 2011 (interim) DB, PC, RT, EDSS- and site-stratified 190 center, 26 countries	1. TER 7 mg QD 2. TER 14 mg QD 3. PLA QD Mean treatment duration: 1. TER 7 mg: 302 d 2. TER 14 mg: 317.5 d 3. PLA: 313 d (44% of the 3 treatment groups received the intended 48 weeks of treatment)	**Demographics** (PLA, TER 7 mg, TER 14 mg): · Age: 38.1, 37.4, 38.1 · Female (%): 69.1, 73.9, 69.8 · Caucasian (%): 83.6, 82.1, 84.9 · Asian race (%): 13.7, 13.7, 12.8 · from U.S. (%): 19.1, 18.7, 17.9 · Disease duration (yr): 4.87, 5.3, 5.27 · Time since last attack (mo): 5.28, 5.22, 5.31 · Relapses (no.) in prior year: 1.4, 1.4, 1.7 · MS subtype (%) RR: 97.3, 96.3, 98.9 SP: 1.1, 0.8, 0.6 PR: 1.6, 2.9, 0.6 · Previously treated w DMD (%): 34.2, 30.3, 34.2 · EDSS: 2.66, 2.75, 2.70 · EDSS ≤3.5: 77.5, 74.9, 73.6 **Inclusion Criteria:** · Age 18–55 · EDSS≤5.5 and ambulatory · ≥1 relapse over the preceding 12 mo or 2 relapses over the preceding 24 mo and no relapses 30 d before randomization **Exclusion Criteria:** · Similar to TEMSO trial above · use of natalizumab, IV immunoglobulins, cladribine, glatiramer acetate, mitoxantrone, or other immunomodulatory agents in preceding 6 mo or other interferons or cytokine therapy in prior 4 mo	Modified ITT: 1. 378 2. 349 3. 365 Attrition: 1. 85 2. 74 3. 72	**Primary outcome:** Annualized confirmed relapse rate: 1. 0.371 (0.300 to 0.459; < 0.001) 2. 0.321 (0.258 to 0.400; <0.001) 3. 0.531 (0.444 to 0.636) *Relative risk reduction v. PLA:* *TER 7 mg: 30%* *TER 14 mg 42.7%* % relapse-free patients 1. 76.5% 2. 77.1% 3. 66%	NA 10.5/10 11.1/9	NA	NA	Quality Rating: Poor Internal Validity: Because this is an interim report, insufficient information exists to fully assess internal validity. However, the following are noted: · Protocol violation as of interim analysis 2.5% (n=27). Most frequent protocol violation was treatment compliance <80%: n=8 TER 14mg, 4 TER 7 mg, 2 PLA · Compliance rates 77.6-80.3% (similar in all 3 arms) · Mean EDSS score on low end of scale: 2.68 · High attrition rates: 22.4% TER 7 mg, 21.1% TER 14 mg, 19.7% PLA External Validity: Because this is an interim report, insufficient information exists to fully assess external validity. However, the following are unlikely to change: · Patient population predominantly female and Caucasian and Asian. ·Patients ambulatory and 77% of patients with EDSS≤3.5.

								· Most patients had not taken DMD in previous 2 years. · 18.6% of patients from U.S. Analysis: Based on patient characteristics one would be unable to draw conclusions about efficacy and safety in racial populations other than Caucasian or Asian, in SP/PRMS populations. How U.S. patients would respond to TER has some uncertainty, as the study may not reflect the U.S., which may have an MS population with more experience with DMDs.

DB: double blind, PC: placebo controlled, RT: randomized trial, TER: teriflunomide, PLA: placebo
EDSS: Expanded Disability Status Scale (ranges from 0 to 10, with higher scores indicating greater disability)
RR: relapsing remitting, SP: secondary progressive, PR: progressive relapsing, MS: multiple sclerosis, DMD: disease modifying drug
D/C: discontinuation. AEs: adverse events, NA: not applicable

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY[1,4]

TER is a novel immunomodulator with anti-proliferative and anti-inflammatory properties. Its exact mechanism of action is unknown; however, it blocks *de novo* pyrimidine synthesis by selectively and reversibly inhibiting the mitochondrial enzyme dihydroorotate dehydrogenase. TER's cytostatic effect on proliferating peripheral T-cells and B-cells may reduce the number of activated lymphocytes entering the central nervous system.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	100%
Protein Binding	>99%
Elimination	Biliary excretion of unchanged drug and renal excretion of metabolites (37.5% feces and 22.6% urine over 21 days)
Half-Life	About 18 days*
Metabolism	Unchanged TER (major) Hydrolysis (primary pathway to minor metabolites)

*Without an accelerated elimination procedure, the plasma concentrations of TER fall to <0.02 mg/L after an average of 8 months or as much as 2 years. An accelerated elimination procedure can be used at any time after stopping TER. Elimination can be accelerated by either:

- giving cholestyramine 8 g every 8 hours for 11 days (cholestyramine 4 g three times daily can be used if cholestyramine 8 g three times daily is intolerable) OR
- giving 50 g oral activated charcoal powder every 12 hours for 11 days.

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS*
7 mg or 14 mg tablets	Oral	Once daily	7 mg or 14 mg daily	No dosage adjustment	No dosage adjustment for mild and moderate impairment. Contraindicated in severe impairment (PK not established).	Efficacy and safety not established	Clinical studies did not include subjects >65 years	Taken with or without food

* Before starting TER, screen patients for latent tuberculosis infection with a TB skin test, exclude pregnancy, confirm use of reliable contraception in women of childbearing potential, check BP, obtain a complete blood cell count within the 6 months prior to starting therapy, instruct patients receiving TER to report symptoms of infections, and obtain serum transaminase and bilirubin levels within the 6 months prior to starting therapy.

After starting TER, monitor ALT levels at least monthly for 6 months after, consider additional ALT monitoring when TER is given with other potentially hepatotoxic drugs, consider stopping TER if serum transaminase levels increase (>3 times the ULN), monitor serum transaminase and bilirubin particularly in patients who develop symptoms

suggestive of hepatic dysfunction, stop TER and start accelerated elimination in those with suspected TER-induced liver injury and monitor liver tests weekly until normalized, check BP periodically and manage elevated BP, check serum potassium level in TER-treated patients with hyperkalemia symptoms or acute renal failure, monitor for signs and symptoms of infection.

Monitor for hematologic toxicity when switching from TER to another agent with a known potential for hematologic suppression, because systemic exposure to both agents will overlap.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

Hepatotoxicity: Risk of hepatotoxicity is expected with TER because leflunomide has caused severe, including fatal, liver injury. Taking TER concomitantly with other potentially hepatotoxic drugs may increase the risk of severe liver injury. Transaminase and bilirubin levels should be obtained within 6 months before initiating therapy. ALT levels should be monitored at least monthly for 6 months after starting TER. Suspected cases of liver injury should stop TER and start the accelerated elimination procedure. TER is contraindicated in patients with severe hepatic impairment, and, normally, should be avoided in those with pre-existing acute or chronic liver disease or ALT >2 times the upper limit of normal (ULN). Patients with pre-existing liver disease may be at risk of developing elevated transaminase levels.

Teratogenicity: TER is contraindicated in pregnant women or women of childbearing potential not using reliable contraception, because TER has caused major birth defects in pregnant animals. Pregnancy must be excluded before starting TER and avoided during TER treatment or before completing an accelerated TER elimination. Women receiving TER who wish to become pregnant must discontinue TER and undergo accelerated elimination, which includes verifying TER plasma concentrations <0.02 mg/L.

Co-administration of teriflunomide with leflunomide is contraindicated.

Warnings and Precautions:

Risk of pancytopenia, agranulocytosis, and thrombocytopenia may exist for TER as they have been reported postmarketing with leflunomide.

Patients with active acute or chronic infections should not start TER until infections are resolved. Suspending TER treatment and using accelerated elimination in those who develop an infection should be considered. TER is not recommended for patients with severe immunodeficiency, bone marrow disease, or severe, uncontrolled infections. Vaccination with live vaccines is not recommended.

TER has the potential to be immunosuppression, which could increase the risk of malignancy, particularly lymphoproliferative disorders. No apparent increase in the incidence of malignancies was reported in TER clinical trials, but larger, longer-term studies are needed to determine a risk.

In PLA-controlled trials, peripheral neuropathy was reported more frequently in patients taking TER (1.2% TER 7 mg, 1.9% TER 14 mg, 0% PLA). Age >60 years, concomitant neurotoxic drugs, and diabetes may increase the risk. Consider stopping TER and performing accelerated elimination in patients who develop symptoms of peripheral neuropathy.

In trials, 10 of 844 (1.2%) of TER-treated subjects v. 0 of 421 PLA-treated subjects had transient acute renal failure with a creatinine measurement increased ≥100% above baseline. Seven of the 10 subjects had a nadir CrCl <30 mL/minute. While continuing TER, the 10 subjects had normal serum creatinine levels 6-48 days following the creatinine increase. Acute uric acid nephropathy likely explains the cases of transient acute renal failure, since TER can cause increased renal uric acid clearance.

In trials, treatment-emergent hyperkalemia >7.0 mmol/L occurred in 8/829 (1.0%) of TER-treated subjects v. 1/414 (0.2%) of PLA-treated subjects. Two TER-treated subjects had hyperkalemia >7.0 mmol/L with acute renal failure.

Hypertension was reported as an adverse reaction in 4% of patients treated with 7 mg or 14 mg of TER v. 2% on placebo. In trials, mean change from baseline in systolic BP was 2.9 mmHg and 2.7 mmHg for TER 7 mg and 14 mg, respectively, and -1.3 mmHg for PLA. The change from baseline in diastolic BP was 1.4 mmHg and 1.3 mmHg for TER 7 mg and 14 mg, respectively, and -0.9 mmHg for PLA.

Interstitial lung disease and worsening of pre-existing interstitial lung disease have been reported during treatment with leflunomide. A similar risk would be expected for TER. New onset or worsening pulmonary symptoms, such as cough and dyspnea, with or without associated fever, may be a reason to stop TER.

Co-administration of TER with antineoplastic or immunosuppressive therapies used for treating MS has not been evaluated. No specific safety concerns arose in studies of TER used with other IMA (interferon beta, glatiramer acetate) for up to 1 year. The long-term safety of these combinations in treating MS has not been established.

Drug-Drug Interactions: TER may be an inhibitor of CYP2C8 and the BCRP, OATP1B, and OAT3 transporters, as well as a weak inducer of CYP1A2. A 25% decrease in peak INR is observed when TER is co-administered with warfarin, and about 1.5-fold increases in ethinylestradiol and levonorgestrel Cmax and AUC were observed when TER was coadministered with these contraceptive hormones. Clinicians should monitor patients taking drugs metabolized by CYP2C8 (e.g., repaglinide, paclitaxel, pioglitazone, or rosiglitazone) or CYP1A2 (e.g., duloxetine, alosetron, theophylline, and tizanidine), and warfarin and consider the type or dose of oral contraceptives used with TER. Studies to confirm transporter-based interactions have not been done.

Food-Drug Interactions: None

Allergy/Cross Reactive Substances: TER has the potential to cause SJS or TENs, as rare cases of these skin reactions have been reported in patients taking leflunomide for rheumatoid arthritis.

Pregnancy/Lactation rating: Pregnancy category X. TER is contraindicated in women who are pregnant or are of childbearing potential and not using reliable contraception, because animal studies have demonstrated the drug is teratogenic and embryolethal at doses less than those used clinically. It is unknown whether the drug is excreted in breast milk, but due to the potential for serious adverse reactions in nursing infants, either the drug or nursing should be discontinued. TER has been detected in semen and animal studies have not been performed to evaluate the risk of male-mediated fetal toxicity. Men on TER should use reliable contraception, as well as their female partners, and undergo accelerated elimination before attempting to father a child. TER reduces the epididymal sperm count in male rats at doses less than the maximum recommended human dose (MRHD), but no effects on fertility were observed.

Dose Index (efficacy/toxic):
Studies in mice have shown no evidence of carcinogenicity at plasma exposures corresponding to 3 times the plasma exposure of humans MRHD. Studies in rats were performed at doses producing plasma exposure concentrations below the MRHD. TER and its metabolite were positive for mutagenesis in some in vitro mutagenicity assays, including the chromosomal aberration assay in human lymphocytes. Although TER was negative in the in vitro Ames and HPRT assays and in vivo micronucleus and chromosomal aberration assays, its minor metabolite, 4-trifluoromethylaniline, was positive in the Ames and HPRT assays.

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

NME Drug Name	Lexicomp	USP Online	Clinical Judgment
LA/SA for teriflunomide	None	Not updated since drug approval	Flutamide Teriparatide
LA/SA for Aubagio	None	Not updated since drug approval	None

ADVERSE REACTIONS[1]

Table 1 Adverse Reactions in Study 1 (occurring in ≥ 2% of patients, and reported for teriflunomide 7 mg or 14 mg at ≥ 2% higher rate than for placebo)

	Teriflunomide		
PRIMARY SYSTEM ORGAN CLASS Preferred Term (%)	14 mg (N=358)	7 mg (N=368)	Placebo (N=360)
INFECTIONS AND INFESTATIONS			
Influenza	12%	9%	10%
Upper respiratory tract infection	9%	9%	7%
Bronchitis	8%	5%	6%
Sinusitis	6%	4%	4%
Cystitis	4%	2%	1%
Gastroenteritis viral	4%	2%	1%
Oral herpes	4%	2%	2%
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Neutropenia	4%	2%	0.3%
Leukopenia	1%	2%	0.3%
IMMUNE SYSTEM DISORDERS			
Seasonal allergy	3%	2%	1%
PSYCHIATRIC DISORDERS			
Anxiety	4%	3%	2%
NERVOUS SYSTEM DISORDERS			
Headache	19%	22%	18%
Paraesthesia	10%	9%	8%
Sciatica	3%	1%	1%
Burning sensation	3%	2%	1%
Carpal tunnel syndrome	3%	1%	0.3%
EYE DISORDERS			
Vision blurred	3%	3%	1%
Conjunctivitis	1%	3%	1%
CARDIAC DISORDERS			
Palpitations	2%	3%	1%
VASCULAR DISORDERS			
Hypertension	4%	4%	2%
GASTROINTESTINAL DISORDERS			
Diarrhoea	18%	15%	9%
Nausea	14%	9%	7%
Abdominal pain upper	6%	5%	4%
Toothache	4%	4%	2%
Abdominal distension	1%	2%	0.3%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
Alopecia	13%	10%	3%
Acne	3%	1%	1%
Pruritus	3%	4%	2%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
Musculoskeletal pain	4%	5%	3%
Myalgia	3%	4%	2%
INVESTIGATIONS			
Alanine aminotransferase increased	14%	12%	7%
Gamma-glutamyltransferase increased	3%	5%	1%
Aspartate aminotransferase increased	3%	2%	1%
Weight decreased	2%	3%	1%
Neutrophil count decreased	2%	3%	0.3%
White blood cell count decreased	1%	3%	0%

Appendix 2: Suggested PA Criteria:

Oral MS Drugs

Goal(s):

- To ensure appropriate and safe drug use drugs
- Promote preferred drugs

Length of Authorization: One year

Requires PA:

- **Fingolimod (Gilenya)**
- **Teriflunomide (Aubagio)**

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Does the patient have a diagnosis of relapsing Multiple Sclerosis (ICD-9 340)?	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Will the prescriber consider a change to a Preferred MS product? Message: • Preferred products are evidence-based reviewed for comparative effectiveness and safety by the Pharmacy and Therapeutics Committee.	**Yes:** Inform Provider of covered alternatives in class. http://www.oregon.gov/DHS/healthplan/tools_prov/dl.shtml	**No:** Go to #4
4. Has the patient failed or cannot tolerate a full course of interferon beta 1a or interferon beta 1b, and glatiramer?	**Yes:** Go to #5.	**No:** Pass to RPH; Deny (medical appropriateness)
5. Is the medication being prescribed by or in consultation with a neurologist?	**Yes:** Go to #6.	**No:** Pass to RPH; Deny (medical appropriateness)
6. Is the patient on concurrent treatment with a disease modifying drug (i.e. interferon beta-1B, glatiramer acetate, interferon beta 1A, natalizumab, mitoxantrone)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #7
7. Is the prescription for fingolimod?	**Yes:** Go to #8	**No:** Approve up to one year

8. Does the patient have evidence of macular edema (ICD-9 362.07)?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #9
9. Does the patient has preexisting cardiac disease, risk factors for bradycardia, or is on antiarrhythmics, beta-blockers, or calcium channel blockers?	**Yes:** Go to #10.	**No:** Approve up to one year
10. Has the patient had a cardiology consultation before initiation?	**Yes:** Approve up to one year	**No:** Pass to RPH; Deny (medical appropriateness)

Clinical Notes:

- Because of bradycardia and atrioventricular conduction, patients must be observed for six hours after initial dose in a clinically appropriate area.
- Patients on antiarrhythmics, beta-blockers or calcium channel blockers or with bradycardia risk factors (h/o MI, age >70 yrs, electrolyte disorder, hypothyroidism) may be more prone to development of symptomatic bradycardia and should be initiated on fingolimod with caution and cardiology evaluation should be done before considering treatment.
- Injectable disease modifying treatments remain first line agents in MS therapy.
- An ophthalmology evaluation should be repeated 3- 4 months after fingolimod initiation with subsequent evaluations based on clinical symptoms.

DUR Board Action: 3-29-2012
Revision(s): 5-30-2013 (MH)
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Oregon Health Authority

Abbreviated Drug Evaluation: Repository corticotropin injection

Month/Year of Review: March 2013
Generic Name: Repository corticotropin injection
PDL Class: None

End date of literature search: February 2013
Brand Name (Manufacturer): Acthar Gel® (Questcor Pharmaceuticals)
Dossier Received: Yes

FDA Approved Indication:
Repository corticotropin is an injectable formulation of the adrenocorticotropic hormone (ACTH) analogue indicated as monotherapy for the treatment of infantile spasms in infants and children less than 2 years of age and for the treatment of exacerbations of multiple sclerosis (MS) in adults. It may also be used for the following disorders that are corticosteroid responsive: rheumatic; collagen; dermatologic; allergic states; ophthalmic; respiratory; and edematous state.[1]

Conclusions:

- There remains very low to insufficient evidence for the treatment of infantile spasms. Most trials are open label or retrospective analysis.
- There is low quality evidence that ACTH may be effective and that vigabatrin is possibly effective for the short term treatment of infantile spasms; however, there remains insufficient evidence if treatment will result in better long-term developmental outcomes.
- There is insufficient evidence to support the use of repository corticotropin injection in the use of aiding in the diagnosis of adrenocortical insufficiency and this indication was removed from the product label in 2010.
- There is insufficient evidence comparing repository corticotropin injection in corticosteroid responsive disorders and no evidence proving superior efficacy or safety to systemic corticosteroids. Available evidence is based on retrospective analyses and case series.
- There is low quality evidence that ACTH is beneficial compared to placebo in improving the symptoms of MS acute exacerbations and insufficient evidence that treatment with ACTH prevents new exacerbations or reduces long term disability.
- There is insufficient evidence demonstrating a difference in rate of recovery between high dose glucocorticoids and ACTH in the treatment of MS exacerbations. ACTH may be an option in those patients who cannot tolerate steroids.
- There is insufficient evidence to support the use of repository corticotropin injection in conditions not responsive to corticosteroid therapy (tobacco cessation, acute gout, childhood epilepsy)

Recommendations:

- Prior authorize repository corticotropin injection to allow coverage for the treatment of infantile spasms in patients less than 2 years of age and restrict other use for those who cannot tolerate appropriate glucocorticoid therapy.

Background:

Acthar Gel® is an injectable formulation (IM or SQ) of ACTH. It works by stimulating the adrenal cortex to secrete cortisol, corticosterone, aldosterone, and a few other androgenic substances.[2] The three most common indications of ACTH are adrenocortical testing, MS, and infantile spasms (West syndrome). ACTH was originally approved in 1952 for a broad range of corticosteroid-responsive conditions in which systemic corticosteroids (prednisone) are commonly used today. Currently, these labeled indications include rheumatic disorders, collagen diseases, dermatologic diseases, allergic states, ophthalmologic diseases, respiratory diseases, and edematous states. Previously, cosyntropin was available only as the brand-name product Cortrosyn® which is indicated for diagnostic testing of adrenal function.[3] Cosyntropin products have been used off-label to treat a variety of diseases. In 2008, Questcor implemented a new strategy for Acthar Gel®, including a price increase to continue manufacturing and distributing this agent.[2]

Infantile spasms, or West syndrome, is a rare disorder that includes a type of epileptic seizure and an electroencephalogram (EEG) finding called hypsarrhythmia. Onset usually occurs before age of one. While the seizures generally resolve by the age of 3, long-term prognosis is poor, with a high incidence of developmental delay, structural neurological abnormalities and persistent seizure activity.[4] The goal of infantile spasms treatment is to stop the seizures, normalize the EEG, and optimize the neurodevelopmental outcome. The FDA approved repository corticotropin injection for the treatment of infantile spasms in 2010. FDA approval was based on one randomized controlled trial and one supportive trial demonstrating efficacy in the cessation of spasms and amelioration of the EEG, not in the prevention of other seizure types, improvement in long-term developmental outcomes, or any other outcomes.[4] Approval was based on a re-analysis of data from previously published studies. No prospectively designed statistical analysis was performed. Other treatment options are corticosteroids, including prednisone, prednisolone, and methylprednisolone, and vigabatrin. The optimum dose and duration of treatment has not sufficiently been defined by the evidence for ACTH. However, short duration of approximately 2 weeks followed by a taper is preferred.[5] The most frequent adverse effects associated with short term use include irritability, increased appetite leading to weight gain, and Cushingoid features.

According to the FDA medical reviewer, the combined endpoint of elimination of spasms and hypsarrhythmia is generally recognized as the most clinically meaningful endpoint for efficacy studies of infantile spasms. For studies with a mean follow-up of at least 12 months, intermediate to long-term outcome measures are EEG without epileptiform abnormalities, absence of seizures, and normal development. [4]

For the treatment of exacerbations of multiple sclerosis (MS), both ACTH and corticosteroids have been used. They reduce inflammatory response by inducing several effects on the immune system. There is limited evidence on effect on outcomes from treating exacerbations and no randomized controlled trials (RCTs) are currently available. The goal in the treatment of MS exacerbations is to reduce short term disability after an exacerbation, prevent new exacerbations, and reduce long term disability.[5] Acute attacks are usually treated with glucocorticoids, such as a 3 to 7 day course of intravenous methylprednisolone.[6] This may sometimes be followed by a tapered dose of oral steroids. Repository corticotropin is typically used in patients who cannot tolerate high-dose glucocorticoids. There is insufficient evidence demonstrating a difference in rate of recovery between high dose glucocorticoids and ACTH in the treatment of MS exacerbations. The most effective dose and duration of repository corticotropin injection have not been determined and a dose of 80 units/day for at least 5 days and for as many as 15 days is commonly used.[7]

Overall, there is a lack of studies comparing the effectiveness of repository corticotropin to corticosteroids in corticosteroid-responsive conditions. There is no reliable evidence in persons who have failed to respond to first line corticosteroids. There remains uncertainties concerning the effect of repository corticotropin on the magnitude of endogenous cortisol production and therefore has a potential for significant adverse effects. Although previously used as an

aid in the diagnosis of adrenocortical insufficiency, this indication was removed from the repository corticotropin label in 2010. There is insufficient evidence to support its use.

Methods:
A Medline literature search ending February 2013 for new systematic reviews, clinical guidelines, and randomized controlled trials (RCTs) comparing repository corticotropin injection was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and 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 for this class update. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

Efficacy Summary:

West Syndrome:
Corticotripin injection was FDA approved for infantile spasms in 2010 based on a 1996 single blinded clinical trial comparing a 2 week course of ACTH 75 u/m2 twice daily to prednisone 1 mg /kg twice daily in 29 infants under 2 years of age (n=29).[4,8] The treating physician was not blinded to treatment assignment, but the EEGs were read by a blinded evaluator.[4] The median age was slightly higher in the prednisone group compared to the ACTH group. The primary outcome was the number in each group who were treatment responders, defined as having a complete suppression of both clinical spasms and hypsarrhythmia on a full sleep cycle video EEG. After treatment, 13 (86.7%) of those randomized to ACTH compared to 4 (28.6%) of those given prednisone responded (p=0.0015). The lack of double blinding and small nature of this study add risk of bias to the results and should be interpreted with caution. In addition, there was not a defined statistical plan and the primary outcomes were not chosen in advance by authors.

Systematic Reviews:
A 2008 systematic review from the Cochrane Collaboration compared the effects of therapies to treat infantile spasms in terms of control of spasms, resolution of hypersarrhythmia, long-term psychomotor development, and subsequent epilepsy rates.[9] Fourteen RCT's were included (n=667), evaluating 9 different medications. Overall, quality and methodology of the included RCT's were poor. Most studies included small numbers of participants and blinding of recipients only occurred in four studies. No studies evaluated long-term psychomotor development. Twelve of the 14 studies had a high risk of bias. In addition, many of the studies did not explicitly distinguish between ACTH and cosyntropin and it cannot be determined which treatment study patients received. The authors concluded that no single treatment has been proven to be more efficacious in treating infantile spasms than any of the others. However, the strongest evidence suggests that hormonal treatment (ACTH) leads to resolution of spasms faster and in more infants than does vigabatrin.

One study included a nested analysis of ACTH versus high-dose prednisolone and found 19 or 25 patients (76%) treated with ACTH had cessation of spasms compared with 21 of 30 (70%) patients treated with prednisolone (OR 1.36, 95% CI 0.41-4.53). However, this was an analysis nested within the comparison of vigabatrin with hormonal treatment. Effects on reduction in spasms, time to relapse, and psychomotor development were not reported. [9]

Clinical Guidelines

A 2004 practice parameter from the American Academy of Neurology concluded that repository corticotropin injection is probably an effective agent in the short-term treatment of infantile spasms.[6] The guidelines also concluded that there is insufficient evidence to determine whether oral corticosteroids are effective, and that vigabatrain was possibly effective but there are significant concerns about retinal toxicity.

These practice guidelines were updated in 2012 through a literature search up to 2011.[10] Main conclusions of the updated guidelines are as follows:

- Data is insufficient regarding the equivalence of other corticosteroids to ACTH as being effective for short-term treatment of infantile spasms (Level U recommendation based on non-randomized trials and consensus opinion). Data is inadequate or conflicting
- Low dose ACTH is an alternative to high-dose ACTH based on Class I (RCT) evidence showing similar efficacy.
- ACTH or vigabatrin may be offered for short-term first line treatment of infantile spasms. However, evidence suggests that ACTH may be offered over vigabatrin (Level C recommendation; possibly effective) and may result in better long-term cognitive outcomes than vigabatrin.
- Insufficient evidence exists to support other antiepileptic drugs.

Multiple Sclerosis

Systematic Reviews:

A 2000 Cochrane review evaluated the efficacy and safety of corticosteroids or ACTH in reducing short term and long term morbidity associated with MS.[5] Only six trials were identified for the evaluation and risk of bias was high. However, all trials did suggest a benefit of ACTH or high doses of methylprednisolone in improving acute exacerbation of symptoms within the first five weeks of treatment (OR 0.378, 95% CI 0.24-0.57). There was insufficient evidence to determine if steroids or ACTH treatment prevented new exacerbations or worsening of long-term disability. There was also insufficient evidence to support the use of one drug, methylprednisolone or ACTH, over the other. Indirect comparisons indicated that methylprednisolone may show a greater benefit compared to ACTH and that the intravenous administration may give greater effect than oral administration.

Randomized Controlled Trials

Since the systematic review, one small, prospective, open-label, poor quality trial compared a 5-day course of self-administered ACTH for exacerbations of MS.[11] Of the 20 study patients, 19 completed the study and results suggested that a five-day course of patient administered ACTH gel therapy may relieve symptoms of acute exacerbations of MS. There were small, non-significant, differences favoring the intramuscular route compared to the subcutaneous route.

A small, open-label, pilot study comparing monthly pulse ACTH therapy added to beta interferon to methylprednisone has been completed. However, it has not been published and only the abstract is available.[12]

Clinical Guidelines

2003 Guidance from NICE recommends that any individual who experiences an acute episode should be offered a course of high-dose corticosteroids.[13(p8)] Recommendations include IV methylprednisolone, 500mg-1g daily, for between 3 and 5 days. An update of the clinical guidance is scheduled for 2013.

Guidelines from the American Academy of Neurology conclude that glucocorticoid treatment has been demonstrated to have a short-term benefit on the speed of functional recovery in acute attacks of MS. They give a Type A recommendation to consider treatment with glucocorticoids for any patient with an acute attack of MS.[14]

Other Indications

For the treatment of corticosteroid-responsive conditions, no randomized clinical studies were found. Only retrospective case series or open-label studies were identified from the literature search. There is no quality evidence of the effectiveness of ACTH gel in those who have failed to respond to corticosteroids.

Nephrotic Syndrome:

The clinical practice guidelines for glomerulonephritis from the Kidney Disease Improving Global Outcomes (KDIGO) were updated in 2013.[15] For the treatment of idiopathic membranous nephropathy, the guidelines state that there have been preliminary reports of uncontrolled studies demonstrating effects of ACTH in gel formulation. However, no RCT's have been conducted with this formulation and no recommendations can be made for the use of ACTH for treatment. They also conclude there is insufficient evidence to use in the treatment of patients resistant to first-line therapy. [15]

In a retrospective case series published in 2011, Bomback, et al. evaluated all known cases of idiopathic nephrotic syndrome treated with ACTH gel through prescription.[16] Data in the United States was available for 21 patients. Three of these patients were using it as primary therapy while the remaining patients ha failed previous immunosuppressive regimens. Overall 11 patients (52%) achieved a complete or partial remission and 4 (19%) achieved complete remission. Important limitations of this data include the observational study method, lack of randomization, lack of control, short follow-up, and small number of patients. No formal statistical analysis was able to be performed and therefore it is difficult to interpret these results.

On additional, open label, prospective, nonblinded study, evaluated the use of ACTH gel on 15 patients with resistant glomerular diseases (2012). Resistant disease was defined as failure to achieve sustained remission with at least 2 prior immunosuppressive regimens (idiopathic membraneous nephropathy), failure to achieve remission with corticosteroids and at least 1 other immunosuppressive regimen (minimal change disease/focal segmental glomerulosclerosis), or resistant disease despite maximum tolerated doses of renin-angiotensin-aldosterone blockade (IGA nephropathy). Patients received ACTH gel 40 units subcutaneously twice weekly for 2 weeks, followed by 80 units twice weekly for 22 weeks. The primary outcome was remission status at the completion of ACTH therapy.[17] Again, no formal statistical analysis was able to be completed due to the small number and pilot study design. Overall, 4 subjects achieved partial remission and 3 subjects discontinued therapy early due to adverse events. Two because of worsening glycemic control and one due to weight gain. The many limitations including small sample, lack of control group, short-term follow up, and lack of randomization make it difficult to interpret these results.

Dermatoymyositis

A single retrospective case series provides clinical observations on treating patients with refractory dermatomyositis and polymyositis uding ACTH gel.[18] Patients observed had either failed or were unable to tolerate the side effects of previous therapy with steroids, intravenous immunoglobulins, and steroid-sparing drugs. The author reported that improvement in manual muscle testing at 3 months was seen in all patients, including improved muscle strength, decreased pain, and resolution of skin involvement but further studies are needed. [18]

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Appendix 1: Specific Drug Information

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose
80 USP units per mL	IM or SubQ	Every 24-72 hours	Infantile Spasms: 75 U/m2 twice daily. After 2 weeks of treatment, dosing should be gradually tapered and discontinued over a 2-week period Acute Exacerbations of MS: 80-120 units daily for 2-3 weeks. A taper may be necessary. In the treatment of other disorders and diseases, dosing needs to be individualized. The usual dose is 40-80 units IM or SubQ every 24-72 hours.	Has not been studied.	Has not been studied. Enhanced effect in liver cirrhosis.	Indicated for the treatment of infantile spasms in children age 2 and under.

Other Dosing Considerations:

For the treatment of infantile spasms, the following is one suggested tapering schedule: 30 U/m2 in the morning for 3 days; 15 U/m2 in the morning for 3 days; 10 U/m2 in the morning for 3 days; and 10 U/m2 every other morning for 6 days.

Dosing is typically based on body surface area (BSA). For calculation of body surface area, use the following formulary:

$$BSA(m^2) = \sqrt{\frac{weight\ (\text{kg}) \times height\ (\text{cm})}{3600}}$$

For the treatment of MS, although drug dependence does not occur, sudden withdrawal after prolonged use may lead to adrenal insufficiency or recurrent symptoms which makes it difficult to stop the treatment. It may be necessary to taper the dose.

For other indications in those over 2 years of age, dosage should be individualized based on the disease and general medical condition of each patient. Frequency and dose should be determined by considering severity of the disease and the initial response of the patient.

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

Contraindications:

Patients with scleroderma, osteoporosis, systemic fungal infections, ocular herpes simplex, recent surgery, history of a peptic ulcer, congestive heart failure, uncontrolled hypertension, or sensitivity to proteins of porcine origin.

Administration of live or attenuated vaccines

Children under 2 years of age with suspected congenital infections.

Warnings and Precautions:

Infections – increased susceptibility to new infection and increased risk of exacerbation, dissemination or reactivation of latent infections.

Adrenal insufficiency after prolonged therapy

Cushing's Syndrome

Elevated blood pressure, salt and water retentio

Vaccination

Masking of symptoms of other underlying disease/disorders

GI perforation and bleeding

Behavioral and mood disturbances

Comorbid Diseases – symptoms of diabetes and myasthenia gravis may be worsened

Negative effects on growth and physical development

Appendix 2: Suggested PA Criteria

Repository Corticotropin Injection (Acthar Gel®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which corticotropin has been shown to be effective and safe.

Length of Authorization: 4 weeks

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the diagnosis monotherapy for infantile spasms in infants and children under 2 years of age (ICD-9 345.6) ?	**Yes:** Approve up to 4 weeks (2 weeks of treatment, and 2 weeks of taper)	**No:** Go to #3
3. Is the diagnosis for acute exacerbation or relapse of multiple sclerosis (ICD-9 340)?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny (medical appropriateness)
4. Has the patient tried and unable to tolerate IV methylprednisolone or oral administration of high-dose methylprednisolone?	**Yes:** Approve up to 5 weeks (3 weeks of treatment, followed by taper)	**No:** Go to #5
5. Is the prescription for adjunctive therapy for short term administration in corticosteroid-responsive conditions including • The following rheumatic disorders: psoriatic arthritis, rheumatoid arthritis, juvenile rheumatoid arthritis, ankylosing spondylitis.(ICD-9 696.0, 714, 714.3, 720.0, 710.0)? OR • The following collagen diseases: systemic lupus erythematosus, systemic deramtomyositis (ICD-9 710.0, 710.3, 710.4)?, OR • Dermatologic diseases such as erythema multiforme, Stevens-Johnson syndrome (ICD-9 695.1, 695.13, 695.14)?, OR • Ophthalmic diseases such as keratitis, iritis, uveitis, optic neuritis, or chorioretinitis (ICD-9 970, 364.0-364.3, 377.3, 363.2)?, OR • For the treatment of respiratory diseases including Symptomatic Sarcoidosis (ICD-9 • For treatment of an edematous state (ICD-9 782.3)?	**Yes:** Go to #6	**No:** Go to #6.
6. Are there contraindications or intolerance to any, or therapeutic failure with at least one intravenous corticosteroid?	**Yes:** Approve x 6 months	**No:** Pass to RPH; Deny (medical appropriateness)

Dosing:

Infantile spasms in children under 2 years of age

- Must be administered intramuscularly
- 75 U/m^2 twice daily over a 2 week period
- Dose should then be tapered over a 2 week period to avoid adrenal insufficiency

Acute exacerbations of multiple sclerosis in adults

- May be given intramuscularly or subcutaneously
- 80-120 U daily for 2-3 weeks
- It may be necessary to taper the dose

Other indications for adults and children over 2 years of age

- Dosage should be individualized according to the disease under treatment and the general medical condition of each patient.
- The usual dose is 40-80 U every 24-72 hours

DUR Board Action: 5-30-2013 (MH)
Revision(s):
Initiated:

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Oregon Health Authority

Abbreviated Class Evaluation: Fat-Soluble Vitamins for the use of Cystic Fibrosis

Month/Year of Review: May 2013

End date of literature search: April 2013

Research Questions:

- Is there evidence to support the use of fat-soluble vitamins for patients with Cystic Fibrosis (CF)?
- Are certain reformulations of fat-soluble vitamins more effective than safer than individual components or other formulations?

Conclusions:

- There is limited, low quality evidence to demonstrate a benefit or harm with fat-soluble vitamin supplementation in patients with CF.
- Therapy is guided by consensus recommendations and clinical practice guidelines which all recommend routine supplementation with vitamins A, D, E and K in patients who are pancreatic insufficient with CF.

Recommendations:

- Due to the consensus among CF practitioners of routine supplementation with fat-soluble vitamin preparations in patients with CF, compare and add appropriate formulations (Source CF®, Vitamax® or ADEK®) to the list of supplements that are included in the rebate policy.
- Further evaluate the vitamin and supplement policy for appropriate exclusions to the rebate list.

Background:

Cystic fibrosis (CF) is the most common lethal genetic disease in white populations and is caused by a mutation in a gene that encodes cystic fibrosis transmembrane conductance regulator protein (CFTR).[1] Symptoms appear throughout life with variability in timing and severity. Short and long-term complications include failure to thrive, stunting, wasting, vitamin and mineral deficiencies, recurrent pulmonary infections, decreased lung function, and recurrent hsopitalizations.[2] About 85-90% of infants with cystic fibrosis develop pancreatic insufficiency and leads to fat-soluble-vitamin deficiency and malnutrition. The use of pancreatic enzyme replacement therapy can help manage malnutrition; however, adequate caloric intake and fat-soluble-vitamin deficiencies are imperative in controlling disease. [1] Patients with CF also have malabsorption of bile acids, which are necessary for absorption of fat-soluble vitamins.[3] Poor absorption of the fat-soluble vitamins (A, D, E, and K) can lead to acrodermatitis, anemia, neuropathy, night blindness, osteoporosis, and bleeding disorders. Although there is limited evidence from randomized controlled trials, standard of care includes supplementation with fat-soluble-vitamins. Many clinical practice guidelines support this. There is a strong correlation between nutritional status and pulmonary function. Water-soluble vitamins are well absorbed and routine supplementation is not necessary.

After diagnosis, the goals of CF are to maintain normal growth and development and to delay onset of pulmonary disease. The goal of nutritional treatment of infants in the newborn period is normal growth. [2] Symptomatic vitamin A and vitamin E deficiency has been reported in patients with CF and many newly diagnosed infants have low levels of one or more fat-soluble vitamins. [2] Some particular groups are at a higher risk of having decreased levels. These include patients who are homozygous for F508del and those with hypoalbuminemia or elevated alkaline phosphatase. These vitamins are available as sole supplements as well as in combination form with other vitamins (either as liquid or a tablet). The availability of different formulations differs in different health services.

Methods:

A Medline literature search ending February 2013 for new systematic reviews, clinical guidelines, and randomized controlled trials (RCTs) comparing fat-soluble vitamins in the use of CF was conducted. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, Clinical Evidence, Up To Date, Dynamed, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and 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 for this class update. RCTs will be emphasized if evidence is lacking or insufficient from those preferred sources.

Efficacy Summary:

Systematic Reviews:

Recently the Cochrane Collaboration completed systematic reviews for the supplementation of fat-soluble vitamins in the treatment of CF. Evidence was extremely limited for all vitamins and ultimately, authors found insufficient high quality evidence and recommended the guidelines be adhered to until further evidence is available. Guidelines from the Cystic Fibrosis Foundation, European Cystic Fibrosis Society, and the UK Cystic Fibrosis Trust currently exist.

A recent Cochrane systematic review attempted to determine if vitamin A supplementation in children and adults with CF reduces the frequency of vitamin A deficiency disorders, improves general and respiratory health, or increases the frequency of vitamin A toxicity.[5] However, the authors only identified one study in their literature search. This was ultimately excluded because it was not placebo controlled. There were no randomized controlled trials identified and

therefore authors could not draw any conclusions on the benefits or harms of regular administration of vitamin A in people with cystic fibrosis. They further described that until further data is available, country or region specific guidelines on the use and monitoring of vitamin A should be followed.

Another 2012 Cochrane systematic review evaluated vitamin D supplementation in children and adults with CF.[6] Three studies were included in the analysis, although only data from two were available. One study compared 800 IU of vitamin D and placebo for 12 months in pancreatic insufficient adults. The two studies showed no clear benefit or harm identified with short-term vitamin D supplementation compared to placebo (n=41). Only effects on bone mineral density (BMD) were evaluated; there were no data on the effects on growth and nutrition. No conclusions on the longer term effects could be drawn from the short term, limited data. Authors conclude there is insufficient evidence to determine a benefit or harm and adherence to relevant CF guidelines should be considered at this time.

A third systematic review from the Cochrane Collaboration assessed the effects of vitamin K supplementation in CF to determine the optimal dose and route of administration for routine and therapeutic use.[4] Only two trials were included in the review (n=32) and had a moderate risk of bias. Both trials were underpowered and of short duration. Patients were from 8 to 35 years old and all were pancreatic insufficient. Neither trial addressed outcomes of interest including coagulopathy, INR, and bone formation outcome measures. One trial demonstrated that serum vitamin K levels appeared to significantly ($p<0.001$) with supplementation. There was no statistically significant difference between the 5 mgd/day and 1 mg/day doses (MD -4.46, 95% CI -12.65 to 3.73). Based on these two trials, authors concluded that there is weak and limited evidence to support the use of vitamin K in patients with CF. However, no harm was seen and until further evidence is available, the present guidelines should be adhered to.

Clinical Guidelines

Cystic Fibrosis Foundation:

The Cystic Fibrosis Foundation commissioned an evidence review to develop evidence-based guidelines for management of infants with CF.[2] Recommendations were graded using the United States Preventive Health Services Task Force (USPSTF) grading system and made consensus recommendations for topics not included in evidence reviews or for topics for which there was limited or no evidence for.

The CF Foundation gives the following recommendations:

- All infants with CF should receive standard, age-appropriate non-fat-soluble vitamins and vitamins A, D, E, and K as recommended in the CF Foundation Consensus Report on Nutrition for Pediatric Patients.
- For infants under 2 years of age, the Foundation recommends that multivitamins designed to provide at least the recommended levels of vitamins A,D,E and K for patients should be prescribed, beginning shortly after diagnosis (Low certainty, Moderate benefit, Consensus Recommendation)
- For infants under 2, the CF Foundation recommends that a trial of zinc supplementation (1 mg elemental zinc/kg/day in divided doses for 6 months) may be given to infants who are not adequately growing despite adequate caloric intake and pancreatic enzyme replacement therapy (Low Certainty, Moderate Benefit, Consensus Recommendation).
- There is insufficient evidence to recommend for or against supplementation with linoleic acid (Grade I)
- There is insufficient evidence to recommend for or against supplementation with docosahexaenoic acid (Grade I)

The CF Foundation updated their Vitamin D guidelines in the treatment of CF due to insufficient prevention of vitamin D insufficiency due to insufficient prevention of vitamin D deficiency.[7] The foundation assembled a multidisciplinary committee with expertise in CF. A systematic review identified 36 articles for inclusion of review. The following recommendations are included:

- All individuals with CF have serum 25-hydroxyvitamin D measured to assess vitamin D status (Consensus Recommendation).
- All individuals with CF should maintain a serum 25-hydroxyvitamin D goal of at least 30 ng/ml.
- All individuals with CF be treated with vitamin D3 (Grade B).
- There was no evidence for the use of calcitriol or other or other analogs of vitamin D in CF patients.
- Although no evidence so support, consensus recommendation that all individuals with CF, from birth to 12 months of age, be treated with an initial dose of 400-500 IU vitamin D3 per day.

The European CF Society

The European CF Society Neonatal Screening Working Group also generated guideline statements from a core group of experts and reviewed then through a modified Delphi consensus process.[8] The goal was to produce guidelines on the management during the first year of life of infants with CF. The quality of identified literature was considered poor and were not reliable to provide clear guidance on management. The process resulted in 44 statements to guide management from over 86 CF specialists from 19 different countries. Therefore, general consensus statements were made and include the following:

- Fat-soluble vitamins need to be supplemented routinely in infants with pancreatic insufficiency.
- There is no agreement on the dose and preparation for Vitamin K supplementation. Recommendations for infants range from 0.3 to 1 mg daily dose.
- Suggested daily doses for fat-soluble vitamins in infants less than 1 year are
    - Vitamin A 1500 IU
    - Vitamin E 40-50 IU
    - Vitamin D 400-800 IU

The CF Trust

The Cystic Fibrosis Trust in the UK created recommendations for the nutritional management of CF.[9] This group describes what consensus groups consider to be best clinical practices. Recommendations were graded based on methods described by the Scottish Intercollegiate Guidelines Network. A Grade A recommendation is based on at least one RCT as part of overall good quality literature and addressing the specific recommendation. Grade B recommendations require well-conducted clinical studies but no RCTs. Level C recommendations required evidence from expert committee reports, opinions, and/or clinical experience of respected authorities. Recommendations from the trust include the following:

- Vitamin A, D and E supplements should be initiated on diagnosis in pancreatic insufficient patients (Grade B)
- In pancreatic sufficient patients, supplementation should be initiated when low levels are detected (Grade B)
- Vitamin K should be initiated if there is evidence of liver disease or prolonged prothrombin time (Grade B)
- Recommended dose of Vitamin A is:
    - < 1 year: 4,000 IU (1,200 mcg) daily
    - >1 year: 4,000 to 10,000 IU (1,200 to 3,000 mcg) daily
- Vitamin D recommendations:
    - Infants: 400 IU (10 mcg) daily
    - Children: 400 to 800 IU (10 to 20 mcg) daily
    - Adults: 800 to 2,000 IU (20 to 50 mcg) daily
- Vitamin E recommendations:
    - Birth to 1 year: 10 to 50 mg daily
    - 1 year to 10 years: 50 to 100 mg daily
    - 10 years: 100 to 200 mg daily

- Recommended dose of Vitamin K has not been established; suggested children and adults receive 10 mg daily (Grade C)

Randomized Controlled Trials

There were no RCT's identified from the literature search evaluating therapy. Only one poor quality, open-label, non-randomized study that evaluated the vitamin re-formulation of AquADEKs softgels over 12 weeks to 14 patients with CF who were all recruited from the CF Center at the University of Denver.[10]

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Oregon Health Authority

New Drug Evaluation: lomitapide

Month/Year of Review: May 2013
Generic Name: lomitapide
PDL Class: Non-Statin Lipid Lowering Agents

End date of literature search: Week 3, March 2013 (MedLine); 4/3/2013 (ClinicalTrials.gov)
Brand Name (Manufacturer): Juxtapid™ (Aegerion Pharmaceuticals, Inc.)
Dossier Received: Redacted version received April 12, 2013

Food and Drug Administration (FDA) Approved Indication:
"Juxtapid™ is a microsomal triglyceride transfer protein inhibitor (MTP) indicated as an adjunct to a low-fat diet and other lipid-lowering treatments, including LDL apheresis where available, to reduce low-density lipoprotein cholesterol(LDL-C), total cholesterol(TC), apolipoprotein B(apo B), and non-high density lipoprotein cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia(HoFH)."[1] There is a Black Box Warning and a Risk Evaluation and Mitigation Strategy is required to determine if the potential benefits of lomitapide outweigh the potential risk of liver injury.[1]

Potential Off-Label Indications:
- Heterozygous familial hypercholesterolemia (HeFH)
- Drug resistant hypercholesterolemia

Research Questions:
- Is lomitapide more effective than statins, statin combination therapy or other recommended therapies to prevent coronary heart disease (CHD) events in patients with hypercholesterolemia?
- Is lomitapide safer than statins, statin combination therapy or other recommended therapies in patients with hypercholesterolemia?
- Are there sub-populations of patients with hypercholesterolemia where lomitapide is more or less effective or safe?

Conclusions:
- There is insufficient evidence from a single uncontrolled, open-label trial of 29 HoFH patients to evaluate lomitapide effectiveness to prevent CHD events.
- The safety database is very small, but there are potential risks of serious acute and/or chronic liver injury. It is teratogenic in animals. There are serious GI effects and known malabsorptions of essential fatty acids and vitamins. There are many drug interactions.
- HoFH patients have limited therapeutic options and lomitapide may be a viable third-line alternative to reduced LDL-C levels.

Recommendations:
- Prior authorize lomitapide to limit use to confirmed adult HoFH patients that have failed or are unable to tolerate maximum lipid-lowering therapy and LDL-C apheresis.

Background: Hypercholesterolemia and specifically high levels of low-density lipoprotein cholesterol (LDL-C) are risk factors for CHD.[2] Currently, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are the first line treatment to reduce LDL-C because they are proven to reduce CHD morbidity and mortality with a relatively low incidence of serious adverse events.[2] Primary prevention recommendations are a minimum 30-40% LDL-C reduction to achieve CHD benefit and secondary prevention recommendations are a minimum of 50% LDL-C reduction.[2] Statins are not tolerated (myalgia or myostitis) or not effective in all patients (e.g. antiretroviral associated dyslipidemia). Some patients with HoFH and HeFH can be refractory to statin therapy because they are genetically lacking LDL-C receptor activity (absent entirely or significantly reduced). Lomitapide has a new mechanism of action and reduces LDL-C levels by inhibiting MTP.[1] This prevents the assembly of apo B and subsequent synthesis of LDL-C.

Familial hypercholesterolemia (FH) has a worldwide prevalence of 0.2% which is mostly comprised of HeFH.[3] FH is characterized by a high LDL-C level from birth, a propensity to tendon xanthomata, and early onset CHD.[4] HeFH is a partial deficiency of the LDL receptor and is associated with total cholesterol levels >300mg/dL and high risk of coronary artery disease by age 30-40 years.[3] HoFH is most often a total LDL receptor deficiency but may also be caused by mutations of apo B or subtilsin/kexing type 9 genes.[3] It is extremely rare but myocardial infarction by age 10 and death by age 20 is common. HoFH is associated with total cholesterol levels > 600-1000mg/dL.[3] HoFH statin LDL-C response is < 10-25% decrease at maximum doses.[5] Cholesterol absorption inhibitors provide addition LDL-C lowering or <10%.[5] LDL-C apheresis is currently the standard of care for HoFH patients resistant to statin therapy and can lower LDL-C by as much as 30-40%.[5,6] However, apheresis needs to be performed on a chronic repetitive basis (i.e. every 1-2 weeks), is associated with LDL-C rebound and is currently performed at only 35 centers in the United States.[5] Liver transplantation is a last resort.[5] HoFH is an FDA orphan indication due to the lack of good therapeutic options.

Clinical Efficacy: The dossier identified 15 Phase I, 6 Phase II and 1 Phase III with safety extension. ClinicalTrials.gov identified nine lomitapide trials: 1 Phase I, 6 Phase II and 2 Phase III of which only 1 was completed and published. Cuchel et al.[7] was a poor quality, non-controlled, open label trial investigating the efficacy and safety of lomitapide in 29 HoFH patients. The study did not evaluate CHD events. The primary endpoint was LDL-C change from baseline to 26 weeks and patients were followed an additional 52 weeks to assess safety. Concomitant lipid-lowing therapies were stable during the efficacy phase but could change during the safety phase. Apheresis was allowed and LDL-C response allowed it to be stopped in 3 patients and the interval extended in another 3. There was a 50% decrease in LDL-C at 26 weeks ($p < 0.0001$) to a median level of 169 mg/dL.[5] Eight patients achieved LDL-C levels <100mg/dL with 4 of these concomitantly receiving apheresis.[5]

Clinical Safety: The safety database is very limited and per the FDA reviewer "can only provide assurance that the true incidence of an ADE is no greater than 10% when the outcome is not observed in the trial."[5] Two patients experienced serious adverse events likely related to drug-drug interactions with CYP3A4 inhibitors.[5] One patient had severe hepatoxity and the other experienced over-anticoagulation while concurrently on warfarin.[5] Thirty-eight percent of patients experienced at least one ALT $\geq$ 3x ULN in the combined efficacy and safety trial but these were not accompanied by other tests of liver dysfunction.[5] The risk of serious liver injury remains undefined due to the small safety database.[5] Diarrhea, nausea, vomiting, dyspepsia or abdominal pain were nearly universal (>90% of patients) and should be managed with a diet where <20% of energy is derived from fat.[5] Lomitapide interferes with dietary fat absorption via its mechanism of action but this can be overcome with dietary supplementation. It is teratogenic in rats and ferrets and carries a FDA pregnancy category X.

NDE: lomitapide

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) CHD events
2) Withdrawals due to ADEs
3) Serious ADEs

Primary Study Endpoints:

1) Percent change in LDL-C from baseline to 28 weeks
2) Withdrawals due to ADEs
3) Serious ADEs

Ref./ Study Design	Drug Regimens / Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARI/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
Cuchel et al.[7] Single-arm Open label MC	L: Lomitapide @ 5mg/day x 2 wks.: increased to 10, 20, 40, +60mg a day at 4-week intervals until an individually determined maximum dose was achieved on the basis of safety and tolerability. f/u 26 weeks for efficacy; 78 weeks for safety. Concomitant lipid-lowing therapies were stable during the efficacy phase but could change during the safety phase.	Patients with HoFH already on lipid-lowering treatment. Demographics: Age: 30.7 years +/- 10.6 Female: 44.8% Caucasian: 86.2% Inclusion: Hx untreated TC > 508 mg/dL + TG <3.4mmol/L + both parents with hx or untreated TC >254 mg/dL OR Genetic documentation of LDL receptor dysfunction ≥ 18 years old Exclusion: Major surgery within 3 months CHF Hx hepatic disease or transaminases 2x ULN SCr >221 micromol/L Recent malignancy Alcohol or drug abuse Know bowel disease or malabsorption Chronic lung diseas3	ITT: L: 29 Total Attrition: L: 6 (20.7%) Loss to follow-up: L: 6 (20.7%)	Primary Outcome: % Δ in LDL-C @ baseline to 26 weeks. N=23 L: -50% (-62%, -39%) to 168mg/dL P <0.0001 3 patients permanently discontinued LDL apheresis 3 permanently increased the time interval between apheresis treatments	NA / NA	Total withdrawals due to AE: L: 5 (17%) [GI distress] SAE: L: 3 (10.3%) [1 –ACS, 1-elective hysterectomy for menorrhagia, 1-angina]	17% / NA 10.3% / NA	**Quality Rating: POOR** **Internal Validity: RoB** Selection: HIGH – No randomization and no control arm. Performance: HIGH- No blinding Detection: MOD-No blinding Attrition: HIGH **External Validity:** Recruitment: Highly selective with long run-in; 12 week screening then 6 week run-in to establish stable lipid-lowering therapies. Apheresis was allowed. Patient Characteristics: Study results apply to HoFH patients only Setting: Lipid clinics Outcomes: LDL-C surrogate, short duration Low Power: 90% to detect 25% difference (n=20)

AMI = acute myocardial infarction;
CA = cancer;
CAD = coronary artery disease
CHD = cardiac heart disease;
CHF = congestive heart failure;
CVA = cardiovascular accident;
DB = Double-Blind;
DM = diabetes mellitus;
f/u = Follow-up;
fx = fracture
Hx = history of;
HTN = hypertension;
L= Lomitapide group
LDL-C = low-density lipoprotein cholesterol;
MC = Multi-Center;
NA = not available or applicable;
P=placebo group;
PC = Placebo Controlled;
PE = pulmonary embolism;
RCT = Randomized Controlled Trial;
SCr = serum creatinine
SQ = subcutaneous;
SVT = supraventricular tachycardia;

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

Lomitapide binds and inhibits MTP which prevents the assembly of apo B and subsequently inhibits the synthesis of LDL-C.[1]

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	7%
Protein Binding	≥ 99.8%
Elimination	< 59.5% recovered in the urine and 33.4% in feces
Half-Life	39.7 hours
Metabolism	Extensively liver metabolized primarily by CYP3A4 and to a small extent by CYP1A2, SB6 2C8 AND 2C19.

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
5mg 10mg 20mg	PO	Take capsules once daily, whole, with water and without food, at least 2 hours after evening meal	Patients with end stage renal disease on dialysis or with baseline mild hepatic impairment should not exceed 40 mg daily	Contraindicated in patients with moderate to severe hepatic impairment or active liver disease.	Safety and effectiveness not established	NA (not studied in sufficient numbers to determine if adjustments are needed)	Initiate at 5mg daily and titrate dose based on acceptable tolerability to 10mg daily at 2 weeks and then at a minimum of 4 week intervals to a maximum of 60mg daily. Before treatment, measure ALT, AST, alkaline phosphatase, and total bilirubin; obtain a negative pregnancy test in females of reproductive potential

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

Black Box Warning for risk of hepatotoxicity. Lomitapide is only available through a restricted REMS program for certified clinicians (1-855-898-27430

It is contraindicated in pregnancy.

It is contraindicated in patients taking strong or moderate CYP3A4 inhibitors.

Warnings and Precautions:

"Gastrointestinal adverse reactions occur in 93% of patients and could affect absorption of concomitant oral medications." [1]

Look-alike / Sound-alike (LA/SA) Error Risk Potential:
Loperamide
Lodoxamide
Loratadine

Appendix 2: Suggested PA Criteria

Lomitapide (Juxtapid®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which lomitapide has been shown to be effective and safe.

Length of Authorization: 6 months

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the client ≥18 years of age AND have a diagnosis of homozygous familial hypercholesterolemia? a) Genetically confirmed OR b) Untreated LDL-C >500mg/dl + xanthoma before 10 yrs. OR c) Both parental heterozygous FH	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Has the patient failed or are they intolerant to maximum statin and combination therapy?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny (medical appropriateness)
4. Has the patient failed or are they not appropriate for LDL-C apheresis?	**Yes:** Go to #5	**No:** Pass to RPH; Deny (medical appropriateness)
5. Is the patient currently on any moderate or strong CYP3A4 inhibitors (e.g. boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole, amprenavir, aprepitant, atazanavir, ciprofloxacin, crizotinib,darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, imatinib, verapamil) ?	**Yes:** Pass to RPH; Deny (medical appropriateness)	**No:** Go to #6.
6. Is the patient male OR female not of child bearing age or confirmed not pregnant?	**Yes:** Approve x 6 months	**No:** Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

Lomitapide is approved only for HoFH, a rare but serious disorder associated with premature cardiovascular morbidity and mortality with few effective treatment options. It is proven effective in reducing LDL-C levels, but there is uncertainty about whether this equates to reduced cardiovascular morbidity and mortality. It is not feasible to do an outcomes study due to the low prevalence of the disease. However, the current safety data does not support the use of lomitapide in patients with lower CHD risk.[1]

1. FDA. Lomitapide Summary Review - Reference ID 3236195. 2012. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/203858Orig1s000SumR.pdf. Accessed April 3, 2013.

P&T Action: *5/30/2013 (KK/??)*
Revision(s):
Initiated:

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Oregon Health Authority

New Drug Evaluation: mipomersen

Month/Year of Review: May 2013
Generic Name: mipomersen
PDL Class: Non-Statin Lipid Lowering Agents
End date of literature search: Week 3, March 2013 (MedLine/Scopus); 2/11/2013 (ClinicalTrials.gov)
Brand Name (Manufacturer): Kynamro™ (Genzyme)
Dossier Received: requested March 1, 2013; Received 4/30/2013

Food and Drug Administration (FDA) Approved Indication:
"KYNAMRO™ is an oligonucleotide inhibitor of apolipoprotein B-100 synthesis indicated as an adjunct to lipid-lowering medications and diet to reduce low density lipoprotein-cholesterol (LDL-C), apolipoprotein B (apo B), total cholesterol (TC), and non-high density lipoprotein-cholesterol (non-HDL-C) in patients with homozygous familial hypercholesterolemia (HoFH)."[1] There is a Black Box Warning and a Risk Evaluation and Mitigation Strategy is required to determine if the potential benefits of mipomersen outweigh the potential risk of liver injury.[1]

Potential Off-Label Indications:
- Heterozygous familial hypercholesterolemia (HeFH)
- Drug resistant hypercholesterolemia

Research Questions:
- Is mipomersen more effective than statins, statin combination therapy or other recommended therapies to prevent coronary heart disease (CHD) events in patients with hypercholesterolemia?
- Is mipomersen safer than statins, statin combination therapy or other recommended therapies in patients with hypercholesterolemia?
- Are there sub-populations of patients with hypercholesterolemia where mipomersen is more or less effective or safe?

Conclusions:
- The three randomized placebo-controlled phase III trials were only 28weeks long and did not evaluate CHD outcomes. LDL-C goal was achieved only in the HeFH study. There is insufficient evidence to determine if mipomersen lowers the incidence of CHD events in patients with HoFH, HeFH or drug resistant hypercholesterolemia.
- The potential for liver injury secondary to chronic fat accumulation is the primary concern. However, 100% of mipomersen patients experienced adverse events (ADEs) including injection-site reactions, flu-like symptoms and proteinuria. Longer-term exposure in more patients is needed to adequately define the risks.
- There are few treatment options for HoFH. Mipomersen is a viable third-line alternative behind LDL-C apheresis.

Recommendations:
- Prior authorize mipomersen to limit use to confirmed HoFH patients that have failed or are unable to tolerate maximum lipid-lowering therapy and LDL-C apheresis.

NDE: mipomersen

Background: Hypercholesterolemia and specifically high levels of low-density lipoprotein cholesterol (LDL-C) are risk factors for CHD.[2] Currently, hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are the first line treatment to reduce LDL-C because they are proven to reduce CHD morbidity and mortality with a relatively low incidence of serious adverse events.[2] Primary prevention recommendations are a minimum 30-40% LDL-C reduction to achieve CHD benefit and secondary prevention recommendations are a minimum of 50% LDL-C reduction.[2] Statins are not tolerated (myalgia or myostitis) or not effective in all patients (e.g. antiretroviral associated dyslipidemia). Some patients with HoFH and HeFH can be refractory to statin therapy because they are genetically lacking LDL-C receptor activity (absent entirely or significantly reduced). Mipomersen has a new mechanism of action and reduces LDL-C levels by reducing the production of apolipoprotein B-100 (apo B-100).[1] Apo B-100 is a precursor to synthesis of LDL-C.

Familial hypercholesterolemia (FH) has a worldwide prevalence of 0.2% which is mostly comprised of HeFH.[3] FH is characterized by a high LDL-C level from birth, a propensity to tendon xanthomata, and early onset CHD.[4] HeFH is a partial deficiency of the LDL receptor and is associated with total cholesterol levels >300mg/dL and high risk of coronary artery disease by age 30-40 years.[3] HoFH is a total LDL receptor deficiency.[3] It is very rare (estimated prevalence of 1 per 1 million people) but myocardial infarction by age 10 and death by age 20 is common. HoFH is associated with total cholesterol levels > 600-1000mg/dL.[3] LDL-C apheresis is currently the standard of care for HoFH patients resistant to statin therapy.[5] However, apheresis needs to be performed on a chronic repetitive basis (i.e. every 1-2 weeks) and is currently performed at only 35 centers in the United States. Liver transplantation is a last resort. HoFH is an orphan indication due to the lack of good therapeutic options.

Clinical Efficacy: ClinicalTrials.gov identified 18 mipomersen randomized controlled trials. Five were Phase I trials, seven were Phase II and seven were Phase III of which four were completed and three were published.[6,7,8] Raal et al.[6] studied mipomersen in HoFH patients. Stein et al.[7] evaluated it in HeFH patients and McGowan et al.[8] in patients with drug resistant hypercholesterolemia.

Mipomersen was approved based upon a single phase III trial of 51 genetically or clinically confirmed HoFH patients.[6] Raal et al.[6] was a fair quality trial that randomized 34 patients to 200mg of subcutaneous mipomersen per week and 17 patients to a matching volume of placebo subcutaneously per week. All patients were allowed to be on maximum tolerated lipid-lowering therapy as long as the doses were stable 12 weeks. LDL-C apheresis was not allowed. Randomization and allocation concealment were well done and described. The groups were only slightly different at baseline with more children and more significant CHD history in the mipomersen group but more metabolic syndrome in the placebo group. There was no loss to follow-up but total attrition was high and uneven in the mipomersen patients due to ADE withdrawal. All mipomersen patients experienced ADEs, primarily injection site reactions. This threatened the blinding and increases the risk of performance bias. CHD outcomes were not assessed it is not likely they will be in the future given the low prevalence of HoFH. The primary outcome was percent change in LDL-C from baseline. The mean treatment time was 25 weeks and follow-up was two weeks after the last dose. There was a mean difference of 21% reduction between groups, favoring mipomersen ($p < 0.0003$) which had a 25% reduction in LDL-C. However, the LDL-C at the end of the study remained very high in both groups: mipomersen 324 mg/dL versus placebo 390mg/dL.

Stein et al.[7] was a fair quality trial that randomized 83 patients to self-administered subcutaneous mipomersen 200mg and 41 patients to an un-described, but self-administered placebo. Both were given weekly for 26 weeks. All patients were genetically or clinically confirmed with HeFH on a stable, maximally tolerated lipid-lowering drug regimen for 12 weeks. LDL-C apheresis was not allowed. There was slightly more patients with cardiovascular history and who smoked in the mipomersen group. Risks for selection, performance and attrition biases were identified. There was inadequate description of randomization, allocation concealment and blinding. Three mipomersen patients were lost to follow-up and nine mipomersen patients withdrew due to ADEs. Again CHD

outcomes were not assessed and the percent change from baseline to 28 weeks in LDL-C was the primary outcome. The mean difference in LDL-C between groups was a decrease of 33% favoring mipomersen (p <0.001) to final LDL-C levels of: mipomersen 104 mg/dL and placebo 143 mg/dL.

McGowan et al.[8] was a good quality trial that randomized 39 patients to self-administered mipomersen 200mg subcutaneously per week to and 19 patients to a self-administered similarly appearing placebo for 26 weeks. It included adults with severe hypercholesterolemia on maximum lipid-lowering therapy and excluded from apheresis. There was a good description of randomization, allocation concealment and blinding. The groups differed in that there was more alcohol use and metabolic syndrome in the mipomersen group but more tobacco use in the placebo group. The mipomersen group experienced more loss to follow-up (13%) and total attrition (36%) than the placebo group (5% and 16% respectively). Blinding may have been broken due to all mipomersen patients experiencing an ADE, most of which were injection site reactions. CHD outcomes were not assessed. The mean difference in the primary outcome, percent change in LDL-C at 28 weeks, was 48% favoring mipomersen (0.001). The final LDL-C for both groups remained high: mipomersen 174mg/dL versus placebo 263mg/dL.

Another trial[9] was identified in the dossier but was not available for review except in abstract form.[10]

Clinical Safety:

According to the FDA Summary Review[11] the primary safety concern with mipomersen is the potential liver injury secondary to chronic fat accumulation. Other safety issues include injection-site reactions, flu-like symptoms and proteinuria. The FDA safety assessment was derived from four phase III trials involving 390 patients that were randomized to mipomersen 2: placebo 1 for 6 months.[9] Table 1 summarizes the FDA Summary Review data.[9]

Table 1- Summary of FDA Summary Review Safety Data

Endpoint	Placebo Percent of Patients	Mipomersen Percent of Patients
Percent fat content change from baseline ≥ 5%	8.3%	61.8%
ALT ≥ 3x Upper Limits of Normal (ULN)	1.0%	16.0%
AST ≥ 3x ULN	0.0%	4.2%
Injection-site reactions	33.0%	84.0%
Flu-like symptoms	16.0%	30.0%
Antibody Response at Week 50	0.0%	33.0%
Proteinuria	0.8%	2.3%
Cardiovascular Events reported as ADE	6.0%	9.0%
Neoplasms	0.5%	1.2%
Withdrawals due to ADE	2.3%	18.0%

NDE: mipomersen

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) CHD events
2) Withdrawals due to ADEs
3) Serious ADEs

Primary Study Endpoints:

1) Percent change in LDL-C from baseline to 28 weeks
2) Withdrawals due to ADEs
3) Serious ADEs

Ref./ Study Design	Drug Regimens / Duration	Patient Population	N	Outcomes/ Efficacy Results (CI, p-values)	ARR/ NNT	Safety Results (CI, p-values)	ARR/ NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
Raal et al.[6] RCT PC DB MC	M: Mipomersen 200mg/week SQ; mean treatment period 159 days. P: Matching SQ placebo /week; mean treatment period 176 days. f/u 28 weeks	Patients with HoFH already on lipid-lowering treatment. Demographics: Mean age: 31.3 years SD 12.4; 7 patients <18 Female: M: 56%, P:59% Group comparison at baseline: Group differences include: more children and significant CV history in control; more metabolic syndrome in mipomersen. Inclusion: ≥12 years old Genetically confirms homozygous FH OR Untreated LDL-C >500mg/dl + xanthoma before 10 yrs. or + both parental heterozygous FH Stable low-fat diet Maximum tolerant lipid-lowering therapy with fasting LDL-C 130mg/dL & weight of ≥40kg. Exclusion: LDL apheresis within 8 weeks CV event within 12 weeks Angina CHF Secondary hyperlipidemia predisposition SCr > 3x ULN Hx of renal or hepatic disease	ITT: M:34 P:17 Total attrition: M: 6 (17.6%) P: 0 (0.0%) Loss to f/u: M: 5 (14.7%) P: 0 (0.0%)	Primary Outcome: % Δ in LDL-C @ baseline to 2 weeks after last dose. M: -24.7% (-31.6%, 17.7%) to 324mg/dL P: -3.3% (-12.1%, 5.5%) to 390mg/dL MD: -21.3% 95% CI (-32.9%, -9.8%) P <0.0003	NA / NA	Total withdrawals due to AE: M: 5 (14.7%) P: 0 (0.00%) RR: NA 95% CI NA p-value NA SAE: M: 2 (7.1%) [ACS, ankle fx] P: 1 (5.9%) [nephrolithiasis] RR: 1.21 95% CI (0.12, 12.40) p-value NA	14.7% / NA 1.3% / 79	**Quality Rating: FAIR** **Internal Validity: RoB** Selection: LOW - Adequate description of randomization and allocation concealment. Stratified by weight (<50kg, ≥50kg). Though baseline group comparison of prognostic factors has small differences. No effect. Performance: MOD- Good description of blinding of patients, caregivers, investigators and outcomes assessors, but all mipomersen patients experienced ADE. Possible bias away from null. Detection: LOW - Good description of blinding of patients, caregivers, investigators and outcomes assessor, but all mipomersen patients experienced ADE. Objective outcome likely not affected. Attrition: HIGH – small sample size, >10% difference between groups in total attrition and loss to follow-up. Possible bias towards the null. **External Validity:** Recruitment: Un-described Patient Characteristics: Study results apply to HoFH patients only Setting: Lipid clinics in 7 countries (United States, Brazil, Canada, Singapore, South Africa, Taiwan, and United Kingdom). 9/6/2007 – 3/25/2009. Outcomes: LDL-C surrogate, short duration and did not get close to LDL-C goal. Low Power: 80% to detect 20% difference.

Stein et al.[7] RCT PC DB MC	M: mipomersen 200mg / week self-administered SQ x 26 weeks P: placebo un-described self-administered SQ x26 weeks f/u 28 weeks	Patients with HeFH and CAD on maximally tolerated lipid-lowering therapies. Demographics: Mean Age: M- 56.2, P-55.9 Female: M-39.8%, P-31.7% White: M-97.6%, P-92.7% Baseline: More in CV history and smoking in mipomersen group generally Inclusion: ≥ 18 years old HeFH (genetic confirmation)OR HeFH defined as untreated LDL-C >2.9mmol/L [190mg/dL] + Simon Broome Register criteria for HeFH + documented stable CAD LDL-C ≥ 100mg/dL ;TG <2.26 200mg/dL Stable max. tolerated dose of lipid-lowering therapy x 12 wks. Exclusion: LDL apheresis within 8 wks. Unstable angina CHF – Class II or IV DM Condition causing 2° hyperlipidemia ALT >1.5x upper limit of normal (ULN) CK ≥ 3x ULN Significant renal or hepatic disease	ITT: M:83 P:41 Total Attrition: M: 10 (12%) P: 0 (0%) Loss to follow-up: M: 3 (4%) P: 0 (0%) Only 1 loss to f/u was excluded from analysis.	Primary outcome: % Δ LDL-C from baseline to 2 weeks after the last dose M: -28.0% (-34, -22.1) to 104 mg/dL P: 5.2% (-0.5, 10.9) to 143 mg/dL MD: -33.2 95% CI: NA p-value: <0.001	NA / NA	Total withdrawals due to AE: M: 9 (10.8%) P: 0 (0.0%) RR: NA 95% CI: NA p-value: NA SAE: M: 6 (7.2%) [basal cell CA, angina, AMI, PE, non-cardiac chest pain] P: 2 (4.9%) [CAD & SVT] RR: 1.5 95% CI: 0.32, 7.11 p-value: NA	10.8% / NA 2.44% / 41	**Quality Rating: FAIR** **Internal Validity: RoB** Selection: LOW - No description of randomization or allocation concealment though baseline group comparison of prognostic factors is fairly even. No effect. Performance: MOD- All mipomersen patients experienced ADE; Possible bias away from null. Detection: LOW - No description of placebo only the assurance that "Patients and study personnel were blinded to treatment assignment and to lipid data." In addition, the hepatic fat assessor was said to be blinded to allocation. Objective outcomes at lower risk from lack of blinding. Attrition: HIGH – small sample size, >10% difference between groups in total attrition. Possible bias towards the null. **External Validity:** Recruitment: Un-described Patient Characteristics: Study results apply to HeFH patients only Setting: Lipid clinics Outcomes: LDL-C surrogate, short duration but mipomersen group did get close to LDL-C goal in primary. Low Power: 90% power to detect 20% difference.

McGowan et al.[8] RCT PC DB MC	M: Mipomersen 200mg / week P: Placebo = 9mg NaCl + 0.0004mg riboflavin / week Both are 1 ml self-administered SQ injections, similar in appearance and administration. f/u 28 weeks.	Adults with sever e hypercholesterolemia on maximum lipid-lowering therapy and excluded from apheresis. Demographics: Mean Age: 50.5 (18-77) Male: 25 (43.1%) White: 49 (84.5%) Baseline comparison: More current alcohol use and metabolic syndrome in mipomersen group; More tobacco use in the placebo group Inclusion: ≥ 18 years old LDL-C ≥5.1 197 mg/dL + CHD OR LDL-C ≥ 301 mg/dL with no CHD Stable low-fat diet with stable weight Maximum tolerated lipid lowering therapy Met LDL-apheresis criteria but was prohibited Exclusion: Significant CVD or cerebrovascular event within 24 weeks CHF DM-I or poorly controlled DM-II HTN Secondary hyperlipidemia predisposition Hx of renal or hepatic disease	ITT: M: 39 P: 19 Total attrition: M: 12 (30.8%) P: 1 (5.2%) Loss to F/U: M: 5 (12.8%) P: 1 (5.3%) There were significant differences between groups in protocol deviations: M: 16 (41%) P: 2 (11%)	Primary Outcome: % Δ in LDL-C @ baseline to 2 weeks after last dose. M: -35.9% 95% CI (-51.3, -15.3) to 174mg/dL P: 12.5% 95% CI (-10.7, 35.8) to 263 mg/dL MD: -48.4% 95% CI NA p-value < 0.001	 NA / NA	Withdrawals due to ADE: M: 8 (20.5%) C: 1 (5.3%) RR 3.90 95% CI (0.52, 28.95) p-value NA SAE: M: 5 (20.0%) [liver toxicity, CVA] P: 1 (6.3%) [MI] RR 3.20 95% CI (0.41, 24.94) p-value NA	 15.3% / 7 13.8% / 7	**Quality Rating: GOOD** **Internal Validity: RoB** Selection: LOW - Good description of adequate randomization & allocation concealment though baseline group comparison of prognostic factors is uneven. No effect. Performance: MOD- Blinding of patients, caregivers, investigators and outcomes assessor is adequate and well described but all mipomersen patients experienced ADE; Possible bias away from null. Detection: LOW - Blinding of patients, caregivers, investigators and outcomes assessor is adequate and well described but all mipomersen patients experienced ADE ; Objective outcomes at lower risk from lack of blinding. Attrition: HIGH – small sample size, >10% difference between groups in total attrition. Possible bias towards the null. **External Validity:** Recruitment: Un-described Patient Characteristics Population studied is limited to adults with severe disease as add-on therapy. Setting: Lipid clinics Outcomes: LDL-C surrogate, short duration and LDL-C goal not achieved. Low Power: 80% power to detect 20% difference.

AMI = acute myocardial infarction;
CA = cancer;
CAD = coronary artery disease
CHD = cardiac heart disease;
CHF = congestive heart failure;
CVA = cardiovascular accident;
DB = Double-Blind;
DM = diabetes mellitus;
f/u = Follow-up;
fx = fracture
Hx = history of;
HTN = hypertension;
LDL-C = low-density lipoprotein cholesterol;
M=mipomersen group;
MC = Multi-Center;
NA = not available or applicable;
P=placebo group;
PC = Placebo Controlled;
PE = pulmonary embolism;
RCT = Randomized Controlled Trial;
SCr = serum creatinine
SQ = subcutaneous;
SVT = supraventricular tachycardia;

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Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY

Mipomersen is an antisense oligonucleotide that reduces the genetic production of apo-B 100 which is the principle apolipoprotein of LDL. Thus, LDL is not produced.[1]

PHARMACOKINETICS[1]

Parameter	Result
SQ Bioavailability	54 – 78%
Protein Binding	≥ 90%
Elimination	< 4% recovered in the urine
Half-Life	1 – 2 months
Metabolism	Metabolized in tissues by endonucleases

INTERACTIONS[1]

Drug interactions are not anticipated via the cytochrome P450 enzymes or via the P-glycoprotein transporter mechanism.

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
200 mg / 1 ml	SQ	Weekly	NA	Withhold dose x 1 week if ALT or AST is ≥ 3 ULN. Resume when ≤ 3 ULN and monitor weekly. If ≥ 5 ULN; withhold and obtain additional liver tests	NA (only 7 patient < 18 were included in the trials)	NA (only 22.6% of patients in trial were ≥ 65 years old)	May cause fetal harm; Pregnancy category B

NDE: mipomersen

DRUG SAFETY[1]

Serious (REMS, Black Box Warnings, Contraindications):

Black Box Warning for risk of hepatotoxicity. Mipomersen is only available through a restricted REMS program. Only certified providers may prescribe and pharmacies may distribute it. Further information is available at www.KynamroREMS.com or by telephone at 1-877-KYNAMRO (1-877-596-2676).[1]

Warnings and Precautions:

"Injection site reactions occur in 84% of patients and typically consist of one or more of the following: erythema, pain, tenderness, pruritus and local swelling. Flu-like symptoms, which typically occur within 2 days after an injection, occur in 30% of patients and include one or more of the following: influenza-like illness, pyrexia, chills, myalgia, arthralgia, malaise or fatigue."[1]

Look-alike / Sound-alike (LA/SA) Error Risk Potential:

Misoprostil
Miconazole
Kalydeco

Appendix 2: Suggested PA Criteria

Mipomersen (Kynamro®)

Goal(s):

- To ensure appropriate drug use and limit to patient populations in which mipomersen has been shown to be effective and safe.

Length of Authorization: 6 months

Approval Criteria		
1. What is the diagnosis?	Record ICD-9 code	
2. Is the client ≥12 years of age AND have a diagnosis of homozygous familial hypercholesterolemia? a) Genetically confirmed OR b) Untreated LDL-C >500mg/dl + xanthoma before 10 yrs. OR c) Both parental heterozygous FH	**Yes:** Go to #3.	**No:** Pass to RPH; Deny (medical appropriateness)
3. Has the patient failed or are they intolerant to maximum statin and combination therapy?	**Yes:** Go to #4.	**No:** Pass to RPH; Deny (medical appropriateness)
4. Has the patient failed or are they not appropriate for LDL-C apheresis?	**Yes:** Approve for 6 months.	**No:** Pass to RPH; Deny (medical appropriateness)

Limitations of Use:

Mipomersen is approved only for HoFH, a rare but serious disorder associated with premature cardiovascular morbidity and mortality with few effective treatment options. It is proven effective in reducing LDL-C levels, but there is uncertainty about whether this equates to reduced cardiovascular morbidity and mortality. It is not feasible to do an outcomes study due to the low prevalence of the disease. However, the current safety data does not support the use of mipomersen in patients with lower CHD risk.[1]

1. FDA Summary Review. Reference ID 3252189. 2013. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203568Orig1s000SumR.pdf. Accessed April 1, 2013.

P&T Action: *5/30/2013 (KK/??)*
Revision(s):
Initiated:

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Month/Year of Review: May 2013
PDL Classes: Cough and Cold

Date of Last Review: May 2010
Source Document: Provider Synergies

Current Status of PDL Class:

- Current Preferred Agents: NONE. Acute Upper Respiratory Infections and Common Cold are below the line on the OHP prioritized list.
- Current Non-Preferred Agents: DIPHENHYDRAMINE, PSEUDOEPHEDRINE, CODEINE, CHLORPHENIRAMINE, DOXYLAMINE, PROMETHAZINE, HYDROXYZINE, GUAIFENESIN, NAPHAZOLINE, OXYMETAZOLINE, PHENYLEPHRINE, BROMPHENIRAMINE, CLEMASTINE, DEXTROMETHORPHAN

Previous Recommendations:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events
- Do not cover

Methods:

A Medline OVID search was conducted with the following search terms: diphenhydramine, pseudoephedrine, codeine, chlorpheniramine, doxylamine, promethazine, hydroxyzine, guaifenesin, homatropine, scopolamine, phenylephrine, brompheniramine, clemastine, dextromethorphan, decongestant, expectorant, antihistamine, antitussive, cough, cold, rhinovirus, coronavirus, parainfluenza virus, respiratory syncytial virus, adenovirus, enterovirus, influenza, sore throat, congestion, sneezing, and fever. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to February week 2 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Trials:

A total of 67 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, two relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Shadkam[1] et al conducted a study comparing the effect of honey, diphenhydramine, dextromethorphan or placebo in relieving nighttime coughing and improving sleep quality in young children with an upper respiratory infection. One hundred-sixty children aged 2 to 5 years old were randomized to one of four treatment groups for a single night intervention. Parents filled out a questionnaire before and after the intervention scoring the severity and frequency of their child's cough, as well the quality of sleep. The mean score for all variables after all four interventions was significantly improved. There was no significant difference between diphenhydramine and dextromethorphan in cough and sleep improvement. This was a low quality study with very little information provided on baseline characteristics, randomization, blinding or allocation concealment.

Eskiizmir[2] et al compared oxymetazoline and xylometazoline to relieve nasal congestion. Relief was measured by airway resistance, nasal airflow, and cross-sectional area of the nasal cavity. Thirty adults were randomized to one of the nasal decongestants or a placebo saline solution. Patients administered a spray to each nostril. Improvement in resistance and airflow were measured after one hour by an analyst blinded to treatment selection. Both oxymetazoline and

xylometazoline significantly improved airway resistance and nasal airflow compared with placebo; however, compared with each other, there was no statistical difference between the two nasal decongestants.

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
No new safety alerts were found, but safety labeling changes were added to codeine[3] and a safety warning was issued for over-the-counter ophthalmic and nasal decongestants[4]. In February 2013, the FDA added a Black Box Warning to codeine to restrict use in children for post-operative pain. Deaths have occurred post-operatively in children with obstructive sleep apnea who received codeine following a tonsillectomy and/or adenoidectomy. These children had evidence of being ultra-rapid metabolizers of codeine causing fatal amounts of morphine in the body. The Contraindication, Warnings/Precautions, Pediatric Use, and Patient Counseling Information sections of the drug label were also updated with this information.

In October 2012, the FDA released a warning concerning the accidental swallowing by children of ophthalmic and nasal decongestants. The eye drops and nasal sprays involved contain the active ingredients tetrahydrozoline, oxymetazoline, or naphazoline and are sold under various brand, generic and store brand names. The children involved (all aged five or younger) experienced serious events requiring hospitalization such as coma, decreased heart rate, decreased breathing, and sedation after ingestion of less than five milliliters. Because these medications are usually not packaged as child-proof, the FDA advises consumers to keep any ophthalmic or nasal products out of reach of children. If ingested, the FDA advises parents contact the toll-free Poison Hotline and seek emergency medical attention immediately.

These warnings are following the 2008 FDA recommendation that these drugs not be used to treat infants and children under 2 years of age because serious and potentially life-threatening side effects can occur. The FDA has yet to complete its safety analysis of these medications in children age 2 to 11. However, many regulatory agencies in other countries such as Australia, New Zealand and the UK have made recommendations that they not be used to treat children under 6 years of age.

New Systematic Reviews:
Two new Cochrane Collaboration systematic reviews were identified. Please see Appendix 2 for the full abstracts.

De Sutter[5] et al reviewed over the counter cold medicine combinations. The trials included in the review were of poor quality with major differences in subjects, interventions, and outcomes making it difficult to pool all results. Combinations examined were antihistamine-analgesic, antihistamine-decongestant, decongestant-analgesic, and antihistamine-analgesic-decongestant. For all ingredient combinations, the reported outcome was global effectiveness described as the odds of treatment failure compared with placebo. For antihistamine-decongestant combinations, six trials were analyzed. The odds ratio of treatment failure was 0.27 (95% CI 0.15 to 0.50), with a number needed to treat (NNT) for an additional benefit of 4. For the antihistamine-analgesic combination medications, one trial was included (N=582); the odds ratio was 0.33 (95% CI 0.23 to 0.46) and the NNT was 6.67. One decongestant-analgesic combination trial was included (OR 0.28; 95% CI 0.15 to 0.52) with a NNT of 4. Two trials pooled with antihistamine-analgesic-decongestant combinations had an OR of 0.47 (95% CI 0.33 to 0.67) and NNT of 5.6.

Smith[6] et al examined the effectiveness of over-the-counter medications in suppressing cough due to upper respiratory infections for adults and children. Twenty-six trials of antitussives, expectorants, mucolytics, antihistamine-decongestants, and antihistamines were included. Relief or reduction in cough was the reported outcome with all results compared to placebo. Results were not pooled and quantified due to the limited number of trials in each group. Overall, the studies were of poor quality and showed conflicting evidence. In total, 11 of the 26 trials showed a positive result, while the other 15 showed no difference between active treatment and placebo. For children: studies showed

antitussives, antihistamines, and antihistamine-decongestant combinations were no more effective than placebo. For adults: antitussives, expectorants, and antihistamine-decongestant combination trials had variable results. A single mucolytic trial showed reduced cough frequency and symptom scores.

Guidelines:
No new or updated guidelines were identified.

Recommendations:

- No further research or review needed at this time.

References:

1. Shadkam MN, Mozaffari-Khosravi H, Mozayan MR. A Comparison of the Effect of Honey, Dextromethorphan, and Diphenhydramine on Nightly Cough and Sleep Quality in Children and Their Parents. *The Journal of Alternative and Complementary Medicine*. 2010;16(7):787–793.

2. Eskiizmir G, Hirçin Z, Özyurt B, Ünlü H. A comparative analysis of the decongestive effect of oxymetazoline and xylometazoline in healthy subjects. *European Journal of Clinical Pharmacology*. 2010;67(1):19–23.

3. Drug Safety and Availability > FDA Drug Safety Communication: Safety review update of codeine use in children; new Boxed Warning and Contraindication on use after tonsillectomy and/or adenoidectomy. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm339112.htm. Accessed March 5, 2013.

4. Drug Safety and Availability > FDA Drug Safety Communication: Serious adverse events from accidental ingestion by children of over-the-counter eye drops and nasal sprays. Available at: http://www.fda.gov/Drugs/DrugSafety/ucm325257.htm. Accessed March 5, 2013.

5. De Sutter AI, Van Driel ML, Kumar AA, Lesslar O, Skrt A. Oral antihistamine-decongestant-analgesic combinations for the common cold. In: The Cochrane Collaboration, De Sutter AI, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD004976.pub3. Accessed March 11, 2013.

6. Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. In: The Cochrane Collaboration, Smith SM, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD001831.pub4. Accessed March 17, 2013.

Appendix 1
Randomized Control Trials

Shadkam MN, Mozaffari-Khosravi H, Mozayan MR. A Comparison of the Effect of Honey, Dextromethorphan, and Diphenhydramine on Nightly Cough and Sleep Quality in Children and Their Parents. *The Journal of Alternative and Complementary Medicine*. 2010;16(7):787–793.

OBJECTIVES: Coughing is a prevalent symptom of upper respiratory infections (URIs) that cause disturbance in the sleep of children and their parents. There is as yet no reliable treatment to control URIs and their related cough; however, drugs such as dextromethorphan (DM) and diphenhydramine (DPH) are now mainly used in the world. The aim of this study is to compare the effect of honey, DM, and DPH on the nightly cough and sleep quality of children and their parents. DESIGN: This was a clinical trial study in which 139 children aged 24-60 months suffering from coughing due to URIs were selected and assigned randomly to 4 groups. The first group received honey (HG), the second one DM (DMG), the third DPH (DPHG), but the fourth group or control group (CG) was assigned to a supportive treatment. OUTCOME MEASURES: After approximately a 24-hour intervention, the 4 groups were reexamined and their cough frequency, cough severity, and sleep quality in children and their parents were recorded by using the questionnaire with Likert-type questions. RESULTS: The mean of cough frequency score HG is 4.09 +/- 0.72 and 1.93 +/- 0.65 before and after the intervention, respectively, while these figures for the CG are 4.11 +/- 0.78 and 3.11 +/- 0.57, respectively. After the intervention, the difference of the mean score of the variables in all groups became statistically significant. The mean score of all variables in HG has stood significantly higher than those in other groups. There is also a significant relationship between the DMG and CG groups, even though there is no statistically difference between DMG and DPHG groups. CONCLUSIONS: The result of the study demonstrated that receiving a 2.5-mL dose of honey before sleep has a more alleviating effect on URIs-induced cough compared with DM and DPH doses.

Eskiizmir G, Hirçin Z, Özyurt B, Ünlü H. A comparative analysis of the decongestive effect of oxymetazoline and xylometazoline in healthy subjects. *European Journal of Clinical Pharmacology*. 2010;67(1):19–23.

BACKGROUND: Oxymetazoline and xylometazoline are locally effective and direct acting drugs that relieve nasal congestion. The aim of this study was to objectively determine and compare the decongestive effects of oxymetazoline and xylometazoline in healthy subjects. METHODS: The study population comprised thirty healthy adults. All subjects underwent active anterior rhinomanometry (AARhm) and acoustic rhinometry (AR) tests following the application of oxymetazoline, xylometazoline, or placebo (physiological saline). The change in nasal resistance, nasal airflow, and different cross-sectional areas (CSAs) of the nasal cavity in the subjects were examined for each solution separately. The measurements were obtained over a 1-h period (baseline and 1, 15, 30, and 60 min post-dosing). All results were analyzed using the Kruskal-Wallis test and the Mann-Whitney U test. RESULTS: A total of 6,300 measurements of AARhm and AR were obtained. The application of placebo did not cause a statistically significant change in nasal resistance, nasal airflow, and CSAs (CSA1, 2, and 3, respectively) of the nasal cavity. In contrast, statistically significant changes in nasal resistance (inspiration $p = 0.000$ and $p = 0.004$; expiration $p = 0.000$ and $p = 0.000$), nasal airflow (inspiration $p = 0.000$ and $p = 0.004$; expiration $p = 0.000$ and $p = 0.000$), and CSAs of the nasal cavity (CSA2 $p = 0.000$ and $p = 0.000$, CSA3 $p = 0.000$ and $p = 0.00$), with the exception of CSA1 ($p = 0.982$ and $p = 0.994$), were obtained after the application of oxymetazoline and xylometazoline. A comparison of oxymetazoline and xylometazoline based on nasal resistance, nasal airflow, and CSAs of the nasal cavity demonstrated no statistically significant difference, except for CSA3. CONCLUSION: Oxymetazoline and xylometazoline are fast-acting and potent topical decongestants that have similar decongestive effects.

Appendix 2
Systematic Reviews

De Sutter AI, Van Driel ML, Kumar AA, Lesslar O, Skrt A. Oral antihistamine-decongestant-analgesic combinations for the common cold. In: The Cochrane Collaboration, De Sutter AI, eds. *Cochrane Database of Systematic Reviews.* Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD004976.pub3. Accessed March 11, 2013.

BACKGROUND: Although combination formulas containing antihistamines, decongestants and/or analgesics are sold over-the-counter (OTC) in large quantities for the common cold, the evidence of effectiveness is limited. OBJECTIVES: To assess the effectiveness of antihistamine-decongestant-analgesic combinations in reducing the duration and alleviating the symptoms of the common cold in adults and children.

SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2011, Issue 4), which contains the Cochrane Acute Respiratory Infections Group's Specialised Register, OLDMEDLINE (1953 to 1965), MEDLINE (1966 to November Week 3, 2011) and EMBASE (1990 to December 2011).

SELECTION CRITERIA: Randomised controlled trials (RCTs) investigating the effectiveness of antihistamine-decongestant-analgesic combinations compared with placebo, other active treatment (excluding antibiotics) or no treatment in children and adults with the common cold.

DATA COLLECTION AND ANALYSIS: Two review authors independently extracted and summarised data on general recovery, nasal obstruction, rhinorrhoea, sneezing, cough and side effects. We categorised the trials according to the active ingredients.

MAIN RESULTS: We included 27 trials (5117 participants) of common cold treatments. Fourteen trials studied antihistamine-decongestant combinations; two antihistamine-analgesic; six analgesic-decongestant; and five antihistamine-analgesic-decongestant combinations. In 21 trials the control intervention was placebo and in six trials an active substance. Reporting of methods in most trials was poor and there were large differences in design, participants, interventions and outcomes. Pooling was only possible for a limited number of studies and outcomes.Antihistamine-decongestant: 12 trials. Eight trials report on global effectiveness, six could be pooled; n = 309 on active treatment, n = 312 placebo) the odds ratio (OR) of treatment failure was 0.27 (95% confidence interval (CI) 0.15 to 0.50); the number needed to treat for an additional beneficial outcome (NNTB) was four (95% CI 3 to 5.6). On the final evaluation day 41% of participants in the placebo group had a favourable response compared to 66% on active treatment. Of the two trials that were not included in the pooling, one showed some global effect, the other showed no effect.Antihistamine-analgesic: three trials. Two reported on global effectiveness, data from one study was presented. (n = 290 on active treatment, n = 292 ascorbic acid). The OR of treatment failure was 0.33 (95% CI 0.23 to 0.46) and the NNTB was 6.67 (95% CI 4.76 to 12.5). After six days of treatment 43% were cured in the control group and 70% in the active treatment group. The second study also showed an effect in favour of active treatment.Analgesic-decongestant: six trials. One trial reported on global effectiveness: 73% benefited compared with 52% in the control group (paracetamol) (OR 0.28, 95% CI 0.15 to 0.52).Antihistamine-analgesic-decongestant: Five trials. Four trials reported on global effectiveness, two could be pooled: global effect reported (less than one severity point on a four or five-point scale) with active treatment (52%) and placebo (34%); the OR of treatment failure was 0.47 (95% CI 0.33 to 0.67) and the NNTB was 5.6 (95% CI 3.8 to 10.2). Two other trials found no beneficial effect. Two other studies did not show any effect.Two studies with antihistamine-decongestant (113 children) could not be pooled. There was no significant effect of the active treatment.Adverse effects: the combination of antihistamine-decongestant had more adverse effects than the control intervention but the difference was not significant: 157/810 (19%) versus 60/477 (13%) participants suffered one or more adverse effects (OR 1.58, 95% CI 0.78 to 3.21). Analgesic-decongestant combinations had significantly more adverse effects than control (OR 1.71, 95% CI 1.23 to 2.37); the number needed to treat for an additional harmful outcome (NNTH) was 14. None of the other two combinations caused significantly more adverse effects. Antihistamine-analgesic: 11/90 with combination suffered one or more adverse effects (12%) versus 9/91 (10%) with control (OR 1.27, 95% CI 0.50 to 3.23). Antihistamine-analgesic-decongestant: in one study 5/224 (2%) suffered adverse effects with active treatment versus 9/208 (4%) with placebo. Two other trials reported no differences between treatment groups but numbers were not reported.

AUTHORS' CONCLUSIONS: Current evidence suggests that antihistamine-analgesic-decongestant combinations have some general benefit in adults and older children. These benefits must be weighed against the risk of adverse effects. There is no evidence of effectiveness in young children.

Smith SM, Schroeder K, Fahey T. Over-the-counter (OTC) medications for acute cough in children and adults in ambulatory settings. In: The Cochrane Collaboration, Smith SM, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD001831.pub4. Accessed March 17, 2013

BACKGROUND: Acute cough due to upper respiratory tract infection (URTI) is a common symptom. Non-prescription, over-the-counter (OTC) medicines are frequently recommended as a first-line treatment, but there is little evidence as to whether these drugs are effective. OBJECTIVES: To assess the effects of oral OTC cough preparations for acute cough in children and adults.

SEARCH METHODS: We searched the Cochrane Central Register of Controlled Trials (CENTRAL) 2012 Issue 3 which contains the Acute Respiratory Infections Group's Specialised Register, MEDLINE (January 1966 to March week 1 2012), EMBASE (January 1974 to March 2012), CINAHL (January 2010 to March 2012), LILACS (January 2010 to March 2012), Web of Science (January 2010 to March 2012) and the UK Department of Health National Research Register (March 2010).

SELECTION CRITERIA: Randomised controlled trials (RCTs) comparing oral OTC cough preparations with placebo in children and adults suffering from acute cough in ambulatory settings. We considered all cough outcomes and secondary outcomes of interest were adverse effects.

DATA COLLECTION AND ANALYSIS: Two review authors independently screened potentially relevant citations, extracted data and assessed study quality. We performed quantitative analysis where appropriate. MAIN RESULTS: Twenty-six trials (18 in adults, eight in children) involving 4037 people (3421 adults and 616 children) were included. In the adult studies six trials compared antitussives with placebo and had variable results. Two trials compared the expectorant guaifenesin with placebo; one indicated significant benefit whereas the other did not. One trial found that a mucolytic reduced cough frequency and symptom scores. Two studies examined antihistamine-decongestant combinations and found conflicting results. Four studies compared other combinations of drugs with placebo and indicated some benefit in reducing cough symptoms. Three trials found antihistamines were no more effective than placebo in relieving cough symptoms. In the children studies antitussives (two studies), antihistamines (two studies), antihistamine decongestants (two studies) and antitussive/bronchodilator combinations (one study) were no more effective than placebo. No studies using expectorants met our inclusion criteria. The results of one trial favoured active treatment with mucolytics over placebo. One trial tested two paediatric cough syrups and both preparations showed a 'satisfactory response' in 46% and 56% of children compared to 21% of children in the placebo group.A minority of studies reported adverse effects and described a low incidence of mainly minor side effects such as nausea, vomiting, headache and drowsiness.

AUTHORS' CONCLUSIONS: There is no good evidence for or against the effectiveness of OTC medicines in acute cough. The results of this review have to be interpreted with caution due to differences in study characteristics and quality. Studies often showed conflicting results with uncertainty regarding clinical relevance. Higher quality evidence is needed to determine the effectiveness of self care treatments for acute cough.

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Month/Year of Review: May 2013
PDL Classes: Topical Antibiotics

Date of Last Review: March 2010
Source Document: Provider Synergies

Current Status of PDL:

- Preferred Agents: BACITRACIN, BACITRACIN ZINC, BACITRACIN/POLYMYXIN B SULFATE, GENTAMICIN SULFATE, MUPIROCIN, NEOMYCIN SULFATE/BACITRACIN ZINC/POLYMYXIN B SULFATE
- Non-Preferred Agents: ALTABAX RETAPAMULIN OINTMENT (ALTABAX®)

Previous Recommendations:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events
- Recommend inclusion of at least mupirocin

Methods:

A Medline OVID search was conducted with the following search terms: bacitracin, polymyxin B, neomycin, gentamicin, mupirocin, retapamulin, MRSA, methicillin resistant staphylococcus aureus, MSSA, methicillin sensitive, staphylococcus aureous, staphylococcus epidermidis, staphylococcus saprophyticus, streptococcus pyogenes, streptococcus saprophyticus, positive haemophilus influenza, negative haemophilus influenza, pseudomonas aeruginosa, skin infection, soft tissue infections, impetigo, minor bacterial infection, minor cut, burn, scrape. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to February week 2 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC), the Center for Disease Control (CDC) and Infectious Diseases Society of America (IDSA).

FDA-Approved Microorganism Indications:

Drug	MRSA	MSSA	Staphylococcus Epidermidis	Staphylococcus saprophyticus	Streptococcus Pyogenes	Streptococcus sp.	Haemophilus. Influenza	Pseudomonas aeruginosa
Bacitracin/bacitracin zinc ointment		X				X		
bacitracin zinc, neomycin, polymyxin B sulfate, hydrocortisone		X				X	X	X
Bacitracin zinc, neomycin, polymyxin B sulfate ointment		X				X	X	X
Bacitracin zinc, neomycin, polymyxin B sulfate, pramoxine		X				X	X	X
Bacitracin zinc, polymyxin B ointment		X				X	X	X
Gentamicin 0.1% cream/ointment		X	X		X		X	X
Mupirocin 2% cream/ointment	X	X	X	X	X			
Neomycin, polymyxin B sulfate, hydrocortisone cream		X				X	X	X

Retapamulin 1% ointment (altabax)		X			X			

New Trials (Appendix 1):
A total of 91 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, one relevant head-to-head clinical trial was identified.

McQuillan et al compared the efficacy of prophylactic topical mupirocin versus a triple antibiotic (bacitracin, polymyxin and gramicidin) ointment in preventing skin infection for patients undergoing peritoneal dialysis. [1] This was a small (n=201), low quality study with multiple opportunities for bias, including unclear blinding and allocation concealment. Seventy-five patients developed an infection during the study. There was no difference in incidence between groups: 36 patients in the mupirocin versus 39 in the triple antibiotic group (p=0.48). There was also no difference between groups in the time to first infection (p=0.41).

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
None

New Systematic Reviews (appendix 2):
A 2012 updated Cochrane systematic review evaluated the treatments for impetigo.[2] Sixty-eight trials were included with a total of 5578 participants; 50 treatments were examined including topical antibiotics (neomycin, bacitracin, polymyxin B, gentamycin, fusidic acid, mupirocin, or retapamulin). Trials were mostly low quality: risk of bias was high with only 15 trials reporting information about blinding. Only one study showed one topical antibiotic as superior over another: gentamycin over neomycin (RR 1.43, 95% CI 1.03 to 1.98). In another single study, the difference between retapamulin over fusidic acid was not statistically significant (RR 1.05, 95% CI 1.00 to 1.11). There were four studies which compared mupirocin with fusidic acid (RR 1.03, 95% CI 0.95 to 1.11) but the difference was not significant. Topical antibiotics were also found to be superior to placebo (RR 2.24, 95% CI 1.61 to 3.13), disinfecting agents (RR 1.15, 95% CI 1.01 to 1.32), and oral erythromycin (RR 1.07, 95% CI 1.01 to 1.13).

Guidelines:
The IDSA 2011 guidelines for the diagnosis and management of skin and soft-tissue infections recommended mupirocin ointment as the topical antibacterial drug of choice in the treatment of impetigo in infants two months and older and in adults.[3]

The 2012 updated version for diabetic foot infection treatment was reviewed. [4] No changes regarding the use of topical antibiotics were found.

Conclusions and Recommendations:
- No further research or review needed at this time.
- Evaluate comparative costs in executive session.

References:

1. McQuillan RF, Chiu E, Nessim S, et al. A Randomized Controlled Trial Comparing Mupirocin and Polysporin Triple Ointments in Peritoneal Dialysis Patients: The MP3 Study. *Clinical Journal of the American Society of Nephrology*. 2011;7(2):297–303. doi:10.2215/CJN.07970811.

2. Koning S, van der Sande R, Verhagen AP, et al. Interventions for impetigo. *Cochrane Database Syst Rev*. 2012;1:CD003261. doi:10.1002/14651858.CD003261.pub3.

3. Liu C, Bayer A, Cosgrove SE, et al. Clinical practice guidelines by the infectious diseases society of america for the treatment of methicillin-resistant Staphylococcus aureus infections in adults and children: executive summary. *Clin. Infect. Dis.* 2011;52(3):285–292. doi:10.1093/cid/cir034.

4. Lipsky BA, Berendt AR, Cornia PB, et al. 2012 Infectious Diseases Society of America Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections. *Clinical Infectious Diseases*. 2012;54(12):e132–e173. doi:10.1093/cid/cis346.

Appendix 1 : Abstracts of Randomized Control Trials

McQuillan RF, Chiu E, Nessim S, et al. A Randomized Controlled Trial Comparing Mupirocin and Polysporin Triple Ointments in Peritoneal Dialysis Patients: The MP3 Study. *Clinical Journal of the American Society of Nephrology*. 2011;7(2):297–303.

Background and objectives: Infectious complications remain a significant cause of peritoneal dialysis (PD) technique failure. Topical ointments seem to reduce peritonitis; however, concerns over resistance have led to a quest for alternative agents. This study examined the effectiveness of applying topical Polysporin Triple ointment (P3) against mupirocin in a multi-centered, double-blind, randomized controlled trial.

Design, setting, participants, & measurements: PD patients routinely applied either P3 or mupirocin ointment to their exit site. Patients were followed for 18 months or until death or catheter removal. The primary study outcome was a composite endpoint of exit-site infection (ESI), tunnel infection, or peritonitis.

Results: Seventy-five of 201 randomized patients experienced a primary outcome event (51 peritonitis episodes, 24 ESIs). No difference was seen in the time to first event for P3 (13.2 months; 95% confidence interval, 11.9–14.5) and mupirocin (14.0 months; 95% confidence interval, 12.7–15.4) (P=0.41). Twice as many patients reported redness at the exit site in the P3 group (14 versus 6, P=0.10).Over the complete study period, a higher rate per year of fungal ESIs was seen in patients using P3 (0.07 versus 0.01; P=0.02) with a corresponding increase in fungal peritonitis (0.04 versus 0.00, respectively; P, 0.05).

Conclusions: This study shows that P3 is not superior to mupirocin in the prophylaxis of PD-related infections. Colonization of the exit site with fungal organisms is of concern and warrants further study. As such, the use of P3 over mupirocin is not advocated in the prophylaxis of PD-related infections.

Appendix 2 : Abstracts of Systematic Reviews

Koning S, Van der Sande R, Verhagen AP, et al. Interventions for impetigo. In: The Cochrane Collaboration, van der Wouden JC, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD003261.pub3.

Background Impetigo is a common, superficial bacterial skin infection, which is most frequently encountered in children. There is no generally agreed standard therapy, and guidelines for treatment differ widely.Treatment options includemany different oral and topical antibiotics as well as disinfectants. This is an updated version of the original review published in 2003.

Objectives To assess the effects of treatments for impetigo, including non-pharmacological interventions and 'waiting for natural resolution'.

Search methods We updated our searches of the following databases to July 2010: the Cochrane Skin Group Specialised Register, the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE (from 2005), EMBASE (from 2007), and LILACS (from 1982). We also searched online trials registries for ongoing trials, and we handsearched the reference lists of new studies found in the updated search.

Selection criteria Randomised controlled trials of treatments for non-bullous, bullous, primary, and secondary impetigo.

Data collection and analysis Two independent authors undertook all steps in data collection. We performed quality assessments and data collection in two separate stages.

Main results We included 57 trials in the first version of this review. For this update 1 of those trials was excluded and 12 new trials were added. The total number of included trials was, thus, 68, with 5578 participants, reporting on 50 different treatments, including placebo. Most trials were in primary impetigo or did not specify this. For many of the items that were assessed for risk of bias, most studies did not provide enough information. Fifteen studies reported blinding of participants and outcome assessors. Topical antibiotic treatment showed better cure rates than placebo (pooled risk ratio (RR) 2. 24, 95% confidence interval (CI) 1.61 to 3.13) in 6 studies with 575 participants. In 4 studies with 440 participants, there was no clear evidence that either of the most commonly studied topical antibiotics (mupirocin and fusidic acid) was more effective than the other (RR 1.03, 95% CI 0.95 to 1.11). In 10 studies with 581 participants, topical mupirocin was shown to be slightly superior to oral erythromycin (pooled RR 1.07, 95% CI 1.01 to 1.13). There were no significant differences in cure rates from treatment with topical versus other oral antibiotics. There were, however, differences in the outcome from treatment with different oral antibiotics: penicillin was inferior to erythromycin, in 2 studies with 79 participants (pooled RR 1.29, 95% CI 1.07 to 1.56), and cloxacillin, in 2 studies with 166 participants (pooled RR 1.59, 95% CI 1.21 to 2.08). There was a lack of evidence for the benefit of using disinfectant solutions. When 2 studies with 292 participants were pooled, topical antibiotics were significantly better than is infecting treatments (RR 1.15, 95% CI 1.01 to 1.32). The reported number of side-effects was low, and most of these were mild. Side-effects were more common for oral antibiotic treatment compared to topical treatment. Gastrointestinal effects accounted for most of the difference. Worldwide, bacteria causing impetigo show growing resistance rates for commonly used antibiotics. For a newly developed topical treatment, retapamulin, no resistance has yet been reported.

Authors' conclusions There is good evidence that topical mupirocin and topical fusidic acid are equally, or more, effective than oral treatment. Due to the lack of studies in people with extensive impetigo, it is unclear if oral antibiotics are superior to topical antibiotics in this group. Fusidic acid and mupirocin are of similar efficacy. Penicillin was not as effective as most other antibiotics. There is a lack of evidence to support disinfection measures to manage impetigo.

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Month/Year of Review: May 2013
PDL Classes: Oral Immunosuppressants

Date of Last Review: April 2010
Source Document: Provider Synergies

Current Status of PDL Class:
- Preferred Agents: AZATHIOPRINE, CYCLOSPORINE, EVEROLIMUS, MYCOPHENOLATE, SIROLIMUS, TACROLIMUS
- Non-Preferred Agents: NONE

Previous Recommendations:
1. Evidence does not support a difference in efficacy/effectiveness
2. Evidence does not support a difference in harm/adverse events
3. Recommend coverage of all entities
4. Recommend preference of generic products

Methods:
A Medline OVID search was conducted with the following search terms: azathioprine, cyclosporine, everolimus, mycophenolate, sirolimus, tacrolimus, oral immunosuppressants, transplantation, homologous transplantation, kidney transplantation, graft rejection, renal transplantation, organ transplantation, organ transplants, liver transplantation, graft rejection, heart transplantation, cardiac transplant, rheumatoid arthritis, inflammatory bowel diseases, myasthenia gravis, pancreas transplantation, Systemic Lupus Erythematosus, Takayasu's Disease, keratoconjunctivitis, Graft vs. Host Disease, lung transplantation, Ulcerative Colitis, Crohn's Disease, Sjogren's Syndrome, small intestine transplantation, and corneal transplantation. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to March week 4 2013.

The Cochrane Collection, Dynamed and Medline OVID were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts. Finally, a search for new or updated guidelines was conducted at the AHRQ National Guideline Clearinghouse (NGC).

New Trials (Appendix 1):
A total of 1005 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo), or outcome (non-clinical). After a review of titles and abstracts for inclusion, 18 relevant head-to-head clinical trials were identified and are discussed below. Seventeen studies were conducted in transplant patients and one trial in psoriasis patients. Because of the nature of the studied populations, these trials were of low quality; blinding, randomization, and allocation concealment were either not performed or not discussed. Please see Appendix 1 for the full abstracts.

Six studies focused on kidney transplant patients. Budde[1] et al conducted a multicenter open-label study in renal transplant patients (n=300) randomized to either cyclosporine or everolimus based regimens. The primary outcome was improved renal function; secondary outcomes included patient tolerance and organ rejection. At twelve months, everolimus patients showed significantly greater glomerular filtration rate (GFR) improvement (mean difference between groups: 9.8 mL/min, 95% CI -12.2 to -7.5). At the end of the trial reject rates were identical (15%) between the two groups. A follow-up study[2] was conducted at 3 years. At this time nearly 30% of everolimus patients had been reintroduced to cyclosporine or started on tacrolimus. The GFR was significantly higher with everolimus compared with cyclosporine (mean difference: 7.5 mL/min, 95% CI 3.6 to 11.4); however rejection rates were higher in the everolimus patients (13% versus 4.8%, p=0.015).

Dantal[3] et al conducted a multicenter open-label trial to measure the benefit of eliminating calcineurin inhibitors (CNI) on kidney function. Renal transplant patients were randomized to a regimen of everolimus and cyclosporine or everolimus and mycophenolate for twelve months. The primary outcome was mean difference in GFR and was not statistically significant between the two groups (p=0.059). The mycophenolate cohort did have an average improvement in GFR not seen in the CNI group; however, the two groups were not well matched at baseline and the CNI group had a much lower average GFR.

Guerra[4] et al looked at the long-term benefits of different immunosuppressant regimens post-renal transplant. Patients (n=150) were randomized in an open-label trial to tacrolimus and sirolimus, tacrolimus and mycophenolate, or cyclosporine and sirolimus. Acute rejection occurred less often (p=0.05) during the first 36 months among those treated with tacrolimus and mycophenolate (14%) than among those treated with tacrolimus and sirolimus (34%) or cyclosporine and sirolimus (31%). Average GFR was consistently higher in the tacrolimus and mycophenolate group (p= 0.008). There were no significant differences in survival between the groups at the end of eight years after transplant.
Mjörnstedt[5] et al also looked at the benefit for renal function of switching from a CNI to another immunosuppressant. Subjects (n=202) were randomized at week seven post-transplant to remain on cyclosporine or switch to everolimus. Improvement in GFR was measured at twelve months. Patients on everolimus saw improvement in average GFR (mean increase of 8.7 mL/min) compared with cyclosporine (mean decrease 0.4 ml/min, p<0.001). Acute rejection was higher for everolimus than cyclosporine (27.5% vs. 11.0%, p=0.004), although there was no difference in overall graft or patient survival.

Santos[6] et al conducted a trial comparing baseline low-dose cyclosporine paired with either everolimus or mycophenolate in kidney transplant patients. After two years patients were measured for differences in creatinine levels, acute rejection and survival rates. There was no significant difference between the everolimus and mycophenolate groups in mean serum creatinine (1.2 mg/dL vs 1.4 mg/dL, p=0.05), acute rejection (31% vs 40%, p=0.05), and patient or graft survival (100%).

Vacher[7] et al compared tacrolimus and mycophenolate with cyclosporine and azathioprine in a twelve month trial with a primary endpoint of acute organ rejection. Kidney transplant patients (n=289) were randomized to one of the two protocol groups. After one year, 14.4% of cyclosporine patients had an acute organ rejection versus 7.7% of tacrolimus patients, although this was nonsignificant (p=0.07). Overall rates of patient and graft survivals were also similar between the two groups.

Three trials focused on liver transplant patients. Abdelmarkel[8] et al looked at the possible benefits in renal function when switching liver transplant patients (n=607) from a CNI (tacrolimus or cyclosporine) to sirolimus. The primary endpoint was difference in GFR at twelve months. No statistical difference was seen in mean GFR between groups (p=0.34). In addition, no difference was seen between groups in rates of organ rejection or death.

Herlenius[9] et al also examined the effect on renal function when changing liver transplant patients from a CNI regimen to another immunosuppressant. Patients with preexisting chronic kidney disease (n=25) were randomized to either sirolimus or mycophenolate in this before and after trial. The average GFR at baseline was 31 mL/min. After three months the average GFR increased to 40 mL/min (p=0.0001) and at twelve months to 42 mL/min (p=0.0006). There was not a significant difference between the two study arms. No long-term outcomes were examined.

Schmeding[10] et al randomized liver transplant patients (n=150) to either standard CNI or mycophenolate treatment for a long-term safety trial. Patients were followed for five years to see if there was any difference in clinical outcomes. No significant difference regarding the incidence of acute rejection was detected and patient survival was identical in the two groups.

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De Simone et al conducted a 24-month, multinational, open-label, randomized trial in liver transplant patients starting 30 days post-transplant in 1,147 patients.[11] Prior to randomization, patients received tacrolimus and corticosteroids, with or without mycophenolate. At day 30, 719 patients were ranomidzed into one of three groups: everolimus initation with tacrolimus elimination, everolimus initation with reduced exposure tacrolimus, or standard-exposure tacrolimus. The first group (tacrolimus elimination) was discontinued early due to a higher incidence of acute rejection. The reduced tacrolimus group was non-inferior to the tacrolimus control group for the primary endpoint of acute rejection, graft loss, or death at 12 months post-transplant (6.7% vs. 9.7%, p<0.001).[11]

Five trials focused on heart transplant patients. Guethoff[12] et al randomized patients to either tacrolimus or cyclosporine and followed them for ten years. Primary efficacy outcomes included acute rejection and overall survival. Members on tacrolimus were significantly less likely to experience an acute rejection (21.7% vs. 65.5%, p<0.004). This did not translate to increases in overall survival for tacrolimus subjects; survival rates at one, five and ten years were 96.7%, 80.0%, and 66.7% for tacrolimus and 90.0%, 83.3%, and 80.0% for cyclosporine (p>0.05 for all years).

Sanchez-Lazero[13] et al examined the rate of cardiac allograft vasculopathy (CAV) in heart transplant patients taking different calcineurin inhibitors. CAV is a leading cause of death in this population. Patients (n=49) were randomized to either cyclosporine or tacrolimus. After one year, no significant difference was detected between the two groups development of CAV (cyclosporine 31.6% vs tacrolimus 38.9%, p=0 .642). Thirteen patients died within the study period; no distinction was made as to which medication regimen these patients were assigned to.

Vigano[14] et al examined the rate of cytomegalovirus (CMV) in heart transplant patients (n=176) randomized to either everolimus or mycophenolate. This twelve month multicenter, open-label study found that the everolimus patients had significantly lower incidence of CMV than the mycophenolate arm (8.8% vs. 32.5%, p<0.001).

Potena[15] et al compared long-term use of low-dose cyclosporine with everolimus or mycophenolate for reducing progression of renal dysfunction in heart transplant patients. Patients (n=34) were one to four years post-transplant with a creatinine clearance (CrCl) of 25 to 60 ml/min. Primary end point was improvement in CrCl after a follow-up of three years. CrCl improved in the mycophenolate group 20% from baseline (p=0.01) but the everolimus group did not have a significant change from baseline. Overall survival and organ rejection rates were not significantly different between the two groups.

Zuckerman[16] et al evaluated the effect on renal function of switching from a CNI to sirolimus in heart transplant patients. The primary outcome was change in GFR after one year. Patients (n=116) were randomized to remain on a CNI (tacrolimus or cyclosporine) or change to sirolimus; baseline GFR for all patients was between 40 and 90 mL/min. After one year, sirolimus patients had a significant increase in GFR compared with those on CNI medications (+3.0 vs.−1.4mL/min, p = 0.004). Acute rejection rates were not significantly different between treatment groups.

Two trials focused on lung transplant patients. Treede[17] et al examined any difference in the incidence of bronchiolitis obliterans syndrome (BOS) with CNI regimens in a multicenter, open-label trial. BOS is the primary cause of death in lung transplant patients. Patients (n=149) were randomized to either cyclosporine or tacrolimus and followed for three years. The rate of BOS, after three years was lower for tacrolimus patients (11.6% vs. 21.3%, p=0.037). Differences in acute rejection and overall survival rates were statistically nonsignificant.

Bhorade[18] et al compared the incidence of organ rejection in lung transplant patients placed on sirolimus. Patients (n=181) were randomized to either sirolimus or azathioprine in a twelve month open-label trial. After one year, there was no significant difference in organ rejection between the two study groups (p=0.82).

One trial focused on psoriasis patients. Akhyani[19] et al randomized patients (n=36) to either mycophenolate or methotrexate for twelve weeks to treat their chronic plaque psoriasis. Patients had a baseline Psoriasis Area and

Severity Index (PASI) score of 10 or greater and the average difference from baseline was the primary outcome. After 12 weeks of treatment, the mean score for the PASI decreased from 16.46 to 3.17 among methotrexate patients and from 17.43 to 3.97 in mycophenolate patients ($p>0.05$). Improvement seen three months after trial discontinuation was also statistically nonsignificant between treatment groups.

New drugs:
None

New Formulations/Indications:
Two new formulations of everolimus have been approved since the last oral immunosuppressant class review. Zortress[20] is an oral tablet indicated for the prophylaxis of organ transplant in adults. It was approved in April of 2010. In February of 2013, it was also approved for the prophylaxis of organ rejection in those receiving a liver transplant.

Afinitor[21] was approved in August of 2012. Afinitor Disperz is a tablet for oral suspension approved for the new indication[22] of treatment in pediatric and adult patients with tuberous sclerosis complex (TSC) who have subependymal giant cell astrocytoma (SEGA) that requires therapeutic intervention but cannot be curatively resected. It is also indicated for the treatment of postmenopausal women with advanced hormone receptor-positive, HER2-negative breast cancer in combination with exemestane, after failure of treatment with letrozole or anastrozole.

New FDA safety alerts:
In September of 2012, the FDA began a Risk Evaluation and Mitigation Strategy (REMS) for mycophenolate[23] to address the increased risk of miscarriage and birth defects if taken during pregnancy. The Mycophenolate REMS includes a Medication Guide, training for health care professionals, and the establishment of a pregnancy registry for women who become pregnant and agree to participate in the registry.

An FDA safety communication was released in April 2011 for azathioprine[24] informing the public that it has received reports of a rare cancer of white blood cells (known as Hepatosplenic T-Cell Lymphoma or HSTCL), primarily in adolescents and young adults being treated for Crohn's disease and ulcerative colitis with medicines known as tumor necrosis factor (TNF) blockers, as well as with azathioprine, and/or mercaptopurine. No labeling changes were associated with this communication. The FDA believes the risks and benefits of using these medications should be carefully weighed when prescribing these drugs to children and young adults.

New Systematic Reviews: (Appendix 2)
Five new systematic reviews were identified. Please see Appendix 2 for the full abstracts.
Asrani[25] et al conducted a systematic review to determine if using sirolimus improves renal function in liver transplant patients with baseline renal insufficiency. Three randomized control trials (RCT) and eight observational studies were included in the analysis. Patients with a glomerular filtration rate (GFR) of less than 60 mL/min were switched from a calcineurin inhibitor (CNI) to sirolimus from the time of transplantation to five years post-transplant. All three RCTs and four of the observational study (n=368) were included in the estimated change in renal function after 12 months (3.38 mL/min, 95% CI -2.93 to 9.69). Isolating the RCT (n=82), the pooled estimated renal function change was significant (10.35 mL/min, 95% CI 3.98 to 16.77), but the average baseline GFR was higher for this population. Sirolimus did not significantly decrease the risk of death (RR 1.12, 95% CI 0.66 to 1.88) or organ rejection (RR 0.8, 95% 0.45 to 1.41). Individual trial quality was poor with high risk of bias in all of the RCT due to lack of blinding, allocation concealment and randomization methodology.

A Cochrane Collaborative systematic review involving oral immunosuppressants was published in2012. Penninga[26] et al planned to examine the efficacy and safety of using low dose CNI (tacrolimus or cyclosporine) in liver transplant

patients. Trials that included a switch to another immunosuppressant were not eligible. No trials were found to meet the author's criteria for inclusion and the review was discontinued.

Sharif[27] et al also examined strategies to minimize the negative effects of CNI therapy. Their analysis focused on kidney transplant patients who had undergone CNI avoidance, CNI minimization, or CNI delayed introduction. Fifty-six studies were included with 11,337 subjects; the median trial length was twelve months. No difference was found in overall graft failure (OR 1.05, 95% CI 0.85 to 1.29) or death (OR 1.11, 95% CI 0.89 to 1.38) between standard versus reduced CNI exposure patients. Acute rejection was measured in 53 studies (n= 10,712) and increased rates of rejection were seen in the reduced CNI exposure group (OR 1.24, 95% 1.01 to 1.53). Breaking the data down for individual regimens, use of sirolimus or everolimus with mycophenolate (n=2688) was associated with an increase in graft failure (OR 0.61, 95% CI 0.39 to 0.96). Individual trial quality was considered fair to poor, with limited information available for allocation concealment and randomization practices. Also, most trials were not blinded.

Penninga[28] et al conducted a systematic review to compare the safety and efficacy of cyclosporine versus tacrolimus for heart transplant patients. Ten randomized control trials (n=956) were reviewed; trial duration was between six months and five years. Both cyclosporine and microemulsion cyclosporine formulations were included. Tacrolimus patients had a significantly lower risk than cyclosporine patients (either type) of experiencing hypertension (RR 0.8, 95% CI 0.69 to 0.93), hyperlipidemia (RR 0.57, 95% CI 0.44 to 0.74), hirsutism (RR 0.17, 95% CI 0.04 to 0.62), and gingival hyperplasia (RR 0.07, 95% CI 0.01 to 0.37). No significant difference was found between groups in rates of acute rejections. Tacrolimus patients also had significantly lower rates of mortality compared with microemulsion cyclosporine (RR 0.64, 95% CI 0.42 to 0.96). Trial quality was rated as poor by the authors for all of the included studies.

Guidelines:

The updated guideline[29] for ulcerative colitis from the American College of Gastroenterology was reviewed; as was the updated lupus nephritis[30] and rheumatoid arthritis[31] guidelines from the American College of Rheumatology. No changes regarding the use of oral immunosuppressants were found.

Similar to 2008, azathioprine, cyclosporine, and gold were not recommended for the treatment of rheumatoid arthritis based on their infrequent use and lack of new data.

Recommendations:

- No further research or review needed at this time.

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Appendix 1: Abstracts of Randomized Control Trials

Budde K, Becker T, Arns W, et al. Everolimus-based, calcineurin-inhibitor-free regimen in recipients of de-novo kidney transplants: an open-label, randomised, controlled trial. *The Lancet*. 2011;377(9768):837–847. doi:10.1016/S0140-6736(10)62318-5.

Background Non-nephrotoxic immunosuppressive strategies that allow reduction of calcineurin-inhibitor exposure without compromising safety or efficacy remain a goal in kidney transplantation. Immunosuppression based on the mammalian-target-of-rapamycin inhibitor everolimus was assessed as a strategy for elimination of calcineurin-inhibitor exposure and optimisation of renal-graft function while maintaining efficacy. Methods In the ZEUS multicentre, open-label study, 503 patients (aged 18–65 years) who had received de-novo kidney transplants were enrolled. After initial treatment with ciclosporin, based on trough concentrations, and enteric-coated mycophenolate sodium (1440 mg/day, orally), corticosteroids (≥5 mg/day prednisolone or equivalent, orally), and basiliximab induction (20 mg, intravenously,

on day 0 [2 h before transplantation], and on day 4), 300 (60%) patients were randomly assigned at 4 · 5 months in a 1:1 ratio to undergo calcineurin-inhibitor elimination (everolimus-based regimen that was based on trough concentrations [6–10 ng/mL] and enteric-coated mycophenolate sodium [1440 mg/day] with corticosteroids), or continue standard ciclosporin-based treatment. Randomisation was done by use of a central, validated system that automated the random assignment of treatment groups to randomization numbers. The primary objective was to show better renal function (glomerular filtration rate [GFR]; Nankivell formula) with the calcineurin-inhibitor-free everolimus regimen at 12 months after transplantation. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00154310. Findings 118 (76%) of 155 everolimus-treated patients and 117 (81%) of 145 ciclosporin-treated patients completed treatment with study drug up to 12 months after transplantation. At this time point, the everolimus regimen was associated with a significant improvement in GFR versus the ciclosporin regimen (71 · 8 mL/min per 1 · 73 m2 *vs* 61 · 9 mL/ min per 1 · 73 m2, respectively; mean difference 9 · 8 mL/min per 1 · 73 m2, 95% CI −12 · 2 to −7 · 5). Rates of biopsy-proven acute rejection were higher in the everolimus group than in the ciclosporin group after randomisation (15 [10%] of 154 *vs* five [3%] of 146; p=0 · 036), but similar for the full study period (23 [15%] *vs* 22 [15%]). Compared with the ciclosporin regimen, higher mean lipid concentrations, slightly increased urinary protein excretion, and lower haemoglobin concentrations were noted with the everolimus regimen; thrombocytopenia, aphthous stomatitis, and diarrhoea also occurred more often in the everolimus group. A higher incidence of hyperuricaemia was noted with ciclosporin. Interpretation Early elimination of calcineurin inhibitor by use of everolimus-based immunosuppression improved renal function at 12 months while maintaining efficacy and safety, indicating that this strategy may facilitate improved long-term outcomes in selected patients.

Budde K, Lehner F, Sommerer C, et al. Conversion From Cyclosporine to Everolimus at 4.5 Months Posttransplant: 3-Year Results From the Randomized ZEUS Study. *American Journal of Transplantation*. 2012;12(6):1528–1540. doi:10.1111/j.1600-6143.2012.03994.x.
The long-term effect of conversion from calcineurin inhibitor (CNI) therapy to an mTOR inhibitor requires clarification. Following completion of the 12-month, open-label, multicenter ZEUS study, in which 300 kidney transplant recipients were randomized to continue cyclosporine (CsA) or convert to everolimus at 4.5 months post transplant, outcomes were assessed at month 36 (n = 284; 94.7%). CNI therapy was reintroduced in 28.4% of everolimus patients by month 36. The primary efficacy endpoint, estimated glomerular filtration rate (Nankivell, ANCOVA)was significantly higher with everolimus versus the CsA group at month 24 (7.6 mL/min/1.73 m2, 95%CI 4.3, 11.0 mL/min/1.73 m2; p < 0.001) and month 36 (7.5 mL/min/1.73 m2, 95%CI 3.6, 11.4 mL/min/1.73 m2; p < 0.001). The incidence of biopsy-proven acute rejection from randomization to month 36 was 13.0% in the everolimus arm and 4.8% in the CsA arm (p = 0.015). Patient and graft survival, as well as incidences of malignancy, severe infections and hospitalization, were similar between groups. Kidney transplant patients who are converted from CsA to everolimus at month 4.5 and who remain on everolimus thereafter may achieve a significant improvement in renal function that is maintained to 3 years. There was a significantly higher rate of rejection in the everolimus arm but this did not exert a deleterious effect by 3 years post transplant.

Abdelmalek MF, Humar A, Stickel F, et al. Sirolimus Conversion Regimen Versus Continued Calcineurin Inhibitors in Liver Allograft Recipients: A Randomized Trial. *American Journal of Transplantation*. 2012;12(3):694–705. doi:10.1111/j.1600-6143.2011.03919.x.
A large prospective, open-label, randomized trial evaluated conversion from calcineurin inhibitor (CNI)- to sirolimus (SRL)-based immunosuppression for preservation of renal function in liver transplantation patients. Eligible patients received liver allografts 6–144 months previously and maintenance immunosuppression with CNI (cyclosporine or tacrolimus) since early post transplantation. In total, 607 patients were randomized (2:1) to abrupt conversion (<24 h) from CNI to SRL (n = 393) or CNI continuation for up to 6 years (n=214). Between-group changes in baseline-adjusted mean Cockcroft–Gault GFR at month 12 (primary efficacy end point) were not significant. The primary safety end point, noninferiority of cumulative rate of graft loss or death at 12months,was not met (6.6% vs. 5.6% in the SRL and CNI groups, respectively). Rates of death at 12 months were not significantly different, and no true graft losses (e.g. liver transplantation) were observed during the 12-month period. At 52 weeks, SRL conversion was associated with higher rates of biopsy-confirmed acute rejection (p = 0.02) and discontinuations (p < 0.001), primarily for adverse events. Adverse events were consistent with known safety profiles. In conclusion, liver transplantation patients showed no demonstrable benefit 1 year after conversion from CNI- to SRL-based immunosuppression.

Akhyani M, Chams-Davatchi C, Hemami M, Fateh S. Efficacy and safety of mycophenolate mofetil vs. methotrexate for the treatment of chronic plaque psoriasis. *Journal of the European Academy of Dermatology and Venereology*. 2010;24(12):1447–1451. doi:10.1111/j.1468-3083.2010.03667.x.
Background Methotrexate (MTX) is a well-known systemic drug for moderate to severe chronic plaque psoriasis. Recently, mycophenolate mofetil (MMF) has been recommended for psoriasis. Objective To compare the efficacy and safety of MMF vs. MTX for the treatment of chronic plaque psoriasis. Methods Thirty-eight consecutive patients with Psoriasis Area and Severity Index (PASI) >10 were randomly assigned for 12 weeks of treatment with either MTX (18 patients; initial dose, 7.5 mg/week) or MMF (20 patients; dose; 2 g/day) and were followed for 12 weeks after discontinuing the treatment. The differences between the two groups were analysed at the end of treatment and follow-up comparing with baseline values. Results After 12 weeks of treatment, the mean ± SD score for the PASI decreased from 16.46 ± 5.29 at baseline to 3.17 ± 2.35 among 15 patients treated with MTX, whereas the score decreased from 17.43 ± 7.42 to 3.97 ± 5.95 among 17 patients treated with MMF (P > 0.05). Twelve weeks after discontinuing the treatment, the scores were 4.77 ± 3.52 and 5.94 ± 4.27, respectively (P > 0.05). PASI -75 were achieved in 58.8% of patients in MMF group and 73.3% in MTX group (P > 0.05). Three months after discontinuing the treatment, PASI-75 remained in 33.3% of patients in MMF and 53.3% of MTX group (P > 0.05). Both drugs were well tolerated and side-effects were minor and transient. Conclusions No significant differences in efficacy were found between MTX and MMF groups. MMF may represent a good alternative for the treatment of psoriasis in patients who are unable to take MTX or other available drugs due to contraindication or toxicity.

Dantal J. Conversion from everolimus with low-exposure cyclosporine to everolimus with mycophenolate sodium maintenance therapy in kidney transplant recipients: A randomized, open-label multicenter study. *Annals of Transplantation*. 2012;17(1):58–67. doi:10.12659/AOT.882637.
Background: Data in kidney transplant recipients regarding elimination of calcineurin inhibitor (CNI) therapy from a *de novo* regimen based on low CNI exposure and an mTOR inhibitor are sparse, and restricted to CNI elimination within the first six months post-transplant. Material/Methods: In a 12-month, randomized, multicenter, open-label study, kidney transplant patients who had received everolimus, low-exposure cyclosporine and corticosteroids from transplantation to month 12 (with proteinuria <1 g/24 h at month 12) were randomized to convert from cyclosporine to mycophenolate sodium 720 mg/day with increased everolimus exposure (6–10 ng/mL [CNI-free group], n=15) or continue unchanged (everolimus 3–8 ng/mL [CNI group], n=15). Results: Median (range) baseline mGFR was 54 (21–87) mL/min and 37 (range 18–69) mL/min (p=0.053) in the CNI-free and CNI groups, respectively, compared to 56 (18–126) mL/min and 32 (12–63) mL/min at month 12 (p=0.007). The between group difference in change in mGFR from baseline to month 12 post-conversion (the primary endpoint) was −14.4 mL/min (95% CI −29.3 to 0.6 mL/min, p=0.059 [least squares mean]). Changes in serum creatinine and estimated GFR to month 12 were significantly in favor of CNI-free patients. One CNI patient experienced biopsy-proven acute rejection. Study drug was discontinued due to adverse events in one CNI-free patient (7%) and three CNI-treated patients (20.0%). Conclusions: Elimination of CNI from a *de novo* regimen of everolimus with low-exposure CNI at one year post-transplant maintained efficacy and led to a non-significant but clinically relevant improvement in renal function, although patients numbers were low (n=30). Findings from this small study require confirmation in a larger controlled trial.

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Bhorade S, Ahya VN, Baz MA, et al. Comparison of Sirolimus with Azathioprine in a Tacrolimus-based Immunosuppressive Regimen in Lung Transplantation. *American Journal of Respiratory and Critical Care Medicine*. 2011;183(3):379–387. doi:10.1164/rccm.201005-0775OC.
Rationale: Lung transplantation has evolved into a life-saving therapy for select patients with end-stage lung diseases. However, long-term survival remains limited because of chronic rejection. Sirolimus is beneficial in preventing cardiac rejection and may decrease rejection after lung transplantation. Objectives: To determine the potential benefit versus risk of sirolimus in lung transplantation. Methods: We conducted a multicenter randomized, open label controlled trial comparing sirolimus (SIR) with azathioprine (AZA) in a tacrolimus-based immunosuppressive regimen in lung transplantation. The primary end point was the incidence of acute rejection at 1 year after transplantation between the two study groups. Measurements and Main Results: One hundred eighty-one patients were randomized to be included in this study. At 1 year after transplantation, there was no significant difference in the incidence of grade A acute rejection between the two study groups. Similarly, the incidence of chronic rejection and graft survival was no different between the two study groups. Cytomegalovirus infection was decreased in the SIR arm compared with the AZA arm (relative risk, 0.67 [95%confidence interval, 0.55, 0.82]; P , 0.01). There was a higher rate of adverse events leading to early discontinuation of SIR (64%) compared with AZA (49%) during the course of this study. Conclusions: Sirolimus, an mTOR inhibitor, did not decrease the incidence of acute rejection at 1 year compared with azathioprine in lung transplantation. These results differ from previous results in cardiac and renal transplantation and emphasize the need for multicenter randomized controlled trials in lung transplantation.

Guerra G, Ciancio G, Gaynor JJ, et al. Randomized Trial of Immunosuppressive Regimens in Renal Transplantation. *Journal of the American Society of Nephrology*. 2011;22(9):1758–1768. doi:10.1681/ASN.2011010006.
The optimal long-term regimen for immunosuppression for kidney transplant recipients is unknown. We conducted a randomized trial involving 150 kidney transplant recipients to compare tacrolimus/sirolimus, tacrolimus/mycophenolate mofetil (MMF), and cyclosporine/sirolimus. All patients received daclizumab induction and maintenance corticosteroids. Median follow-up was 8 yr. post-transplant. Acute rejection (AR) occurred significantly less often among those treated with tacrolimus/MMF (12%) than among those treated with tacrolimus/sirolimus (30%) or cyclosporine/sirolimus (28%). Mean estimated GFR was consistently higher in the tacrolimus/MMF arm, especially after controlling for donor age in a multivariable model during the first 36 mo. (*P* _ 0.008). The rate of dying with a functioning graft was significantly higher among those treated with tacrolimus/sirolimus (26%) than among those treated with tacrolimus/MMF (12%) or cyclosporine/sirolimus (4%). We did not observe significant differences in actuarial graft survival at 8 yr. post-transplant between the groups. Patient noncompliance seemed responsible for 45% (13/29) of observed graft failures, with 11 of these occurring after 36 mo. Significantly more viral infections, protocol violations, and need for antilipid therapy occurred among patients receiving sirolimus, but we did not observe differences between the groups with regard to infections requiring hospitalization or new-onset diabetes. Taken together, these results suggest that maintenance therapy with tacrolimus/MMF is more favorable than either tacrolimus/sirolimus or cyclosporine/sirolimus.

Guethoff S, Meiser BM, Groetzner J, et al. Ten-year results of a randomized trial comparing tacrolimus versus cyclosporine a in combination with mycophenolate mofetil after heart transplantation. *Transplantation*. 2013;95(4):629–634. doi:10.1097/TP.0b013e318277e378.
Background. Long-term results of prospective randomized trials comparing triple immunosuppressive strategies combining tacrolimus (TAC) or cyclosporine A (CsA) with mycophenolate mofetil (MMF) and steroids after heart transplantation (HTX) are rarely published. Therefore, we collected long-term follow-up data of an intervention cohort 10 years after randomization. Methods. Ten-year follow-up data of 60 patients included in a prospective, randomized trial between 1998 and 2000 were analyzed as intention-to-treat (TAC-MMF n=30; CsA-MMF n=30). Baseline characteristics were well balanced. Cardiac allograft vasculopathy (CAV) was graduated in accordance with the new ISHLT classification. Results. Survival at 1, 5, and 10 years was 96.7%, 80.0%, and 66.7% for TAC-MMF and 90.0%, 83.3%, and 80.0% for CsA-MMF (P=ns). Freedom from acute rejection (AR) was significantly higher in TAC-MMF versus CsA-MMF (65.5% vs. 21.7%, log-rank 8.3, P=0.004). Freedom from ISHLTQCAV1 after 5 and 10 years was in TAC-MMF 64.0% and 45.8%, and in CsA-MMF 36.0% (log-rank 3.0, P=0.085) and 8.0% (log-rank 9.0, P=0.003). No difference in long-term results for freedom from coronary angioplasty or stenting, renal dysfunction, diabetes mellitus, CMV infection, or malignancy was detected.
Conclusion. Cross-over effects because of treatment switch may result in impairment of significance between the groups. The long-term analysis resulted in a significant difference in manifestation of CAV between the groups after 10 years. Less rejection in the TAC-group might have contributed to the lower incidence of CAV. Superior freedom from AR and CAV in the TAC-MMF group did not result in better long-term survival.

Herlenius G, Felldin M, Nordén G, et al. Conversion From Calcineurin Inhibitor to Either Mycophenolate Mofetil or Sirolimus Improves Renal Function in Liver Transplant Recipients With Chronic Kidney Disease: Results of a Prospective Randomized Trial. *Transplantation Proceedings*. 2010;42(10):4441–4448. doi:10.1016/j.transproceed.2010.09.113.
Background. Chronic kidney disease (CKD) has emerged as a significant cause of morbidity and a risk factor for mortality after orthotopic liver transplantation (OLT). The use of calcineurin inhibitor (CNI)-based immunosuppression is an important etiologic factor for developing CKD. CNI discontinuation or minimization protocols with replacement of the CNI with non-nephrotoxic drugs, such as mycophenolate mofetil (MMF) or sirolimus (SRL), may have the potential to preserve or recover renal function. Patients and Methods. In this prospective, randomized, single-center study with CNI discontinuation, OLT recipients with CKD (measured glomerular filtration rate [GFRm] 15–45 mL/min/1.73 m2) were randomized to either SRL or MMF-based immunosuppression. The main objective was to study the effect of CNI discontinuation on renal function. Secondary aims were to assess the frequency of biopsy-proven acute rejection episodes (BPAR) and adverse events (AE). Renal function was followed with GFRm using 51-Chromium EDTA clearance at baseline, 3 months, and 1 year. Patients were stratified according to baseline GFRm _ versus _30 mL/min/1.73 m2. The 25 patients were enrolled for MMF (n _ 13) or SRL (n _ 12). The median age at inclusion was 59 years (range, 25–66) and the median number of years after OLT was 4.4 (range, 1–13). Twenty-two patients were followed up for a year; MMF (n _ 12) and SRL (n _ 10). Results. Mean GFRm for the whole cohort (n _ 25) was 31_/_8 mL/min/1.73 m2 at baseline. After 3 months the GFRm (n _ 23) increased to 40_/_10 mL/min/1.73 m2 (*P* _.0001) and at 1 year 42 _/_ 11 mL/min/1.73 m2 (n _ 22). There was no significant difference between the MMF and the SRL study arms. The cohort (n _ 8) with baseline GFRm _30 mL showed a 63% (*P* _ .003) increased filtration after 1 year. There was no significant difference in the frequency or severity of AE between the study arms with the exception of oral ulcerations and persistent hypertriglyceridemia in the SRL group. Two deaths occurred, 1 in each study arm, both probably unrelated to the change in immunosuppression. There were no BPAR episodes. Conclusion. CNI discontinuation and replacement with either MMF or SRL resulted in a significant improvement in renal function even in those patients with severe CKD. The protocol was effective with no acute rejection episodes. The SRL arm showed a higher frequency of oral aphthous ulcerations and hypertriglyceridemia. Future studies addressing long-term renal function after CNI discontinuations are needed.

Mjörnstedt L, Sørensen SS, von zur Mühlen B, et al. Improved Renal Function After Early Conversion From a Calcineurin Inhibitor to Everolimus: a Randomized Trial in Kidney Transplantation. *American Journal of Transplantation*. 2012;12(10):2744–2753. doi:10.1111/j.1600-6143.2012.04162.x.
In an open-label, multicenter trial, *de novo* kidney transplant recipients at low to medium immunological risk were randomized at week 7 post transplant to remain on CsA (n = 100, controls) or convert to everolimus (n = 102), both with enteric-coated mycophenolate sodium and corticosteroids. The primary endpoint, change in

measured GFR (mGFR) from week 7 to month 12, was significantly greater with everolimus than controls: 4.9 (11.8) mL/min versus 0.0 (12.9) mL/min (p = 0.012; analysis of covariance [ANCOVA]). Per protocol analysis demonstrated more marked difference: an increase of 8.7 (11.2) mL/min with everolimus versus a decrease of 0.4 (12.0) mL/min in controls (p < 0.001; ANCOVA). There were no differences in graft or patient survival. The 12-month incidence of biopsy-proven acute rejection (BPAR) was 27.5% (n = 28) with everolimus and 11.0% (n = 11) in controls (p = 0.004). All but two episodes of BPAR in each group were mild. Adverse events occurred in 95.1% of everolimus patients and 90.0% controls (p = 0.19), with serious adverse events in 53.9% and 38.0%, respectively (p = 0.025). Discontinuation because of adverse events was more frequent with everolimus (25.5%) than controls (3.0%; p = 0.030). In conclusion, conversion from CsA to everolimus at week 7 after kidney transplantation was associated with a greater improvement in mGFR at month 12 versus CNI treated controls but discontinuations and BPAR were more frequent.

Potena L, Prestinenzi P, Bianchi IG, et al. Cyclosporine lowering with everolimus versus mycophenolate mofetil in heart transplant recipients: Long-term follow-up of the SHIRAKISS randomized, prospective study. *The Journal of Heart and Lung Transplantation*. 2012;31(6):565–570. doi:10.1016/j.healun.2012.01.002.
BACKGROUND: Cyclosporine nephrotoxicity negatively impacts long-term outcome after heart transplantation (HT). We previously reported 1-year results from a randomized study showing that cyclosporine-lowering strategies based on everolimus or mycophenolate mofetil (MMF) are equally effective for reducing progression of renal dysfunction. It is unknown whether this efficacy could be maintained over the long term. METHODS: Thirty-four recipients 1 to 4 years after HT and with 25 to 60 ml/min of creatinine clearance (CrCl) were randomized to everolimus with a very low dose (C0: 50 to 90 ng/ml, *n* _ 17) or MMF with low dose of cyclosporine (C0: 100 to 150 ng/ml, *n* _ 17). Follow-up was prolonged up to 3 years, and calculated CrCl was the main efficacy measure. RESULTS: Cyclosporine was maintained at 70% and 30% lower than baseline in the everolimus and MMF arms, respectively, throughout the 3-year study period. CrCl remained stable in the everolimus patients (_7% from baseline; *p* _ 0.7), but improved in the MMF patients (_20% from baseline; *p* _0.01), with a trend toward improved values compared with everolimus patients (46 _ 12 vs 56 _ 15 ml/min; *p* _ 0.06). Subgroup analysis revealed that baseline proteinuria markedly influenced the renal function response to everolimus: whereas in patients with baseline proteinuria CrCl significantly worsened (_20%; *p* _ 0.04), it improved in those without (_15%; *p* _ 0.03). Safety was comparable between the two study arms. CONCLUSIONS: Cyclosporine nephrotoxicity improved after a prolonged dose reduction in patients receiving MMF. The everolimus-based strategy provided a similar benefit only to patients without baseline proteinuria. While raising caution against the universal use of everolimus for kidney protection, our long-term results support the need for customized approaches in the management of drug toxicities in maintenance HT recipients.

Sánchez-Lázaro IJ, Almenar-Bonet L, Martínez-Dolz L, et al. Preliminary Results of a Prospective Randomized Study of Cyclosporine Versus Tacrolimus in the Development of Cardiac Allograft Vasculopathy at 1 Year After Heart Transplantation. *Transplantation Proceedings*. 2010;42(8):3199–3200. doi:10.1016/j.transproceed.2010.05.055.
Introduction and aims. Cardiac allograft vasculopathy (CAV) is the leading cause of death after the first year post– heart transplantation (HT). Numerous factors have been implicated in the development of CAV. The aim of this prospective randomized study was to assess the impact of cyclosporine (CsA) and tacrolimus (Tac) on the development of CAV. Materials and methods. From November 2006 to October 2008, 49 HT patients in our center were randomized to receive CsA or Tac. The additional treatment for all patients consisted of daclizumab induction and maintenance treatment with mycophenolate mofetil (1 g/12 hours) and steroids (withdrawal was not attempted). Thirteen patients died before coronary arteriography plus intravascular ultrasound of the left anterior descending artery was performed at 1 year after HT. Hence, the final number of patients included was 36 (18 per group). We considered significant CAV to be the presence of intimal proliferation _1 mm and/or _0.5 mm in 180°. The statistical methods were Student *t* and chi-square tests. Results. There were no differences in baseline characteristics between the two groups. Nor were there significant differences in maximum intimal proliferation between the groups (CsA 0.65 _ 0.29 vs Tac 0.82 _ 0.51 mm; *P* _ .292) or in the development of significant CAV when both criteria were combined (CsA 31.6% vs Tac 38.9%; *P* _ .642). Conclusions. One year after HT, no differences were detected in the development of significant CAV according to the type of calcineurin inhibitor used when combined with daclizumab induction and maintenance treatment with mycophenolate mofetil and steroids.

Santos SM, Carlos CM, Cabanayan-Casasola CB, Danguilan RA. Everolimus with Reduced-dose Cyclosporine Versus Full-dose Cyclosporine and Mycophenolate in De Novo Renal Transplant Patients: A 2-Year Single-Center Experience. *Transplantation Proceedings*. 2012;44(1):154–160. doi:10.1016/j.transproceed.2011.11.055.
background. Although calcineurin inhibitors (CNIs) have improved short-term graft survival, long-term function remains a challenge. CNIs have been implicated in the development of chronic allograft failure. Low-dose cyclosporine with everolimus may mitigate CNI nephrotoxicity and prolong graft survival. We compared the efficacy and safety of de novo everolimus with low-dose cyclosporine and prednisone versus cyclosporine, mycophenolate, and prednisone among kidney transplant patients up to 24 months after transplantation. Methods. Kidney transplant patients given low-dose cyclosporine, everolimus, and prednisone were compared with patients given cyclosporine, mycophenolate, and prednisone from December 2006 to December 2008. All had living donors, panel reactive antibody _15%, and follow-up for 2 years after transplantation. Continuous variables using mean and standard deviation, *t* test and test for proportions were used to determine significant differences between the baseline characteristics of the 2 treatment groups. Generalized linear regression and logistic regression were used to measure the effect of treatment on outcomes. Results. Demographic characteristics were similar in both groups except for age, length of time awaiting kidney transplantation, type of renal replacement therapy, follow-up time, sex distribution, and number of HLA mismatches. These independent variables were used in the generalized linear regression model. There was no significant difference between the everolimus and mycophenolate groups up to 2 years in mean serum creatinine (1.2 mg/dL vs 1.4 mg/dL-, respectively *P* _ .05), acute rejection (12 months: 20% vs 31%; 24 months: 31% vs 40%; *P* _ .05), patient survival (98%), and graft survival (100%). Likewise, there were no significant differences in surgical, infectious, metabolic, and gastrointestinal side effects between the 2 groups. Conclusions. Everolimus with low-dose cyclosporine and prednisone in de novo kidney transplant recipients was similar in efficacy and safety to cyclosporine, mycophenolate, and prednisone. Longer follow-up is needed to see whether everolimus with low-dose cyclosporine will result in improved kidney function.

Schmeding M, Kiessling A, Neuhaus R, et al. Mycophenolate mofetil monotherapy in liver transplantation: 5-year follow-up of a prospective randomized trial. *Transplantation*. 2011;92(8):923–929. doi:10.1097/TP.0b013e31822d880d.
Background. Calcineurin inhibitors (CNIs) play the key role in immunosuppressive protocols yet are often associated with numerous side effects. Renal insufficiency, hypertension, hyperglycemia, and increased risk of secondary malignancy are major problems in short- and long-term follow-up of liver transplant patients. Mycophenolate mofetil (MMF) has proved to be a potent immunosuppressive agent free of the CNI-associated side effects. Patients and Methods. One hundred fifty patients who received liver transplantation at our institution (1998 –2003) were prospectively randomized: 75 patients continued CNI standard therapy, 75 patients were switched to MMF monotherapy, and follow-up was 5 years. Incidence of rejection, renal complication, cardiovascular, neurological and gastrointestinal adverse effects, and diabetes and malignancy development was recorded. Graft biopsies were performed every 2 to 3 years. Results. No significant difference regarding the incidence of acute rejection was detected. A trend to higher rejection frequency was apparent in the MMF monotherapy group. Chronic rejection was absent; organ and patient survival were identical in the two groups. No significant difference occurred concerning the incidence of cardiovascular, gastrointestinal or neurological adverse effects, or the development of malignancies. Renal function improved significantly in patients with renal insufficiency when patients treated with CNI were

switched to MMF monotherapy. Conclusion. MMF monotherapy may serve as safe long-term immunosuppression after liver transplantation for a subgroup of patients. Especially for patients with renal insufficiency MMF offers immunosuppression without the risk of nephrotoxicity.

Treede H, Glanville AR, Klepetko W, et al. Tacrolimus and cyclosporine have differential effects on the risk of development of bronchiolitis obliterans syndrome: results of a prospective, randomized international trial in lung transplantation. *J. Heart Lung Transplant.* 2012;31(8):797–804. doi:10.1016/j.healun.2012.03.008.
BACKGROUND: Chronic lung allograft dysfunction, which manifests as bronchiolitis obliterans syndrome (BOS), is recognized as the primary cause of morbidity and mortality after lung transplantation. In this study we assessed the efficacy and safety of two de novo immunosuppression protocols to Prevent BOS. METHODS: Our study approach was a multicenter, prospective, randomized (1:1) open-label superiority Investigation of de novo tacrolimus vs cyclosporine, with both study arms given Mycophenolate Mofetil and prednisolone after lung transplantation. Cytolytic induction therapy was not employed. Patients were stratified at entry for cystic fibrosis. Primary outcome was incidence of BOS 3 years after Transplant (intention-to-treat analysis). Secondary outcomes were survival and incidence of acute Rejection, infection and other adverse events. RESULTS: Group demographic data were well matched: 110 of 124 tacrolimus vs 74 of 125 cyclosporine Patients were treated per protocol (p _ 0.01 by chi-square test). Cumulative incidence of BOS Grade _1 at 3 years was 11.6% (tacrolimus) vs 21.3% (cyclosporine) (cumulative incidence curves, P _ 0.037 by Gray's test, pooled over strata). Univariate proportional sub-distribution hazards Regression confirmed cyclosporine as a risk for BOS (HR 1.97, 95% CI 1.04 to 3.77, p _ 0.039). Three-year cumulative incidence of acute rejection was 67.4% (tacrolimus) vs 74.9% (cyclosporine) (p _ 0.118 by Gray's test). One- and 3-year survival rates were 84.6% and 78.7% (tacrolimus) vs 88.6% and 82.8% (cyclosporine) (p _ 0.382 by log-rank test). Cumulative infection rates were similar (p _ 0.91), but there was a trend toward new-onset renal failure with tacrolimus (p _ 0.09).

Vacher-Coponat H, Moal V, Indreies M, et al. A randomized trial with steroids and antithymocyte globulins comparing cyclosporine/azathioprine versus tacrolimus/mycophenolate mofetil (CATM2) in renal transplantation. *Transplantation.* 2012;93(4):437–443. doi:10.1097/TP.0b013e31824215b7.
Background. The best immunosuppressive regimen in benefit-risk ratio in renal transplantation is debated. Nowadays, tacrolimus (Tac) and mycophenolate mofetil (MMF) are considered more efficient than cyclosporine A (CsA) and MMF, but recent studies have challenged this assumption. Methods. We conducted a monocentric, prospective, open-labeled, randomized, and controlled trial comparing CsA/azathioprine (Aza) versus Tac/MMF in 289 kidney transplant recipients treated with antithymocyte globulins and prednisone. Primary outcome was the number of patients with clinically suspected acute rejection at 1 year. Secondary outcomes were the number of patients with biopsy-proven acute rejection (BPAR), estimated glomerular filtration rate (eGFR), patient and graft survivals, and adverse events at 1 and 3 years. Results. During the first year, 21 patients had clinically suspected acute rejection with CsA/Aza (14.4%) vs. 11 (7.7%) with Tac/MMF (P_0.07). BPAR, including borderline, was more frequent in the CsA/Aza group (14.4%) than in the Tac/MMF group (5.6%; P_0.013). At 1 year, patient and graft survivals were not different, and eGFR was 48_1 in the CsA/Aza group and 53_1 mL/min/1.73 m2 in the Tac/MMF group (P_0.007). There was no significant difference in diabetes after transplantation (16.8% and 18.8%, respectively). Conclusions. With antithymocyte globulins and steroids, clinically suspected acute rejections did not differ between CsA/Aza and Tac/MMF arms. Analysis of secondary endpoints showed a lower rate of BPAR, including border line, and a higher eGFR in the Tac/MMF group. CsA/Aza allowed a low acute rejection rate, but Tac/MMF seemed as a better regimen regarding severe secondary outcomes.

Viganò M, Dengler T, Mattei MF, et al. Lower incidence of cytomegalovirus infection with everolimus versus mycophenolate mofetil in de novo cardiac transplant recipients: a randomized, multicenter study. *Transplant Infectious Disease.* 2010;12(1):23–30. doi:10.1111/j.1399-3062.2009.00448.x.
Abstract: Cytomegalovirus (CMV) is a major cause of infectious complications following cardiac transplantation, severely affecting short- and long-term outcomes. A 12-month, multicenter, randomized, open-label study in de novo cardiac transplant patients was undertaken to compare the efficacy, renal function, and safety of everolimus plus reduced cyclosporine versus mycophenolate mofetil (MMF) plus standard cyclosporine (ClinicalTrials.gov NCT00150046). CMV specific data was prospectively collected on infections, laboratory evidence, CMV syndrome, and CMV disease. In total, 176 patients were randomized (everolimus 92; MMF 84). Use of CMV prophylaxis was similar between groups (everolimus 20.8%; MMF 24.0%). Patients in the everolimus arm had a significantly lower incidence of any CMV event (8.8% versus 32.5%with MMF, Po0.001), CMV infection as an adverse event (4.4%versus 16.9%, P50.011), laboratory evidence of CMV (antigenemia 7.7%versus 7.7%, Po0.001; polymerase chain reaction assay 2.2% versus 12.0%, P50.015), and CMV syndrome (1.1%versus 8.4%, P50.028). In the donor (D)1/recipient (R)1and D _/R1 subgroups, even after adjusting for use of prophylaxis, the CMV event rate remained significantly lower with everolimus than with MMF (P50.0015 and P50.0381, respectively). In conclusion, de novo cardiac transplant recipients experienced lower rates of CMV infection, CMV syndrome, or organ involvement on an everolimus-based immunosuppressant regimen compared with MMF.

Zuckermann A, Keogh A, Crespo-Leiro MG, et al. Randomized Controlled Trial of Sirolimus Conversion in Cardiac Transplant Recipients With Renal Insufficiency. *American Journal of Transplantation.* 2012;12(9):2487–2497. doi:10.1111/j.1600-6143.2012.04131.x.
This randomized, comparative, multinational phase 3b/4 study of patients 1–8 years post cardiac transplantation (mean 3.9 years) evaluated the effect of conversion from a calcineurin inhibitor (CNI) to sirolimus on renal function in patients with renal insufficiency. In total, 116 patients on CNI therapy with GFR 40–90 mL/min/1.73m2 were randomized (1:1) to sirolimus (n = 57) or CNI (n = 59). Intent-to-treat analysis showed the 1-year adjusted mean change from baseline in creatinine clearance (Cockcroft-Gault) was significantly higher with sirolimus versus CNI treatment (+3.0 vs.−1.4mL/min/1.73m2, respectively; p = 0.004). By on-therapy analysis, values were +4.7 and −2.1, respectively (p < 0.001). Acute rejection (AR) rates were numerically higher in the sirolimus group; 1 AR with hemodynamic compromise occurred in each group. A significantly higher treatment discontinuation rate due to adverse events (AEs; 33.3% vs. 0%; p < 0.001) occurred in the sirolimus group. Most common treatment-emergent AEs significantly higher in the sirolimus group were diarrhea (28.1%), rash (28.1%) and infection (47.4%). Conversion to sirolimus from CNI therapy improved renal function in cardiac transplant recipients with renal impairment, but was associated with an attendant AR risk and higher discontinuation rate attributable to AEs.

Appendix 2: Abstracts of Meta Analyses

Asrani SK, Leise MD, West CP, et al. Use of sirolimus in liver transplant recipients with renal insufficiency: A systematic review and meta-analysis. *Hepatology.* 2010;52(4):1360–1370. doi:10.1002/hep.23835.
Sirolimus is used in patients with renal insufficiency after liver transplantation (LT) and especially in those with calcineurin inhibitor (CNI)–associated nephrotoxicity. We conducted a systematic review of all randomized controlled trials and observational studies to test the hypothesis that the use of sirolimus is associated with an improvement in renal function at 1 year in LT recipients with renal insufficiency [glomerular filtration rate (GFR) < 60 mL/minute or creatinine level ‡ 1.5 mg/dL]. We performed a search of all major databases, conference proceedings, and relevant journals through December 2009 and contacted content experts, corresponding authors, and the pharmaceutical manufacturer. A random effects model was used to determine the pooled estimate of the change in renal function and pooled risk

estimates of adverse events that may be associated with sirolimus-based therapy at 1 year. Eleven studies (three randomized controlled trials and eight observational studies) met the final inclusion criteria. A nonsignificant improvement of 3.38 mL/minute [95% confidence interval (CI)522.93 to 9.69] was observed in methodologically sound observational studies and controlled trials reporting the primary outcome. In controlled trials, baseline GFR >50 mL/min sirolimus use was associated with an improvement of 10.35 mL/minute (95% CI 5 3.98-16.77) in GFR or creatinine clearance. Sirolimus was not significantly associated with death [relative risk (RR) 5 1.12, 95% CI 5 0.66-1.88] or graft failure (RR 5 0.80, 95% CI 5 0.45-1.41), although reporting was incomplete. It was associated with a statistically significant risk of infection (RR 5 2.47, 95% CI 5 1.14-5.36), rash (RR 5 7.57, 95% CI 5 1.75-32.70), ulcers (RR 5 7.44, 95% CI 5 2.03-27.28), and discontinuation of therapy (RR 5 3.61, 95% CI 5 1.32-9.89). Conclusion: Conversion to sirolimus from CNIs is associated with a nonsignificant improvement in renal function in LT recipients with renal insufficiency, although the results are limited by heterogeneity, a risk of bias, and a lack of standardized reporting.

McDonald JW, Tsoulis DJ, MacDonald JK, Feagan BG. Methotrexate for induction of remission in refractory Crohn's disease. In: The Cochrane Collaboration, McDonald JW, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD003459.pub3. Accessed April 22, 2013.

Background Although corticosteroids are effective for induction of remission of Crohn's disease, many patients relapse when steroids are withdrawn or become steroid dependent. Furthermore, corticosteroids exhibit significant adverse effects. The success of methotrexate as a treatment for rheumatoid arthritis led to its evaluation in patients with refractory Crohn's disease. Methotrexate has been studied for induction of remission of refractory Crohn's disease and has become the principal alternative to azathioprine or 6-mercaptopurine therapy. This systematic review is an update of a previously published Cochrane review.
Objectives The primary objective was to assess the efficacy and safety of methotrexate for induction of remission in patients with active Crohn's disease in the presence or absence of concomitant steroid therapy. Search methods We searched MEDLINE, EMBASE, CENTRAL and the Cochrane IBD/FBD group specialized register from inception to June 27, 2012 for relevant studies. Conference proceedings and reference lists were also searched to identify additional studies.
Selection criteria Randomized controlled trials of methotrexate compared to placebo or an active comparator for treatment of active refractory Crohn's disease in adult patients (> 17 years) were considered for inclusion. Data collection and analysis The primary outcome was failure to failure to enter remission and withdrawal from steroids. Secondary outcomes included adverse events, withdrawal due to adverse events, serious adverse events and quality of life. We calculated the relative risk (RR) and 95% confidence intervals (95% CI) for each outcome. Data were analyzed on an intention to treat basis. The Cochrane risk of bias tool was used to assess the methodological quality of included studies. The GRADE approach was used to assess the overall quality of evidence supporting the primary outcome. Main results Seven studies (495 patients) were included. Four studies were rated as low risk of bias. Three studies were rated as high risk of bias due to open label or single-blind designs. The seven studies differed with respect to participants, intervention, and outcomes to the extent that it was considered to be inappropriate to pool the data for meta-analysis. Three small studies which employed low doses of oral methotrexate showed no statistically significant difference in failure to induce remission between methotrexate and placebo or between methotrexate and 6-mercaptopurine. For the study using 15 mg/week of oral methotrexate 33% (5/15) of methotrexate patients failed to enter remission compared to 11% (2/18) of placebo patients (RR 3.00, 95% CI 0.68 to 13.31). For the study using 12.5 mg/week of oral methotrexate 81% (21/26) of methotrexate patients failed to enter remission compared to 77% (20/26) of placebo patients (RR 1.05, 95% CI 0.79 to 1.39). This study also had an active comparator arm, 81% (21/26) o^{24}f methotrexate patients failed to enter remission compared to 59% (19/32) of 6-mercaptopurine patients (RR 1.36, 95% CI 0.97 to 1.92). For the active comparator study using 15 mg/week oral methotrexate, 20% (3/15) of methotrexate patients failed to enter remission compared to 6% of 6-mercaptopurine patients (RR 3.20, 95% CI 0.37 to 27.49). This study also had a 5-ASA arm and found that methotrexate patients were significantly more likely to enter remission than 5-ASA patients. Twenty per cent (3/15) of methotrexate patients failed to enter remission compared to 86% (6/7) of 5-ASA patients (RR 0.23, 95% CI 0.08 to 0.67). One small study which used a higher dose of intravenous or oral methotrexate (25 mg/week) showed no statistically significant difference between methotrexate and azathioprine. Forty-four per cent (12/27) of methotrexate patients failed to enter remission compared to 37% of azathioprine patients (RR 1.20, 95% CI 0.63 to 2.29). Two studies found no statistically significant difference in failure to enter remission between the combination of infliximab and methotrexate and infliximab monotherapy. One small study utilized intravenous methotrexate (20 mg/week) for 5 weeks and then switched to oral (20 mg/week). Forty-five per cent (5/11) of patients in the combination group failed to enter remission compared to 62% of infliximab patients (RR 0.73, 95% CI 0.31 to 1.69) The other study assessing combination therapy utilized subcutaneous methotrexate (maximum dose 25 mg/week). Twenty-four per cent (15/63) of patients in the combination group failed to enter remission compared to 22% (14/63) of infliximab patients (RR 1.07, 95% CI 0.57 to 2.03). A large placebo-controlled study which employed a high dose of methotrexate intramuscularly showed a statistically significant benefit relative to placebo. Sixty-one per cent of methotrexate patients failed to enter remission compared to 81% of placebo patients (RR 0.75, 95% CI 0.61 to 0.93; number needed to treat, NNT=5). Withdrawals due to adverse events were significantly more common in methotrexate patients than placebo in this study. Seventeen per cent of methotrexate patients withdrew due to adverse events compared to 2% of placebo patients (RR 8.00, 95% CI 1.09 to 58.51). The incidence of adverse events was significantly more common in methotrexate patients (63%, 17/27) than azathioprine patients (26%, 7/27) in one small study (RR 2.42, 95%CI 1.21 to 4.89). No other statistically significant differences in adverse events, withdrawals due to adverse events or serious adverse events were reported in any of the other placebo-controlled or active comparator studies. Common adverse events included nausea and vomiting, abdominal pain, diarrhea, skin rash and headache. Authors' conclusions There is evidence from a single large randomized trial which suggests that intramuscular methotrexate (25 mg/week) provides a benefit for induction of remission and complete withdrawal from steroids in patients with refractory Crohn's disease. Lower dose oral methotrexate does not appear to provide any significant benefit relative to placebo or active comparator. However, these trials were small and further studies of oral methotrexate may be justified. Comparative studies of methotrexate to drugs such as azathioprine or 6-mercaptopurine would require the randomization of large numbers of patients. The addition of methotrexate to infliximab therapy does not appear to provide any additional benefit over infliximab monotherapy. However these studies were relatively small and further research is needed to determine the role of methotrexate when used in conjunction with infliximab or other biological therapies

Penninga L, Møller CH, Gustafsson F, Steinbrüchel DA, Gluud C. Tacrolimus versus cyclosporine as primary immunosuppression after heart transplantation: systematic review with meta-analyses and trial sequential analyses of randomised trials. *European Journal of Clinical Pharmacology*. 2010;66(12):1177–1187. doi:10.1007/s00228-010-0902-6.

Purpose We conducted a systematic review of randomized trials to compare the benefits and harms of tacrolimus versus cyclosporine as primary immunosuppression after heart transplantation. Methods and results We searched electronic databases and bibliographies up to April 2010. Our review followed the Cochrane and PRISMA guidelines. The meta-analysis included 10 randomized trials with 952 patients. Tacrolimus was significantly superior to cyclosporine (both formula combined) with regard to hypertension (relative risk [RR] 0.8; 95% confidence interval [CI] 0.69–0.93, p=0.003), hyperlipidaemia (RR 0.57; 95% CI 0.44–0.74, p<0.0001), hirsutism (RR 0.17 95% CI 0.04–0.62, p=0.008), and gingival hyperplasia (RR 0.07 95% CI 0.01–0.37, p=0.002). No significant differences between the two calcineurin inhibitors were found with regard to acute rejections causing haemodynamic instability, diabetes, renal dysfunction, infection, malignancy, or neurotoxicity. Tacrolimus was significantly superior to microemulsion cyclosporine with regard to mortality (RR 0.64; 95% CI 0.42–0.96, p=0.03), acute severe biopsy-proven rejection (RR 0.71; 95% CI 0.56–0.90, p=0.004), hyperlipidaemia (RR 0.57; 95% CI 0.41–0.79, p=0.0009), hirsutism (RR 0.17 95% CI 0.04–0.62, p=0.008), and gingival hyperplasia (RR 0.07; 95% CI 0.01–0.37, p=0.002). Tacrolimus was significantly superior to oil-based cyclosporine with regard to hypertension (RR 0.66; 95% CI 0.54–0.80, p<0.0001), and Hyperlipidaemia (RR 0.57; 95% CI 0.38–0.87, p=0.009). Conclusion Tacrolimus seems to be superior to cyclosporine in heart transplant patients with regard to

hypertension, hyperlipidaemia, gingival hyperplasia and hirsutism. In addition, tacrolimus seems to be superior to microemulsion cyclosporine in heart transplant patients with regard to a number of outcomes, including death. More trials with a low risk of bias are needed to determine if the results of the present meta-analysis can be confirmed.

Penninga L, Wettergren A, Chan A-W, Steinbrüchel DA, Gluud C. Calcineurin inhibitor minimisation versus continuation of calcineurin inhibitor treatment for liver transplant recipients. In: The Cochrane Collaboration, Penninga L, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD008852.pub2. Accessed April 29, 2013.

Background The therapeutic success of liver transplantation has been largely attributable to the development of effective immunosuppressive treatment regimens. In particular, calcineurin inhibitors were essential in reducing acute rejection and improving early survival. Currently, more than 90% of all liver transplant recipients are treated with the calcineurin inhibitor cyclosporine or tacrolimus. Unfortunately, calcineurin inhibitors cause adverse events, such as nephrotoxicity, and because of this, minimisation (reduction and withdrawal) regimens of calcineurin inhibitor have been developed and studied. However, the benefits and harms of these minimisation regimens are unclear. Objectives To assess the benefits and harms of calcineurin inhibitor minimisation for liver transplant recipients without substitution by another immunosuppressive agent. Search methods We searched The Cochrane Hepato-Biliary Group Controlled Trials Register, Cochrane Central Register of Controlled Clinical Trials (CENTRAL) in *The Cochrane Library,* MEDLINE (OvidSP), EMBASE (OvidSP), Science Citation Index Expanded and the World Health Organization (WHO) international clinical trials registry platform (www.who.int/ictrp) until August 2011. In addition, we searched bibliographies of relevant articles as well as US Food and Drug Administration (FDA) and European Medicines Agency (EMA) drug approval reviews for additional trials. Selection criteria We planned to select all randomised clinical trials investigating calcineurin inhibitor reduction or withdrawal in liver transplant recipients, irrespective of blinding, publication status, or language. Quasi-randomised clinical studies and cohort studies that were obtained through the searches were considered only for the reporting of harms. Trials investigating substitution of one calcineurin inhibitor by another calcineurin inhibitor were excluded. Trials investigating calcineurin inhibitor withdrawal concurrently with switching over to a mammalian target of rapamycin (mTOR) inhibitor-based regimen (everolimus or sirolimus) or mycophenolate mofetil-based regimen are the subject of a separate review. Data collection and analysis Search strategies were used to obtain titles and abstracts of studies that were relevant for the review. Two authors independently scanned the references and assessed trial eligibility. Main results A total of 1299 references were identified by the searches. After removal of duplicates, 794 references were left. Out of these, two abstract reports of one ongoing randomised trial fulfilled the inclusion criteria of the review. This ongoing trial studies total withdrawal of immunosuppression in patients who receive a calcineurin inhibitor (cyclosporine or tacrolimus) or mycophenolate mofetil as the only immunosuppressive agent. The trial compares withdrawal of calcineurin inhibitor or mycophenolate mofetil with continuation of calcineurin inhibitor or mycophenolate mofetil. However, no trial results on the outcomes of interest to this review were available. Authors' conclusions This review shows that strategies regarding calcineurin inhibitor minimisation, that is, reduction or withdrawal, without substitution versus continuation of calcineurin inhibitor treatment lack evidence from randomised trials. More research with calcineurin inhibitor reduction and withdrawal regimens is needed to optimise dosing and timing of calcineurin inhibitor treatment in order to achieve optimal patient and graft survival with a minimum of adverse events. Specifically regarding calcineurin inhibitor reduction versus no reduction, we recommend that randomised trials evaluating calcineurin inhibitor reduction versus continuation of calcineurin inhibitor treatment are conducted. Regarding calcineurin inhibitor withdrawal, we recommend that mechanisms for tolerance and 'graft acceptance' are clarified, and patient groups likely to tolerate calcineurin inhibitor withdrawal are identified in order to select the right patients for total withdrawal of calcineurin inhibitors without substitution with another immunosuppressive drug. The randomised trials should only be performed in highly selected patients.

Sharif A, Shabir S, Chand S, Cockwell P, Ball S, Borrows R. Meta-Analysis of Calcineurin-Inhibitor-Sparing Regimens in Kidney Transplantation. *Journal of the American Society of Nephrology*. 2011;22(11):2107–2118. doi:10.1681/ASN.2010111160.

Calcineurin-inhibitor-sparing strategies in kidney transplantation may spare patients the adverse effects of these drugs, but the efficacy of these strategies is unknown. Here, we conduct a meta-analysis to assess outcomes associated with reducing calcineurin inhibitor exposure from the time of transplantation. We search Medline, Embase, and Cochrane Register of Controlled Trials for randomized controlled trials published between 1966 and 2010 that compared *de novo* calcineurin-inhibitor-sparing regimens to calcineurin-inhibitor-based regimens. In this analysis, we include 56 studies comprising data from 11337 renal transplant recipients. Use of the contemporary agents belatacept or tofacitinib, in combination with mycophenolate, decreased the odds of overall graft failure (OR 0.61; 95% CI 0.39–0.96; *P* _0.03). Similarly, minimization of calcineurin inhibitors in combination with various induction and adjunctive agents reduces the odds of graft failure (OR 0.73; 95% CI 0.58–0.92; *P* _ 0.009). Conversely, the use of inhibitors of mammalian target of rapamycin (mTOR), in combination with mycophenolate, increases the odds of graft failure (OR 1.43; 95% CI 1.08–1.90; *P* _ 0.01). Calcineurin-inhibitor-sparing strategies are associated with less delayed graft function (OR 0.89; 95% CI 0.80–0.98; *P* _ 0.02), improved graft function, and less new-onset diabetes. The more contemporary protocols did not seem to increase rates of acute rejection. In conclusion, this meta-analysis suggests that reducing exposure to calcineurin inhibitors immediately after kidney transplantation may improve clinical outcomes.

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