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

Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, March 28, 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. ProDUR Report — R. Holsapple (HP)
- b. RetroDUR Report — T. Williams (OSU)
- c. Quarterly Utilization Reports — R. Citron (OSU)
- d. Oregon State Drug Reviews — K. Sentena (OSU)
    1. *The Future of Newer Obesity Medications*

III. HERC COVERAGE GUIDANCE
- a. Therapies with Marginal Benefit or High Cost Guideline — C. Livingston (HERC)
- b. Ampyra Example — R. Citron (OSU)
- c. Public Comment
- d. Discussion of Process for Referral to HERC

IV. NEW BUSINESS
- a. Tapentadol* — T. Williams (OSU)
    1. Drug Use Evaluation
    2. Public Comment
    3. Discussion of Clinical recommendations to OHA
- b. Colony Stimulating Factor Use in Patients with Heaptitis C* — K. Ketchum (OSU)
    1. Drug Use Evaluation
    2. Public Comment
    3. Discussion of clinical recommendations to OHA
- c. Intramuscular Antipsychotics* — K. Ketchum (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. Anticoagulant Abbreviated Class Update* K. Sentena (OSU)
1. Apixaban New Drug Evaluation
2. Public Comment
3. Discussion of clinical recommendations to OHA

e. Targeted Immune Modulators* M. Herink (OSU)
1. Tofacitinib New Drug Evaluation
2. Public Comment
3. Discussion of clinical recommendations to OHA

f. Linaclotide* M. Herink (OSU)
1. New Drug Evaluation
2. Public Comment
3. Discussion of clinical recommendations to OHA

g. Drug Class Scans* M. Herink (OSU)
1. Topical Analgesics
2. Topical Steroids
3. Antifungals
4. Topical Antifungals
2. Public Comment
3. Discussion of clinical recommendations to OHA

V. EXECUTIVE SESSION

VI. RECONVENE for PUBLIC RECOMMENDATIONS

VII. ADJOURN

**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)*

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Oregon Drug Use Review / Pharmacy & Therapeutics Committee
Thursday, January 31, 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; Phillip Levine, PhD; Tracy Klein, PhD, FNP; William Origer, MD
Members Present by Phone: David Pass, MD; James Slater, PharmD; Stacy Ramirez, PharmD; Zahia Esber, MD
Staff Present: Israel Harden, 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: Bing-Bing Liang, PharmD; Brandy Fouts, PharmD
Audience: Kenith Fritsche (OSU); Paul Banken (NNI); Amir Karimzadeh (Forest); Jamie Damm (Vertex); Jeff Evans (Astellas); Venus Holder (Lilly); Linda Posta (Astellas); Jennifer Kammerer (Astellas); Shannon Beatty (MedImmune); Paul Nielsen (MedImmune); David Barba (Forest); Jeana Colabianchi (Sunovion); Steve Fuldon (Otsuka); Lori Howarth (Bayer); Bruce Smith (GSK); Jim Graves (BMS); Barry Benson (Merck); Cheryl Fletcher (Abbvie); Richard Kosesan

I. CALL TO ORDER
a. The meeting was called to order at approximately 1pm.
b. The Committee reviewed the revised membership report.
c. No new conflicts of interest were declared.
d. The November 29, 2012 meeting minutes were reviewed.

ACTION: Approved as is.

e. Dr. Douglass presented a department update.

II. OPERATING PROCEDURES
a. Mr. Citron presented amended operating procedures document. Dr. Klein recommended changing “physicians” to “prescribers” in item 5 of the Conduct of Meetings section of the document.

ACTION: Approved as amended.

b. Ms. Ketchum presented on quality assessment and evidence grading methods.

ACTION: Approved as is.

c. Dr. Herink presented on clinical procedures.

ACTION: Approved as is.

**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)*

III. NEW BUSINESS

a. Dr. Williams presented on FDB drug file updates.

ACTION: Approved.

b. Dr. Herink presented an abbreviated new drug evaluation on Retisert implant and recommended asking the HERC to evaluate the surgical procedures of both the fluocinolone and dexathemasoneocular implants for line placement.

ACTION: Approved.

c. Dr. Liang presented an abbreviated class update on overactive bladder medications and recommended comparing costs of agents in class in executive session and continue to include both ER and IR options as preferred alternatives. Dr. Liang also presented a new drug evaluation on mirabegron recommending making it non-preferred. Linda Posta from Astellas provided public comment.

***ACTION:** After Executive Session, the Committee recommended continuing ER and IR options as alternatives, but make hyoscyamine rapid tabs preferred and to make Oscimin®, hyoscyamine drops, mirabegron and Gelnique® non-preferred. The Committee also recommended making tolterodine non-preferred with a 90 day grandfather.

d. Dr. Fouts presented a new drug evaluation on aclidinium bromide and recommended making it non-preferred. Amir Karimzadeh from Forest presented public comment.

***ACTION:** After Executive Session, the Committee approved the recommendations.

e. Dr. Herink presented an abbreviated new drug evaluation on Combivent Respimat® recommending making Combivent Respimat® and Combivent MDI® non-preferred and require a step through therapy with either a short acting beta agonist OR a short acting anticholinergic and grandfather current utilizers.

***ACTION:** After Executive Session, the Committee approved the recommendations.

f. Dr. Herink presented drug class scans recommending:

1. Macrolide Antibiotics – no further review at this time and make all erythromycin pruducts non-preferred.

***ACTION:** After Executive Session, the Committee approved the recommendations.

2. Fluoroquinolone Antibiotics – no further review at this time and make Noroxin® non-preferred.

***ACTION:** After Executive Session, the Committee approved the recommendations.

3. GI: PPI's and H2A's – no further review at this time, update prior authorization criteria, make omeprazole tablets, all OTC H2A products and cimetidine non-preferred, grandfathering cimetidine indefinitely.

***ACTION:** After Executive Session, the Committee approved the recommendations.

4. Antihistamines – no further review at this time and make all OTC products non-preferred.

***ACTION:** After Executive Session, the Committee approved the recommendations.

IV. The meeting was adjourned at approximately 3:30pm.

**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)*

ProDUR Report for December 2012- February 2013

High Level Summary by DUR Alert

DUR Alert	# Alerts	# Overrides	# Cancellations	# Non-Response	% of all DUR Alerts
ER (Early Refill)	56,879	12,455	200	44,168	67.60%
PG (Pregnancy/Drug Interaction)	2,899	1,898	16	982	3.35%
ID (Ingredient Duplication)	13,860	4,025	54	9,744	16.40%
TD (Therapeutic Duplication)	5,794	1,898	11	3,853	6.80%

ProDUR Report for December 2012- February 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	% Change from Dec. to Jan/Feb
ER	Remeron (Mirtazapine)-Dec	164	38	126	1,575	10.4%	23.2%	
	Remeron (Mirtazapine)-Jan/Feb	491	83	408	3,737	13.1%	16.9%	-27.0%
	Hydrocodone Bit/APAP-Dec	127	48	79	1,984	6.4%	37.8%	
	Hydrocodone Bit/APAP-Jan/Feb	254	62	192	4,625	5.5%	24.4%	-35.4%
	Oxycodone HCl-Dec	92	54	38	1,077	8.5%	58.7%	
	Oxycodone HCl-Jan/Feb	164	72	91	2,128	7.7%	43.9%	-25.2%
	Lorazepam-Dec	921	309	610	9,586	9.6%	33.6%	
	Lorazepam-Jan/Feb	1,286	224	1,062	17,284	7.4%	17.4%	-48.1%
	Alprazolam-Dec	574	172	401	6,330	9.1%	30.0%	
	Alprazolam-Jan/Feb	980	162	816	11,977	8.2%	16.5%	-44.8%
	Diazepam-Dec	385	97	288	4,058	9.5%	25.2%	
	Diazepam-Jan/Feb	551	87	464	7,709	7.1%	15.8%	-37.3%
	Buspar (Buspirone)-Dec	272	69	203	2,368	11.5%	25.4%	
	Buspar (Buspirone)-Jan/Feb	589	93	496	5,497	10.7%	15.8%	-37.8%
	Lamictal (Lamotrigine)-Dec	628	178	450	5,276	11.9%	28.3%	
	Lamictal (Lamotrigine)-Jan/Feb	1,401	283	1,117	11,856	11.8%	20.2%	-28.7%
	Depakote (Divalproex Sodium)-Dec	400	127	273	3,335	12.0%	31.8%	
	Depakote (Divalproex Sodium)-Jan/Feb	845	181	663	7,308	11.6%	21.4%	-32.5%
	Clonazepam-Dec	185	64	120	1,944	9.5%	34.6%	
	Clonazepam-Jan/Feb	264	47	217	2,859	9.2%	17.8%	-48.5%
	Gabapentin-Dec	112	35	76	901	12.4%	31.3%	
	Gabapentin-Jan/Feb	289	81	208	1,989	14.5%	28.0%	-10.3%
	Abilify (Aripiprazole)-Dec	571	143	427	4,167	13.7%	25.0%	
	Abilify (Aripiprazole)-Jan/Feb	1,117	216	901	9,558	11.7%	19.3%	-22.8%
	Seroquel (Quetiapine)-Dec	703	251	451	4,803	14.6%	35.7%	
	Seroquel (Quetiapine)-Jan/Feb	1,463	306	1,156	10,759	13.6%	20.9%	-41.4%
	Risperdal (Risperidone)-Dec	574	174	399	4,475	12.8%	30.3%	
	Risperdal (Risperidone)-Jan/Feb	1,261	227	1,033	9,872	12.8%	18.0%	-40.6%
	Zyprexa (Olanzapine)-Dec	292	73	214	2,535	11.5%	25.0%	
	Zyprexa (Olanzapine)-Jan/Feb	748	150	598	5,774	13.0%	20.1%	-19.8%
	Geodon (Ziprasidone)-Dec	185	59	126	1,379	13.4%	31.9%	
	Geodon (Ziprasidone)-Jan/Feb	361	70	289	2,925	12.3%	19.4%	-39.2%
	Albuterol-Dec	100	34	66	1,805	5.5%	34.0%	
	Albuterol-Jan/Feb	254	50	203	4,608	5.5%	19.7%	-42.1%
	Lithium Carbonate-Dec	247	85	160	1,917	12.9%	34.4%	
	Lithium Carbonate-Jan/Feb	513	113	400	4,145	12.4%	22.0%	-36.0%
	Wellbutrin (Bupropion)-Dec	612	139	472	6,163	9.9%	22.7%	
	Wellbutrin (Bupropion)-Jan/Feb	1,305	182	1,123	13,938	9.4%	13.9%	-38.6%
	Prilosec (Omeprazole)-Dec	152	57	95	1,599	9.5%	37.5%	
	Prilosec (Omeprazole)-Jan/Feb	326	78	248	3,543	9.2%	23.9%	-36.2%
	Zoloft (Sertraline)-Dec	848	243	605	7,667	11.1%	28.7%	
	Zoloft (Sertraline)-Jan/Feb	1,904	317	1,587	17,581	10.8%	16.6%	-41.9%
	Celexa (Citalopram)-Dec	719	153	565	7,042	10.2%	21.3%	
	Celexa (Citalopram)-Jan/Feb	1,581	224	1,356	15,870	10.0%	14.2%	-33.4%
	Prozac (Fluoxetine)-Dec	649	157	492	6,622	9.8%	24.2%	
	Prozac (Fluoxetine)-Jan/Feb	1,524	228	1,296	15,542	9.8%	15.0%	-38.2%
	Lexapro (Escitaloprim)-Dec	397	96	300	3,420	11.6%	24.2%	
	Lexapro (Escitaloprim)-Jan/Feb	716	116	600	7,080	10.1%	16.2%	-33.0%
	Paxil (Paroxetine)-Dec	235	52	183	2,465	9.5%	22.1%	
	Paxil (Paroxetine)-Jan/Feb	536	80	456	5,735	9.3%	14.9%	-32.5%
	Trazodone-Dec	1,061	282	779	8,676	12.2%	26.6%	
	Trazodone-Jan/Feb	2,269	338	1,931	19,378	11.7%	14.9%	-44.0%
	Cymbalta (Duloxetine)-Dec	592	143	448	5,566	10.6%	24.2%	
	Cymbalta (Duloxetine)-Jan/Feb	1,212	139	1,073	11,404	10.6%	11.5%	-52.5%
	Effexor (Venlafaxine)-Dec	307	66	241	3,617	8.5%	21.5%	
	Effexor (Venlafaxine)-Jan/Feb	742	103	639	7,984	9.3%	13.9%	-35.4%
	Amitriptyline-Dec	391	101	290	4,211	9.3%	25.8%	
	Amitriptyline-Jan/Feb	1,052	143	909	9,894	10.6%	13.6%	-47.4%
	Straterra (Atomoxetine)-Dec	209	43	166	1,891	11.1%	20.6%	
	Straterra (Atomoxetine)-Jan/Feb	398	50	348	4,075	9.8%	12.6%	-38.9%

ProDUR Report for December 2012- February 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)-Jan/Feb	0	5	22	1	26	0	0	1
	Hydrocodone Bit/APAP-Jan/Feb	0	0	24	0	13	0	0	1
	Oxycodone HCl-Jan/Feb	4	2	32	0	15	0	0	3
	Lorazepam-Jan/Feb	7	12	75	0	45	1	0	7
	Alprazolam-Jan/Feb	5	15	51	0	30	0	0	3
	Diazepam-Jan/Feb	2	3	31	0	18	0	0	4
	Buspar (Buspirone)-Jan/Feb	2	4	34	1	15	0	0	0
	Lamictal (Lamotrigine)-Jan/Feb	5	8	85	5	57	0	0	5
	Depakote (Divalproex Sodium)-Jan/Feb	1	5	46	3	54	0	0	3
	Clonazepam-Jan/Feb	3	1	14	0	11	0	0	2
	Gabapentin-Jan/Feb	0	1	40	1	13	0	0	1
	Abilify (Aripiprazole)-Jan/Feb	7	15	56	4	64	0	1	3
	Seroquel (Quetiapine)-Jan/Feb	7	19	71	0	80	1	0	6
	Risperdal (Risperidone)-Jan/Feb	3	12	60	3	68	0	1	4
	Zyprexa (Olanzapine)-Jan/Feb	1	11	32	1	31	0	0	2
	Geodon (Ziprasidone)-Jan/Feb	0	5	9	0	21	0	2	2
	Albuterol-Jan/Feb	0	4	6	0	15	0	0	1
	Lithium Carbonate-Jan/Feb	4	4	33	1	24	0	1	2
	Wellbutrin (Bupropion)-Jan/Feb	7	11	31	1	48	1	1	4
	Prilosec (Omeprazole)-Jan/Feb	2	0	19	1	25	0	0	5
	Zoloft (Sertraline)-Jan/Feb	9	13	119	3	53	0	1	5
	Celexa (Citalopram)-Jan/Feb	5	10	63	5	63	0	0	1
	Prozac (Fluoxetine)-Jan/Feb	7	15	62	4	49	0	1	2
	Lexapro (Escitaloprim)-Jan/Feb	5	11	34	1	30	0	0	1
	Paxil (Paroxetine)-Jan/Feb	3	6	15	3	15	0	0	2
	Trazodone-Jan/Feb	11	17	128	2	82	0	1	4
	Cymbalta (Duloxetine)-Jan/Feb	6	12	36	2	24	0	2	0
	Effexor (Venlafaxine)-Jan/Feb	4	10	22	0	12	0	1	1
	Amitriptyline-Jan/Feb	2	9	55	0	24	0	0	3
	Straterra (Atomoxetine)-Jan/Feb	0	5	11	0	15	0	0	0
	TOTALS	**112**	**245**	**1316**	**42**	**1040**	**3**	**12**	**78**

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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	33		92		26
Unique Patients Sent Interventions	0	0	0	0	0	0		92		26
% Sent	-	-	-	-	-	0%		100%		100%
Quarter 2 Jan-Mar										
Unique Patients	0	0	0	0	255	0		26		5
Unique Patients Sent Interventions	0	0	0	0	0	0		26		5
% Sent	-	-	-	-	0%	-		100%		100%
Quarter 3 Apr-Jun										
Unique Patients	0	0	0	0	138	0		0		0
Unique Patients Sent Interventions	0	0	0	0	0	0		0		0
% Sent	-	-	-	-	0%	-		-		-
Quarter 4 Jul-Sep										
Unique Patients	1	0	0	0	41	0		0		0
Unique Patients Sent Interventions	0	0	0	0	0	0		0		0
% Sent	0%	-	-	-	0%	-		-		-
Year to date summary										
Unique Patients	1	0	0	0	434	33		118		31
Unique Patients Sent Interventions	0	0	0	0	0	0		118		31
% Sent	0%	-	-	-	0%	0%		100%		100%
ROI per intervention	$51	NA	NA	NA	NA	NA		$49		$220
Estimated program savings	$0	NA	NA	NA	NA	NA		$5,782		$6,820

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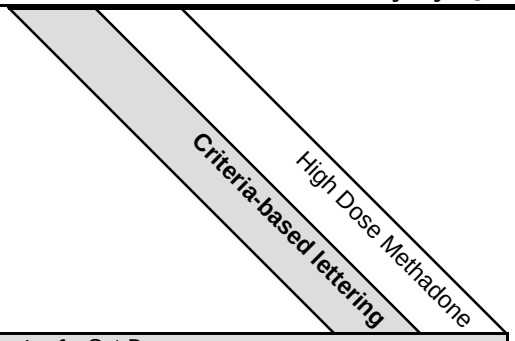
Retro-DUR Intervention History by Quarter - FFY 2012-2013 Le



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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OHP FFS Average Cost PMPM Top 40 Drugs (brand name) - Fourth Quarter 2012

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**	**2012**	**2011**	**%**	**2012**	**2011**	**%**	**2012**	**2011**	**%**
1	7	ABILIFY	$3.63	$3.32	9.5%	0.54	0.56	-3.0%	$672	$596	12.8%
2	11	CYMBALTA	$1.76	$1.42	24.1%	0.72	0.68	5.8%	$245	$209	17.4%
3	10	METHYLPHENIDATE ER	$1.43	$1.36	5.2%	0.84	0.81	3.7%	$170	$167	1.5%
4	33	SYNAGIS	$1.02	$1.30	-21.6%	0.04	0.06	-33.1%	$2,540	$2,168	17.2%
5	71	REMODULIN	$0.94	$1.47	-36.5%	0.00	0.01	-38.8%	$21,623	$20,641	4.8%
6	15	PROAIR HFA	$0.74	$0.49	49.5%	1.35	0.93	44.8%	$55	$53	3.2%
7	58	LANTUS	$0.71	$0.55	30.7%	0.31	0.29	8.0%	$228	$188	21.1%
8	7	SEROQUEL XR	$0.62	$0.59	6.5%	0.13	0.15	-12.3%	$476.08	$392.06	21.4%
9	99	PULMOZYME	$0.60	$0.41	45.3%	0.02	0.02	23.2%	$2,615.98	$2,224.85	17.6%
10	42	HUMIRA	$0.59	$0.53	10.9%	0.03	0.03	7.0%	$2,068.49	$1,997.57	3.6%
11	11	STRATTERA	$0.57	$0.56	1.0%	0.24	0.27	-11.2%	$235.60	$207.02	13.8%
12	77	LOVENOX	$0.54	$0.10	438.1%	0.05	0.01	589.8%	$1,107	$1,415	-21.8%
13	11	INTUNIV	$0.51	$0.34	50.2%	0.25	0.19	30.4%	$203	$176	15.2%
14	51	FLOVENT HFA	$0.50	$0.47	8.1%	0.30	0.30	-0.1%	$167.63	$155.17	8.0%
15	33	TRUVADA	$0.50	$0.92	-45.7%	0.05	0.09	-49.8%	$1,046.28	$972.43	7.6%
16	15	ADVAIR DISKUS	$0.50	$0.48	2.8%	0.19	0.20	-4.6%	$262.94	$244.28	7.6%
17	42	ENBREL	$0.47	$0.43	9.8%	0.02	0.02	-5.3%	$2,003.95	$1,727.55	16.0%
18	33	ATRIPLA	$0.46	$1.02	-54.6%	0.03	0.06	-56.7%	$1,711.39	$1,633.36	4.8%
19	12	DEXTROAMPHETAMINE-AMPHETAMINE	$0.46	$0.46	-0.3%	0.28	0.26	9.2%	$164.63	$179.25	-8.2%
20	40	OXYCONTIN	$0.46	$1.07	-56.8%	0.10	0.21	-50.7%	$454.51	$516.53	-12.0%
21	58	NOVOLOG	$0.44	$0.36	23.4%	0.18	0.16	12.5%	$247.30	$225.39	9.7%
22	15	SPIRIVA	$0.42	$0.38	8.9%	0.16	0.16	5.2%	$255.83	$247.10	3.5%
23	40	HYDROCODONE-ACETAMINOPHEN	$0.41	$0.41	-0.6%	2.63	2.89	-9.0%	$15.52	$14.23	9.1%
24	15	COMBIVENT	$0.38	$0.38	0.5%	0.17	0.17	-0.9%	$218.69	$215.78	1.3%
25	23	TOBI	$0.38	$0.35	8.8%	0.01	0.01	-13.1%	$5,559.14	$4,435.88	25.3%
26	12	VYVANSE	$0.37	$0.37	-0.2%	0.22	0.23	-6.4%	$168.60	$158.40	6.4%
27	7	INVEGA SUSTENNA	$0.35	$0.24	42.6%	0.03	0.02	37.9%	$1,161.01	$1,122.89	3.4%
28	7	ZIPRASIDONE HCL	$0.32			0.16			$206.56		
29	58	HUMALOG	$0.32	$0.32	1.7%	0.13	0.12	4.5%	$248.47	$256.35	-3.1%
30	1	OMEPRAZOLE	$0.32	$0.30	7.5%	1.82	1.65	10.5%	$17.52	$17.99	-2.6%
31	30	XELODA	$0.29	$0.11	168.1%	0.01	0.01	34.1%	$2,725.42	$1,362.39	100.0%
32	69	CREON	$0.28	$0.30	-7.4%	0.03	0.03	5.4%	$906.03	$1,032.33	-12.2%
33	30	REVLIMID	$0.27	$0.09	199.6%	0.00	0.00	161.5%	$7,298.80	$6,420.14	13.7%
34	7	INVEGA	$0.26	$0.24	11.7%	0.04	0.04	-8.2%	$687.56	$565.32	21.6%
35	11	MODAFINIL	$0.26			0.03			$925.36		
36	7	LATUDA	$0.26	$0.12	121.5%	0.04	0.02	82.6%	$573.41	$472.59	21.3%
37	99	COPAXONE	$0.25	$0.22	13.4%	0.01	0.01	-5.6%	$4,145.73	$3,452.09	20.1%
38	33	REYATAZ	$0.25	$0.45	-45.0%	0.03	0.05	-44.9%	$872.21	$876.10	-0.4%
39	30	TEMODAR	$0.25	$0.25	-0.9%	0.01	0.01	-8.0%	$4,180.36	$3,879.39	7.8%
40	48	VIMPAT	$0.25	$0.20	25.0%	0.05	0.04	13.3%	$536.53	$484.88	10.7%
		Aggregate	$53.64	$59.70	-10.1%	101.43	100.68	0.7%	$63	$77	-17.7%
		75th Percentile			35.9%			26.1%			13.2%
		50th Percentile (Median)			1.6%			-0.7%			0.9%

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OHP FFS Average Cost PMPM Top 30 Drug Class – Fourth Quarter 2012

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**	**2012**	**2011**	**%**	**2012**	**2011**	**%**	**2012**	**2011**	**%**
1	7	Ataractics, Tranquilizers	$6.99	$10.69	-34.7%	6.0	6.2	-3.2%	$117	$173	-32.5%
2	11	Psychostimulants, Antidepressants	$4.76	$4.70	1.3%	9.1	9.1	0.5%	$52	$52	0.7%
3	33	Antivirals	$4.13	$6.11	-32.4%	0.6	0.8	-21.9%	$630	$798	-21.1%
4	99	Miscellaneous	$3.27	$2.74	19.3%	1.5	1.5	3.5%	$203	$182	11.4%
5	15	Bronchial Dilators	$2.93	$3.42	-14.3%	3.3	3.5	-5.5%	$88	$97	-9.6%
6	48	Anticonvulsants	$2.79	$2.51	11.1%	5.5	5.4	2.7%	$46	$42	8.4%
7	58	Diabetic Therapy	$2.45	$2.28	7.8%	2.1	2.1	-1.7%	$119	$109	9.2%
8	10	CNS Stimulants	$2.19	$2.34	-6.3%	1.8	1.9	-6.1%	$123	$124	-0.1%
9	40	Narcotic Analgesics	$1.89	$2.96	-36.3%	6.3	7.4	-14.1%	$30	$40	-26.4%
10	30	Antineoplastic	$1.85	$0.99	87.8%	0.3	0.3	-1.6%	$420	$258	62.7%
11	71	Other Hypotensives	$1.79	$2.17	-17.3%	2.8	2.8	-0.3%	$64	$78	-17.6%
12	42	Antiarthritics	$1.43	$1.35	5.6%	2.1	2.1	-0.3%	$68	$64	6.1%
13	51	Gluco Corticoids	$1.29	$1.21	6.6%	1.8	1.9	-5.5%	$71	$63	12.4%
14	63	Oral Contraceptives	$1.20	$1.10	8.7%	2.6	2.6	0.4%	$47	$43	8.0%
15	12	Amphetamine Preps	$1.19	$1.30	-8.0%	0.9	0.9	-4.6%	$132	$137	-3.3%
16	1	Antacids	$0.99	$1.17	-15.3%	3.5	3.6	-2.6%	$28	$32	-13.1%
17	64	Other Hormones	$0.96	$0.74	29.9%	0.1	0.1	9.1%	$808	$696	16.2%
18	41	Non-narcotic Analgesics	$0.82	$0.87	-6.5%	5.8	5.2	12.4%	$14	$17	-17.8%
19	27	Other Antibiotics	$0.79	$0.76	4.2%	0.8	0.8	-4.5%	$99	$93	7.3%
20	77	Anticoagulants	$0.77	$0.98	-21.5%	0.5	0.5	-6.7%	$161	$192	-16.0%
21	6	Laxatives	$0.75	$0.66	13.4%	6.0	5.4	10.4%	$12	$12	2.9%
22	87	Electrolytes and Misc Nutr	$0.66	$0.64	3.7%	3.0	2.9	3.8%	$22	$22	1.2%
23	65	Lipotropics	$0.59	$1.09	-45.9%	2.1	2.1	-0.2%	$28	$52	-46.1%
24	80	Fat Soluble Vitamins	$0.42	$0.37	13.7%	4.3	3.6	18.3%	$10	$10	-4.0%
25	69	Enzymes	$0.42	$0.41	2.6%	0.0	0.0	4.9%	$837	$854	-2.1%
26	23	Streptomycins	$0.41	$0.43	-4.5%	0.0	0.0	-20.8%	$1,514	$1,163	30.1%
27	82	Multivitamins	$0.38	$0.36	8.0%	3.7	3.4	7.3%	$10	$10	-0.2%
28	76	Other Cardiovascular Preps	$0.32	$0.32	-0.6%	1.8	1.8	-2.2%	$17	$17	0.7%
29	14	Antihistamines	$0.31	$0.30	3.5%	2.7	2.5	7.4%	$11	$12	-4.2%
30	49	Antinauseants	$0.27	$0.18	54.8%	0.9	0.7	26.3%	$29	$23	22.5%
		Aggregate	$53.64	$59.70	-10.1%	101.43	100.68	0.7%	$63	$77	-17.7%
		75th Percentile			20.9%			13.7%			8.4%
		50th Percentile (Median)			3.5%			0.5%			0.3%

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Pharmacy Utilization Summary Report: January 2012 - December 2012

	2012												
	JANUARY	FEBRUARY	MARCH	APRIL	MAY	JUNE	JULY	AUGUST	SEPTEMBER	OCTOBER	NOVEMBER	DECEMBER	
Eligibility													**AVG/YTD**
Total Members	610,951	614,598	617,154	618,741	619,071	619,994	618,940	619,527	621,079	619,870	618,962	621,328	618,351
FFS Members	98,287	94,464	95,551	98,227	93,871	95,264	97,124	95,914	103,154	101,337	85,412	80,358	94,914
Standard	6,499	5,939	5,581	5,743	5,631	5,627	5,694	5,626	6,046	6,171	4,095	3,486	5,512
Plus	66,336	63,022	64,361	66,770	62,683	63,941	65,530	64,208	70,631	68,720	54,699	50,213	63,426
Medicare Wrap	25,452	25,503	25,609	25,714	25,557	25,696	25,900	26,080	26,477	26,446	26,618	26,659	25,976
Gross Figures													
Total Cost	$14,591,516	$14,226,609	$14,624,426	$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	$149,677,281
FFS Drugs	$4,345,792	$4,283,674	$4,444,328	$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	$48,019,636
Mental Health Carveout Drugs	$10,245,723	$9,942,935	$10,180,099	$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	$101,657,644
Total Rx	185,830	179,850	187,659	182,966	190,235	178,304	180,179	184,181	172,761	192,095	170,300	167,020	2,171,380
FFS Drugs	81,700	80,086	83,719	80,994	84,688	78,210	79,057	81,158	78,188	87,765	70,784	67,627	953,976
Mental Health Carveout Drugs	104,130	99,764	103,940	101,972	105,547	100,094	101,122	103,023	94,573	104,330	99,516	99,393	1,217,404
Cost/Rx	$78.52	$79.10	$77.93	$70.69	$67.86	$66.31	$67.22	$66.22	$63.22	$63.19	$62.84	$62.86	$68.83
FFS Drugs	$53.19	$53.49	$53.09	$53.13	$51.09	$50.71	$50.63	$49.29	$48.14	$48.17	$46.00	$45.82	$50.23
Mental Health Carveout Drugs	$98.39	$99.66	$97.94	$84.63	$81.32	$78.49	$80.19	$79.56	$75.68	$75.83	$74.82	$74.46	$83.41
Generic	$43.44	$43.70	$42.08	$33.94	$30.75	$28.48	$28.36	$27.45	$25.05	$24.95	$23.67	$22.86	$31.23
Brand	$340.62	$343.87	$344.36	$345.71	$343.71	$349.80	$357.92	$356.92	$350.83	$350.39	$355.44	$354.94	$349.54
PMPM Figures													
Cost PMPM	$60.99	$61.53	$63.01	$57.76	$59.96	$54.31	$54.31	$54.94	$48.01	$54.48	$50.15	$50.47	$55.83
Standard	$151.10	$151.21	$166.02	$151.50	$156.18	$146.71	$143.20	$152.43	$126.19	$136.17	$119.27	$129.53	$144.13
Plus	$62.79	$64.07	$66.03	$58.64	$62.90	$55.47	$55.50	$56.30	$49.01	$56.55	$56.50	$58.67	$58.54
Medicare Wrap	$15.99	$18.05	$14.76	$17.91	$17.18	$16.52	$16.00	$17.11	$15.84	$17.75	$13.38	$13.49	$16.17
FFS Drugs	$44.22	$45.35	$46.51	$43.81	$46.09	$41.63	$41.21	$41.71	$36.49	$41.72	$38.12	$38.56	$42.12
Mental Health Carveout Drugs	$16.77	$16.18	$16.50	$13.95	$13.86	$12.67	$13.10	$13.23	$11.52	$12.76	$12.03	$11.91	$13.71
Rx PMPM	1.00	1.01	1.04	0.99	1.07	0.98	0.98	1.01	0.91	1.03	0.99	1.00	1.00
Standard	1.95	2.04	2.21	2.10	2.22	2.07	2.05	2.19	1.92	2.16	2.04	2.00	2.08
Plus	0.86	0.88	0.91	0.85	0.93	0.84	0.83	0.86	0.77	0.89	0.86	0.87	0.86
Medicare Wrap	1.02	0.99	1.02	0.99	1.05	0.99	1.02	1.03	0.96	1.04	0.99	1.01	1.01
FFS Drugs	0.83	0.85	0.88	0.82	0.90	0.82	0.81	0.85	0.76	0.87	0.83	0.84	0.84
Mental Health Carveout Drugs	0.17	0.16	0.17	0.16	0.17	0.16	0.16	0.17	0.15	0.17	0.16	0.16	0.16
Utilization Percentages													
Generic %	88.2%	88.2%	88.1%	88.2%	88.1%	88.2%	88.2%	88.2%	88.3%	88.3%	88.2%	88.0%	88.2%
FFS Drugs	90.2%	90.4%	90.3%	90.5%	90.6%	90.7%	90.8%	90.8%	90.7%	90.8%	91.1%	91.0%	90.7%
Mental Health Carveout Drugs	86.6%	86.5%	86.4%	86.4%	86.2%	86.3%	86.2%	86.2%	86.3%	86.1%	86.1%	85.9%	86.2%
PDL %	91.3%	91.7%	92.0%	92.2%	92.9%	93.2%	93.2%	94.0%	94.2%	91.7%	91.4%	91.1%	92.4%

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: January 24, 2013

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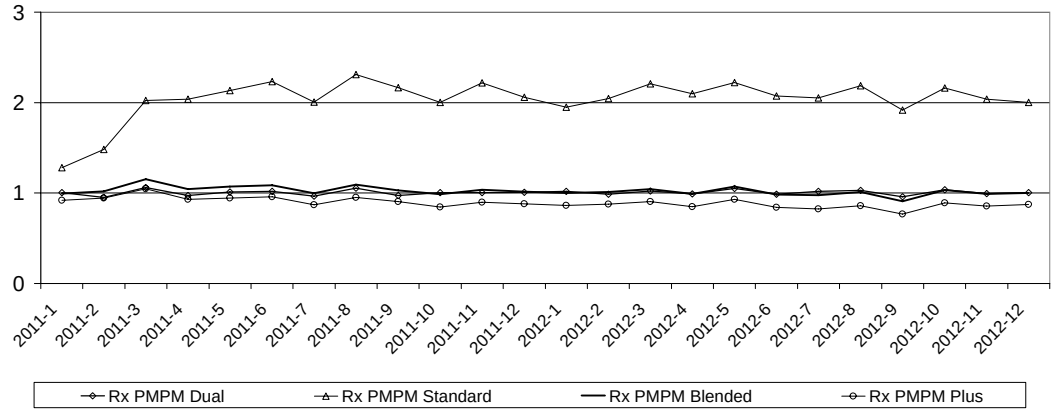
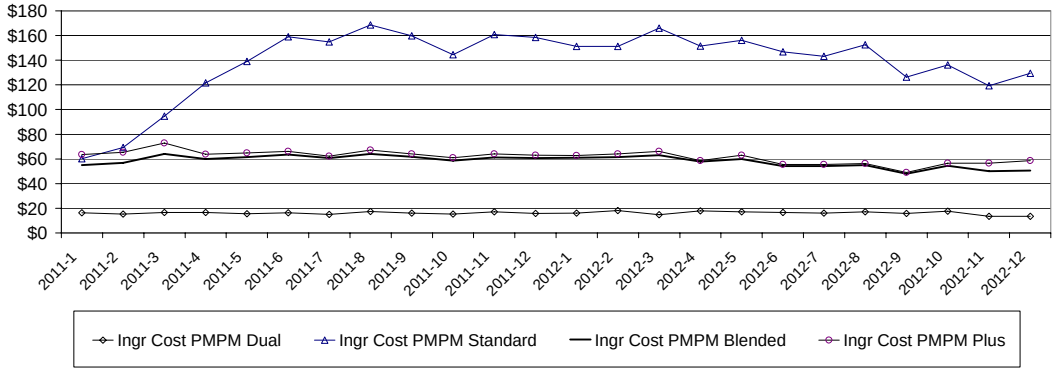
Pharmacy Utilization Summary Report: 2011-2012

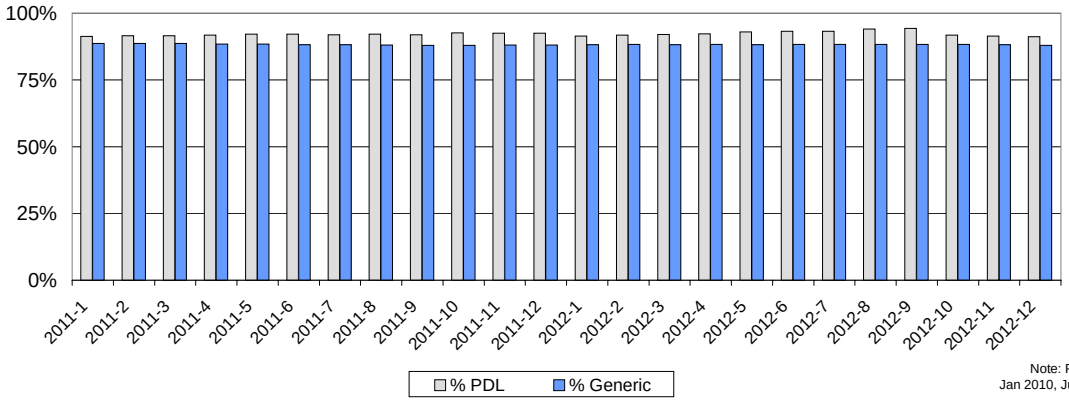
RX Dispensed PMPM



Ingredient Cost PMPM



Percent Generic and PDL



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

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The Future of Newer Obesity Medications

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Obesity has become a major health crisis in the United States. The 2009-2010 Centers for Disease Control (CDC) report stated that over 1/3 of the adult population was considered obese.[1] In the state of Oregon, about 60% of the adult population is considered overweight or obese, and in 2006, medical costs related to obesity were over 1.6 billion for the state.[2] Many chronic diseases, such as hypertension, type 2 diabetes, and hyperlipidemia can result from being obese. The high prevalence of obesity has led to the development and approval of many weight loss medications to assist in weight loss and prevent long-term morbidity and mortality. However, due to limited efficacy along with intolerable and serious side effects, most have been removed from the market. Two new centrally acting obesity medications were approved for long-term weight loss in the summer of 2012: lorcaserin hydrochloride (Belviq®) and phentermine/topiramate controlled-release (Qsymia®). The question now remains, will these medications help put an end to the health crisis, or will they be pulled from the market like their predecessors?

Obesity Guidelines

Currently, the World Gastroenterology Organization (WGO) Global Guidelines recommend diet, exercise, and behavioral modifications as first-line treatment steps to losing weight.[3] If weight loss is not achieved, medications can be added on depending on patient's body mass index (BMI) and co-morbidities. Patients who are overweight (BMI 25.0-29.9 kg/m^2) or fit into obesity class I (BMI 30.0-34.9 kg/m^2) with co-morbidities present are considered candidates for weight loss medications, along with patients who are in the class II (BMI 35.0-39.9) or class III (BMI ≥40) obesity category with or without co-morbidities. Bariatric surgery is only recommended as a last resort for obese individuals with a BMI ≥40 or BMI ≥35 with co-morbid conditions, including diabetes.

According to the 2007 Food and Drug Administration (FDA) Industry Guidance for Obesity Treatment, a product can be considered effective for weight management after one year of treatment if either of the following occurs: 1) the difference in mean weight loss between the active-product and placebo-treated groups is at least 5 percent and the difference is statistically significant, or 2) if the proportion of subjects who lose greater than or equal to 5 percent of baseline body weight in the active-product group is at least 35 percent, weight loss is approximately double the proportion in the placebo-treated group, and the difference between groups is statistically significant.[4] Attrition rates in studies evaluating weight loss medications are generally high, averaging above 30% and are, in part, a function of weight loss.[5] Under the Oregon Health Plan, medical treatment of obesity is limited to intensive counseling on nutrition and exercise, provided by health care professionals. Pharmaceutical agents are not covered services for the treatment of obesity.

Past and Present: Weight Loss Medications

Currently, there are several short-term (generally 12 weeks or less) weight loss medications available on the market, such as phentermine. Orlistat is the only medication available for long-term use (generally a year or longer). Orlistat has a peripheral mechanism of action, blocking fat absorption from the gut and, in combination with lifestyle modifications, has been shown in clinical trials to cause a ≥5% reduction in baseline body weight at one year.[6,7] In 2010, safety concerns surfaced about orlistat causing rare cases of severe liver injury, and in 2012, case reports of oxalate nephrolithiasis and oxalate nephropathy with renal failure led to the release of a new warning.[8,9] The long-term weight loss medication, sibutramine, was pulled off the market by the FDA in October 2010 due to the safety concerns identified in outcomes from the Sibutramine Cardiovascular Outcomes Trial (SCOUT), which demonstrated a 16% increase in the risk of major adverse cardiovascular events (hazard ratio [HR] for nonfatal myocardial infarction, 1.28; 95% CI 1.04, 1.57; p-value=0.02; HR for nonfatal stroke, 1.36; 95% CI 1.04, 1.77; p-value=0.03).[10] The difference in mean percent change in body weight between sibutramine and placebo was 3.5%. Additionally, two serotonergic weight loss medications, flenfluramine and dexfenfluramine, were pulled off the market in the 1990's because use was linked to pulmonary hypertension and cardiac valvulopathy.[11, 12]

Lorcaserin

Lorcaserin, a selective serotonin 2c agonist thought to decrease appetite and increase satiety, was approved by the FDA in June 2012 for adults with a BMI of 30 kg/m^2 or greater or with a BMI of 27-30 kg/m^2 and at least one co-morbid condition.[14] The serotonin 2c selectivity is assumed to reduce the risk for cardiac valvulopathy.[12]

Approval was based on three fair quality, randomized, placebo-controlled phase III clinical trials that studied the medication adjunctively with a reduced calorie diet and exercise for chronic weight management in non-diabetics (BLOOM and BLOSSOM) and in the diabetic population (BLOOM-DM).[12,15,16] The majority of the subjects in all of the trials were white women in their mid-40's to 50's that were relatively healthy, reducing the generalizability to the overall population. All patients were asked to participate in 30 minutes of exercise daily and reduce their caloric intake by 600 kcal/day, which are potential confounding variables.

All three trials resulted in a statistically significant weight loss of ≥5% and ≥10% for both doses compared to placebo. The combined data from BLOOM and BLOSSOM (n=6139) demonstrated that 10 mg of lorcaserin twice daily resulted in 47.1% of non-diabetic patients experiencing a weight reduction of ≥5% from baseline, which was statistically significantly greater than placebo (relative risk [RR] 2.09; 95% CI 1.94, 2.26; p-value<0.0001) with an absolute risk reduction (ARR) of 25% and a number needed-to-treat (NNT) of 4.[12,16] In diabetic patients (BLOOM-DM; n=499), 37.5% of patients experienced a weight reduction of ≥5% from baseline (RR 2.32; 95% CI 1.67, 2.38; p-value<0.0001). These results met the second FDA criteria for approval. However, there was only a 3% mean difference in weight loss between lorcaserin and placebo in diabetic patients and 3.3% in nondiabetic patients, not meeting the other FDA approval criteria for demonstrating minimal clinical efficacy.

In BLOOM-DM, mean hemoglobin A1c (a measure of glycemic control) decreased from baseline significantly more in the lorcaserin 10 mg twice-daily group as compared to placebo (-1.0% vs. -0.5%; p-value<0.001).[15] Antihyperglycemic medications could be dose-adjusted after the twelfth week of the BLOOM-DM trial though, so it remains unknown if the hemoglobin A1c reduction was solely due to weight loss from lorcaserin or as a result of medication adjustments.

The clinical trials did not demonstrate a significant difference in FDA-defined valvulopathy between lorcaserin and placebo (pooled RR 1.16; 95% CI 0.81, 1.67).[12,16] However, they were not powered to evaluate the effect on long-term cardiovascular outcomes. The most common adverse effects reported in the trials were headache, upper respiratory infection, nausea, dizziness, and fatigue. In addition, lorcaserin may increase the risk of psychiatric, cognitive, and serotonergic adverse events.

Phentermine/Topiramate

A fixed dose combination of phentermine and topiramate was approved by the FDA in July 2012 for adults with a BMI of 30 kg/m^2 or greater or a BMI of 27-30 kg/m^2 with at least one co-morbid condition. The mechanism of action is unclear at this time, but the combination is thought to reduce appetite and

food consumption through norepinephrine release (phentermine), and augment the activity of gamma-aminobutyrate and inhibit carbonic anhydrase (topiramate). The approved doses of phentermine/topiramate are 7.5mg/46mg and 15mg/92mg with two tapering doses of 3.75mg/23mg and 11.25mg/69mg. Dose adjustment is necessary in moderate to severe renal impairment and in moderate hepatic impairment. It is not recommended for children under 18 and should be used with caution in adults over 65 due to minimal data in both populations. Phentermine/topiramate was approved with a risk evaluation and mitigation strategy (REMS) informing prescribers and female patients of the risk of birth defects and the importance of pregnancy prevention.

Approval was based on two fair to good quality, randomized, double-blind, placebo-controlled phase III clinical trials (EQUIP and CONQUER) that studied varying doses of the medication compared to placebo for chronic weight management for 56 weeks.[17,18] All study participants were asked to reduce their caloric intake by 500 kcal/day and initiate an exercise routine. A double-blind extension study (SEQUEL) was completed following CONQUER, which assessed efficacy and safety of phentermine/topiramate for a total of 108 weeks in the most adherent patients from CONQUER.[19] EQUIP included obesity class II and III patients (BMI ≥35 kg/m^2), while CONQUER and SEQUEL included overweight and obesity class I through III patients (BMI ≥27 kg/m$^{2)}$ with one or more co-morbidities. Unlike lorcaserin, this medication met both of the FDA efficacy criteria endpoints.

EQUIP demonstrated significantly more patients achieving a weight loss ≥5% of baseline body weight for phentermine/topiramate 15mg/92mg and 3.75 mg/23mg compared to placebo (74.4%, 51.1%, and 24.8% respectively; p-value<0.0001 for all comparisons).[17] Mean percent change in weight loss was also significantly greater with high and low dose phentermine/topiramate compared to placebo (-10.9%, -5.1%, and -1.6%, respectively; p-value<0.0001 for all comparisons). There was a statistically significant difference in withdrawals due to adverse events between the high dose of phentermine/topiramate 15mg/92mg and placebo (16% vs. 8.4%; RR 1.91 95% CI 1.33, 2.76; p-value<0.001). [17] The higher dose of phentermine/topiramate had more significant adverse events than the titration dose and placebo; the most common events (p-values<0.0001) included paresthesia, dry mouth, constipation, dysgeusia, depression, irritability, anxiety, and concentration and attention impairment. [17]

The CONQUER trial compared the higher dose of phentermine/topiramate 15mg/92mg and lower dose of 7.5mg/46mg to placebo. In the intention-to-treat analysis, the change in body weight at 56-weeks was greater in the higher and lower dose groups compared to placebo (least square mean -9.8%, -7.8%, and -1.2%, respectively; p-value<0.0001).[18] The proportion of patients achieving at least 5% weight loss was 70% (RR 3.36; 95% CI 2.98, 3.80), 62% (RR 2.98; 95% CI 2.59, 3.41), and 21% (p-value<0.0001 for all comparisons to placebo) for phentermine/topiramate 15mg/92mg, 7.5mg/46mg versus placebo, respectively. There was no statistically significant difference in serious adverse events, but there was again a statistically significant difference in withdrawal rate between the high dose and placebo (19% vs. 9% for 15mg/92mg vs. placebo; RR 2.16; 95% CI 1.70, 2.78; p-value<0.0001). [18]

In the extension trial (SEQUEL), participants continued to receive the original treatment to which they were randomly assigned during the CONQUER study.[19] Further participation into SEQUEL was optional, potentially biasing toward inclusion of only subjects with positive outcomes. There continued to be a significantly greater mean percentage change from baseline body weight for both the high dose and the medium dose compared to placebo (-10.5%, -9.4%, and -1.8%, respectively). [19] The proportion of patients achieving at least 5% weight loss was 79.7% (RR 2.70; 95% CI 2.22, 3.27), 74.3% (RR 2.51; 95% CI 2.02, 3.07), and 28.9% (p-value<0.0001 for all comparisons to placebo). [19] The incidence of individual adverse events was lower in the second year (weeks 56-108) than in the first year (weeks 0-56). There was a reduction seen in blood pressure that was accompanied by a mean increase in heart rate of 1.7 beats per minute with the 15mg/92mg dose. The long-term clinical significance of this is unknown.

Summary

Newer weight loss medications are currently being developed to try to meet the market demand for a new pivotal weight loss drug. A variety of centrally acting mechanisms and polytherapies are being explored. The treatment of obesity with centrally acting drugs is an area of continued debate regarding whether the benefits justify the risks. To date, no clinical outcome study has been performed to demonstrate that long-term treatment with anti-obesity drugs has a positive effect on morbidity and mortality.

Phentermine/topiramate and lorcaserin were associated with greater weight loss compared to placebo. Phentermine/topiramate was associated with a higher incidence of medical events related to psychiatric, cognitive, and cardiac disorders compared to lorcaserin. It remains unknown if these new agents will demonstrate long-term effectiveness with tolerable harms in the general population.

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HERC Approved 1/10/13

ANCILLARY GUIDELINE XXX, THERAPIES WITH MARGINAL BENEFIT OR HIGH COST

It is the intent of the Commission that therapies that exhibit one or more of the following characteristics generally be given low priority on the Prioritized List:

i. Marginal or clinically unimportant benefit,
ii. Very high cost in which the cost does not justify the benefit
iii. Significantly greater cost compared to alternate therapies when both have similar benefit

Where possible, the Commission prioritizes pairings of condition and treatment codes to reflect this lower priority, or simply does not pair a procedure code with one or more conditions if it exhibits one of these characteristics.

As codes for prescription drugs and certain other ancillary services are not included on the Prioritized List, it is more difficult to indicate the importance of these services through the prioritization process. The Commission recognizes the evidence-based reviews being conducted by the Pharmacy and Therapeutics Committee and hereby prioritizes those services found in Table XX located at www… (e.g. *as of October 1, 2013*) to be prioritized on the line listed below that corresponds with the condition being treated:

ICD-9-CM Codes	Condition classification	Line
001-139, 771, V01-V09, V12.0, V18.8	Infectious & parasitic diseases	683
140-209, V10, V16, V58.0-V58.1, V67.1-V67.2	Malignant neoplasms	622
210-239	Benign neoplasms	656
240-279, 775, V12.1-V12.2, V18.0-V18.1	Endocrine, nutritional and metabolic diseases & immunity disorders	684
280-289, V12.3, V18.2-V18.3, V58.2	Diseases of the blood and blood-forming organs	685
290-319, V11, V17.0, V18.4, V67.3	Mental, behavioral and	681

1

	neurodevelopmental disorders	
320-359, 740-742, 779, V12.4, V17.2, V58.72	Diseases of the nervous system	687
360-389, 743-744, V19.0-V19.3, V57.4, V58.71	Diseases of the sensory organs	686
390-459, 745-747, 773-774, 776, V12.5, V17.1, V17.3-V17.4, V58.73	Diseases of the circulatory system	685
460-519, 748, 769-770, V12.6, V17.5-V17.6, V57.0, V58.74	Diseases of the respiratory system	689
520-579, 749-751, 777, V12.7, V18.5, V58.75	Diseases of the digestive system	692
580-629, 752-753, V13.0, V13.2, V18.6-V18.7, V25-V26, V56, V58.76	Diseases of the genitourinary system	690
630-679, V13.1, V22-V24, V27-V28	Complications of pregnancy, childbirth and the puerperium	690
680-709, 757, 778, V13.3, V19.4, V58.77	Diseases of the skin and subcutaneous tissue	688
710-739, 754-756, V13.4-V13.5, V17.7-V17.8, V54, V57.1-V57.2, V57.8, V58.78, V67.4	Diseases of the musculoskeletal system and connective tissue	691
758-766, 768, 780-799, V13.6-V13.9, V14-V15, V18.9, V19.6-V19.8, V20-V21, V29-V39, V40-V53, V55, V57.3, V57.9, V58.3-V58.6, V58.8-V58.9, V59-V66, V67.0, V67.5-V67.9, V68-V91	Symptoms, signs and ill-defined conditions	692
767-768, 772, 800-999	Injury and poisoning	663

OREGON HEALTH AUTHORITY
DRUG USE REVIEW/PHARMACY AND THERAPEUTICS COMMITTEE

Therapies with Marginal Benefit and High Cost Policy

NOTE: This Policy and associated recommendations are independent from the PMPDP recommendations.

GOAL:
Adopt a policy to assist the Pharmacy and Therapeutics Committee in identifying drugs that meet the criteria for a recommendation to the HERC Committee for further evaluation for the Prioritized List.

1. After a thorough clinical review of the evidence for a particular therapy in addition to cost discussion in executive session, the P&T Committee can recommend the drug be considered as part of this policy and recommendation to the HERC Committee.

2. Therapies that exhibit one or more of the following can be considered by the Committee:
   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

EXAMPLE:

Question: Does the benefit seen with dalfampridine (Ampyra®) outweigh the cost associated with therapy? If not, should it be evaluated for a lower priority line of MS treatments on the prioritized list?

Indication: Dalfampridine extended release tablets are indicated for the improvement of walking in patients with multiple sclerosis (MS), as demonstrated by increased walking speed.

Efficacy:
- Dalfampridine is not a disease modifying agent and, therefore, does not reduce relapse rates or slow disease progression. No studies have been performed addressing whether the use of dalfampridine decreases hospitalization rates, reduces resources used for home care, or improves the performance of activities of daily living.
- Dalfampridine may increase walking speeds in some patients with MS (only about 27% of patients respond). The absolute difference in walking speed seen between responders and non-responders is about 2 seconds over 25 feet.
- It is not known whether a small increase in walking speed can help improve the ability to carry out daily activities or if can help those who already are wheelchair bound.
- If it works, patients should see an improvement within 2 to 6 weeks.

Safety:
- Dalfampridine has been shown to increase the risk of seizures.
- Other side effects include dizziness, asthenia, weakness, trouble sleeping, and balance disorder.

Cost:
- The wholesale acquisition cost for dalfampridine, dosed 10mg twice daily, is about $1,056 per 30-day supply, or $12,850 per year.

Alternative Treatment Options:

- Dalfampridine is the only approved drug for the indication of improvement in walking in multiple sclerosis patients.
- Current first-line treatment consists of disease-modifying agents aimed to slow the progression of MS and reduce the associated disability.

FURTHER ACTIONS:

1. Compare costs of proposed medication to alternative therapies (if, and when available).
2. Consider an appropriate definition of “marginal benefit”.
3. Consider what is considered “high cost”.
4. Consider different pricing definitions and which is most efficient to use for evaluation.

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Month/Year of Review: March 2013
Generic Name: Dalfampridine
Brand Name: (Manufacturer): Ampyra™
Class: Potassium Channel Blocker for MS symptoms

End date of literature search: January 3, 2012
Manufacturer: Acorda Therapeutics, Inc
Dossier received: Yes
Comparator Therapies: None

FDA Approved Indications:[1]
Dalfampridine extended release tablets are indicated for the improvement of walking in patients with multiple sclerosis (MS), as demonstrated by increased walking speed.

Conclusions:

1. **Does FAM produce changes in disability or impairment scales assessing motor function?**
   The differences between FAM-treated and placebo-treated patients for change in walking speed and MSWS-12 were small and achieved inconsistent statistical significance.

   In the phase 2 trial, there was no statistically significant difference between FAM-treated and placebo-treated patients for mean percent change in walking speed as assessed by the T25FW. Therefore, post-hoc data analysis was performed to identify a new endpoint—response to treatment—that would achieve statistical significance in the phase 3 trials.

   Statistical significance was indeed achieved for the primary endpoint in the two phase 3 clinical trials. However, FDA analysis shows the absolute difference in walking speed between responders and non-responder is about 2 seconds over 25 feet. No information is available for distances beyond 25 feet.

   Other limitations of the studies include lack of long-term data and lack of clarity on how one would determine in practice who could potentially respond to FAM. Three unpublished extension studies have been completed that address the long-term efficacy and safety of FAM; however, no studies have been published addressing quality of life or activities of daily living.

2. **Does FAM change disease progression, hospitalization rates, improve the performance of activities of daily living, or reduce resources used for home care?**
   FAM is not a disease-modifying agent and, therefore, does not reduce relapse rates or slow disease progression. No studies have been performed addressing whether the use of FAM decreases hospitalization rates, reduces resources used for home care, or improves the performance of activities of daily living.

3. **Does FAM improve quality of life?**
   Quality of life was not measured in the phase 3 studies. The phase 2 study reported the MSQLI was used as a secondary efficacy measure but did not report the results, thus there is no evidence FAM improves quality of life.

4. **How does FAM compare with non-pharmacologic therapies, such as exercise therapy?**
   No head-to-head comparisons have been performed between FAM and exercise therapy or any other therapy. While exercise is recommended for those with MS, there is little consistent data concerning its efficacy in improving walking in MS.[2]

5. **Is FAM safe?**

The most concerning adverse event for FAM-treated patients is the risk of seizures. Doses exceeding 10 mg twice daily have been associated with increased seizure risk. Also, seizure risk has not been truly evaluated in studies of FAM, because patients with a history of seizure and evidence of epileptiform activity on EEG have been excluded and safety evaluations have been performed in just 807 MS patients taking FAM SR.

The following scenarios could result in a patient potentially having a seizure: (1) FAM could be prescribed to patients who have not had their renal function checked and to patients who may be prone to seizures; (2) patients may inadvertently take two doses at once or less than 12 hours apart or may cut, crush, or chew tablets; and (3) the dosage form could fail and "dump" on occasion. FAM also could present an as yet unidentified risk to patients with decreased seizure threshold due to alcohol use, brain damage, or concomitant use of drugs that lower the seizure threshold.

Ampyra does have a Risk Evaluation and Mitigation Strategy (REMS), including a medication guide and annual letters to prescribers and pharmacists with warnings about the potential risk of seizure. Extension trials that may shed more light on safety have yet to be published.

Other noteworthy adverse events are the rate of UTIs (NNH 25) and the rates of dizziness (NNH 33), asthenia (NNH 33), weakness (NNH 33), and balance disorder (NNH25) in patients who are having difficulty with mobility. Nevertheless, the overall discontinuation rate due to adverse events for FAM-treated patients was just 4% compared with 2% for placebo-treated patients.

No evidence of mutagenicity, carcinogenicity, or impaired fertility has been observed in animals given doses well above the MRHD. However, decreased offspring viability and growth has been observed in animals given doses similar to the MRHD. Therefore, managing the risks and benefits of using FAM in pregnancy is real, especially given that MS is a chronic disease that disproportionately affects women.

6. **Is the benefit of FAM commensurate with the cost?**
   Because FAM is the only approved drug for the indication improvement in walking in MS patients, one cannot compare its cost to other drugs. One could ask whether the improvement in walking leads to direct or indirect healthcare cost savings, but no pharmacoeconomic studies have been performed for FAM.

Recommendations:

Evaluate as part of the marginal benefit/high cost drug policy and refer to the Health Evidence Review Commission for evaluation of cost effectiveness.

Summary:
FAM, also known as fampridine and 4-aminopyridine, is the first symptomatic therapy approved for MS patients with impaired walking mobility. MS is a chronic, progressive, immune-mediated disorder that destroys axonal myelin sheaths, resulting in neurodegeneration and the accumulation of neurologic deficits over time. Symptoms that arise are myriad but may include impaired walking mobility. Nearly 50 percent of those with MS will require the use of a walking aid within 15 to 25 years of diagnosis.

MS has no cure; therefore, the mainstays of treatment are disease-modifying agents that slow the progression of the disease and symptomatic and supportive therapies. FAM is a potassium channel inhibitor that may act by increasing action potential conduction in demyelinated axons, thereby improving walking speed.

Efficacy: Low level evidence from two phase 3 studies and one phase 2 study show dalfampridine (FAM) statistically increases walking speed in a subset of patients with MS called timed-walk responders (TWRs). However, FDA analysis of the absolute difference in walking speed over 25 feet between responders and non-responders is small.
The phase 2 study was negative and compared three doses of sustained-release FAM with placebo in MS patients. The primary endpoint was mean percent change in walking speed during treatment using the Timed 25-Foot Walk (T25FW), which measures patients' ability to safely and quickly walk 25 feet.

Though statistical significance for the endpoint was not achieved, researchers used post-hoc analysis to create a novel primary endpoint, referred to as "response to treatment," for the two phase 3 trials. This endpoint, which has not been validated, defines a responder as one who has a walking speed for at least three visits during the trials' double-blind treatment period was faster than the maximum speed in five non-treatment visits.

Using "response to treatment" as the primary efficacy endpoint, the two phase 3 studies compared FAM 10 mg bid to placebo and used the change in 12-item MS walking scale (MSWS-12) between baseline and treatment's end to address validity and clinical significance. The MSWS-12 assessed MS patients' perspectives on their ambulatory disability. Both studies achieved statistical significance for the endpoint (NNT 3–4), and researchers found a statistically significant decrease in MSWS-12 score from baseline for responders compared to non-responders, independent of treatment group.

However, FDA analysis showed that at the end of the double-blind (DB) treatment period for phase 3 study MS-F203 the difference in walking speed between responders and non-responders over 25 feet was 1.75 seconds (s) (1.99 s for placebo-treated responders versus non-responders and 1.60 s FAM for responders versus non-responders) and for phase 3 study MS-F204 was 1.71 s (1.54 s for placebo-treated responders versus noon-responders and 2.15 s for FAM responders versus non-responders).

Neither phase 3 study directly addressed what impact being a responder would have on the quality of life of MS patients or their activities of daily living, health, or homecare requirements. No information was available concerning distances walked beyond 25 feet. The studies also were unable to address how one would use FAM in practice, given that only a subset of patients were deemed responders and no method exists to identify potential responders prior to treatment.

Safety: In clinical trials, the most common serious adverse events occurring in FAM-treated patients were urinary tract infections (NNH 25) and multiple sclerosis relapse (NNH 100). However, seizure risk has been the focus of concern because of past experience with immediate release fampridine and higher doses of sustained-release FAM. Patients with a history of seizure and evidence of epileptiform activity on EEG were excluded from the trials, so it has been impossible to quantify the actual risk to patients taking FAM 10 mg BID. Accordingly, patients with history of seizure disorder have been contraindicated from taking FAM, and patients should be cautioned to not exceed the maximum recommended semidaily dose. However, prescribing information has not recommended EEG.

FAM may have negligible benefit relative to its annual cost and its associated safety risks. Should criteria be developed to restrict FAM's use, the following should be included: FAM should be limited to those who (1) have a walking disability that requires the use of a walking aid, (2) be able to complete the T25FW in 8–45 s, and (3) do not have moderate or severe renal impairment or a history of seizure disorder or epileptiform activity on EEG. Physician reassessment by T25FW should be required after a 12-week trial.

BACKGROUND/CURRENT LANDSCAPE

FAM is the first drug approved for the improvement of walking in MS patients, and the measure of efficacy used in the two pivotal FAM phase 3 trials on which FAM's approval has been based is a novel one. Because MS has no cure, disease modifying agents and symptomatic therapies are the mainstay for managing the disease.

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 to 2.5 times more frequently in women than in men.[3, 4]

Symptoms of MS 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.[3, 4] Nearly 50 percent of those with MS will require the use of a walking aid within 15 to 25 years of diagnosis.[5]

The three major subtypes of MS are relapsing remitting, secondary progressive, and primary progressive. About 85 to 90 percent of patients present with relapsing remitting MS, which is marked by episodes of worsening or new neurological symptoms followed by periods of inactivity. Most patients with relapsing remitting MS develop secondary progressive MS within twenty to forty years, which is characterized by steady neurological decline with few or no clinically recognized relapses. About 10 to 15 percent of patients present with primary progressive MS, which is characterized by steady neurologic decline from onset for at least a year without distinct relapses.[3, 4]

The course of MS is highly unpredictable and varies from person to person. About 10 percent of patients have a relatively benign course and do well for more than 20 years, while about 70 percent develop secondary progression. Life expectancy may be slightly shorter for those with MS. In rare cases, patients with fulminant MS die within months of disease onset.[6]

The total mean annual cost of MS in 2004, which is after the introduction of disease modifying agents, has been estimated to be about $47,000 per patient.[7] Both direct and indirect costs rise continuously with each stepwise increase in disability as measured by the Expanded Disability Status Scale (EDSS).[8]

MS is managed by disease-modifying agents and symptomatic and supportive therapies. First-line disease-modifying agents for slowing the progression of MS and reducing the associated disability include interferon (IFN)-β1b (Betaseron), IFN-β1a (Avonex), IFN-β1a (Rebif), glatiramer acetate (Copaxone), natalizumab (Tysabri), and mitoxantrone (Novantrone).[3, 4] Many agents are used to treat the symptoms of MS, such as baclofen or tizanidine for spasticity and gabapentin or amitriptyline for neuropathy. Non-pharmacologic therapies for MS symptoms include physical therapy for spasticity, gait dysfunction, and imbalance as well as exercise for osteoporosis and walking mobility.[3–5] Now FAM has been approved for the improvement of walking.

In clinical trials of disease modifying agents, the most often used primary efficacy endpoint has been relapse rate, while disease progression as measured by change in Expanded Disability Status Scale (EDSS) score has been more often used as a secondary efficacy endpoint. 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.[9–11] An EDSS of 4.0 and 6.0 typically would correspond to limited walking ability and to the need for unilateral support for walking.[12]

In most clinical trials of disease modifying agents, progression has been defined as a sustained 3- or 6-month increase in EDSS of at least one point recorded in a period when the patient had no exacerbation. From the pooled data of three trials, the calculated relative risk of progression at 2 years for MS patients taking beta-interferon versus placebo was 0.70 (0.55–0.88, p=0.002).[9]

The measure of efficacy used in the two pivotal FAM phase 3 trials is a novel one that appears to have been created for the purpose of achieving clinical significance. The primary efficacy measure, called response to treatment, is defined as a consistent improvement in walking speed as measured by the Timed 25-Foot Walk (T25FW). The T25FW is a timed test of walking that measures patients' ability to safely and quickly walk 25 feet in his or her usual manner.[13] Four feet per second is normal walking speed. [14]

The T25FW is a component of the MS Functional Composite (MSFC), which was developed in the mid-1990s by the Clinical Outcomes Assessment Task Force of the National MS Society to overcome the limitations of the EDSS.[10, 14, 15] The MSFC, which was a secondary efficacy measure in a pivotal phase 2 FAM trial, is a composite measure of impairment and disability and, in addition to the T25FW, measures two other clinical dimensions: (1) the 9-Hole Peg Test (9HPT), which tests arm function and (2) the Paced Auditory Serial-Addition Task (PASAT), a cognitive function test.[15]

In FAM phase 3 trials, the 12-item MS walking scale (MSWS-12) was used to validate the clinical significance of the primary efficacy endpoint.[13] The MSWS-12 assesses MS patients' perspectives on their ambulatory disability. Patients rate the degree of limitation they've experienced in walking due to MS in the previous 2 weeks for each of 12 walking-related items. The ratings are summed and turned into a scale of 0 to 100, with higher scores indicating greater limitation on walking abilities.[17]

COMPARATIVE CLINICAL EFFICACY[13, 18, 19]

Relevant Endpoints:

1) Disability

2) Quality of Life

3) Clinical Exacerbation/relapse

4) Withdrawals due to adverse effects

5) Seizure

Study Endpoints:

1) Response to treatment: A timed walk responder is defined as a patient with a faster walking speed, as measured by the T25FW, for at least 3 of 4 visits during the DB treatment period than the maximum speed for any of the first 5 off-drug visits. Clinical significance of the timed-walk response was validated using the MSWS-12

2) Average change from baseline in MSWS-12 score during treatment period.

3) Mean change in walking speed from baseline during the treatment period.

Evidence Table

Ref./Study Design[1]	Drug Regimens[1]	Patient Population[1,2]	N^	Duration[1]	Efficacy Results[3] (CI, p-values)	ARR/NNT[3,4]	Safety Results (CI, p-values)	ARR/NNH[3,4]	Quality Rating/Comments[5]
MS-F203									Fair
Goodman 33 center Phase III 6/05–6/06 MC, DB, PC, RCT	1. FAM 10 mg BID 2. PLA	Inclusion criteria: • Aged 18–70 • clinically defined multiple sclerosis • able to complete two trials of the T25FW in an average time of 8–45 s at screening Exclusion criteria: • onset of multiple sclerosis exacerbation within 60 days of screening • history of seizures or evidence of epileptiform activity on a screening electroencephalogram • any condition that would interfere with the conduct or interpretation of the study • additional restrictions on changes in concomitant medications to avoid related changes in MS symptoms during the trial Patient characteristics: PLA, FAM total, FAM responders, FAM non-responders Age (mean yrs): 50.9, 51.5, 51.4, 51.6 Female (%): 60, 71, 76, 69 White (%): 93, 93, 91, 93 MS course (%) Relapsing-remitting: 29, 27, 19, 31 Primary progressive: 19, 14, 14, 13 Secondary progressive: 49, 55, 62, 51 Progressive relapsing: 3, 4, 5, 4 Treatment w/ interferon or glatiramer (%): 71, 66, 65, 67 MS duration (mean yrs): 12.7, 13.4, 14.1, 13.1 EDSS score (mean): 5.8, 5.8, 5.8, 5.7 T25FW (feet/s): 2.1, 2.1, 2.1, 2.0 LEMMT score: 4, 4.1, 4, 4.1 Ashworth score: 1, 1, 0.9, 0.9 MSWS-12 score: 68.5, 70.7, 70.3, 70.1 SGI score: 4.7, 4.6, 4.6, 4.6	224 72	Treatment period: 14 weeks Phases: 1. Screening 2. SB placebo run-in, beginning 1 week after screening: 2 weeks (visits 0 and 1, separated by 1 week) 3. DB treatment period, beginning 3 weeks after screening: 14 weeks (visits 2 and 3, separated by 2 weeks, and visits 4, 5, and 6, separated by 4 weeks) 4. Non-treatment follow-up, beginning 17 weeks after screening: 4 weeks (visits 7 and 8, separated by 2 weeks)	Timed walk responders (TWR): 1. FAM: 35% [p<0.0001; OR 4.75; CI: 2.08 to 10.86] 2. PLA: 8% Other analyses: Average change from baseline in MSWS-12 score during treatment period, independent of treatment group: Timed walk responders: –6.84 [–9.65 to –4.02, p=0.002] Timed walk non-responders: 0.05 [–1.48 to 1.57] Mean change from baseline in walking speed during treatment period: FAM TWR: 0.51 ft/s [CI: 0.41 to 0.61] FAM TWNR: 0.16 ft/s [CI: 0.11 to 0.21] PLA (TWR + TWNR): 0.1 ft/s [CI: 0.03 to 0.17]	27 / 4	Seizure: 1. FAM: 0.4% (n=1) 2. PLA: 0% Withdrew due to adverse events: 1. FAM: 4.8% 2. PLA: 0%	0.4 / NA 4.8 / 21	Internal validity concerns • The definition of a responder seems arbitrary • Appropriateness of questionnaire used to determine clinical significance of findings unclear • Defined ITT population as all randomized patients who had at least one efficacy assessment of T25FW and MSWS-12 during the DB treatment period • Vague exclusion criteria • Did not report how adherence to treatment was ensured, but stated was 97% • Did not state what concomitant medications, other than immunomodulators, or non-pharmacologic therapies patients were using that may have affected mobility • Patients included in the phase II trial, from which the primary endpoint was derived, were required to be able to complete the T25FW in 8–60 s, but in this trial, the requirement was 8–45 s External validity concerns • In speaking of the drug's mechanism of action, the study stated "only some patients would be expected to have axons susceptible to the drug effects at any given time." Therefore, it is unclear which patients at what time would benefit from this medication and at what point patients who had benefited would stop benefiting • Ambulatory deficits in MS caused by multiple factors; unclear which affected by FAM. • Lack of validation of the primary endpoint and unclear clinical significance of the primary endpoint, e.g., impact on activities of daily living, number of hospitalizations, home care needs, quality of life • Study duration short and lacked follow-up regarding long-term benefit • Patients excluded who have history of seizure and epileptiform activity on EEG • Exclusion criteria so vague that it is unknown whether or not patients who are commonly treated were excluded • Patients predominantly Caucasian • Setting from which patients drawn not described

MS-F204									Fair
Goodman 39 center 5/07–2/08 Phase III MC, DB, PC, RCT	1. FAM 10 mg BID 2. PLA	**Inclusion and exclusion criteria similar to MS-F203** **Patient characteristics: PLA, FAM** Age (mean yrs): 51.7, 51.8 Female (%): 62.2, 73.3 White (%): 88.2, 94.2 MS course (%) Relapsing-remitting: 33.6, 35.8 Primary progressive: 17.6, 8.3 Secondary progressive: 47.1, 51.7 Progressive relapsing: 1.7, 4.2 Immunomodulator treatment (%): 83, 83 MS duration (mean yrs): 13.1, 14.43 EDSS score (mean): 5.6, 5.8 T25FW (feet/s): 2.2, 2.1 LEMMT score (mean): 4.0, 3.9 Ashworth score (mean): 0.8, 0.9 MSWS-12 (mean): 67.7, 73.8 SGI score (mean): 4.4, 4.3	119 118	Treatment period: 9 weeks Phases: 1. Pre-screening:1 week 2. SB placebo run-in, beginning 1 week after screening: 2 weeks (visits 0 and 1, separated by 1 week) 3. DB treatment, beginning 3 weeks after screening: 9 weeks (visits 2, 3, 4, 5, and 6 separated by 2 weeks) 4. Follow-up, beginning 12 weeks after screening: 2 weeks (visits 7 & 8, separated by 2 wks)	Timed walk responders: 1. FAM: 42.9% [p<0.0001] 2. PLA: 9.3% Average change from baseline in MSWS-12 during DB treatment period, independent of treatment group: 1. TWR: –6.84 [CI: –9.57 to –2.52, nominal p<0.001] 2. TWNR: 0.85 [CI: –0.72 to 2.43] Average change in walking speed visits 3–6: 1. FAM TWR: 0.51 ft/s (CI: 0.43 to 0.59) 2. FAM TWNR: 0.12 ft/s (CI: 0.05 to 0.19) 3. PLA (TWR + TWNR): 0.17 ft/s [CI: 0.10 to 0.23]	33.6 / 3	Seizure: 1. FAM: 0% 2. PLA: 0.84% (n=1) Withdrawals due to adverse events: 1. FAM: 3.3% 2. PLA: 3.4%	NA NA	• Internal and external validity issues similar to MS-F203, as the two studies principally differed only as follows: shorter duration of DB treatment period (9 weeks v. 14 weeks); 1:1 randomization to active drug and placebo; and an additional visit at the end of the treatment period to obtain data on efficacy and drug plasma concentration near the dosing interval's end. • The FAM group has a higher baseline MSWS-12 score (p=0.006)
MS-F202									Poor
Goodman 24 center Phase II 2/03–12/03 MC, DB, PC, RCT	1. FAM 10 mg BID 2. FAM 15 mg BID 3. FAM 20 mg BID 4. PLA	**Inclusion criteria:** • Aged 18–70 • clinically defined multiple sclerosis • able to complete two trials of the T25FW in an average time of 8–60 s at screening **Exclusion criteria:** • recent MS relapses or changes in medications **Patient characteristics: PLA, FAM 1 mg, FAM 15 mg, FAM 20 mg:** Mean age: 49, 49.8, 47.7, 52.2 % female: 57, 69, 68, 60 % Caucasian: 94, 96, 88, 91	51 50 57 47	Treatment period: 12 weeks Phases: 1. Screening (visit 0) 2. SB placebo run-in, beginning 1 week after screening: 2 weeks (visits 1 and 2, separated by 1 week) 3. DB dose escalation, beginning 3 weeks after screening: 2 weeks	Mean percent change in walking speed during treatment relative to baseline (placebo run-in) using the T25FW 1. FAM 10 mg: 8% [NS] 2. FAM 15 mg: 11% [NS] 3. FAM 20 mg: 6.5% [NS] 4. PLA: 3% Post-hoc responder analysis (someone whose walking speed for at least three visits during the DB treatment period was faster than the	NA NA NA 27 / 4 28 / 4 30 / 3	Seizure: FAM 10 mg: 0% 2. FAM 15 mg: 0% 3. FAM 20 mg: 0.04% 4. PLA: 0% Withdrawal due to adverse events: 1. FAM 10 mg: 0% 2. FAM 15 mg: 0.02% 3. FAM 20 mg: 0.09% 4. PLA: 0.02%	NA NA 0.04 / NA NA NA 0.07 / NA	Primary endpoint statistical significance not achieved. **Internal validity concerns** • Did not indicate what % of patients were on immunomodulators and what immunomodulators they were on • Did not state what concomitant medications or non-pharmacologic therapies patients were using that may have affected mobility • Allowed changes in dosing of concomitant medications when necessary • Used modified ITT **External validity concerns** • Ambulatory deficits in MS caused by multiple

		MS course (%) Relapsing-remitting: 28, 19, 30, 16 Primary progressive: 26, 23, 24, 26 Secondary progressive: 47, 58, 46, 58 MS duration (mean yrs): 13.9, 10.7, 11.8, 11.8 EDSS score (mean): 5.87, 5.83, 5.64, 5.74 MSFC scores T25FW (feet/s): 1.87, 1.94, 1.99, 2.04 9-HPT (dominant hand, s): 33.9, 35.7, 33.5, 35.3 9-HPT (non-dominant hand, s): 35.7, 30.6, 31.3, 37.2 PASAT-3: 45.7, 49.2, 48.7, 47.5 Composite score: –0.10, 0.04, 0.04, 0.01 LEMMT score: 4.05, 3.98, 4, 3.98 Ashworth score: 1.2, 0.88, 0.89, 0.88 MSWS-12 score: 75.7, 76.3, 74.6, 76.8 CGI score: 3.74, 3.82, 3.8, 3.91 SGI score: 4.38, 4.32, 4.56, 4.25		(visits 3 and 4, separated by 1 week) 4. DB stable dose, beginning 5 weeks after screening: 12 weeks (phone visits 5 and 6, separated by 1 week; clinic visits 7, 8, and 9, separated by 4 weeks) 5. Dose reduction, beginning 17 weeks after screening: 1 week (visit 10) 6. Non-treatment washout and follow-up, beginning 18 weeks after screening: 2 weeks (visit 11)	maximum speed measured in the five non-treatment visits): 1. FAM 10 mg: 35.3% 2. FAM 15 mg: 36.0% 3. FAM 20 mg: 38.6% 4. PLA: 8.5%				factors; unclear which affected by FAM • Clinical significance of the primary endpoint unclear, e.g., impact on activities of daily living, number of hospitalizations, home care needs, quality of life • Setting from which patients drawn not described • No progressive relapsing patients in the study • Patients predominantly Caucasian • Setting from which patients drawn not described

[1]Study design abbreviations: DB = double-blind, RCT = randomized trial, PC = placebo-controlled, FAM = fampradine, PLA = placebo
[2]MS disability tests: T25FW: timed 25-foot walk (maximum time allowed to complete is 180 s, or 0.14 ft/s), EDSS: expanded disability status scale, MSFC: MS functional composite, 9-HPT: 9-hole peg test, PASAT: paced auditory serial addition test, LEMMT: lower extremity manual muscle test, MSWS-12: 12-item MS walking scale, SGI: subject global impression (assesses physical wellbeing, 1=terrible to 7=delighted), CGI: clinical global impression (1=not ill to 7=extremely ill)
[3]Results abbreviations: ARR = absolute risk reduction, TWR: timed walk responders, TWNR, timed walk non-responders, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval.
[4]NNT/NNH are reported only for statistically significant results
[5]Quality Rating: (Good- likely valid, Fair- likely valid/possibly valid, Poor- fatal flaw-not valid)
^Modified ITT: all randomized subjects who received at least one efficacy evaluation (T25FW for MS-F202 and 203 and T25FW and MSWS-12 for MS-F204) during the DB period.

Summary of Findings

Sustained-release FAM was approved by the FDA for improvement of walking in patient with MS based on two pivotal phase 3 clinical trials: MS-F203 and MS-F204.[13, 19] Both have been published. The phase 2 trial, MS-F202, also provides evidence concerning the efficacy of FAM and the origins of the primary endpoint used in the phase 3 trials.[18] (See Clinical Efficacy Evidence Table)

Study MS-F202 was a dose comparison trial of sustained-release FAM that randomized 206 patients 1:1:1:1 to receive FAM 10 mg bid, FAM 15 mg bid, FAM 20 mg bid, or placebo. Enrolled in the study were patients 18–70 years old with clinically defined MS who were able to complete two trials of the T25FW in an average time of 8–60 seconds (s) at screening. The study population had an average EDSS >5.64. The primary efficacy endpoint was mean percent change in walking speed during treatment using the T25FW.[18]

Statistical significance for the primary endpoint was not achieved for MS-F202. Therefore, researchers performed a post-hoc analysis that found a greater percentage of FAM-treated patients had a "consistent" improvement in walking speed. This newly created, as-yet-to-be-validated endpoint was called "response to treatment," and responders were defined as those whose walking speed for at least three visits during the double-blind treatment period of the trial was faster than the maximum speed in five non-treatment visits, four before and one after treatment.[18]

The response rate for patients treated with FAM 10, 15, and 20 mg was 35.3%, 36.0%, and 38.6% and for placebo 8.5% (p value not given), giving an NNT of 3.55 (95% CI 2.16–4.94).[18] Therefore, response to treatment was used as the primary endpoint for the phase 3 trials.

Published phase 3 study MS-F203 randomized 301 patients 3:1 to receive FAM 10 mg bid or placebo, respectively, during a 14-week, double-blind treatment period. Enrolled in the study were patients 18–70 years old with clinically defined MS who were able to complete two trials of the T25FW in an average time of 8–45 s at screening. The study population had an average EDSS of 5.8.[13]

Patients who were unable to complete the T25FW within 45 s were excluded from the trial, implying that FAM lacks benefit in more severely disabled patients. This was corroborated by the FDA report in which reviewers said "the sponsor in 2005 alluded to the lack of reliability of the data in more disabled subjects when walking speed exceeded 45 second."[14]

Study MS-F203 found that, for a group of MS patients able to complete the T25FW within 45 s, the percentage of time walked responders (TWR) in the FAM group was 35% compared with 8% in the placebo group ($p<0.001$, OR 4.75; 95% CI 2.08–10.86), giving an NNT of 4.[13]

The phase 3 study MS-F204 was similar to that of MS-F203, except the double-blind treatment period was 9 weeks long. The investigators did not reveal why the lengths of the treatment phases of the two studies were different. The study found that the percentage of responders in the FAM group was 43% compared with 9% in the placebo ($p<0.001$), giving an NNT of 3.[19]

Though the phase 3 studies showed statistical significance for their primary endpoint, questions about the clinical significance of the endpoint remained, given that the endpoint has not yet been shown to be a valid one for assessing FAM or any other MS drug. The studies addressed this by asking patients to complete the MSWS-12 and calculating the average change from baseline in the score. Researchers found a statistically significant decrease in MSWS-12 score for responders compared to non-responders, independent of treatment group: –6.84 (–9.65 to –4.02) versus 0.05 (–1.48 to 1.57), respectively, ($p=0.002$) for study MS-F203 and –6.04 (–9.75 to –2.52) versus 0.85 (–0.72 to 2.43).[13, 19]

The positive findings for the change in MSWS-12 are questionable. The MSWS-12 may be an inappropriate instrument to use to validate the results of the T25FW. Also, the analysis using the MSWS-12 should have been performed on the intent-to-treat population rather than responders versus non-responders. Therefore, the achieved change in MSWS-12 may not truly represent clinical significance.[14]

Investigators also performed an assessment of average change from baseline in walking speed for the responders versus placebo group. The changes in walking speed for FAM responders compared with total placebo group in study MS-F203 were 0.51 feet/s (0.41 to 0.61) and 0.1 feet/s (0.03 to 0.17), respectively.[13] FDA analysis of MS-F203 showed that this translated to a 1.75 s difference in walking speed between total non-responders and responders, a 1.99 s difference between placebo-treated responders and non-responders, and a 1.6 s difference between FAM-treated responders and non-responders.[14] The changes in walking speed for FAM responders versus total placebo group in

study MS-F204 were 0.51 ft/s (0.43 to 0.59) versus 0.17 ft/s (0.10 to 0.23) for placebo group.[19] FDA analysis of MS-F204 showed that this translated to a 1.71 s difference in walking speed over 25 feet between total non-responders and responders, a 1.54 s difference between placebo-treated responders and non-responders, and a 2.15 s difference between FAM-treated responders and non-responders.[14]

Before FAM should be considered an option for improving the lives of MS patients, longer-term studies should be performed with more clinically relevant outcomes that include the impact FAM would have on the quality of life of MS patients or their activities of daily living, health, or homecare requirements. The phase 2 study included the Multiple Sclerosis Quality of Life Inventory (MSQLI) as a secondary efficacy measure but the scores were not reported.[18] Extension studies (MS-F202 EXT, MS-F203 EXT, MS-F204 EXT), which have been completed but not yet published, may shed light on the long-term efficacy of FAM, but primarily in terms of walking speed.

Finally, assuming FAM allows patients to achieve clinically meaningful changes in mobility, it is unclear how one would use FAM in practice given that only a subset of patients are responders and no method is available to identify which patients would potentially respond.

DRUG SAFETY

Serious (REMS, Black Box Warnings, Contraindications):[1]

FAM should not be used in those with a history of seizure or with moderate or severe renal impairment.

Precautions: Those with mild renal impairment may have seizure risk approaching those taking FAM 15 mg bid in clinical trials. FAM should not be taken with any other product containing 4-aminopyridine, such as compounded products. FAM may increase the incidence of urinary tract infections (UTIs).

Tolerability (Drop-out rates, management strategies)

Both the product information sheet and the FDA make it unclear how many MS patients have been exposed to FAM, as the reported figures do not add up. The reported figures are as follows: FAM has been evaluated in 917 MS patients.[1] A total of 601 MS patients have been exposed to FAM for at least 6 months and 405 for at least 1 year, with the majority receiving doses of at least 10 mg bid. A total of 807 MS patients have been exposed to FAM SR (67 in clinical pharmacology trials, 532 in placebo controlled trails, 208 in uncontrolled trials) and 187 patients have been exposed to other forms of FAM, 89 each in clinical pharmacology and in placebo controlled trials.[14]

Despite this lack of clarity, FAM has been used on relatively few patients and that time on the market will tell the prevalence of side effects related to treatment.

In open-label extension studies, a dose-dependent increase in the incidence of seizures was seen in patients with MS at rates of 0.41 per 100 person-years (95% CI 0.13–0.96) for FAM 10 mg twice daily and 1.7 per 100 person-years (95% CI 0.21–6.28) for FAM 15 mg twice daily. Patients with a history of seizures or with evidence of epileptiform activity on EEG were excluded from clinical trials. Therefore, FAM product information states the seizure risk in patients with epileptiform activity is unknown and could be "substantially higher than that observed in FAM clinical studies."[1]

Initially, FAM was studied in MS patients using an immediate release formulation, and seizures occurred in 6/178 patients receiving doses greater than 20 mg/day. This side effect is correlated with plasma concentration. The sustained release formulation was developed as a method to control the fluctuations and high peaks in serum levels seen with the immediate release formulation, and thus serious adverse effects.[14, 20]

Ampyra™ REMS includes a medication guide and annual letters to prescribers and pharmacists describing the proper distribution and safe use of Ampyra™, including warnings about the potential risk of seizure and about the use of compounded formulations.

Adverse events resulted in discontinuation in 4% (15/400) of patients treated with FAM 10 mg twice daily and 2% (5/238) of those treated with placebo.[1]

Pregnancy/Lactation rating:[1] Pregnancy category C. The effects of FAM on labor and delivery are unknown. The safety of FAM in pregnant and nursing women and in patients less than 18 years old has not been tested. FAM should only be used if the benefit justifies the potential risk to the fetus. In animals, FAM given during pregnancy and lactation leads to decreased offspring viability and growth at doses similar to the MRHD.

Unanswered safety questions:
The risk of FAM to patients who are at increased risk for seizures from brain damage, alcohol use, or concurrent use of other medications that decrease the seizure threshold is unknown. Long-term studies are needed to better define the risk of seizures in MS patients. FAM has not been tested in geriatric patients in sufficient number to make a determination about its safety.

Dose Index (efficacy/toxic):[1]
Animal studies have shown no evidence of carcinogenicity at plasma exposures corresponding to 18 times the plasma exposure of humans using the maximum recommended human dose (MRHD), 20 mg daily. However, studies in rats have shown a statistically significant increase in uterine polyps at doses 9 times the MRHD. No evidence of mutagenicity has been demonstrated from *in vivo* and *in vitro* toxicology assays. No adverse effects on fertility have been observed in male and female rats at doses of 1, 3, and 9 mg/kg/day (relationship to the MRHD not given).

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 (Lexicomp, USP Online LASA Finder, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

NME Drug Name	Lexicomp	USP Online	First DataBank	ISMP	Clinical Judgment
LA/SA for dalfamprindine	Delavirdine Desipramine	None		None	None
LA/SA for Ampyra	Anakinra	None		None	None

ADVERSE REACTIONS[1]

In clinical trials, the most commonly observed adverse reactions—incidence ≥2% and at a rate greater than or equal to placebo—reported in the prescribing information for FAM are presented in the following table.

Adverse Reaction	Placebo (N=238)	FAM 10 mg bid (N=400)	NNH
Urinary tract infection	8%	12%	25
Insomnia	4%	9%	20
Dizziness	4%	7%	33
Headache	4%	7%	33
Nausea	3%	7%	25
Asthenia	4%	7%	33
Back pain	2%	5%	33
Balance disorder	1%	5%	25
Multiple sclerosis relapse	3%	4%	100
Paresthesia	3%	4%	200
Nasopharyngitis	2%	4%	50
Constipation	2%	3%	100
Dyspepsia	1%	2%	100
Pharyngolaryngeal pain	1%	2%	100

DOSE & AVAILABILITY[1]

STRENGTH	FORM	ROUTE	FREQUENCY	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
10 mg	Extended release tablets	Oral	Twice daily (12 hours apart)	Creatinine clearance should be determined before using FAM. FAM should not be used in those with moderate renal or severe renal impairment*				• May be taken with or without food. • The recommended dose is not to be exceeded. • The FDA has required studies to evaluate the efficacy of lower doses.[13]

*Renally impaired patients would need a dose lower than 10 mg twice daily to avoid the risk of adverse effects such as seizure, and a lower dosage form is unavailable. Seizure risk in patients with mild renal impairment is unknown; however, their FAM plasma levels may approach 15 mg twice daily, a dose that might increase seizure risk.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	96%
Cmax	17.3 ng/mL to 21.6 ng/mL
Protein Binding	1–3%
Elimination	Primarily renal
Half-Life	5.2–6.5 hours
Metabolism	Minor CYP3E1

After 24 hours, 95.9% of a FAM dose is eliminated in the urine 90.3% unchanged, while 0.5% is eliminated in the feces. Two inactive, minor metabolites are produced.

ALLERGIES/INTERACTIONS[1]

Drug-Drug: None

Food-Drug: None

Allergy/Cross Reactive Substances: None

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Tapentadol Drug Use Evaluation

Recommendations

- Add tapentadol to the list of medications subject to the High Dose Opioid PA Criteria
- Apply quantity limits consistent with PA Criteria, package insert dosages, and tablet optimization
- Do not grandfather patients currently receiving tapentadol

Introduction

As addressed in previous Drug Use Evaluations (DUE), opioid analgesic misuse and abuse have generated significant concerns in the medical community, legislative bodies, and the media.[1,2] These DUEs did not address the use of tapentadol, a novel synthetic mu opioid receptor agonist with norepinephrine re-uptake inhibition (NRI). The efficacy of tapentadol has been demonstrated to be non-inferior to currently available opioids for the approved indications. The side effect profile is comparable to other mu opioid receptors, with slightly lower incidence of GI effects, but higher incidence of sympathetic stimulation. Unlike most opioids, tapentadol has a maximum daily dose due to NRI effects.[3,4]

Analysis

Based on clinical trials of tapentadol, equivalents doses of morphine are 0.24-0.36mg tapentadol to 1mg morphine.[3] When compare to oxycodone the range is 0.24-0.72mg tapentadol to 1mg of morphine equivalents.[5–7] These data suggest a reasonable conversion factor of 0.4 mg tapentadol to 1mg morphine, which is consistent with publically available conversion tools.[8] Table 1 lists quantity limits with morphine equivalents for each strength and formulation. Quantity limits also allow for gradual titration according to recommendations in the package inserts.[3,4]

Recent FFS pharmacy claims indicate 2 members with more than 6 prescriptions and only two members currently receiving Tapentadol. Based on this limited use, no grandfather of existing therapy is recommended.

Generic	Brand	Form	Strength (mg)	Daily Quantity Limit	High Dose PA Limit	Morphine Equivalents Daily for High Dose PA Limit	Comment
TAPENTADOL HCL	NUCYNTA	TABLET	50	6	6	120	tablet optimization Dosing Q4-6hr
TAPENTADOL HCL	NUCYNTA	TABLET	75	6	4	120	tablet optimization Dosing Q4-6hr
TAPENTADOL HCL	NUCYNTA	TABLET	100	6	3	120	Maximum Dose 600mg daily[3]
TAPENTADOL HCL	NUCYNTA ER	TAB ER 12H	50	2	6	120	BID dosing
TAPENTADOL HCL	NUCYNTA ER	TAB ER 12H	100	2	3	120	BID dosing
TAPENTADOL HCL	NUCYNTA ER	TAB ER 12H	150	2	2	120	BID dosing
TAPENTADOL HCL	NUCYNTA ER	TAB ER 12H	200	2	1	80	BID dosing
TAPENTADOL HCL	NUCYNTA ER	TAB ER 12H	250	2	1	100	Maximum Dose 500mg daily[4]

Table 1 – Recommended Quantity Limits for Tapentadol

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Drug Use Evaluation: Colony Stimulating Factor use in patients with Hepatitis C

BACKGROUND

Colony stimulating factors (CSFs) have been suggested for the off-label treatment of neutropenia caused by peg-interferon alfa treatment for hepatitis C.[1] The use of CSFs for the treatment of neutropenia is thought to increase the sustained virologic response (SVR) by maintaining therapeutic levels of peg-interferon alfa.

Although CSFs for the treatment of neutropenia seems promising, it is unlikely that the benefits of use for outweigh the risks. Patient who are treated with CSFs are at an increased risk of developing myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).[2]

There is low level of evidence supporting CSFs superiority over temporarily reducing the peg-interferon alfa dose.[3] According the American Association for the Study of Liver Guidelines and Veterans Affairs (VA) guidelines CSFs should only be considered when the patient experiences persistent neutropenia despite dose reduction of peg-interferon alpha. Factors that put patients with hepatitis C at a higher risk for neutropenia and possibly a higher response rate to CSFs include HIV infection, liver cirrhosis, or a liver transplant.[4,5]

Goal: To evaluate CSFs use in hepatitis C patient. If inappropriate use was found, further prior authorization criteria would be brought to the committee for review. Specifically, these questions were addressed:

1) What is proportion of hepatitis C patients who are also on CSF?
2) What proportion of hepatitis C patients on CSFs also have the following risk factors for developing infection: Cirrhosis, Liver transplant, HIV co-infection?
3) What is proportion of hepatitis C patients on CSFs, that failed a previous dose reduction of peg-interferon?

METHODS

Paid fee-for-service (FFS) medical and drug claims from July 1, 2011 to June 30, 2012 were used to identify patients with hepatitis C and treated with CSFs. Hepatitis C patients were identified with medical claims with ICD9 equal to 070.41, 070.44, 070.51, 070.54, 070.70, 070.71, V12.09 or V02.62 in any position or a drug claim for either peg-interferon alfa-2B or peg-interferon alfa-2A (see Appendix 1). Only those patients also treated with CSFs as identified in Appendix 1 were included.

Medical and pharmacy claim profiles were generated for all patients and reviewed by a fourth year Doctor of Pharmacy student.

RESULTS

There were 5,545 patients with a diagnosis of hepatitis .Of this population, 11 patients (<0.2%) were also on CSF therapy. Ten of these 11 patients had a concomitant diagnosis of a malignant neoplasm. These 10 patients were likely using a CSF to treat chemotherapy induced neutropenia. The last patient was a complex case with a history of diabetes mellitus, chronic back pain and appeared to have significant infectious complications from a back surgery. There was a single billing for CSF during this time.

CONCLUSION/RECOMMENDATIONS

While this analysis was fraught with the limitations of missing information that all administrative claims analyses are, there was no apparent inappropriate CSF use in the population with a hepatitis C . Since there is no apparent inappropriate use of CSFs in the population of patients with hepatitis C, there is no need for prior authorization at this time.

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6. Appendix 1:

Peg-interferon drug claim selection codes

GSN	GEN NAME	BRAND
45877	PEGINTERFERON ALFA-2B	PEGINTRON
45878	PEGINTERFERON ALFA-2B	PEGINTRON
48814	PEGINTERFERON ALFA-2B	PEGINTRON
48815	PEGINTERFERON ALFA-2B	PEGINTRON
58877	PEGINTERFERON ALFA-2B	PEGINTRON REDIPEN
58878	PEGINTERFERON ALFA-2B	PEGINTRON REDIPEN
58879	PEGINTERFERON ALFA-2B	PEGINTRON REDIPEN
58880	PEGINTERFERON ALFA-2B	PEGINTRON REDIPEN
51151	PEGINTERFERON ALFA-2A	PEGASYS
53612	PEGINTERFERON ALFA-2A	PEGASYS

CSF drug selection codes

a. Drug claim with GSN =

GSN	GEN NAME	BRAND
15917	FILGRASTIM	NEUPOGEN
15927	SARGRAMOSTIM	LEUKINE
29260	SARGRAMOSTIM	LEUKINE
45996	FILGRASTIM	NEUPOGEN
45997	FILGRASTIM	NEUPOGEN
46004	FILGRASTIM	NEUPOGEN
49872	PEGFILGRASTIM	NEULASTA

b. Medical claim with J-code =

J1440	Filgrastim 300 mcg injection
J1441	Filgrastim 480 mcg injection
J2820	Sargramostim injection
J2505	Injection, pegfilgrastim 6mg

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Drug Use Evaluation: Intramuscular Antipsychotics

The Pharmacy and Therapeutics Committee (P & T) reviewed costs of the second generation antipsychotics in September 2012. Staff recommended to limit billing of intramuscular (IM) antipsychotics to professional claims. P & T members were concerned group homes and long-term care (LTC) facilities used pharmacy billing for these services and that closing pharmacy billing would limit access and potentially harm patients. A drug use evaluation was requested before acting on the recommendation. The primary goal of the evaluation was to establish the impact on LTC patients of a requirement to bill IM antipsychotics via professional claims.

Methods:

Paid claims for IM antipsychotics from January 1, 2012 through June 30, 2012 were included in the analysis. Both drug and professional claims were included. Drugs were identified using the codes in Appendix 1. Claims for Medicare Part D patients as identified with benefit packages 'BMM' and 'BMD, were excluded.

Patients were identified as living in a long-term care or group home using two methods. The first was if the claim was billed by a pharmacy enrolled as a Nursing Home Pharmacy specialty. The alternative method identified patients with case descriptors equal to one of the following: 'APD','CBF','DAN','DDB','DDC','DDG','DDS','EXT','IHC','MAN','MAR','MPS','NFC','RTF'.

Patients were also evaluated for concurrent use of oral drugs. Concurrent use was defined as an overlap of 'Days Supply' spans of 60 days. It was assumed the 'Days Supply' for all medical claims was 30 days. Oral drugs were as defined as 'Drug Route' code equal to "PO" and 'Form' code not equal to "UL", which indicates orally dissolving or buccal forms.

Additionally, the net daily reimbursement rates were compared for both programs. Drug claims were reimbursed at Average Acquisition Cost, less Rebate Per Unit, multiplied by the recommended units per day. Professional claims were reimbursed by Average Sales Price, less Rebate Per Unit (using appropriate unit conversion factor), multiplied by the recommended units per day.

Results

Table 1 displays the gross costs and utilization of the drugs. Notably, 85% were billed on drug claims and only 15% on professional claims. Additionally, the majority of claims are reimbursed at a lower rate using drug claim methodology (Appendix 2 – Executive Session).

Table 1 – Gross Cost and Utilization of IM Antipsychotics

Drug Category	Total Paid Claim Amount	% Total	Gross Claim Count	% Total	Avg. Reimbursed / Claim (excludes rebate)
Drug Claims					
RISPERIDONE MICROSPHERES	$1,292,919	49.80%	1,983	41.71%	$652
PALIPERIDONE PALMITATE	$1,167,589	44.97%	1,026	21.58%	$1,138
HALOPERIDOL DECANOATE	$66,692	2.57%	746	15.69%	$89
OLANZAPINE PAMOATE	$31,563	1.22%	33	0.69%	$956
FLUPHENAZINE DECANOATE	$19,553	0.75%	224	4.71%	$87
OLANZAPINE	$3,050	0.12%	17	0.36%	$179
HALOPERIDOL LACTATE	$1,004	0.04%	17	0.36%	$59
ZIPRASIDONE MESYLATE	$188	0.01%	2	0.04%	$94
	$2,582,557	99.47%	4,048	85.15%	$3,256
Professional Claims					
Paliperidone palmitate inj	$6,085	0.23%	15	0.32%	$406
Haloperidol injection	$3,416	0.13%	421	8.86%	$8
Ziprasidone mesylate	$1,965	0.08%	54	1.14%	$36
Chlorpromazine hcl injection	$923	0.04%	71	1.49%	$13
Risperidone, long acting	$566	0.02%	42	0.88%	$13
Olanzapine long-acting inj	$529	0.02%	20	0.42%	$26
Fluphenazine decanoate 25 MG	$87	0.00%	80	1.68%	$1
Haloperidol decanoate inj	$68	0.00%	3	0.06%	$23
	$13,638	0.53%	706	14.85%	$527
Total:	**$2,596,196**	**100.00%**	**4,754**	**100.00%**	**$3,782**

Table 2 displays the demographics of patients using IM antipsychotics. Only 792 patients were identified, average age 42 years old, 53% female and predominantly white. Using case descriptors to identify LTC residence, 15% of patients resided in LTC facilities. Pharmacies enrolling with the Division of Medical Assistance Programs (DMAP) with the specialty of "Nursing Home Pharmacy" dispensed 25% of claims (not displayed).

Table 2: Demographics of all IM Antipsychotic Users

		All Users	
Total		792	(%)
Age			
	Mean	41.6	
	Range	6-98	
	<6	0	0.00%
	6-12	3	0.38%
	13-18	28	3.54%
	19-65	730	92.17%
	>65	31	3.91%
Female		419	52.90%
Race			
	White	621	78.41%
	American Indian	24	3.03%
	Black	58	7.32%
	Asian	25	3.16%
	Other	64	8.08%
LTC Residence		121	15.28%

Table 3 identified 202 (26%) of the 792 patients were concurrently on other oral drugs for 60 days while treated with IM antipsychotics.

Table 3 – Patient with Concurrent Use of Oral Drugs for 60 days

Drug	Patient Count	%
N=	792	
RISPERIDONE MICROSPHERES	89	11.24%
PALIPERIDONE PALMITATE	65	8.21%
HALOPERIDOL DECANOATE	42	5.30%
FLUPHENAZINE DECANOATE	6	0.76%
	202	25.51%

Discussion

The majority (85%) of IM antipsychotic claims are billed using drug claims. Fifteen percent of patients resided in LTC facilities and 25% of claims were billed by pharmacies serving LTC facilities. There was no financial or clinical advantage to moving claims to the professional billing.

However, 26% of patients were concurrently taking oral drugs while treated with IM antipsychotics. The difference in monthly drug cost between IM and oral antipsychotics is more than $600 on average. There are multiple reasons why a patient may still be a candidate for IM therapy while taking other oral drugs, most notably poor compliance. However, if 10% of patients on IM risperidone and paliperidone while concurrently on oral therapy for 60day were switched to oral antipsychotics (i.e.2.5% of the total), the potential savings would have been $450,000 during the study period (net rebate).

Recommendations:

1) Continue to allow billing of IM antipsychotics via the drug claims
2) Insure professional claims and drug claims are reimbursed at the same but lowest rate.
3) Consider engaging pharmacists via RetroDUR to evaluate patients for conversion to oral antipsychotics.

Appendix 1 – Drugs of Interest

GSN	Description
61911	ABILIFY 9.7 MG/1.3 ML VIAL
3788	CHLORPROMAZINE HCL
3790	CHLORPROMAZINE HCL
3820	FLUPHENAZINE 2.5 MG/ML VIAL
3818	FLUPHENAZINE DEC 25 MG/ML VL
3968	HALOPERIDOL 5 MG/ML AMPUL
13076	HALOPERIDOL DEC 100 MG/ML AMP
11876	HALOPERIDOL DEC 100 MG/ML VIAL
3967	HALOPERIDOL DEC 50 MG/ML VIAL
3966	HALOPERIDOL DECAN 50 MG/ML AMP
3970	HALOPERIDOL LAC 5 MG/ML VIAL
50386	OLANZAPINE 10 MG VIAL
50386	ZYPREXA 10 MG VIAL
65794	OLANZAPINE PAMOATE 300 MG VIAL
65793	OLANZAPINE PAMOATE 405 MG VIAL
65795	OLANZAPINE PAMOATE 210 MG VIAL
65450	PALIPERIDONE 117 MG PREF SY
65451	PALIPERIDONE 156 MG PREF SY
65452	PALIPERIDONE 234 MG PREF SY
65448	PALIPERIDONE 39 MG PREF SYR
65449	PALIPERIDONE 78 MG PREF SYR
52934	RISPERIDONE MICROSPHERES 25 MG SYR
52936	RISPERIDONE MICROSPHERES 50 MG SYR
62640	RISPERIDONE MICROSPHERES 12.5 MG SYR
52935	RISPERIDONE MICROSPHERES 37.5 MG SYR
3849	TRIFLUOPERAZINE 2MG/ML VIAL
50102	GEODON 20MG

Jcode	Description
J0400	Aripiprazole injection
J3230	Chlorpromazine hcl injection
J2680	Fluphenazine decanoate 25 MG
J1631	Haloperidol decanoate inj
J1630	Haloperidol injection
J2358	Olanzapine long-acting inj
J2426	Paliperidone palmitate inj
J2794	Risperidone, long acting
J3486	Ziprasidone mesylate

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Abbreviated Class Update: Anticoagulants

Month/Year of Review: March 2013
Last Review: April 2010 (injectable anticoagulants)
January 2012 (warfarin, dabigatran, rivaroxaban)

End date of literature search: January 2013
Source: Provider Synergies
OSU DURM

Current PDL Status:

Preferred

Anticoagulant Class	Drug
Vitamin K Antagonists (VKA)	warfarin
Low Molecular Weight Heparins (LMWH)	dalteparin
Low Molecular Weight Heparins (LMWH)	Lovenox® (brand only)
Unfractionated Heparin (UFH)	heparin

Non-preferred

Anticoagulant Class	Drug
Low Molecular Weight Heparins (LMWH)	enoxaparin
Direct Factor Xa Inhibitors (FXI)	apixaban (pending review)
Direct Factor Xa Inhibitors (FXI)	fondaparinux
Direct Factor Xa Inhibitors (FXI)	rivaroxaban
Direct Thrombin Inhibitor (DTI)	dabigatran
Direct Thrombin Inhibitor (DTI)	desirudin

Research Questions:

- Is there evidence of efficacy* differences between the different anticoagulant products?
- Is there evidence of safety* advantages between the available anticoagulants products?
- Are there indications or subpopulations where one agent may be more effective or safer than other available agents?

* There were no head to head efficacy and safety comparisons for the newer oral anticoagulants. Systematic reviews strength of evidence recommendations were based on indirect comparisons as they relate to these newer oral agents. Limitations to using indirect comparisons include differences in patient populations, study design and implementation.

Conclusions:

Table 1. Orthopedic Prophylaxis Summary of Evidence

Outcome/Indication	Treatment	Strength of Evidence	Source
PE	LMWH favored over UFH	Moderate and High	AHRQ[1]
	No significant difference between enoxaparin, apixaban, dabigatran and rivaroxaban (indirect comparison of symptomatic events)	Moderate to High	DERP[5]
DVT	LMWH favored over UFH	Moderate and High	AHRQ[1]
	Fondaparinux favored over LMWH	Low and Moderate	AHRQ[1]
	DTI favored over UFH	Moderate	AHRQ[1]
	LMWH favored over VKA	Low	AHRQ[1]
	Apixaban* and rivaroxaban favored over enoxaparin (symptomatic events)	Moderate to High	DERP[5]
	Enoxaparin favored over dabigatran* (symptomatic events)	Moderate to High	DERP[5]
VTE	LMWH equal to DTIs	Low	AHRQ[1],CADTH[4]
	Apixaban*, dabigatran* and rivaroxaban similar efficacy (indirect comparison of symptomatic events)	Moderate	DERP[5]
	Rivaroxaban favored over enoxaparin (symptomatic events)	Moderate to High	DERP[5]
	LMWH favored over fondaparinux, apixaban*, dabigatran*, rivaroxaban or UFH	Moderate	ACCP[2]
	No preference		AHA[10]
HIT	LMWH favored over UFH	Moderate and High	AHRQ[1]
Mortality	LMWH favored over DTI	Moderate	Cochrane[3]
	No significant difference between enoxaparin, apixaban*, dabigatran* and rivaroxaban	Moderate to High	DERP[5]
Major Bleeding	LMWH favored over UFH	Moderate and High	AHRQ[1]
	LMWH favored over fondaparinux	Moderate	AHRQ[1]
	VKAs favored over LMWH	High	DERP[5], AHRQ[1]
	Apixaban*, dabigatran* and rivaroxaban similar	Moderate	DERP[5]
Total Bleeds	LMWH favored over DTI	Low	Cochrane[3]
Clinically Major Bleeding (major bleeds or clinically relevant minor bleeding)	Apixaban* favored over rivaroxaban (indirect comparison)	Moderate	DERP[5]
	Apixaban* favored over dabigatran* (indirect comparison)	Moderate	DERP[5]
	Rivaroxaban similar to dabigatran* (indirect comparison)	Moderate	DERP[5]
Clinically Relevant Bleeding	Enoxaparin similar to dabigatran* (indirect comparison)	Moderate to High	DERP[5]
	Apixaban* favored over dabigatran*, rivaroxaban and enoxaparin (indirect comparison)	Moderate to High	DERP[5]

	Dabigatran*, apixaban* and enoxaparin favored over rivaroxaban (indirect comparison)	Moderate to High	DERP[5]
Composite of asymptomatic and symptomatic DVT, non-fatal PE and all-cause death	Apixaban* inferior to enoxaparin (30 mg twice daily) for TKR Apixaban* superior to enoxaparin (40 mg once daily) for TKR (ARR: 9.33%/NNT 11) Apixaban* superior to enoxaparin (40 mg once daily) for THR (ARR: 2.5%/ NNT 40)	Moderate Moderate Moderate	Primary[7] Primary[8] Primary[9]
Composite of VTE and all-cause mortality	Dabigatran* 220 mg daily is noninferior to enoxaparin (40 mg daily) for THR	Moderate	Primary[6]
* Not FDA approved for orthopedic prophylaxis ARR - absolute risk reduction, NNT – number needed to treat			

Table 2. Acute DVT Treatment

Outcome	Treatments	Strength of Evidence	Source
Recurrent DVT of the leg	LMWHs favored over subcutaneous UFH Fondaparinux favored over subcutaneous UFH	Moderate Low	ACCP[2] ACCP[2]
Recurrent VTE	Rivaroxaban is noninferior to enoxaparin/VKA	Moderate	Primary[11]

Table 3. Treatment of PE Summary of Evidence

Outcome	Treatments	Strength of Evidence	Source
PE	LMWH favored over IV UFH and SQ UFH Fondaparinux is favored over IV UFH and SQ UFH VKAs strongly recommended LMWH or fondaparinux favored over SQ UFH No preference to agents	Low and Moderate Low and Moderate Moderate Moderate and Low	AHRQ[1] AHRQ[1] ACCP[2] ACCP[2] AHA[10]
Cancer and PE	LMWH favored over VKA VKA favored over dabigatran and rivaroxaban	Moderate Low	ACCP[2] ACCP[2]
Symptomatic Recurrent VTE	Rivaroxaban is noninferior to Enoxaparin/VKA	Moderate	Primary[12]

Table 4. Long-term Anticoagulation Summary of Evidence

Outcome	Treatments	Strength of Evidence	Source
DVT	VKA favored over LMWH LMWH favored over dabigatran and rivaroxaban	Low Low	ACCP[2] ACCP[2]
Recurrent VTE	LMWH favored over VKA	High	Cochrane[13]
Cancer and PE	LMWH favored over VKA	Moderate	ACCP[2]

Table 5. Atrial Fibrillation Summary of Evidence

Outcome/Indication	Treatments	Strength of Evidence	Source
Atrial Fibrillation	Dabigatran favored over VKAs	Moderate	ACCP[2]
Stroke	Dabigatran favored over warfarin	Moderate to High	DERP[5], CADTH[15]
	Apixaban favored over warfarin	Moderate	DERP[5], CADTH[15]
Systemic Embolism	Apixaban favored over warfarin	Moderate	DERP[5]
Mortality	Apixaban, dabigatran (110 mg and 150 mg) and rivaroxaban similar (indirect comparison)	Moderate	DERP[5]
Major Bleeds	Apixaban favored over dabigatran 150 mg and rivaroxaban (indirect comparison)	Moderate	DERP[5], CADTH[15]
	Apixaban favored over warfarin	Moderate to High	DERP[5], CADTH[15]
Gastrointestinal Bleeds	Apixaban favored over dabigatran 150 mg and rivaroxaban (indirect comparison)	Moderate	DERP[5]
	Warfarin favored over dabigatran and rivaroxaban	Moderate to High	DERP[5]
Intercranial Bleeds	Apixaban, dabigatran and rivaroxaban favored over warfarin	Moderate to High	DERP[5], CADTH[15]
Composite of Stroke or Systemic Embolism	Apixaban superior to warfarin (ARR 0.33/NNT 303)	Moderate	Primary[14]
Myocardial Infarction	Warfarin superior to dabigatran 150 mg Apixaban favored over dabigatran (both doses)		CADTH[15]
ARR - absolute risk reduction, NNT – number needed to treat			

Recommendations:

- LMWH clinical efficacy and safety is similar between agents so preference should be based on cost.
- Fondaparinux should remain an option for patients with a history of heparin induced thrombocytopenia (HIT) or allergy to other agents.
- Rivaroxaban and enoxaparin are considered first line for orthopedic prophylaxis (moderate to high evidence). Preference should be based on cost.
- For the treatment of AF, dabigatran (ARR 0.6%/NNT 167, 3-9 fewer events per 1000 treated[15]) and apixaban (ARR 0.33%/NNT 303, 1-6 fewer events per 1,000 treated[15]) have relatively small efficacy benefits compared to warfarin and limited long-term efficacy and safety data. Both agents are recommended as second line after warfarin.
- Recommend rivaroxaban and dabigatran as second line options, after warfarin and enoxaparin, for the treatment of DVT and PE.

Reason for Review:
The injectable anticoagulant class was reviewed by the Oregon Health Resources Commission (HRC) in April 2010. The comparative effectiveness resource used for this review did not included oral anticoagulants or comparison of injectable anticoagulants to the newly released oral anticoagulants.[7] This review will analyze the comparative effectiveness of injectable and oral anticoagulants compared to the new oral anticoagulants, apixaban, dabigatran and rivaroxaban, and incorporation of important updates related to this class since the last review. New evidence-based guidelines have been released and new systematic reviews were also updated and will be included in this review.

Previous HRC Conclusions/April 2010 (only injectable anticoagulants were evaluated):
- There is no evidence to suggest a difference in the efficacy and harms of LMWHs.
- There is evidence that fondaparinux has superior efficacy compared enoxaparin but with an increased risk of bleeding.
- Fondaparinux has been shown to be non-inferior to dalteparin.

Background:
Anticoagulants are used in the prevention and treatment of thrombosis, including VTE. VTEs are a result of DVT or PE which can be secondary to surgery and other medical conditions. Thrombosis may result from abnormalities in the vascular and coagulation systems.[16] Damage to the endothelial lining of blood vessels trigger activation of the coagulation cascade leading to thrombus formation.[17] Injectable anticoagulants work by enhancing antithrombin (AT) which is responsible for inhibiting a variety of clotting factors.[17] Oral anticoagulants exhibit anticoagulant activity through blocking the formation of vitamin K clotting factors (warfarin), direct thrombin inhibition (dabigatran) and factor Xa inhibition (rivaroxaban and apixaban).[18-21]

The most important outcomes in assessing therapy for the prevention and treatment of VTE include the occurrence or reoccurrence of VTE, major bleeding and all-cause mortality. Additional relevant outcomes are: minor bleeding, cardiovascular events and withdrawals due to adverse events. Early research relied primarily on symptomatic VTE and fatal PE as measures of antithrombotic prophylaxis efficacy. Current literature has incorporated the use of the surrogate outcome, asymptomatic DVT, detected by mandatory venography.[22] The ACCP guidelines find this outcome "fundamentally unsatisfactory" due to the inability to weigh the risks and benefits of efficacy (knowledge of symptomatic events) compared to serious bleeding.[22] The guidelines provide suggestions to estimate reductions in symptomatic thrombosis, dependent upon available evidence. Many studies that evaluate the effectiveness of anticoagulants in orthopedic patients rely on asymptomatic DVT events to determine treatment differences and are not powered to detect a difference in the frequency of symptomatic events, due to low occurrence rates.[4]

Strokes, systemic embolisms and mortality rates are the most important outcomes in evaluating treatment for AF. Important secondary outcomes are ischemic and hemorrhagic strokes. Important safety outcomes include major bleeds, GI bleeds and myocardial infarctions (MI).

VTE Prophylaxis
For patients undergoing THR or TKR prophylactic anticoagulants are considered standard practice. ACCP guidelines recommend the use of LMWHs over other available treatment options (moderate evidence).[2] A minimum treatment duration of 10-14 days is recommended (moderated evidence).[2] There is moderate evidence suggesting thromboprophylaxis be continued for up to 35 days from the day of the surgery.[2] The FDA approved doses for subcutaneous enoxaparin prophylaxis in patients undergoing hip replacement surgery is 30 mg every 12 hours or 40 mg once daily and for knee replacement surgery is 30 mg given every

12 hours.[23] This is in contrast to the common European dosing regimen of enoxaparin 40 mg given once daily for prophylaxis in patients undergoing knee replacement, which is used in some trial designs.

Acute VTE Treatment

ACCP guidelines recommend the use of LMWH, fondaparinux, IV UFH or subcutaneous UFH for the acute treatment of DVT and PE. The treatment duration is indication dependent, however, long-term anticoagulation is recommended, ranging from 3 months to extended therapy.[2] Treatment with VKAs are recommended over LMWH for extended anticoagulation in most patients (Grade I, low evidence), except those with cancer in which LMWHs are preferred, based on moderate evidence.[2]

Atrial Fibrillation

Patients with AF are at increased risk of stroke and systemic embolism, which is estimated based on the $CHAD_2$ Classification Scheme (Table 1). The $CHADS_2$ risk stratification scheme estimates stroke risk in patients with AF based on: presence of heart failure, presence of hypertension, age ≥75 years, presence of diabetes mellitus, and a history of previous stroke or transient ischemic attack.[24] The greater the number of risk factors present, the greater the risk of stroke. CHEST guidelines on antithrombotic and thrombolytic therapy recommend anticoagulation for patients with AF and a $CHAD_2$ score ≥1.

Table 1. $CHADS_2$ Classification Scheme for Stroke Risk[24]

	Risk Factor	Points
C	Congestive Heart Failure	1
H	Hypertension	1
A	Age ≥75 years	1
D	Diabetes	1
S_2	History of stroke or TIA	2

Injectable Anticoagulants - FDA-Approved Indications[23,25-29]

Drug	DVT Prophylaxis				DVT Treatment (with warfarin)	Other
	Abdominal Surgery	Hip Replacement	Knee Replacement	Hip Fracture Surgery		
Dalteparin (Fragmin®)	+	+	---	---	---	Unstable angina and non-Q-wave MI, DVT prophylaxis, extended VTE treatment in cancer patients
Enoxaparin (Lovenox®)	+	+	+	----	+ (without PE in outpatient setting, with or without in inpatient setting)	Unstable angina and non-Q-wave MI, DVT prophylaxis, acute STEMI or with subsequent PCI
Fondaparinux (Arixtra®)	+	+	+	+	+ (inpatient setting only, with or without PE)	Acute PE if treated in the hospital with warfarin

Heparin	+	---	---	----	+	- Low-dose for prevention of postoperative VTE and PE in patients undergoing abdominothoracic surgery or for those at risk of developing thrombosis - Prophylaxis and treatment of PE - A-fib with embolization - Acute and chronic consumptive coagulopathies - Prevention of clotting in arterial and cardiac surgery - Prophylaxis and treatment of peripheral arterial embolism
Desirudin (Iprivask®)	---	+	---	---	---	

* MI- myocardial infarction, DVT – deep vein thrombosis, VTE- venous thromboembolism, STEMI- ST segment elevation myocardial infarction, PCI-percutaneous coronary intervention

Oral Anticoagulants – FDA Approved Indications[18-21]

Drug	DVT/PE Prophylaxis	DVT/PE Treatment	Atrial Fibrillation	Cardiac Valve Replacement	Post- MI
Warfarin (Coumadin®)	+	+	+	+	+
Dabigatran (Pradaxa®)	---	---	+ (nonvalvular only)	---	---
Rivaroxaban (Xarelto®)	+ (Studied in THR and TKR)	+	+ (nonvalvular only)	---	---
Apixaban (Eliquis®)	---	---	+ (nonvalvular only)	---	---

* MI- myocardial infarction, DVT – deep vein thrombosis, THR- total hip replacement, TKR- total knee replacement

Methods:

A Medline literature search ending in January 2013 for new systematic reviews and randomized controlled trials (RCTs) comparing anticoagulants to each other or to other anticoagulants was performed. 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. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources. After review of the citations from Medline and the manual searches, the following were reviewed: three clinical treatment guidelines[2,10,29], five systematic reviews[3-5,13,15] and eleven RCTs [6-9,11,12,14,32-35].

Systematic Reviews:

Cochrane[3] – Prevention of VTE

A recent Cochrane analysis evaluated the effectiveness of DTIs compared to VKAs and LMWHs for the prevention of VTE in patients undergoing THR or TKR. Fourteen randomized controlled trials with dabigatran or ximelagatran were included in the efficacy analysis (21,642 patients) and safety analysis (27,360 patients). Currently, ximelagatran is not available due to hepatic toxicities. Outcomes of interest were major VTE events (symptomatic and asymptomatic), all-cause mortality, total bleeding events and liver function tests, measured by alanine aminotransferase (ALT) >3 times the upper limit of normal. Included randomized clinical trials were 7-14 days of treatment with the exception of one dabigatran study, which allowed for extended prophylaxis up to 35 days.

When DTIs were compared to LMWHs there were no major differences in the rate of major VTE events (OR 0.91, 95% CI 0.69-1.19)(low evidence). A sensitivity analysis of major VTE events found that this finding remained true regardless of surgery type or doses studied. When only symptomatic VTEs were included, again there was no difference found between LMWHs and DTIs. Due to the infrequent nature of symptomatic events, the sample size needed to properly evaluate the differences between treatments would require thousands of patients, which was not attainable in this analysis. The time of initiation of anticoagulation, before compared to after surgery, was shown to impact the efficacy of anticoagulant more than the drug. A sensitivity analysis found that when DTIs were initiated before surgery less VTEs resulted compared to LMWH. The opposite effect was true when DTIs were started after surgery.

All-cause mortality and total bleeding events were found to be higher with DTIs compared to LMWHs with moderate and low evidence, respectively. When follow up events were included, the difference in all-cause mortality was statistically significantly higher with DTIs compared to LMWHs (OR 2.06, 95% CI 1.10 to 3.87). ALT elevations >3 times the upper normal limit occurred less frequently with DTIs compared to LMWH (OR 0.41, CI 0.23-0.72) (low evidence).

Cochrane concluded that there was insufficient evidence to recommend dabigatran over enoxaparin and DTIs had similar efficacy as VKAs for the prevention of VTE in patients undergoing orthopedic surgery.

Cochrane[13]- Treatment of Symptomatic Venous Thrombosis

A second Cochrane Systematic Review was released in October 2012. The long-term treatment of symptomatic venous thrombosis with either VKAs or LMWHs was analyzed. A literature search up to February 2012 resulted in fifteen open-label trials involving 3, 197 patients with symptomatic VTE. Trials included four formulations of VKA (warfarin, coumarin, acenocoumarol and phenprocoumon) and 7 types of LMWH (enoxaparin, fragmin, tinzaparin, dalteparin, nadroparin, and reviparin). Trials were classified based on methodological quality (concealed randomization, double-blinded treatment and blinded assessment of outcomes measures). Category I trials were considered to have high methodological quality and Category II trials had a lower level of methodological quality. Additional analyses were performed for Category I (7 trials) and Category II (8 trials) designations. The primary outcomes of the analysis were recurrent symptomatic VTE, major bleeds and mortality at three months.[6]

The incidence of recurrent VTE during treatment was higher with VKAs (5.2%) compared to LMWHs (4.5%), (OR 0.82, 95% CI 0.59 to 1.13).[6] Analysis of Category I trials found similar results in favor of LMWH (OR 0.80, 95% CI 0.54 to 1.18). When only Category I trials using the same initial treatment were analyzed (2 trials), treatment favored VKAs (OR 1.95, 95% CI 0.74 to 5.19). Thirteen trials found no significant difference between VKAs and LMWHs in rates of major bleeding. Pooled analysis data of major bleeding showed a significant trend favoring LMWHs (OR 0.50, 95% CI 0.31 to 0.79). When considering only Category I trials, major bleeding rates favored LMWHs, but were not statistically different, from VKAs (OR 0.62, 95% CI 0.36 to 1.07). Mortality rates were similar for VKAs and LMWHs, 3.6% and 3.9%, respectively.[6] International normalized ratios (INR) were reported in six trials. Four trials reported 64-69% of patients with mean INRs in therapeutic range and two trials reported patients with INRs that were considered good (30-38%) or acceptable/intermediate (43-56%).[6]

AHRQ - Venous Thromboembolism Prophylaxis in Orthopedic Surgery[1]

A comparative effectiveness review was done to evaluate the role of prophylaxis on VTE in patients undergoing orthopedic surgery. One hundred and seventy seven controlled trials and observational studies were included. Comparative efficacies between classes of agents and of individual agents within classes were evaluated. Approval of rivaroxaban occurred after the completion of this report and therefore data from the RECORD trials were included as an addendum but not in the pooled analyses. There is insufficient evidence to compare the benefits or risk of harms between the different LMWH treatments.[1] LMWHs were found to have a better balance of efficacy and harms when compared to UFH. This was substantiated with moderate evidence for PE (OR 0.48 [0.24 to 0.95]), DVT (RR 0.80 [0.65 to 0.99]), and HIT (OR 0.12 [0.03 to 0.43)] and with high evidence for proximal DVT (RR 0.60 [0.38 to 0.93]) and major bleeding (OR 0.57 [0.37 to 0.88]). Strong conclusions of benefits and harms of LMWH and oral antiplatelet agents, fondaparinux, injectable or oral DTIs or oral VKAs were not able to be drawn. LMWHs may be inferior to factor Xa inhibitors (fondaparinux) when evaluating proximal DVT (RR 1.99 [1.57 to 2.51]) and distal DVT (OR 2.19 [1.52 to 3.16]) but are associated with less risk of major bleeding (OR 0.65 [0.48 to 0.89]) (moderate evidence). UFH was found to have an increased incidence of DVT and proximal DVT compared to DTI (moderate evidence). Observational studies found that LMWHs were associated with decreased mortality but this was not supported by RCT findings. UFH was associated with a higher rate of major bleeding and death when compared to fondaparinux.

There were few studies to do a comparative analysis between agents within the same class. Enoxaparin was found to have similar benefits and harms as dalteparin and tinzaparin.

CADTH- Dabigatran or Rivaroxaban Versus Other Anticoagulants for Thromboprophylaxis After Major Orthopedic Surgery: Systematic Review of Comparative Clinical-Effectiveness and Safety[4]

A Health Technology Assessment was performed to compare the clinical effectiveness and safety of the new oral anticoagulants, dabigatran and rivaroxaban, to currently used anticoagulants (LMWH, fondaparinux, UFH and warfarin) in the prevention of thrombosis following orthopedic surgery. A total of nine phase II and phase III trials of patients undergoing TKR and THR were included. No difference in efficacy was found between dabigatran and enoxaparin when the results from the phase III trials (RENOVATE1[15], RE-MODEL[16], and REMOBILIZE[17]) were pooled for a meta-analysis (n=8,210). Rates of bleeding, liver enzyme elevations and acute coronary events were also similar between groups. Rivaroxaban was compared to enoxaparin in three phase III RCTs (RECORD 1[18], RECORD 2[19] and RECORD 3[20]) using the 40mg once daily enoxaparin dose. Rivaroxaban was shown to be superior to enoxaparin based on the primary endpoint of any DVT, non-fatal PE, and all-cause mortality. Comparable rates of major bleeding, liver enzyme elevation, and acute coronary events were found between treatment groups. RECORD 4[21], compared rivaroxaban to enoxaparin 30mg twice daily, is ongoing but preliminary results suggest a significantly significant reduction in the primary endpoint events in favor of rivaroxaban with low rates of bleeding in both groups.

DERP – Newer Oral Anticoagulant Drugs (draft)[5]

A recently released review from DERP analyzes the safety and efficacy of the newer oral anticoagulants in patients with AF, those undergoing orthopedic surgery and medically ill. The report included the new oral anticoagulants: apixaban, dabigatran, edoxaban (not approved in US) and rivaroxaban. Clinical evidence was graded from insufficient to high and studies had to meet appropriate inclusion criteria, which left 8 systematic reviews available for analysis. No direct comparisons between new oral agents were available.

Orthopedic Prophylaxis

In patients undergoing orthopedic surgery there was moderate strength of evidence that apixaban, dabigatran and rivaroxaban were similar in preventing symptomatic VTE events. This was based on the indirect comparison of apixaban to dabigatran (compared to dabigatran RR, 1.16; 95% CI, 0.31 to 4.28), rivaroxaban compared to dabigatran (RR, 0.68; 95% CI, 0.21 to 2.23) and rivaroxaban compared to apixaban (RR, 0.59; 95% CI, 0.26 to 1.33). Comparison of

enoxaparin to newer oral agents for orthopedic prophylaxis showed no significant difference in the outcomes of all cause mortality and symptomatic PE (moderate to high evidence). A reduced risk of symptomatic VTE was found with rivaroxaban compared to enoxaparin (RR, 0.48; 95% CI, 0.31 to 0.75)(moderate to high evidence). Symptomatic DVTs were lower with apixaban and rivaroxaban compared to enoxaparin; enoxaparin compared to apixaban (RR, 0.41; 95% CI, 0.18 to 0.95), enoxaparin compared to rivaroxaban (RR 0.40; 95% CI, 0.22 to 0.72) (moderate to high evidence). Symptomatic DVT events favored enoxaparin compared to dabigatran (RR, 0.82; 95% CI, 0.17 to 3.99) (moderate to high evidence).

When comparing the evidence of harms of the newer oral agents in patients undergoing orthopedic prophylaxis, DERP found the risk of major bleeding was similar between the groups, based on indirect comparisons (moderate evidence). For the composite outcome of clinically major bleeding (either major bleeding or clinically relevant minor bleeding) rivaroxaban had a higher incidence compared to apixaban (RR, 1.52; 95% CI, 1.19 to 1.95) (moderate evidence). This translates into a clinically relevant bleeding risk increase of 52% with rivaroxaban compared to apixaban, based on indirect comparisons. For the outcome of clinically major bleeding there was a lower risk with apixaban compared to dabigatran and no difference between rivaroxaban and dabigatran (moderate evidence). When compared to enoxaparin the risk of clinically relevant bleeding was similar to dabigatran (moderate to high evidence). For this same outcome, the risk was lower with apixaban (RR, 0.82; 95% CI, 0.69 to 0.98) compared to enoxaparin and higher with rivaroxaban (RR 1.12; 95% CI 0.94 to 1.35) when compared to enoxaparin.

Atrial Fibrillation

In patients with non-valvular AF there was no difference, based on indirect comparisons, in all cause mortality between apixaban, rivaroxaban, dabigatran 110 mg and dabigatran 150 mg (moderate evidence). Rivaroxaban was associated with an increased incidence of stroke when compared to dabigatran 150 mg (OR, 1.35; 95% CrI, 1.03 to 1.79) (moderate evidence). However, rivaroxaban was associated with less myocardial infarctions than dabigatran 150 mg (OR, 0.63; 95% CrI, 0.42 to 0.93). When compared to warfarin, apixaban demonstrated a reduced risk of stroke and systemic embolism (OR, 0.80; 96% CrI, 0.66 to 0.95) and all cause mortality (OR, 0.90; 95% CrI, 0.80 to 0.998)(moderate evidence). Dabigatran was also shown to have a reduced risk of stroke when compared to warfarin, (OR, 0.65; 95% CrI, 0.52 to 0.81) (moderate to high evidence).

Subgroup analysis found patients with AF and INRs that were therapeutic at least 66% of the time, the new oral agents were not superior to warfarin. In individuals over the age of 75, the newer agents decreased the risk of stroke/systemic embolism compared to warfarin but this was only true for dabigatran in patients under 75. Apixaban was the only agent that decreased the risk of major bleeds compared to warfarin in patients over 75, however, in patients under 75 years dabigatran and apixaban had less risk of major bleeds compared to warfarin. Patients with a $CHAD_2$ score >2 benefited from apixaban treatment with less strokes and less major bleeds.

When assessing harms in patients with AF, dabigatran 150mg had increased risk of major bleeding compared to apixaban (RR 1.35; 95% CrI, 1.11 to 1.66) and increased risk of gastrointestinal (GI) bleeding compared to apixaban (RR 1.65; 95% CrI 1.16 to 2.38) (moderate evidence). Rivaroxaban demonstrated an increased risk of major bleeding and major GI bleeding compared to apixaban, OR 1.48 (95% CrI, 1.21 to 1.82) and OR 1.83 (95% CrI, 1.30 to 2.57), respectively (moderate evidence). Compared to warfarin, apixaban had less risk of major bleeds (OR 0.70; 95% CrI, 0.61 to 0.81) and intracranial bleeds (OR 0.42; 95% CrI, 0.30 to 0.58) (moderate to high evidence). Dabigatran 150mg and rivaroxaban were found to have less intracranial bleeds (OR 0.42 and OR 0.66) but increased risk of GI bleeds (OR 1.45 and OR 1.61), compared to warfarin (moderate to high evidence).

Long-term Anticoagulation

Mortality and recurrent VTE rates were similar between dabigatran and rivaroxaban compared with warfarin (moderate evidence).

CADTH – Antithrombotic Agents for the Prevention of Stroke and Systemic Embolism in Patients with Non-Valvular Atrial Fibrillation (draft)[15]

A just released systematic review from CADTH evaluated 12 trials to compare the clinical evidence of antithrombotic agents in patients with AF, which included the following treatments: new oral anticoagulants (NOAC) apixaban, dabigatran and rivaroxaban; warfarin; or ASA ± clopidogrel. The analysis evaluated key endpoints (stroke and systemic embolism, major bleeding, all-cause mortality, extracranial hemorrhage, intracranial hemorrhage and myocardial infarction) as well as subgroup analyses ($CHADS_2$ score, age and TTR) and risk/benefit analysis. Indirect comparisons were used to compare the clinical efficacy of the new NOACs due to lack of direct comparison data.

For stroke and systemic embolism apixaban and dabigatran 150 mg were superior to warfarin (OR 0.8 for apixaban and OR 0.7 for dabigatran). These results translate into 1-6 fewer events per 1,000 patients treated per year with apixaban and 3-9 fewer events per 1,000 patients treated per year with dabigatran. Dabigatran 150 mg was superior to dabigatran 110 mg (dose not available) for stroke and systemic embolism. All anticoagulants were favored over low-dose ASA and the combination of low-dose ASA and clopidogrel. Compared to warfarin, major bleeding rates were lower with apixaban (OR 0.7) and dabigatran 110 mg (OR 0.8). Dabigatran 150 mg and rivaroxaban were associated with higher bleeding rates than apixaban, OR 1.34 and 1.48, respectively. Clopidogrel + low-dose ASA were also found to have significantly higher bleeding rates than apixaban. Mortality rates were significantly less with apixaban compared to warfarin, with 8 fewer events per 1000 patients treated in year. Apixaban was shown to have significantly lower rates of extracranial hemorrhage than warfarin (OR 0.8) and dabigatran 150 mg, rivaroxaban and medium dose ASA all had significantly higher rates compared to apixaban. All NOACs had lower rates of intracranial hemorrhage which were statistically significant and ranged from 1 to 7 fewer events per year and per 1,000 patients treated. NOACs were also superior to low-dose ASA + clopidogrel. Myocardial infarction rates were higher with dabigatran 150 mg compared to warfarin, OR 1.4. Apixaban was found to have lower MI rates compared to dabigatran (110 mg and 150 mg), medium dose ASA and low-dose ASA + clopidogrel.

The subgroup analyses found that in patients with $CHAD_2$ scores <2, apixaban and dabigatran 110 mg, when compared to warfarin, were found to have significantly lower bleeding rates. In these same patients dabigatran 150 mg proved more effective, based on lower rates of strokes and systemic embolism, than dabigatran 110 mg. NOACs and warfarin were also shown to be more effective than low-dose ASA and low-dose ASA + clopidogrel combination. In this same subgroup, major bleeding rates were significantly lower with apixaban and dabigatran 110 mg compared to low-dose ASA + clopidogrel. In patients with a $CHAD_2$ score of ≥2 both dabigatran 150 mg and apixaban were found to have less rates of stroke and systemic embolism compared to warfarin, OR 0.7 and 0.8, respectively. In this same population, NOACs were also more effective than low-dose ASA alone and in combination with clopidogrel. Major bleeding rates were found to be lower with apixaban compared to warfarin, rivaroxaban and dabigatran 150 mg in patients with a $CHAD_2$ score ≥2.

Dabigatran 150 mg was found to be more effective than warfarin, based on stroke and systemic embolism rates, in patients 75 years or older. Patients in this age group were also found to have lower rates of stroke and systemic embolism when treated with any anticoagulant compared to low-dose aspirin. For those patients that were <75 years old, warfarin was shown to prevent more strokes and systemic embolisms significantly more than low-dose ASA and low-dose ASA + clopidogrel.

There was no significant difference among treatments for stroke and systemic embolism rates in centers with good INR control (TTR ≥66%). In centers with poor INR control (<66%), dabigatran 150 mg was found to have a reduced rate of strokes and systemic embolisms compared to warfarin and rivaroxaban. In two separate groups, patients younger than 75 years of age and in patients with poor INR control (TTR <66%), apixaban and dabigatran (both doses) were found to

have less major bleeding compared to warfarin. In patients with good INR control (TTR ≥66%) apixaban was associated with less major bleeding than warfarin and for those over 75 years old, apixaban was found to have less major bleeding than all the anticoagulants. When comparing patients on warfarin with poor INR control (TTR <66%) to patients on NOACs, major bleeding rates were found to be less in the NOAC group.

The benefit to risk profile, which takes into account stroke and systemic embolism rates compared to major bleeds, found no major differences between the NOACs but demonstrated a positive risk/benefit finding for NOACs when compared to warfarin. However, risk differences were small, mostly under 10 fewer events per 1,000 patients treated per year between NOACs and warfarin. Antiplatelets were shown to lave a less favorable benefit/risk profile compared to NOACs independent of stroke risk, age, or INR control.

New Guidelines:

Antithrombotic Therapy for VTE disease: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians (ACCP) Evidence-Based Clinical Practice Guidelines[2]

The ACCP guideline on therapy for VTE updates the 8th edition of the guideline that was released in 2008. Treatment and management of thrombotic events are discussed and graded. Evidence was analyzed by the expert panel utilizing the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system for evaluating outcomes. Recommendations were considered strong (Grade 1) or weak (Grade 2) based on a benefit to risk ratio, the quality of the evidence and the impact of the recommendation. A strong recommendation was written as "recommended" where a weak recommendation was written as "suggested". Pharmacological classes are recommended for prevention and treatment, however, specific treatments are rarely suggested.

For VTE prophylaxis in patients undergoing orthopedic surgery (TKR and THR), LMWHs are weakly recommended over fondaparinux, apixaban, dabigatran, rivaroxaban, or UFH (moderate evidence). LMWHs are weakly recommended over VKAs or aspirin (low evidence).

In patients requiring treatment of proximal acute DVT of the leg or PE, LMWH and fondaparinux are recommended over IV UFH and SQ UFH based on a weak recommendation (low to moderate evidence). For patients with DVT of the leg or PE, long-term therapy treatment with a VKA is weakly recommended over LMWH. If these same patients decide to not use VKA therapy, then the use of LMWHs are weakly recommended over dabigatran or rivaroxaban for long-term use.

In patients with DVT of the leg or PE and cancer, LMWHs are weakly recommended over VKA therapy. VKA treatment is preferred over dabigatran and rivaroxaban for long-term treatment (low evidence).

For patients who have nonrheumatic AF and low risk of stroke, aspirin is weakly recommended (moderate evidence). For patients at intermediate and high risk of stroke ($CHAD_2$ score ≥1), anticoagulation is strongly recommended (moderate to high evidence). Dabigatran is weakly recommended over VKAs (moderate evidence). For patients with other types of AF, VKAs are recommended, with and without additional agents.

Management of Massive and Submassive Pulmonary Embolism, Iliofemoral Deep Vein Thrombosis, and Chronic Thromboembolic Pulmonary Hypertension: A Scientific Statement From the American Heart Association[10]

In 2011 The American Heart Association (AHA) published recommendations for treating massive and submassive PE, iliofemoral deep vein thrombosis (IFDVT) and chronic thromboembolic pulmonary hypertension. Recommendations were based on systematically reviewed evidence and given a rating based on the American Heart Association Levels of Evidence. Size of treatment effect was based on class I-III (the lower the class the greater the benefit over risk) and estimate of certainty (precision) of treatment effect (level A-C, with level A having strong evidence and level C having weaker evidence).

Therapy recommendations for the treatment of acute massive, submassive, and low-risk PE were similar to other guidelines. Therapeutic anticoagulation with LMWH, IV or SQ UFH or fondaparinux was recommended (Class I; Level of Evidence A). IFDVT involves thrombosis in any part of the iliac vein or the common femoral vein and some evidence suggests that IFDVT presents a greater risk of poor outcomes. Recommendations for initial anticoagulation for IFDVT include IV UFH, LMWH, or fondaparinux (Class I; Level of Evidence A) or SQ UFH (Class I; Level of Evidence B). Direct thrombin inhibitors are recommended for patients with suspected or proven HIT (Class I; Level of Evidence B). Warfarin is recommended for patients without cancer requiring long-term anticoagulation for IFDVT (Class I; Level of Evidence A) and LMWH is preferred for patients with cancer (Class I; Level of Evidence A).

NICE- Venous Thromboembolic Diseases: the Management of Venous Thromboembolic Diseases and the Role of Thrombophilia Testing[30]

NICE released a clinical guideline for VTE management in June 2012. Clinical evidence was evaluated based on the GRADE method with outcome evidence ratings ranging from very low to high. Treatments included in this review are; UFH, LMWH, synthetic pentasaccharides (fondaparinux) and VKAs. Rivaroxaban is discussed in a separate NICE review. Pharmacological treatment is recommended for DVT and PE based on patient comorbidities, with no specific anticoagulant preferred. Comparisons between fondaparinux and LMWHs included only low and very low quality studies with no certainty of a difference in VTE related mortality, recurrent VTE rates and major bleeds. Fondaparinux was compared to UFH in which a clinical important decrease in recurrent VTE favoring fondaparinux was found in patients with and without cancer (low evidence). LMWHs were compared to UFH with uncertain findings favoring LMWHs for the outcomes of all cause mortality, recurrent VTE, and major bleeds (very low and low evidence). It is unlikely that there is any difference in all cause mortality between LMWHs and VKAs (moderate evidence). In a study including cancer and non-cancer patients, LMWHs were shown to possibly have a clinically important decrease in recurrent VTE rates compared to VKAs (moderate evidence). This finding was not sustained for a subgroup analysis containing only non-cancer patients but was sustained for the cancer patient group. An option of LMWH or fondaparinux is suggested, with selection dependent upon co-morbidities, contraindications, and costs. UFH and LMWHs are preferred for patients with renal failure. For patients with hemodynamic instability and an increased risk of bleeding UFH is recommended. LMWHs are recommended for at least six months in patients with cancer with VTE, otherwise VKA treatment is suggested.

New Safety Alerts, Indications:

DABIGATRAN- FDA Safety Review

Pradaxa (dabigatran etexilate mesylate): Drug Safety Communication- Safety Review of Post-Market Reports of Serious Bleeding Events[31]

On November 2, 2012 the FDA updated a previous report of risk of serious bleeding with dabigatran. The FDA evaluated reports with the new use of dabigatran and warfarin and found that bleeding rates associated with dabigatran did not appear higher compared to warfarin. The FDA is continuing to monitor this safety issue.

FDA Drug Safety Communication: Pradaxa (dabigatran etexilate mesylate) should not be used in patients with mechanical prosthetic heart valves[32]

In December 2012, the FDA warned healthcare professionals and patients that a recent study in Europe (RE-ALIGN) demonstrated an increased risk of strokes, heart attacks, and blood clots forming on the mechanical heart valves in patients treated with dabigatran compared to warfarin. Bleeding after valve surgery was also higher in the dabigatran group. A contraindication against the use of dabigatran in patients with mechanical heart valves was added to the prescribing information for dabigatran.

RIVAROXABAN- New Indication

On November 2, 2012 the FDA approved the addition of treatment of DVT, PE and the reduction in the risk of recurrence of DVT and PE to rivaroxaban labeling. For this indication rivaroxaban should be given with food and be dosed at 15 mg twice daily for the first 21 days and then 20 mg once daily for continued treatment. This oral treatment regimen streamlines treatment of thrombosis by eliminating the need for initial treatment with an injectable agent. The clinical evidence used for this approval was based on the EINSTEIN-DVT and EINSTEIN-EXT studies which are presented below.

The EINSTEIN Investigators (See Evidence Table below)[11]

Rivaroxaban was studied in a phase III, parallel group, non-inferiority, open-label, RCT in over 3,400 patients with acute symptomatic DVT without PE in the EINSTEIN-DVT trial. Patients were randomized to rivaroxaban 15mg twice daily for 3 weeks and then 20mg once daily or enoxaparin and a vitamin K antagonist (warfarin or acenocoumarol) for 3, 6, or 12 months.

Rivaroxaban was found to be non-inferior to standard treatment (enoxaparin plus VKA) for the prevention of recurrent VTE in patients with acute DVT (low evidence). The primary endpoint was experienced by 2.1% of the rivaroxaban group and 3.0% for the enoxaparin/VKA group (HR 0.68; 95% CI, 0.44-1.04; $p<0.001$ for noninferiority). Similar rates of major bleeding (8.1%) were found in both groups (low evidence). The open-label design of this trial introduces a potential for bias that could influence treatment outcomes.

The EINSTEIN Investigators (See Evidence Table below)[11]

The EINSTEIN-EXTENSION study was a placebo-controlled, double-blind, phase III continuation study in over 1,000 patients with a confirmed symptomatic DVT or PE previously treated with a VKA or rivaroxaban for 6 or 12 months (EINSTEIN-DVT, EINSTEIN-PE), that there was equipoise with respect to the need for continued anticoagulation. Patients were randomly assigned to rivaroxaban 20mg daily or placebo for an additional 6 or 12 months. The average patient was 58 years old and approximately 40% female. The primary efficacy analysis was recurrent venous thromboembolism and major bleeding was the primary safety analysis.

Rivaroxaban was found to be more effective than placebo in preventing VTE with extended treatment (HR 0.18; 95% CI 0.09 to 0.39; $p<0.001$) (low evidence). Rivaroxaban was associated with more major bleeding than placebo (low evidence). Extension study design may bias efficacy and safety results based on enrollment of patients already able to tolerate/respond to treatments.

The EISTEIN-PE Investigators (See Evidence Table below)[12]

In a phase III, open-label trial of 4,832 patients, rivaroxaban was compared to enoxaparin followed by warfarin in patients 18 years or older with a confirmed diagnosis of PE (EINSTEIN-PE). Patients were treated for 3, 6 or 12 months determined by treating physician before randomization. Patients were a mean age of 58 years old with equal males and females enrolled. A majority of patients had intermediate anatomical extent of PE and 25% had concurrent symptomatic DVT.

An average of 19% of patients has a history of previous VTE and 64% were deemed to have PEs that were unprovoked. The primary outcome was symptomatic recurrent VTE and major or clinically relevant nonmajor bleeding was the primary safety outcome.

Rivaroxaban was found to be non-inferior to enoxaparin/VKA treatment for the outcome of symptomatic recurrent VTE when treating PE (low evidence). The primary outcome occurred in 2.1% of the rivaroxaban group and 1.8% of the enoxaparin/VKA group (HR: 1.12, 95% CI 0.75 to 1.68, p=0.003 for noninferiority). Major bleeding events were significantly lower in the rivaroxaban group compared to enoxaparin/VKA treatment, 1.1% and 2.2%, respectively (low evidence). The open-label study design may bias treatment results.

New Primary Literature:

Dabigatran vs. Enoxaparin:
Eriksson, et al (See Evidence Table below)[6]
A fair quality phase III, double-blind, RCT compared dabigatran 220mg daily to enoxaparin 40mg SQ daily for thromboprophylaxis after THR (RE-NOVATE II[23]). This study was similar to RE-NOVATE[15] with the exception being that RE-NOVATE II enrolled a more diverse population, only evaluated the 220mg dabigatran dose and included patients from North America (17%). Just over 2,000 patients were randomized to treatment for 28-35 days. Patients were mostly white with an average age of 62. The primary endpoint was the composite of total VTE and all-cause mortality and the main safety outcome was major bleeding.

Dabigatran was found to be non-inferior, but not superior, to enoxaparin for the primary endpoint (7.7% for dabigatran and 8.8% for enoxaparin, ARR -1.1%, 95% CI -3.8% to 1.6%) (moderate evidence). Rates of major bleeds were similar for dabigatran (1.4%) and enoxaparin (0.9%), (RR 1.5, CI 0.67 to 3.6, p=0.40). Limitations to these findings include; results expressed as composites which can overestimate results, evaluation of asymptomatic DVTS which the importance and clinical relevance is unknown, and a large number of patients being excluded from the primary endpoint analysis due to lack of venography.

New Drug Evaluation- Apixaban

FDA Indications:
Apixaban is a factor Xa inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with nonvalvular AF.

Potential Off-label Indications:
Apixaban may be used for anticoagulant prophylaxis following orthopedic surgery, treatment of DVT and PE, in medically ill patients and in those with acute coronary syndromes.

Atrial Fibrillation

Clinical Efficacy Data (see evidence table below):

The clinical efficacy of apixaban use in AF was demonstrated in two good quality trials, ARISTOTLE[14] and AVERROES[33]. Both trials were phase III, double-blind, double-dummy design comparing apixaban to warfarin (ARISTOTLE) or aspirin (AVERROES). Both trials allowed for a reduced apixaban dose of 2.5 mg twice daily if patients had two or more of the following criteria: ≥80 years old, ≤60 kg weight, or serum creatinine level of 1.5 mg per deciliter (133 µmol/L) or more. Studies enrolled patients with AF and at least one risk factor for stroke. In both trials, patients were on average 70 years old with a $CHAD_2$ score of 2. ARISTOTLE included warfarin naïve patients and experienced warfarin users. AVERROES was terminated early at 1.1 years of mean follow-up due to a clear benefit of apixaban treatment and ARISTOTLE follow-up was a median of 1.8 years. The primary end point in both trials was the occurrence of stroke (ischemic and hemorrhagic) or systemic embolism and a key secondary efficacy end point was all-cause mortality. The primary safety outcome was major bleeding.

ARISTOTLE was a good quality, large (n=18,201), multi-center trial enrolling patients with AF from 40 countries.[14] Patients were randomized to apixaban 5 mg twice daily or warfarin (adjusted to an INR goal of 2.0-3.0). Apixaban was superior to warfarin based on the primary outcome rates of 1.27% per year for apixaban compared to 1.60% per year for warfarin (HR 0.79, 95% CI 0.66 to 0.95; p= 0.01), which was primarily driven by the reductions in hemorrhagic stroke. The incidence of hemorrhagic stroke was significantly lower with apixaban (0.24%/year) than with warfarin (0.47%/year) (HR 0.51, 95% CI 0.35 to 0.75, p<0.001). The rate of ischemic strokes were also lower with apixaban but not significantly so. All-cause mortality rates were lower with apixaban (3.52%/year) compared with warfarin (3.94%/year), (HR 0.89, 95% CI, 0.80 to 0.998; p=0.47).

AVERROES compared the safety and efficacy of apixaban to aspirin in 5,599 patients with AF that were not candidates for warfarin treatment.[33] In this good quality trial, patients were assigned to apixaban 5 mg twice daily or aspirin 81 to 324 mg daily with a mean follow up of 1.1 years. Apixaban was found to be superior to aspirin for the primary endpoint, with incidence rates of 1.6% per year for apixaban and 3.7% per year for aspirin (HR 0.45, 95% CI 0.32 to 0.62, p<0.001). Ischemic stroke rates were significantly less with apixaban than with aspirin, 1.1%/year vs. 3.0%/year, respectively. Hemorrhagic stroke rates were also lower for apixaban compared to aspirin but not significantly so. All-cause mortality rates were 3.5%/year for apixaban patients and 4.4%/year for aspirin patients (HR 0.79, 95% CI 0.62 to 1.02, p=0.07).

Clinical Safety:

Safety of apixaban was studied in two phaseIII trials involving 11,886 patients, with the majority taking 5 mg twice daily of apixaban (n=11,284).[14,33] The combined treatment duration of the two studies were ≥24 months for 3,369 patients and ≥12 months for 9,375 patients. Bleeding was the most common reason for treatment discontinuation which occurred more often with warfarin (2.5%/year) than with apixaban (1.7%/year) in ARISTOTLE and more often with apixaban (1.5%/year) than with aspirin (1.3%/year) in AVERROES. Major bleeding rates were significantly higher with warfarin (3.09%/year) than with apixaban (2.13%/year) (HR 0.69, 95% CI 0.60 to 0.80, p<0.0001) in ARISTOTLE. In AVERROES the incidence of major bleeds per year was higher with apixaban than with aspirin, 1.4% and 1.2%, respectively (HR 1.13, 95% CI 0.74 to 1.75, p=0.57).

Conclusion:

Apixaban was shown to be superior to warfarin, based on one good quality study, for the prevention of stroke in AF and is associated with significantly less major bleeding (moderate evidence).

Off-label Uses

Orthopedic Prophylaxis

Clinical Efficacy Data (see evidence table below):

The clinical efficacy and safety of apixaban use in orthopedic prophylaxis was demonstrated in three phase III, randomized, double-blind, double-dummy clinical trials involving 11,659 patients (ADVANCE 1-3).[7,8,9] Patients were eligible for the trials if they were scheduled for TKR or revision (ADVANCE 1-2)[7,8] or THR or revision (ADVANCE 3)[9]. Mean treatment durations were 11-12 days in the TKR trials and 34 days in the THR trial. The primary endpoint in all trials was the rate of symptomatic and asymptomatic DVT, non-fatal PE and all-cause mortality. The primary safety endpoint for all trials was bleeding rates.

ADVANCE-1[7]

ADVANCE-1 was a fair quality ,multi-center trial involving 3,195 patients eligible for thromboprophylaxis after TKR. Patients were randomized to apixaban 2.5 mg twice daily or enoxaparin 30 mg every 12 hours for a mean treatment duration of 11 days. Primary outcome rates were based on venography results which were available for approximately 70% of patients. Apixaban was shown to be inferior to enoxaparin. Rates of the primary outcome occurred in 104 (9.0%) apixaban patients compared to 100 (8.8%) of enoxaparin patients (RR 1.02; 95% CI 0.78 to 1.32, p=0.06 for noninferiority). Symptomatic VTE and VTE related death were also lower in the enoxaparin group. Apixaban was associated with 16 (1.0%) pulmonary embolisms compared to 7 (0.4%) in the enoxaparin group.

ADVANCE-2[8]

In a good quality trial ADVANCE-2 compared apixaban 2.5 mg twice daily to the European TKR dosing regimen of enoxaparin of 40 mg every 24 hours in patients requiring thromboprophylaxis after TKR. In this multi-center (Non-US) trial over 3,000 patients were treated a mean duration of 12 days, which was also the mean length of hospital stay in each group. Approximately 65% of patients were available for the primary efficacy analysis. Apixaban was shown to be noninferior and superior to enoxaparin for the primary outcome. The primary outcome occurred in 147 (15%) of apixaban patients and 243 (24%) of enoxaparin patients (RR: 0.62; 95% CI 0.51 to 0.74, p<0.0001 for superiority). Symptomatic VTE and VTE related death were the same in both groups (n=7). PE rates were slightly higher for apixaban compared to enoxaparin, 4 and 0, respectively.

ADVANCE-3[9]

ADVANCE-3 was a good quality study in 5,407 patients requiring thromboprophylaxis for THR. Patients from 160 sites primarily based in Europe and North America, received apixaban 2.5 mg twice daily or enoxaparin 40 mg every 24 hours. Patients were treated for a mean duration of 34 days. The primary efficacy analysis involved approximately 70% of randomized patients. Apixaban was associated with 27 (1.4%) occurrences of the primary outcome compared to enoxaparin with a rate of 74 (3.9%), (RR: 0.36 (95% CI 0.22 to 0.54, p<0.001 for noninferiority and superiority). Symptomatic VTE and VTE related death were higher in the enoxaparin group but not significantly different from apixaban. The rate of PE was 4 (0.2%) in the enoxaparin group compared to 0 in apixaban group.

Clinical Safety:

The safety of apixaban inpatients undergoing TKR and THR was evaluated in over 11,000 patients in three phase III trials (ADVANCE 1-3).[7,8,9] Adverse reactions and discontinuations due to adverse events were similar between the groups. The primary safety outcome was bleeding. Major bleeds and clinically relevant non-major bleeds were found to be significantly less with apixaban compared to enoxaparin in ADVANCE-1. The rate of major bleeds in the apixaban group was 0.7% (n=11) compared to enoxaparin which was 1.4% (n=22) (Risk Difference: -0.81; 95% CI -1.49 to 0.14, p=0.05). Major or clinically relevant non-major bleeding occurred in 46 (2.9%) of apixaban patients and 68 (4.3%) of enoxaparin treated patients (Risk Difference: -1.46; 95% CI, -2.75 to 0.17, p=0.03). In ADVANCE-2 and

ADVANCE-3 the incidence of major bleeds and the composite endpoint of clinically relevant non-major bleeds or major bleeds were similar in the apixaban and enoxaparin treatment groups.

Conclusion:
The off-label use of apixaban was found to be superior to the European dosing regimen of enoxaparin, based on one fair quality trial, but not to the US approved dosing regimen of enoxaparin, in patients requiring thromboprophylaxis for TKR (low evidence). One good quality trial found off-label use of apixaban, in patients undergoing THR, to be superior to enoxaparin (moderate evidence). Rates of bleeding were found to be similar for apixaban and enoxaparin in patients requiring thromboprophylaxis for TKR or THR (moderate evidence).

Medically Ill Patients

Clinical Efficacy Data (see evidence table below):
In one, phase III, fair-quality trial 6,528 medically ill, hospitalized patients were randomized to receive apixaban 2.5 mg twice daily for 30 days or enoxaparin 40 mg once daily for 6-14 days (ADOPT).[34] The trial included acutely ill patients with congestive heart failure (CHF) or respiratory failure or other medical disorders with at least one additional risk factor for VTE. The primary outcome measure was 30-day composite of death related to VTE, PE, symptomatic DVT or asymptomatic proximal-leg DVT which occurred in 2.71% of apixaban patients and 3.06% of enoxaparin patients (RR: 0.87; 95% CI 0.62 to 1.23, p=0.44). The study was underpowered due to high attrition rates, with approximately 36% of patients not included in primary efficacy analysis.

Clinical Safety:
The safety of apixaban in medically ill patients was studied in ADOPT, which included 3,184 patients on apixaban for 30 days.[34] The primary safety outcome was bleeding events. Major bleeds occurred in 15 (0.47%) of patients treated with apixaban and 6 (0.19%) of patients treated with enoxaparin (RR: 2.58; 95% CI 1.02 to 7.24, P=0.04). Major and clinically relevant non-major bleeding events were also lower with enoxaparin compared to apixaban, 2.08% versus 2.67%, respectively.

Conclusion:
There is insufficient evidence for the use of apixaban for thromboprophylaxis in medically ill, hospitalized patients at this time, and may be associated with significantly more major bleeds.

Acute Coronary Syndrome

In one phase III, double-blind, placebo-controlled, fair quality trial of 7,392 patients with acute coronary syndrome apixaban 5 mg twice daily was found to have increased rates of major bleeds without a counterbalance of reduced ischemic events and for this reason the trial was stopped prematurely.[35]

Extended Treatment of VTE

In one phase III, double-blind, placebo-controlled, randomized trial of 2,482 patients, apixaban 2.5 mg and apixaban 5 mg twice daily were compared to placebo (AMPLIFY-EXT)[36]. Patients were included if they had a prior VTE and completed 6 to 12 months of anticoagulation and for whom there was clinical equipoise regarding continuing or discontinuing treatment. Patients were on average 57 years old with slightly more males than females. The primary outcome studied was symptomatic recurrent VTE or death from VTE. The major safety endpoints was major bleeding.

Clinical Efficacy:
In one fair quality trial, both doses of apixaban were superior to placebo for the primary outcome (low evidence).[36] There was 3.8% of patients with symptomatic recurrent VTE or death from VTE in the apixaban 2.5 mg group (A2.5 vs. placebo: RR: 0.33; 95% CI, 0.22 to 0.48, p<0.001) compared to 4.2% for apixaban 5 mg (A5 vs. placebo: RR: 0.36; 95% CI, 0.25 to 0.53, p<0.001) and 11.6% of placebo patients.

Clinical Safety:
Apixaban had similar rates of major bleeding and clinically relevant non-major bleeding rates (low evidence).

Conclusion:
Additional evidence is needed to recommend apixaban for extended treatment in patients previously treated for VTE (low evidence).

COMPARATIVE CLINICAL EFFICACY:

Relevant Endpoints:
Mortality
Thromboembolic events (DVT, PE, stroke)
Cardiovascular events
Bleeding

Primary Study Endpoints:
Surgery Prophylaxis: Total VTE and mortality
DVT/PE Treatment: Recurrent VTE and mortality
AF: Stroke or systemic embolism and mortality
Medically Ill: Cardiovascular death, myocardial infarction or ischemic stroke
ADVANCE 1-3: Recurrent VTE, clinically relevant bleeding
All studies: bleeding

Evidence Table

RE-NOVATE II[6]									
Eriksson, et al Phase III, RCT, DB 19 Countries	1. Dabigatran (D) 220mg QD * started 1-4 hours after surgery with a half-dose 2. Enoxaparin (E) 40mg QD * started the evening before surgery	Age:62 yrs Female: 52% Inclusion: Patients 18 and older undergoing unilateral THR Exclusion: Bleeding disorder, uncontrolled hypertension, surgery, condition or medication predisposing pt. to bleeding, abnormal liver fxn and , renal insufficiency	1. 1036 2. 1019	Median Tx duration: 32 days Median f/u: 93 days	<u>Total VTE + all-cause mortality :</u> D: 7.7% E: 8.8% ARR: -1.1% (95% CI -3.8 to 1.6%, p<0.0001 for noninferiority) <u>Total DVT:</u> D: 7.6% E: 8.6% ARR: -1.0% (95% CI -3.7 to 1.7%, p=0.48) <u>Symptomatic DVT:</u> D: 0.0% E: 0.4% p=0.06 <u>Symptomatic non-fatal PE:</u> D: 0.1% E: 0.2% p=0.62 <u>VTE Mortality</u> D: 2.2% E: 4.2% ARR: -1.9% (95% CI -3.6 to -0.2%, p=0.03 for superiority)	N/A NS NS NS ARR 1.9% NNT 52	<u>Major Bleeding:</u> D: 1.4% E: 0.9% p=0.40 <u>Withdrawal due to Adverse Events</u> D: 5.9% E: 5.2%	NS NS	**Quality Rating: Fair** **Internal Validity: RofB** Selection: computer-generated scheme using telephone randomization procedure Performance: double-dummy design used to conceal treatment assignments from patients and clinical monitors Detection: treatment group assignments were concealed from investigators and staff Attrition: large number (21%) excluded from mITT analysis due to lack of venography. The number was similar between groups and is consistent with other similar studies (power estimate took into account expected exclusions). **External Validity** Recruitment: recruited from 108 centers in 19 countries. Patient Characteristics: population was predominately White (90%) and Asian (9%). 2.5% had a DVT or PE history. Outcomes: Primary endpoint results expressed as composites can exaggerate outcomes but are included for completeness. Primary endpoint including symptomatic and asymptomatic (venography). The importance and clinical relevance of asymptomatic DVT is unknown.
EINSTEIN-DVT[11]									
The	1. Rivaroxaban 15mg twice daily X 3	Age: 56 years Female: 43.5%	1. 1731	Median Tx duration: 3, 6, or 12 months	<u>Recurrent VTE (composite of DVT, non-fatal PE or fatal PE):</u>		<u>Composite of major or clinically relevant nonmajor bleeding:</u>		**Quality Rating: Fair** **Internal Validity: RofB**

Einstein Investigator Phase III, RCT, Open-label, PG, non-inferiority study	weeks then 20mg once daily 2. Enoxaparin + either warfarin or acenocoumarol (vitamin K antagonist)	Inclusion: Acute symptomati DVT Exclusion: Additional VKA indication, CrCl <3(ml/min, significant liver disease, active bleeding, uncontrolled HTN, pregnant/breastfe ding, concomitant CYP-450 3A4 inhibitors	 2. 171		R: 36 (2.1%) E-VKA: 51 (3.0%) HR: 0.68 (95% CI 0.44-1.04 p<0.001 for noninferiority) Mortality: R: 38 (2.2%) E-VKA: 49 (2.9%) HR: 0.67 (95% CI 0.44 to 1.02, p=0.06)	ARR: 0.9% NNT: 111 NS	R: 139 (8.1%) E-VKA: 138 (8.1%) HR: 0.97 (95% CI 0.76-1.22, p=0.77) Major Bleeding: R: 14 (0.8%) E-VKA: 20 (1.2%) HR: 0.65 (95% CI 0.33 to 1.30, p=0.21)	NS NS	Selection: Patients were randomized via computerized voice-response system. Performance: study was open label allowing for potential bias. Detection: Outcomes were assessed by centra adjudication committee that were unaware of treatment assignment. Attrition: Low rates of lost to follow-up. **External Validity:** Recruitment: Details not provided. Patient Characteristics: Patients on warfarin in TTR 58% of the time, which is slightly lower then other similar studies. Included patients with active cancer but not other groups that are unable to take VKAs. Outcomes: Direct outcomes were used to determine treatment effect. Composite outcomes can overestimate treatment effect. Outcomes are unknown beyond 12 months.
EINSTEIN-Extension[11]									
The Einstein Investigators Phase III, DB, PG	1. Rivaroxaban 20mg daily 2. Placebo	Age: 58 yrs Female: 41%/43% Inclusion: objectively confirmed, symptomatic DVT o PE with 12 month prior treatment with warfarin or acenocoumarol Exclusion: additional VKA indication, CrCl <30 ml/min, significant liver disease, active bleeding, uncontrolled HTN, pregnant/ breastfeeding, concomitant CYP-450 3A4 inhibitors	1. 602 2. 594	Tx duration: 6 or 12 months	Recurrent VTE: R: 8 (1.3%) P: 42 (7.1%) HR 0.18; (95% CI 0.09 to 0.39, p<0.001) Morality: R: 1 (0.2%) P: 2 (0.3%)	ARR: 5.8% NNT: 17	Major Bleeding: R: 4 (0.7%) P: 0 (0.0%) p=0.11 Clinically Relevant Non-major Bleeding: R: 32 (5.4%) P: 7 (1.2%)	NS	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via computerized voice-response system. Performance: double-blind design. Placebo comparison limits clinical applicability. Detection: Outcomes were assessed by centra adjudication committee that were unaware of treatment assignment. Attrition: Low rates of lost to follow-up. **External Validity:** Recruitment: Patients previously on therapy (EINSTEIN-DVT or routine care) and if there was equipoise to continuing treatment. Patient Characteristics: Patients were previously exposed to treatment. Outcomes: Direct outcomes were used to determine treatment effect. Composite outcomes can overestimate treatment effect.

EINSTEIN-PE[12]									
The EINSTEIN-PE Investigators Phase III, PG, open-label, RCT	1. Rivaroxaban 15 mg twice daily for 3 weeks and then 20 mg once daily 2. Enoxaparin followed by dose-adjusted VKA	Mean Age: 58 years Male: 53% Inclusion: 18 years and older, with acute symptomatic PE with objective confirmation, with or without symptomatic DVT Exclusion: Prior anticoagulation, placement of vena cava, thromboectomy, fibrinolytic agent for current episode contraindication to anticoagulation treatment, additional indication for anticoagulation, and renal or liver disease.	1. 2419 2. 2413	Tx duration: 3, 6, or 12 months	<u>Symptomatic Recurrent VTE:</u> R: 50 (2.1%) E-VKA: 44 (1.8%) HR: 1.2 (95% CI, 0.75 to 1.68, p=0.003, for noninferiority)	NA	<u>Composite of major or clinically relevant nonmajor bleeding</u>: R: 249 (10.3%) E-VKA: 274 (11.4%) HR: 0.90 (95% CI, 0.76 to 1.07, p=0.23) <u>Major Bleeding:</u> R: 26 (1.1%) E-VKA: 52 (2.2%) HR: 0.49 (95% CI, 0.31 to 0.79, p=0.003) <u>Mortality:</u> R: 58 (2.4%) E-VKA: 50 (2.1%) HR: 1.13 (95% CI, 0.77 to 1.65, p=0.53)	NS NA NS	**Quality Rating: Fair** **Internal Validity: RofB** Selection: Patients were randomized via computerized voice-response system. Performance: open-label design lends itself to potential treatment bias. Detection: Details on outcome assessment not described. Attrition: Rates were low. **External Validity:** Recruitment: Patients were from 263 sites in 38 countries. Patient Characteristics: Similar baseline characteristics. Patients in enoxaparin treatment group were treated for a median duration of 8 days. Average TTR for warfarin treated patients was 62.7%. Outcomes: Direct outcomes used.
ARISTOTLE[14]									
Granger, et al Phase III, RCT, DB, DD	1. Apixaban 5 mg bid 2. Warfarin (INR adjusted to 2.0-3.0)	Median Age: 70 yrs Female: 35% Mean $CHAD_2$ Score: 2.1 Inclusion: AF or flutter diagnosis and 1 risk factor for stroke Exclusion Criteria: AF with a reversible cause, moderate or severe mitral	1. 9120 2. 9081	Median F/U: 1.8 yrs.	<u>Stroke or Systemic Embolism (per year):</u> A : 212 (1.27%) W: 265 (1.60%) HR 0.79 (95% CI, 0.66 to 0.95, p= 0.01 for superiority) <u>Ischemic Stroke:</u> A: 162 (0.97%) W: 175 (1.05%) HR: 0.79 (95% CI, 0.65 to 0.95, p=0.42) <u>Hemorrhagic Stroke:</u>	ARR: 0.33 NNT: 303 NS	<u>Major Bleeding:</u> A: 327 (2.13%) W: 462 (3.09%) HR 0.69 (95% CI, 0.6 to 0.80) P<0.001		**Quality Rating: Good** **Internal Validity: RofB** Selection: Randomization details not provided Baseline characteristics were well matched. Performance: Patients and investigators were blinded to treatment allocation including encrypted INR device used in DD study design. Detection: Outcomes assessors were blinded to treatment assignment. Attrition: Efficacy data was analyzed based on an ITT analysis which included all patients that were randomized. For safety outcomes, all patients who took at least one dose of study drug were included. Attrition accounted for

		stenosis, other indication for anticoagulation, recent stroke, ASA >165 mg/day or need for both ASA and clopidogrel and renal insufficiency			A: 40 (0.24%) W: 78 (0.47%) HR: 0.51 (95% CI, 0.35 to 0.75, p<0.001) <u>Myocardial Infarction:</u> A: 90 (0.53%) W: 102 (0.61%) HR: 0.88 (95% CI, 0.66 to 1.17, p=0.37) <u>Mortality:</u> A: 603 (3.52%) W: 669 (3.94%) HR: 0.89 (95% CI, 0.80 to 0.998, p=0.047)	ARR: 0.23% NNT: 435 NS ARR: 0.42% NNT: 238			2.1% of patients. **External Validity:** Recruitment: Patients from approximately 40 countries and 1000 centers were included. Patient Characteristics: Study included warfarin naïve users (~43%) and patients with varying degrees of AF risk based on $CHAD_2$ score. Mean time in therapeutic range for warfarin users was 62%. Outcomes: Direct outcomes were used to determine treatment effect. Composite outcomes can overestimate treatment effect.
AVERROES[33]									
Connolly, et al Phase III, RCT DB, DD	1. Apixaban 5 mg bid 2. Aspirin 81-324 mg daily	Age: 70 yrs. old Female: 41% Mean $CHAD_2$: 2 Inclusion Criteria: Patients were 50 yr or older with AF, at least one risk factor for stroke and not receiving or candidates for VKA therapy. Exclusion Criteria: Patient requiring anticoagulation for other indications than AF, serious bleeding in previou 6 months or at high risk of bleeding, alcohol or drug abuse, mental health issues, reduced life	1.2808 2.2791	Mean F/U: 1.1 yrs.	<u>Stroke or Systemic Embolism(per year):</u> A: 51 (1.6%) ASA: 113 (3.7%) HR 0.45 (95% CI, 0.32 to 0.62, p<0.001) <u>Ischemic Stroke:</u> A: 35 (1.1%) ASA: 93 (3.0%) HR: 0.37 (95% CI, 0.25 to 0.55, p<0.001) <u>Hemorrhagic Stroke:</u> A: 6 (0.2%) ASA: 9 (0.3%) HR: 0.67 (95% CI, 0.24 to 1.88, p=0.45) <u>Mortality:</u> A: 111 (3.5%) ASA: 140 (4.4%) HR 0.79 (95% CI, 0.62 to 1.02, p= 0.07)	ARR: 2.1% NNT: 48 ARR: 1.9% NNT: 53 NS NS	<u>Major Bleeding:</u> A: 44 (1.4%) ASA: 39 (1.2%) HR: 1.13 (95% CI, 0.74 to 1.75, p=0.57)	NS	**Study Rating: Good** **Internal Validity: RofB** Selection: Patients randomized via central, computerized, automated voice-response system. Baseline characteristics were well matched. Performance: Use of double-blind, double-dummy design was used to minimize bias. Detection: Outcomes assessors were blinded to treatment assignment. Attrition: Study was stopped early due to clear benefit of apixaban. Data was available on all randomized patients. **External Validity:** Recruitment: Included patients from 36 countries and 522 centers. Patient Characteristics: Patients included warfarin naïve (60%) and those with multiple risk factors for stroke. Most patients randomized to active ASA group received 81 mg of ASA (64%). Nine percent of patients in both groups took ASA in addition, 50% of the time.

		expectancy of less than 1 yr., severe renal insufficiency, increased LFTS/bilirubin or aspirin allergy.							Outcomes: Direct outcomes were used. Composite outcomes can overestimate treatment effect.
ADVANCE-1[7]									
Lassen, et al Phase III, RCT DB, DD	1. Apixaban 2.5 mg twice daily* 2. Enoxaparin 30 mg every 12 hours* * Treatment started 12-24 hours post surgery	Mean Age: 66 years Female: 60% Inclusion: Patients ≥ 18 years of age scheduled for TKR on one or both knees. Exclusion: active bleeding, contraindications to anticoagulation, required ongoing anticoagulation or antiplatelet therapy, uncontrolled hypertension, activ hepatobiliary disease, significant renal disease and contraindications to venography.	1. 1599 2. 1596	Mean Treatment: 11 days Mean start of medication: 20 hours	<u>Composite of asymptomatic and symptomatic DVT, non-fatal PE or death from any cause:</u> A: 104 (9.0%) E: 100 (8.8%) RR 1.02 (95% CI 0.78 to 1.32, p=0.06 for noninferiority) <u>Symptomatic VTE and VTE related death:</u> A: 19 (1.2%) E: 13 (0.81%) RR 1.46 (95% CI 0.72 to 2.95) <u>All PE:</u> A: 16 (1.0%) E: 7 (0.4%) <u>Mortality:</u> A: 3 (0.2%) E: 3 (0.2%)	NS NS NS	<u>Major Bleeds:</u> A: 11 (0.7%) E: 22 (1.4%) Risk Difference: -0.81 (95% CI -1.49 t 0.14, p=0.05) <u>Major or clinically relevant non-major bleeding:</u> A: 46 (2.9%) E: 68 (4.3%) Risk Difference: -1.46 (95% CI, -2.75 to 0.17, p=0.03)	NA NA	**Study Rating: Good** **Internal Validity: RofB** Selection: Patients randomized via central, interactive telephone system. Well matched baseline characteristics. Performance: Use of double-blind, double-dummy design was used to minimize bias. Detection: Outcomes assessment done by blinded, independent central adjudication committee. Attrition: There was a high level of attrition (~30%) which was similar between groups and characteristic for studies dependent upon venography for primary outcome rates. **External Validity:** Recruitment: Included patients from 14 countries and 129 sites. Patient Characteristics: Most patients were white (95%), from North America and under went unilateral knee replacement. Mean hospital stay was 6 days. Outcomes: Use of composite outcomes can overestimate treatment effect. Endpoints were driven mostly by asymptomatic events, which clinical relevance is still unknown.
ADVANCE-2[8]									
Lassen, et al Phase III, DB, DD, RCT	1. Apixaban 2.5 mg twice daily (started 12-24 hours post surgery) 2. Enoxaparin	Mean Age: 66.5 years Female: 71.5% Inclusion: Patients ≥ 18 years of age scheduled to have	1. 1528 2. 1529	Mean treatment: 12 days	<u>Composite of asymptomatic and symptomatic DVT, non-fatal PE and all-cause death:</u> A: 147 (15.1%) E: 243 (24.4%)	ARR: 9.3%	<u>Major Bleeds</u> A: 9 (0.6%) E: 14 (0.9%) P= 0.30 Absolute Risk Difference: -0.33% (95% CI -0.95 to 0.29,	NS	**Study Rating: Good** **Internal Validity: RofB** Selection: Patients randomized via an interactive, central telephone system. Performance: Double-blind, double-dummy treatment design minimized bias. The

	40 mg once daily (started 12 hours before surgery)	unilateral or bilateral elective knee replacement, including revision. Exclusion: Same as above.			RR: 0.62 (95% CI 0.51 to 0.74, p<0.0001 for superiority) <u>Symptomatic VTE or VTE-related death:</u> A: 7 (0.46%) E: 7 (0.46%) RR: 1.00 (95% CI 0.35 to 2.85) <u>All PE:</u> A: 4 (0.26%) E: 0 (0%) Mortality: A: 2 (0.13%) E: 0 (0%)	NNT: 11 NA NA	p=0.301) <u>Major or clinically relevant non-major bleeding:</u> A: 53 (3.5%) E: 72 (4.8%) Absolute Risk Difference: -1.24% (95% CI -2.66 to 0.18, p=0.088)	NS	European dosing regimen of enoxaparin 40 mg daily was used as the comparator. Detection: Outcome assessment done by assessors blinded to treatment assignment. Attrition: Approximately 35% of patients in both groups were not included in primary efficacy analysis. This rate is consistent with other studies with a similar design, however, higher than projection of 30%. **External Validity:** Recruitment: Patients were recruited from 27 countries and 125 sites. Patient Characteristics: Patients were recruited from non-US sites and majority of patients were white females. Mean hospital stay and treatment duration was 12 days, therefore, majority of drug treatments were done as an inpatient. Outcomes: Use of composite outcomes may overestimate treatment benefit. More clinically relevant symptomatic VTE rates were the same, however, trial was not powered to determine superiority.
ADVANCE-3[9]									
Lassen, et al Phase III, DD. DB, RCT	1. Apixaban 2.5 mg twice daily (started 12-24 hours post surgery) 2. Enoxaparin 40 mg every 24 hours (started 12 hours before surgery)	Mean Age: 60 yrs. Female: 52% Inclusion: Patients ≥ 18 years of age scheduled for elective total hip replacement or revision of previous inserted hip prosthesis. Exclusion: active bleeding, contraindications to anticoagulation or required ongoing anticoagulation or	1. 1949 2. 1917	Mean treatment duration: 34 days	<u>Composite of asymptomatic or symptomatic DVT, non-fatal PE or all-cause mortality:</u> A: 27 (1.4%) E: 74 (3.9%) RR: 0.36 (95% CI 0.22 to 0.54, p<0.001 for noninferiority and superiority) <u>Symptomatic VTE and VTE-related death:</u> A: 4 (0.1%) E: 10 (0.4%) RR: 0.40 (95% CI 0.01 to 1.28, p=0.11)	ARR: 2.5% NNT: 40 NS	<u>Major Bleeds</u> A: 22 (0.8%) E: 18 (0.7%) Absolute Risk Difference: 0.1 (95% CI -0.3 to 0.6, p=0.54) <u>Major or clinically relevant non-major bleeding:</u> A: 129 (4.8%) E: 134 (5.0%) Absolute Risk Difference: 0.2 (95% CI -1.4 to 1.0 p=0.72)	NS NS	**Study Rating: Good** **Internal Validity: RofB** Selection: Patients randomized via an interactive telephone system. Performance: Double-blind, double-dummy treatment design minimized bias. Detection: Blinding of outcome assessors was not described. Attrition: There were 28% of apixaban treated patients and 29% of enoxaparin treated patients that had venograms that could not be evaluated and were excluded from the analysis. **External Validity:** Recruitment: Patients were recruited from 21 countries and 160 sites. Patient Characteristics: Patients were

		antiplatelet therapy.			All PE: A: 0 (0%) E: 4 (0.2%) Mortality: A: 3 (0.1%) E: 1 (<0.1%)				predominately white and primarily treated in Europe and North America. Mean hospitalization days were 9. Outcomes: Use of composite outcomes may overestimate treatment benefit.
APPRAISE-2[35]									
Alexander, et al Phase III, DB, PC , RCT	1. Apixaban 5 mg twice daily 2. Placebo* * In addition to standard anti-platelet therapy	Mean Age: 67 years Females: 32% Inclusion Criteria: Patients with acute coronary syndrome (ACS) at high risk and taking standard treatment for ACS (aspirin or aspirin plus any P2Y12-receptor antagonist) Exclusion Criteria: Severe hypertension, severe renal dysfunction, active bleeding or at high risk of bleeding, known coagulopathy, prior stroke, class IV heart failure, and shortened predicted life expectancy.	1. 3705 2. 3687	Median treatment duration: 175 days for apixaban and 185 days for placebo	Composite of cardiovascular death, myocardial infarction or ischemic stroke: A: 279 (7.5%) P: 293(7.9%) HR: 0.95 (95% CI 0.80 to 1.11, p=0.51) Myocardial Infarction: A: 182 (4.9%) P: 194 (5.3%) HR: 0.93 (95% CI, 0.76 to 1.14, p=0.51) Mortality: A: 155 (4.2%) P: 143 (3.9%) HR: 1.08 (95% CI, 0.86 to 1.35, p=0.51)	NS NS NS	Major Bleeding: A: 46 (1.3%) P: 18 (0.5%) HR: 2.59 (95% CI 1.50 to 4.46, p=0.001) * Trial was stopped early due to excess of clinically important bleeding events	ARR: 0.8% NNH: 125	**Study Rating: Fair** **Internal Validity: RofB** Selection: Patients randomized in a blinded fasion via interactive voice-response system. Performance: Double-blind treatment design minimizes bias. Detection: Blinding of outcome assessors was not described. Attrition: Trial was stopped early due to excess of clinically important bleeding events. **External Validity:** Recruitment: Patients were recruited from 39 countries and 858 sites. Patient characteristics: Patients were high risk with more than half having protocol-defined high-risk characteristic. Most patients were taking aspirin (97%) and a high percent(81%) were also taking aspirin and a P2Y12-receptor antagonist. Outcomes: Composite outcome may overestimate treatment effect.
ADOPT[34]									
Goldhaber, et al Phase III, DB, DD, PC, RCT	1. Apixaban 2.5 mg twice daily for 30 days 2. Enoxaparin	Mean Age: 67 years Males: 49% Inclusion: 40 years or older, hospitalized for	1. 2211 2. 2284	Mean treatmen duration: A: 25 days E: 7 days	30-day composite of death related to VTE, PE, symptomatic DVT or asymptomatic proximal-leg DVT: A: 60 (2.71%)	NS	Major Bleeds A: 15 (0.47%) E: 6 (0.19%) RR: 2.58 (95% CI 1.0 to 7.24, p=0.04)	ARR: 0.28% NNH: 357	**Study Rating: Fair** **Internal Validity: RofB** Selection: Patients randomized through a central telephone system with computer-generated randomization list. Trial was

	40 mg once daily for 6-14 days	CHF, acute respiratory failure, infection (without septic shock), acute rheumatic disorder or inflammatory bowel disease and had an expected hospital stay of at least 3 days. Except for patients with CHF and respiratory failure, patients also had to have one additional risk factor and be moderately or severely restricted in mobility. Exclusion Criteria: Diagnosis of VTE, disease requiring ongoing anticoagulation, active liver disease, anemia or thrombocytopenia, severe renal disease, taking 2 or more antiplatelets or aspirin at more than 165 mg day, recent surgery, previous anticoagulant prophylaxis within 14 days, actively bleeding or at high risk for bleeding or invasive procedure scheduled.			E: 70 (3.06%) RR: 0.87 (95% CI 0.62 to 1.23, p=0.44) <u>Symptomatic DVT:</u> A: 5 (0.15%) E: 16 (0.49%) <u>Mortality:</u> A: 131 (4.1%) E: 133 (4.1%)	NS NA	<u>Major and clinically relevant non-major bleeding:</u> A: 85 (2.67%) E: 67 (2.08%) RR: 1.28 (95% CI 0.9 to 1.76 p=0.12)	NS	underpowered for primary efficacy outcome. Performance: Different treatment durations makes efficacy comparison difficult. Enoxaparin was given only as an inpatient for a minimum of 6 days. Detection: Primary outcome adjudication done by blinded, independent central adjudication committee. Attrition: Approximately 36% of patients were not included in primary efficacy analysis. **External Validity:** Recruitment: Patients were recruited from 35 countries and 302 sites. Patient Characteristics: Included primarily white patients with CHF or acute respiratory failure. Outcomes: Composite outcome may overestimate treatment effect. Screening of hospitalized patients for VTE with compression ultrasonography not routinely done.
AMPLIFY-EXT[36]									
Agnelli G,	1. Apixaban 2.5 mg twice	Average Age: 56.5 years	1. 840	Tx duration: 12 months	<u>Symptomatic Recurrent VTE or Death from VTE:</u>		<u>Major Bleeds:</u> A2.5: 2 (0.2%)		**Study Rating: Fair**

et al Phase III, DB PC, RCT	daily (A2.5) 2. Apixaban 5 mg twice daily (A5) 3. Placebo	Male: 57.5% DVT initial diagnosis: 65% Inclusion: Patients 18 years o older with objectively confirmed VTE wh had competed 6-12 months of anticoagulation therapy and there was clinical equipoise regarding continuing or discontinuing treatment Exclusion: Contraindications t anticoagulant therapy, dual antiplatelet therapy, or aspirin dose greater than 165 mg daily.	2. 811 3. 826		A 2.5: 32 (3.8%) A5: 34 (4.2%) P: 96 (11.6%) A2.5 vs P: RR: 0.33 (95% CI, 0.22 to 0.48, p<0.001) A5 vs. P: RR: 0.36 (95% CI 0.25 to 0.53, p<0.001)	A2.5-ARR: 7.8% NNT 13 A5-ARR: 7.4% NNT: 14	A5: 1 (0.1%) P: 4 (0.5%) A2.5 vs P: RR 0.49 (95% CI 0.09 to 2.64 A5 vs. P: RR: 0.25 (95% CI 0.03 to 2.24 <u>Major or clinically relevant non-major bleeding:</u> A2.5: 27 (3.2%) A5: 35 (4.3%) P: 22 (2.7%) A2.5 vs P: RR: 1.20 (95% CI 0.69 to 2.10 A5 vs P: RR: 1.62 (95% CI 0.96 to 2.73	NS NS	**Internal Validity: RofB** Selection: Patients randomized through an interactive voice-response system. Performance: Placebo comparison limits clinical applicability. Detection: Details on outcome assessment were not provided. Attrition: There were low levels of attrition (4 patients) **External Validity:** Recruitment: Patients were recruited from AMPLIFY trial (ongoing) in which they have already been accustomed to treatment with either apixaban or enoxaparin and warfarin. Patient Characteristics: Most patients (~90%) had unprovoked VTE, relatively young and were similar at baseline. Outcomes: Composite outcome may exaggerate treatment effect.

[1]**Study design:** DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel -group, XO = crossover, DD = double dummy.
[2]**Results abbreviations**: RRR = relative risk reduction, RR =relative risk, OR= Odds Ratio, HR = Hazard Ratio, ARR = absolute risk reduction, ARI = absolute risk increase NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval, ITT= intention-to-treat analysis, mITT-modified intention-to-treat analysis
[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)
Clinical Abbreviations: TTR= time in therapeutic range, SQ-subcutaneous, DVT- deep vein thrombosis, PE-pulmonary embolism, VTE- venous thromboembolism.

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Appendix 1: Drug Information[19]

Pharmacology: apixaban works by directly inhibiting free and clot-bound factor Xa and prothrombinase activity, resulting in decreased thrombus formation.

Table 1. Pharmacokinetics[19]

Parameter	Apixaban
Half-life	12 hours (chronic dosing)
Metabolism	Metabolized mainly via CYP3A4
Elimination	27% renal and 25% hepatic
Renal Dose Adjustment	Decrease dose to 2.5 mg twice daily in patients with any 2 of the following: serum creatinine ≥1.5 mg/dL, age ≥80 years or body weight ≤60kg. Not recommended if creatinine clearance is <15 mL/min or on dialysis.

Hepatic Dose Adjustment	No adjustment is needed in mild hepatic impairment. Use with caution in patients with moderate hepatic impairment due to possible intrinsic coagulopathy. Not recommended in patients with severe hepatic impairment.

Contraindications/Warnings[19]:

- **Black Box Warning:** Discontinuing apixaban causes patients to be at an increased risk of thrombotic events. An increased rate of stroke was demonstrated in trials when patients were transferred from apixaban to warfarin. It is recommended to strongly consider coverage with another anticoagulant if apixaban is being discontinued for reasons other than bleeding.
- **Contraindications:** Apixaban should not be used in patients with active pathological bleeding or severe hypersensitivity to apixaban.
- **Warning:** An increased rate of stroke was demonstrated in trials when patients were transferred from apixaban to warfarin. It is recommended to strongly consider coverage with another anticoagulant if apixaban is being discontinued for reasons other than bleeding. Apixaban increases the risk of bleeding which can be fatal. There is no antidote for apixaban.

Dose[19]

The recommended dose of apixaban is 5 mg twice daily for most patients with AF. The dose should be decreased to 2.5 mg twice daily for patients with any 2 of the following: ≥80 years of age, body weight ≤60 kg or serum creatinine ≥1.5 mg/dL.

Renal Impairment: See above. No data available on those patients with creatinine clearance <15 mL/min or on dialysis. Limited data available for patients with CrCl < 50 or <30 ml/min.

Hepatic Impairment: No dose adjustment in required in mild hepatic impairment.

Drug Interactions: The dose of apixaban should be reduced to 2.5 mg twice daily when co-administered with drugs that are strong dual inhibitors of cytochrome P450 3A4 and P-glycoprotein inhibitors. Co-administration of antiplatelet agents, fibrinolytics, heparin, aspirin and chronic NSAID use increases the risk of bleeding.

Switching from warfarin to apixaban: warfarin should be discontinued and apixaban starting when the INR is below 2.0.

Switching from apixaban to warfarin: apixaban will interfere with INR values and therefore INR measurements may not be useful in determining the warfarin dose. For continuous anticoagulation, it is recommended to discontinue apixaban and start a parenteral anticoagulant and warfarin at the time the next dose of apixaban would have been taken.

Switching from apixaban to other anticoagulants other than warfarin: discontinue the one being taken and begin the other at the next scheduled dose.

APPENDIX 2:
Suggested PA Criteria

Oral Direct Factor Xa Inhibitors (Rivaroxaban and Apixaban)

Goal(s):

- Promote safe and effective use of oral direct factor Xa inhibitors.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
What diagnosis is the factor Xa being prescribed for?	Record the ICD9 code:	
1. Does the patient have a diagnosis requiring short-term (<45 days) anticoagulation (i.e. total knee replacement: ICD9 - 81.54 or 81.55) or total hip replacement: ICD9 – 81.51 or 81.52)?	**Yes:** Go to #2.	**No:** Go to #3
2. Is the request for rivaroxaban?	**Yes:** Approve for up to 35 days.	**No:** Deny with the allowance of a 14 days of apixaban (or until patient is deemed adequately anticoagulated)*. Recommend a preferred agent.
3. Does the patient have a diagnosis of nonvalvular atrial fibrillation (ICD9 – 427.3x)?	**Yes:** Go to #4	**No:** Go to #7
4. Will the prescriber consider a change to the preferred oral anticoagulant, warfarin?	**Yes:** Approve. Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #5

5. Is the patient unable to tolerate the preferred oral anticoagulants due to one of the following: - unstable INR - allergy - contraindications to therapy - drug-drug interactions - intolerable side effects	**Yes:** Go to # 6	**No:** Deny with the allowance of a 14 days of rivaroxaban or apixaban (or until patient is deemed adequately anticoagulated)*. Recommend trial of warfarin.
6. Is the request for the second line agent, apixaban?	**Yes:** Approve for 1 year.	**No:** Deny with the allowance of a 14 days of rivaroxaban (or until patient is deemed adequately anticoagulated)*. Recommend trial of apixaban.
7. Does the patient have a diagnosis requiring acute or chronic DVT or PE treatment?	**Yes:** Go to #8	**No:** Deny (Medical Appropriateness)
8. Will the prescriber consider a change to a preferred anticoagulant?	**Yes:** Approve. Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #9
9. Is the patient unable to tolerate the preferred anticoagulant due to one of the following: - unstable INR - allergy - contraindications to therapy - drug-drug interactions - intolerable side effects	**Yes:** Go to #10	**No:** Deny with the allowance of a 14 days of rivaroxaban or apixaban (or until patient is deemed adequately anticoagulated)*. Recommend preferred anticoagulant.
10. Is the request for the rivaroxaban?	**Yes:** Approve for up to 1 year.	**No:** Deny with the allowance of a 14 days of apixaban (or until patient is deemed

		adequately anticoagulated)*. Recommend rivaroxaban trial.
* Patients switching from rivaroxaban or apixaban to other anticoagulants have been shown to have an increased risk of thrombotic events. Adequate anticoagulation is recommended during the switch from rivaroxaban or apixaban to another anticoagulant. Rivaroxaban and apixaban effect INR measurements, therefore, the appropriate dose of warfarin based on INR can not be used. Adding a parenteral anticoagulant, in addition to warfarin, at the time the next dose of rivaroxaban or apixaban is due is recommended.		

P&T Action: 3/28/13 (KS), 8/30/12 (KS), 1/26/12(KS)
Revision(s):
Initiated: 4/9/12

Oral Direct Thrombin Inhibitors (Dabigatran)

Goal(s):

- Promote safe and effective therapies for oral direct thrombin inhibitors.

Length of Authorization: 1 year

Covered Alternatives: Listed at; http://www.oregon.gov/DHS/healthplan/tools_prov/pdl.shtml

Approval Criteria		
1. Does the patient have a diagnosis of nonvalvular atrial fibrillation?	**Yes:** Go to #2	**No:** Go to #5
2. Will the prescriber consider a change to a preferred product warfarin?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #3
3. Is the patient unable to take warfarin therapy due to one of the	**Yes:** Go to #4	**No:** Deny.

following: - unstable INR - warfarin allergy - contraindications to warfarin therapy - drug-drug interactions - intolerable side effects		Recommend warfarin trial.
4. Does the patient have normal renal function (CrCl >30 mL/min) and is prescribed dabigatran 150mg twice daily or reduced renal function (CrCl 15-30 mL/min) and is prescribed dabigatran 75mg twice daily?	**Yes:** Approve for up to 1 year.	**No:** Deny (Medical Appropriateness)
5. Does the patient have a diagnosis requiring acute or chronic DVT or PE treatment?	**Yes:** Go to #6	**No:** Deny (Medical Appropriateness)
6. Will the prescriber consider a change to the preferred anticoagulant?	**Yes:** Additional information can be found at: http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/clinical.html	**No:** Go to #7
7. Is the patient unable to tolerate the preferred anticoagulant due to one of the following: - unstable INR - allergy - contraindications to warfarin therapy - drug-drug interactions - intolerable side effects	**Yes:** Approve for up to 1 year.	**No:** Deny. Recommend trial of preferred anticoagulant.

DUR Board Action: 3/28/13(KS), 1/26/12(KS)
Revision(s):
Initiated: 1/26/12 (KS)

Appendix 2: Suggested PA Criteria

Targeted Immune Modulators (TIMS)

Goal(s):

- *Cover TIMs according to OHP list guidelines.*
- *Promote use that is consistent with National Guidelines and medical evidence.*
- *Promote use of high value products.*

Requires PA: Non-preferred products

Preferred Products: Adalimumab (Humira®), Etanercept (Enbrel®)

Length of Authorization: 12 months

Generic Name	Trade Name	Indication
Abatacept	Orencia	RA, Juvenile RA, Juvenile idiopathic arthritis
Adalimumab	Humira	RA, Psoriatic arthritis, ankylosing spondylitis, Juvenile idiopathic arthritis, Crohn's disease, Plaque psoriasis, ulcerative colitis
Anakinra	Kineret	RA
Certolizumab	Cimzia	RA, Crohn's disease
Etanercept	Enbrel	RA, psoriatic arthritis, ankylosing spondylitis, juvenile idiopathic arthritis, plaque psoriasis
Golimumab	Simponi	RA, psoriatic arthritis, ankylosing spondylitis
Infliximab*	Remicade	RA, Crohn's disease, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis, plaque psoriasis
Natalizumab*	Tysabri	Crohn's disease
Rituximab*	Rituxan	RA
Tocilizumab*	Actemra	RA, juvenile idiopathic arthritis
Ustekinumab	Stelara	Plaque psoriasiss
Tofacitinib	Xeljanz	RA

Abbreviations: RA, rheumatoid arthritis
* Must be billed via J-code and payment requires trial of preferred self-administered drug first.

Approval Criteria : Nicotine Replacement Therapy (NRT)	
1. What is the diagnosis?	Record ICD-9 code

2. Is the diagnosis covered by OHP?	**Yes:** Go to #3	**No:** Pass to RPH; Deny (medical appropriateness)
3. Will the provider change to a preferred product?	**Yes:** Inform provider of covered alternatives in class..	**No:** Go to #4
4. Is the diagnosis psoriasis (ICD-9: 696.1-696.2, 696.8) and the product requested FDA approved for psoriasis (see table above)? * Moderate/Severe psoriasis treatments are covered on the OHP.	**Yes:** Refer to anti-psoriatics PA criteria at http://www.dhs.state.or.us/policy/healthplan/guides/pharmacy/OR%20Medicaid%20PA%20Criteria/PA%200711.pdf	**No:** Go to #5
5. Is the diagnosis ankylosing spondylitis (ICD-9 720) and the product requested is FDA approved for ankylosing spondylitis?	**Yes:** Approve treatment for up to 1 year	**No:** Go to #6
6. Is the diagnosis rheumatoid arthritis (ICD-9 714.xx) or psoriatic arthropathy (ICD-9 696.0) and the product requested FDA approved for rheumatoid arthritis (see table above)?	**Yes:** Go to #7	**No:** Go to #8
7. Has the patient had a trial and inadequate response to methotrexate or other first line DMARDs (leflunomide, sulfasalazine, hydroxychloroquine, penicillamine) and a disease duration of ≥6 months? Or, An intolerance or contraindication to oral DMARDs?	**Yes:** Approve treatment for up to 1 year	**No:** Pass to RPH; Deny (medical appropriateness)
8. Is the diagnosis Crohn's disease (ICD-9 555) and the product requested FDA approved for Crohn's (see table above)?	**Yes:** Go to #9	**No:** Pass to RPH; Deny (medical appropriateness)
9. Has the patient had a trial and inadequate response to conventional therapy including immunosuppressive therapy (mercaptopurine, azathioprine) and/or corticosteroid treatments? Or, Has an intolerance or contraindications to conventional therapy?	**Yes:** Approve treatment for up to 1 year	**No:** Pass to RPH; Deny (medical appropriateness)

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Oregon Health Authority

New Drug Evaluation: Linaclotide

Month/Year of Review: November, 2012
End date of literature search: November, 2012
Generic Name: Linaclotide
Drug Class: Prosecretory Gastrointestinal Agent
Brand Name (Manufacturer): Linzess® (Forest Laboratories, Inc.; Ironwood Pharmaceuticals, Inc.)

FDA Approved Indication: Treatment of irritable bowel syndrome with constipation (IBS-C) and for the treatment of chronic idiopathic constipation (CIC).[1]

Research Questions:
- Is linaclotide more effective than lubiprostone, laxatives, or other non-pharmacological agents for the reduction of constipation symptoms in IBS-C and CIC?
- Is linaclotide better tolerated than lubiprostone, the only other agent that is FDA approved for both non-emergency IBS-C and CIC?
- Are there specific populations for which linaclotide is better tolerated or more effective?

Conclusions:
- There is a moderate level of evidence that linaclotide reduces symptoms of constipation and pain associated with CIC and IBS-C. There is insufficient evidence to determine whether linaclotide improves clinical outcomes associated with health related quality of life.
- There are no comparative analyses published to date to determine if linaclotide is more effective or better tolerated than lubiprostone for CIC and IBS-C.
- It is unknown at this time whether linaclotide has the potential to cause the development of anti-linaclotide antibodies and cross-reaction with endogenous peptides.
- There is insufficient evidence to make conclusions of any improved efficacy or safety of linaclotide in specific subpopulations.

Recommendations:
- IBS and constipation are below the Oregon Health Plan line on the prioritized list. Include prior authorization to cover for only OHP covered diagnoses.

Background:
Irritable bowel syndrome (IBS) is a gastrointestinal disorder characterized by abdominal pain and discomfort that is accompanied by altered bowel habits.[2] The condition is the most frequently diagnosed GI disorder with a prevalence of 10-15% of the population in North America.[3] Up to 50% of all visits to the

gastroenterologist are for IBS, with female populations predominating at a ratio of 2:1 compared to males. While younger patients and women are more likely to be diagnosed with IBS, the disorder affects both sexes and all age groups. Patients may describe a constellation of symptoms ranging from cramping pain, diarrhea, alternating diarrhea and constipation, and periods of normal bowel habits interspersed with either constipation or diarrhea. Blood in the stool, nocturnal diarrhea, greasy stools or large volume diarrhea are not associated with IBS and indicate further investigation is warranted to isolate an organic cause.[2,3]

Irritable bowel syndrome with constipation is a subset of IBS that affects approximately one third of all IBS patients.[4] Symptoms that accompany IBS-C include abdominal bloating, hard stools, straining, and a sensation of incomplete evacuation.[2,4] Historical agents for the treatment of IBS-C included Tegaserod, a 5-HT4 partial agonist that was removed from the market in 2007 following increased cardiovascular events related to the medication; it is now only available as a prokinetic agent on an emergency IND basis. The only other approved agent in the U.S. for the treatment of IBS-C is lubiprostone, an E1 prostaglandin analogue chloride channel activator that increases chloride transport, intestinal fluid secretion and intestinal motility.[4] However, lubiprostone is only approved for adult, female patients with IBS-C. The most common side effect from lubiprostone is nausea, with an overall dose-related incidence ranging from 7 to 29%.[5] Lubiprostone is also approved for the treatment of chronic idiopathic constipation (CIC), a condition that is separate from IBS-C.

The symptoms of chronic idiopathic constipation are similar to IBS-C, i.e. bloating, straining during defecation, hard stools, abdominal discomfort, and a sense of incomplete evacuation.[2,6,7] Chronic idiopathic constipation is more prevalent in females, older individuals, and individuals of lower economic status or lower educational level.[7,8] The estimated prevalence of the disorder ranges from 4-20%, based on cross-sectional surveys of U.S. and European populations.[8] CIC by definition has no known cause, and is not associated with neurologic or metabolic disorders, lesions of the GI tract, or disorders such as diabetes or anorexia nervosa.

Constipation is the hallmark symptom that is shared between IBS-C and CIC. Insight into the placement of pharmacological therapy into the treatment algorithm for constipation may be gleaned from prucalopride guidance provided by NICE.[9] Although prucalopride is not available in the U.S., the guidance suggests a stepwise approach to the treatment of constipation before pharmacologic therapy is considered. First line options for treating constipation should focus on lifestyle and dietary modifications; short courses of laxatives may be administered if dietary and lifestyle modifications fail. A 2005 systematic review supports the use of specific laxatives in a stepwise fashion after first line options, citing adequate hydration, increased fiber intake, and nonstrenuous exercise as initial recommendations for treating constipation.[10] Reviewers analyzed data from randomized trials comparing non-pharmacological agents to placebo. The authors concluded that good evidence existed to support additional therapy with polyethylene glycol for the treatment of chronic constipation (Grade A). Moderate evidence supported the use of psyllium and lactulose (Grade B). There was insufficient evidence to support the use of bisacodyl, senna, milk of magnesia, or stool softeners for chronic constipation.

Patients who do not respond to lifestyle modifications or non-pharmacological treatment of IBS-C and CIC may wish to augment therapy with pharmacological options. Linaclotide is a new medication that will become available in the 4th quarter of 2012 as an additional treatment option for both IBS-C and CIC.[1] The agent is a synthetic, 14-amino acid peptide that is structurally related to endogenous guanylin peptides. The drug binds to and activates the guanylate cyclase C receptor on the luminal surface of intestinal epithelium. Once bound, activation of the receptor causes an increase in both intracellular and extracellular cGMP levels. Within intestinal epithelial cells, increases in cGMP initiate a signal-transduction cascade that activates the cystic fibrosis transmembrane conductance regulator. Ultimately, this causes secretion of chloride and bicarbonate into the intestinal lumen, leading to increased luminal fluid secretion and accelerated intestinal transit. FDA approved dosing includes linaclotide 290 mcg for irritable bowel syndrome with constipation, while the 145 mcg dose is indicated for

chronic idiopathic constipation.[1] Approved doses have been modified to reflect potencies determined through analytical analysis during product development and differ slightly from the doses reported in phase II trials.[12]

Clinical Efficacy:

A total of 4 Phase III, randomized, placebo controlled, parallel group, multicenter trials have been published that evaluate the efficacy of linaclotide in the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation.[4,6,11] All studies evaluated the clinical efficacy and safety of linaclotic in the treatment of CIC or IBS-C. Baseline demographic characteristics in the CIC trials were similar and well-matched; baseline demographics in the IBS-C trials were similar except for sex in trial MCP-103-302, which had a higher proportion of males in the placebo arm (p=0.038). Baseline clinical characteristics were simi in all trials with the exception of abdominal fullness (P=0.011), stool consistency (P=0.046) and straining (P=0.020) in IBS-C trial LIN-MD-31. Patients in all trials were predominantly white, female, under age 65, and with a mean age range of 43 to 49 years. Efficacy data was evaluated for all primary endpoints at 12 week based on intention-to-treat populations who reported at least one post-randomization, complete spontaneous bowel movement (CSBM). For all studies, patient were allowed to continue a stable, continuous regimen of fiber, bulk laxatives, or stool softeners if constant dose was maintained. Oral or suppository bisacodyl to 15 mg was allowed as rescue medication for severe constipation at 72 hrs after the last bowel movement or for intolerable constipation.

Of the phase III trials, two were fair quality trials that evaluated linaclotide vs. placebo in patients with CIC. Trials LIN-MD-**01** and MCP-103-**303** were identical, except for the inclusion of an additional 4-week randomized withdrawal after week 12 in trial 303.[6] Data for both trials were reported in the same publication, w a total of 1276 patients stratified post-randomization to receive 145 mcg linaclotide, 290 mcg linaclotide, or identical placebo once daily. Eligible patients include men and women ages 18 years or older with less than three spontaneous bowel movements (SBMs) per week plus one or more signs or symptoms during greate than 25% of bowel movements for a minimum of 12 weeks: straining; lumpy/hard stools; or sensation of incomplete evacuation. Patients must have also had les than or equal to six SBMs per week and less than three CSBMs during the baseline 14 weeks.

The primary efficacy endpoint for trials 01 and 303 was three or more CSBMs per week and an increase of one or more CSBMs from baseline during at least 9 ou of 12 weeks of treatment. This endpoint has been established as the FDA primary efficacy endpoint for CIC. It includes CSBM as a more clinically meaningful endpoint than spontaneous bowel movement, since constipation sufferers often complain about a sense of incomplete evacuation regardless of stool frequency.[6,12] The primary efficacy analysis was the difference in responder rate between linaclotide treatment arms and placebo. A total of 1272 patients reported at least one post-randomization CSBM and were included in the ITT analysis. There were statistically significant differences for all linaclotide doses compared to placebo, however the overall response rates that met the primary endpoint criteria were low for both studies. In trial 01, 16.0% of the 145 mcg arm and 21.3% of the 290 mcg arm attained the primary endpoint, compared to 6.0% of the placebo arm (NNT = 10 & 7, respectively; P≤0.01 & ≤0.001, respectively). trial 303, 21.2% of the 145 mcg arm and 19.4% of the 290 mcg arm vs. 3.3% of the placebo arm met the criteria for the primary endpoint (NNT=6 & 6, respective P≤0.001 for both linaclotide arms).

Secondary endpoint analyses for trials 01 and 303 revealed statistically significant differences for all endpoints, including stool frequency, stool consistency, severity of straining, abdominal discomfort, bloating, and constipation severity. The FDA considered the following secondary endpoints to be appropriate for inclusion in labeling: weekly change from baseline in number of CSBMs and SBMs, and change from baseline stool consistency based on the validated 7-point Bristol Stool Form Scale.[12] A score of 1 on the BSFS is indicative of constipation, while a score of 7 indicates diarrhea. For all linaclotide arms, CSBMs increased by approximately two per week compared to less than one for placebo, while SBMs increased by approximately three per week compared to an increase of one for placebo (all P-values <0.001). Overall, mean baseline stool consistency scores for all arms were approximately a 2 (lumpy, indicative of constipation). At 12 week

linaclotide arm mean scores increased to 4 (smooth, soft stool) vs. 3 (cracks, suggesting hardness) for placebo, all P-values <0.001. In regard to other secondary endpoints, the FDA determined in its summary review that the scoring systems used to assess observed treatment changes for severity of straining, abdominal discomfort, bloating, and constipation severity were problematic.[12] The ordinal scales utilized for these secondary endpoints were not validated. Patients were also asked to rate constipation symptoms compared to baseline, i.e. over an extended period of time & introducing the potential for recall bias. For example, weekly questions to evaluate bloating and abdominal discomfort were considered problematic because wording did not specify "severity" even though response options included "none, mild, moderate, severe, or very severe" on an ordinal scale of 1 to 5. In addition, mean and median baseline scores were in the range of on all arms (moderate), but only dropped to a range considered to be mild constipation for both linaclotide and placebo arms.

Two additional phase III trials have been published evaluating the efficacy of linaclotide. Trials LIN-MD-**31** and MCP-103-**302** were fair quality trials evaluating 29 mcg linaclotide vs. placebo in patients with IBS-C, with the same design methods for primary endpoint assessments.[4,11] Trial 31 included an additional 4-week randomized withdrawal period, while trial 302 gathered additional efficacy and safety data as tertiary analyses beyond the 12-week primary endpoint through 2(weeks. Eligible patients included men and women ages 18 years or older who met modified Rome II criteria for IBS-C, plus abdominal pain or discomfort with at least 2 of 3 features reported for a minimum of 12 weeks in the 12 months before screening: relieved w/defecation; onset associated with a change in the frequency of stool; or onset associated with a change in the form of stool before taking tegaserod or lubiprostone. Patients must also have had less than three SBMs per week and one or more signs or symptoms during greater than 25% of bowel movements for a minimum of 12 weeks: straining; lumpy/hard stools; a sensation of incomplete evacuation during greater than 25% of bowel movements, plus an average score of at least 3 for daily abdominal pain and an average of less than three CSBMs per week and less than or equal to five SBMs per week. Both trials included the same four primary efficacy endpoints assessed at 12 week

A total of 804 patients in trial 31 and 800 patients in trial 302 completed at least one post-randomization report and were evaluated in the ITT populations. Primary efficacy endpoints included: a) responders with at least a 30% reduction in abdominal pain and an increase of at least one CSBM from baseline in at leas out of 12 weeks (the FDA primary endpoint established for IBS-C),[12] b) at least a 30% reduction in the average daily worst abdominal pain for at least 9 out of 12 wks, c) at least three CSBMs and an increase of at least one CSBM from baseline for at least 9 out of 12 weeks, and 4) a combined responder (a+b). Similar to the CIC trials, the primary efficacy analysis was the difference in responder rate between linaclotide treatment arms and placebo. The percent response to treatmen by study is tabulated below. All results for trial 302 were statistically significant with P-values <0.0001; P-values for trial 31 were <0.0001, except for endpoint b (P=0.0262) and endpoint d (P=0.0004). Similar to the CIC trials, overall response rates to linaclotide were low even though results were statistically significant when compared to placebo.

Primary Efficacy Endpoints[4,11,12]	MCP-103-302		LIN-MD-31	
	Linaclotide 290 mcg (N=401)	Placebo (N=403)	Linaclotide 290 mcg (N=405)	Placebo (N=395)
6/12 Week APC +1 Responder[a]				
Responder %	33.7	13.9	33.6	21.0
NNT	5		8	
9/12 Week Abdominal Pain Responder[b]				
Responder %	38.9	19.6	34.3	27.1
NNT	5		14	
9/12 Week CSBM 3+1 Responder[c]				
Responder %	18.0	5.0	19.5	6.3
NNT	8		8	
9/12 Week APC 3+1 Responder[d]				
Responder %	12.7	3.0	12.1	5.1
NNT	10		14	

[a]FDA endpoint: ≥30% abdominal pain reduction and increase ≥1 CSBM fr baseline in the same week for ≥6/12 weeks.; [b]≥30% decrease in avg daily worst abdominal pain for 9/12 weeks; [c]≥3 CSBMs & an increas ≥1 CSBM from baseline for 9/12 weeks; [d]combined responder: decrease of ≥30% in avg daily worst abdominal pain score, ≥3 CSBMs, & a increase of ≥1 CSBM from baseline in the same wk for ≥9/12 weeks.

Of note, in the IBS-C phase III trials the FDA defined primary endpoint was not as rigorous as the 9 out of 12 week "APC 3+1 responder". Responder rates trended down as the endpoint for the IBS-C trials became more rigorous. While primary endpoints were assessed at 12 weeks, differences in responder rates in trial 302 did remain statistically significant with a sustained effect at 26 weeks for linaclotide vs. placebo. Response rates in the linaclotide arm were 32.4%, 36.9%, 15.7%, 12.0% vs. 13.2%, 17.4%, 3.5%, 2.5% for placebo for primary endpoints a-d, respectively (P<0.0001 for all analyses; endpoints a-d defined in table above). For trial 302 primary endpoints, NNTs remained in a similar range of 5 to 11 at 26 weeks, compared to a range of 5 to 10 at 12 weeks.

A total of 10 secondary endpoints were analyzed in trials 31 and 302. However, the FDA expressed concerns with secondary endpoints similar to the CIC trials, specifically in regard to abdominal discomfort, bloating, and severity of straining.[12] Reviewers concluded that the following two secondary endpoints could be included in the narrative: 1) change from baseline in the 12-week CSBM frequency rate, and 2) change from baseline in week-12 abdominal pain. From baseline t 12 weeks, the difference in the CSBM frequency rate between linaclotide and placebo was approximately 1.5 CSBMs. For mean abdominal pain scores, the difference between linaclotide and placebo was approximately a decrease of 0.7 points on a scale of 0 to 10. In comparison to the CIC trials, mean scores for sto consistency increased from approximately 2 to 4.3-4.5 for linaclotide treated arms, and from 2 to 3 for placebo arms.

Additional data regarding the efficacy of linaclotide for CIC and IBS-C is available from two phase II, multicenter, randomized, double blind, placebo-controlled dose-range finding trials evaluating the efficacy of linaclotide.[13,14] Primary endpoints did not match the defined endpoints of the phase III trials and were not included in the FDA's Summary Review. However, primary endpoints were similar to secondary endpoints from the phase III trials and provide additional efficac data in regard to appropriate dosing regimens for linaclotide. Both trials evaluated four dosing regimens of linaclotide 75 µg, 150 µg, 300 µg, and 600 µg vs. placebo.

102

The phase IIa trial published by Lembo et al. evaluated linaclotide vs. placebo in an ITT population of 307 patients with chronic constipation.[13] The primary endpoint was the mean change from baseline to 4 weeks in weekly SBM rates. It is unclear if additional endpoints were established a priori or if additional

endpoints were considered secondary assessments. Similar to the phase III trials, ordinal scales used for severity assessments of additional endpoints were not validated. However, for the primary endpoint there was a linear dose response in the mean frequency of SBMs from baseline to 4 weeks, with increases of 2.6, 3.3, 3.6 and 4.3 SBMs for doses of 75, 150, 300, and 600 µg respectively, compared to 1.5 for placebo ($P<0.05$). There was also a trend toward improvement in mean weekly CSBM frequency and stool consistency with increasing dose; however, results should be interpreted with caution given that the description of additional endpoints is vague in regard to hierarchy and whether they were ad hoc analyses. While bowel function trended toward greatest improvement at the 600 µg dose, there were also more side effects reported at this dose, with diarrhea as the most common adverse event. Authors concluded that the 150 µg and 300 µg doses of linaclotide provided the best balance of efficacy and safety for patients with chronic constipation.

The phase IIb trial published by Johnston et al. evaluated linaclotide vs. placebo in an ITT population of 419 patients with IBS-C.[14] The primary endpoint was the mean change from baseline to 12 weeks in weekly CSBM rates. Similar to the phase IIa trial, it is unclear if a hierarchy of additional endpoints was established and ordinal scales for severity measures were not validated. Results for the primary endpoint across all arms were statistically significant (all $P<0.01$). Mean increases for CSBM frequency ranged from 2.5 to 3.6, with the largest increase of 3.6 CSBMs occurring in the 300 µg arm ($P<0.001$). Diarrhea was the only dose-dependent side effect. Authors concluded that the 300 µg dose provided comparable efficacy to the 600 µg dose with fewer GI side effects, and recommended the dose be selected for phase III studies.

To date, comparative efficacy data of linaclotide vs. commonly used laxatives is lacking. However, a recent systematic review and meta-analysis was published that provides some insight into how linaclotide compares to other therapies for chronic constipation.[8] Twenty-one randomized controlled trials were evaluated for the effectiveness of laxatives and pharmacological therapies in the treatment of CIC, including linaclotide. Authors concluded the following agents were more effective than placebo: linaclotide (RR 0.84; 95% CI 0.80-0.87); lubiprostone (RR 0.67; 95% CI 0.56-0.80); laxatives (RR 0.52; 95% CI 0.46-0.60; included PEG, sodium picosulfate and bisacodyl). Prucalopride was also found to be more effective than placebo (RR 0.82; 95% CI 0.76-0.88), but it is not available in the U.S. Numbers needed to treat to prevent one patient from failing to respond to therapy ranged from 3 to 6.

There are no published comparative efficacy trials comparing linaclotide to lubiprostone. However, overall response rates to lubiprostone vs. placebo in an adult female, IBS-C population in two double-blind, placebo controlled trials was 13.8/7.8% and 12.1/5.7%.[15] The primary endpoint for the lubiprostone IBS-C trials was based on the patient's response to a global symptom relief scale and was less rigorous than the endpoints in the linaclotide CIC/IBS-C trials. It is therefore difficult to interpret any differences in response rates to linaclotide vs. lubiprostone. Head-to-head trials are needed to evaluate the efficacy of linaclotide compared to other available agents for the treatment of chronic constipation.

In conclusion, the overall strength of evidence is moderate in support of linaclotide's efficacy in the treatment of CIC and IBS-C. However, statistically significant results may not be clinically meaningful to patients. Overall response rates to linaclotide are low, and the measures utilized to evaluate clinically relevant symptom reduction for abdominal pain and symptom severity were suboptimal in phase II and phase III trials. For phase III trial primary efficacy endpoints, a response to 9 out of 12 weeks in the case of CIC and to 6 out of 12 weeks for IBS-C means up to 50% of the time the patient may experience no relief from symptoms. In addition, the impact of linaclotide on health-related quality of life was not assessed as a pre-defined primary or secondary endpoint. Patients in the general population who have constipation may be older, since prevalence increases with age. The data may not accurately reflect any differences in response due to sex as the study populations were predominantly female. Finally, the FDA primary endpoints for IBS-C and CIC are relatively new and have not been fully vetted in clinical trials. Therefore, it is difficult to determine the clinical meaningfulness of the endpoints, e.g. with an increase of one CSBM per week over baseline the patient may still experience discomfort and/or pain if their baseline number of CSBMs was zero. Patients should still seek to optimize all other options for treating IBS-C and CIC before trying linaclotide.

Clinical Safety:

The safety of linaclotide in patients under the age of 18 has yet to be determined. There is a black box warning for patients up to 6 years of age and use is discouraged in pediatric patients 6 through 17 years of age. The FDA has requested that the manufacturer perform additional safety analyses in animal and human models to determine the safety profile for this population. This request follows data demonstrating toxicity in neonatal and juvenile mice. In addition, the FDA has expressed concern that the greatest safety risk of linaclotide is the theoretical development of anti-linaclotide antibodies and cross-reaction with endogenous peptides. No data is available to date to assess this risk; however the manufacturer is required to perform additional anti-drug antibody assays plus a clinical trial in adults to determine the risk of developing antibody responses in response to treatment.[1,12]

The most common adverse drug event in all four phase III trials was diarrhea, with an overall incidence of 16% at the 145 mcg dose of linaclotide and 20% at 290 mcg linaclotide.[12] Likewise, data from the phase II trials suggests a trend of increasing incidence of diarrhea with increased doses of linaclotide. Two open-label, long-term safety studies have since been conducted on linaclotide. Although published data is not available, the outcomes have been included in the FDA Summary Review.[12] Nearly a third of both CIC and IBS-C patients reported diarrhea as an adverse event. Overall, in the long-term studies diarrhea was reported as severe in 3% of patients. The agent carries a pregnancy rating of "C".

Seven known deaths occurred from all study populations, however none were attributed to the drug. One patient died during screening prior to study drug exposure, two patients died from cancer, one patient fell from a ladder, and three deaths were attributed to narcotic use. There was no evidence linking linaclotide to renal or hepatic toxicity, correlating to low systemic exposure to the drug. None of the data from the randomized controlled trials established a causal link between linaclotide and diverticulitis, gall bladder disease, ischemic colitis, or hematological disorders; however, there was a higher percentage of patients with low RBC levels in the 290 microgram arms of the IBS-C and CIC trials compared to placebo and the lower dose arm (0.5%/0.2%/0.2%, respectively). The meaning of this finding is unclear, as there was no statistical difference between HCT or Hgb between study arms.[12]

COMPARATIVE CLINICAL EFFICACY

Relevant Endpoints:

1) Reduced symptom severity or elimination of symptoms
   -Improved bowel function
   -Reduced pain/discomfort associated with disease state
2) Improved health-related quality of life
3) Tolerability

Primary Study Endpoints (Phase III Trials):

1) CIC trials: Patients with at least 3 CSBMs per week and an increase of at least one CSBM per wk from baseline for at least 9 weeks during the 12-week treatment period (FDA defined 1° endpoint)
2) IBS-C trials: Responders with ≥30% abdominal pain reduction and an increase of at least one CSBM from baseline in the same week for at least 6 out of 12 weeks (FDA defined 1° endpoint)
3) IBS-C trials: ≥30% reduction of average daily worst abdominal pain for at least 9 out of 12 wks
4) IBS-C trials: at least 3 CSBMs & an increase of at least one CSBM from baseline for 9 out of 12 weeks
5) IBS-C trials: Combined responder: decrease of ≥30% in avg daily worst abdominal pain score, ≥3 CSBMs, & an increase of ≥1 CSBM from baseline in the same wk for ≥9/12 weeks

Ref./Study Design	Drug Regimens/ Duration	Patient Population (R1/R2/P)	N	Outcomes/ Efficacy Results (CI, p-values)	NNT	Safety Results (CI, p-values)	NNH	Quality Rating; Internal Validity Risk of Bias/ External Validity Concerns
1. Lembo AJ, et al. [6] **Trial MCP-103-303 (CIC)** DB, PC, PG, MC, RCT Phase III	R1: Linaclotide 145 µg R2: Linaclotide 290 µg P: Placebo Duration: 12 weeks Trials 303 and 01 were identical, except Trial 303 had an additional 4-wk randomized withdrawal after 12 weeks.	Mean age: 47/48/49 years Male: 13/12/12.9% White: 72.7/75.6/76.6% Age ≥65 yrs: 12.4/12.5/13.4% Inclusion Criteria: Men & women ≥18 yrs with <3 SBMs/wk + one or more s/sx during >25% BMs for min of 12 weeks: straining; lumpy/hard stools; sensation of incomplete evacuation. Plus: ≤6 SBMs/wk & <3 CSBMs during baseline 14 wks. Exclusion Criteria: loose or watery stool in absence of laxative for >25% BMs in preceding 12 wks; mushy stool for >1 SBM during baseline, Rome II criteria for IBS; hx pelvic floor dysfunction; alarm sx confirmed by colonoscopy. Patients on a stable, continuous regimen of fiber, bulk laxatives, or stool softeners allowed to continue if constant dose was maintained. PO or suppository bisacodyl up to 15 mg/day allowed as rescue medication for severe constipation at 72 hrs after last BM or for intolerable constipation.	N=643 ITT = 642 R1: 217 R2: 216 P: 209	FDA 1° endpoints: Patients with ≥ 3 CSBMs/week and an ↑ of at least one CSBM/wk from baseline for ≥ 9 weeks during the 12-wk treatment period [n (%)]: R1: 46 (21.2); P≤0.001 R2: 42 (19.4); P≤0.001 P: 7(3.3) OR (linaclotide: Placebo): R1: 7.72, 95% CI (3.41,17.47) P≤0.0001 R2: 7.21, 95% CI (3.14,16.59) P≤0.0001 2° endpoints: CSBMs change from baseline (no./wk): R1: 1.9 R2: 2.0 P: 0.5 P<0.001 SBMs change from baseline (no./wk): R1: 3.0 R2: 3.0 P: 1.1 P<0.001 Stool consistency, change from baseline score: R1: 1.9 R2: 1.8 P: 0.6 P<0.001	NNT R1: 6 R2: 6	**Pooled data 303/01** (R1/R2/P; CI & P-values not reported): Any events: 60.5%/55.7%/52.1% The most common dose-related ADE (%): Diarrhea: 16/14.2/4.7 Other ADEs in ≥3% of patients: flatulence, ab pain, URI, ab distention, nasopharyngitis, sinusitis, upper ab pain Mortality: 0% (one pt died from fentanyl OD) Serious ADEs (%): 1.4/2.6/2.1 Discontinuation due to ADEs (%): 7.9/7.3/4.2 1st occurrence of diarrhea ADE reported in 1st 2 weeks: 61.7% Diarrhea graded as severe ADE (R/P; %): 1.5/0.2	NNH R1: 9 R2: 10	**Quality Rating:** Fair **Analysis:** ITT; total of 1272 patients (trials 01 & 303); 4 patients out of 1276 did not report any post-randomization CSBMs. Sensitivity analyses including the 4 non-reporting patients revealed similar results. Observed-cases approach to missing post-baseline data with last-observation-carried-forward applied. **Overall Attrition:** R1/R2/P (%) 14.3/18.4/15.3 **Risk of Bias** **Internal Validity:** Selection: Low bias; randomization and allocation concealment clear; via offsite IVRS Performance: Low bias, blinding of patients and study monitors; unclear how PK samples at wk 7 were blinded but linaclotide levels were not detectable Attrition: Low bias; Less than 20% overall, with <10% difference between treatment groups. Adherence to IVRS: 88.3% Level of adherence to study medication, crossovers, and contamination not discussed. **External Validity:** Patient Characteristics: similar between groups; may not reflect general population Setting: geographic region used as a fixed effect term for analysis instead of trial center as some sites had small numbers of patients Outcomes: 200 patients provided 90% power to detect treatment differences in the primary endpoint. 2°outcomes that required pts to recall current symptoms compared to baseline subject to bias (e.g., severity, straining).

2. Lembo AJ, et al. [6] **Trial LIN-MD-01 (CIC)** DB, PC, PG, MC, RCT Phase III	R1: Linaclotide 145 µg R2: Linaclotide 290 µg P: Placebo Duration: 12 weeks Trials 303 and 01 were identical, except Trial 303 had an additional 4-wk randomized withdrawal after 12 weeks.	Mean age: 49/47/47 years Male: 8.5/11.4/8.8% White: 78.9/75.2/78.1% Age ≥65 yrs: 11.3/10.4/12.6% Same inclusion/exclusion criteria as Trial 303	N=633 ITT= 630 R1: 213 R2: 202 P: 215	<u>FDA 1° endpoints:</u> Patients with ≥ 3 CSBMs/week <u>and</u> an ↑ of at least one CSBM/wk from baseline for ≥ 9 weeks during the 12-wk treatment period [n (%)]: R1: 34 (16.0); P≤0.01 R2: 43 (21.3); P≤0.001 P: 13(6.0) OR (linaclotide: Placebo): R1: 2.93 95% CI (1.50,5.72) P≤0.0012 R2: 4.22 95% CI (2.20,8.10) P≤0.0001 <u>2° endpoints:</u> CSBMs change from baseline (no./wk): R1: 2.0 R2: 2.7 P: 0.6 P <0.001 SBMs change from baseline (no./wk): R1: 3.4 R2: 3.7 P: 1.1 P <0.001 Stool consistency, change from baseline score: R1: 1.8 R2: 2.0 P: 0.6 P<0.001	NNT R1: 10 R2: 7	**<u>Pooled data 303/01</u>** (R1/R2/P CI & p-values not reported)**:** ADEs, any events (%): 60.5/55.7/52.1 The most common dose-related ADE (%): Diarrhea: 16/14.2/4.7 Other ADEs in ≥3% of patients flatulence, URI, ab pain, ab distention, nasopharyngitis, sinusitis, upper ab pain Mortality: 0% (one pt died from fentanyl OD) Serious ADEs (%): 1.4/2.6/2.1 Discontinuation due to ADEs (%): 7.9/7.3/4.2 1st occurrence of diarrhea ADE reported in 1st 2 weeks: 61.7% Diarrhea graded as severe ADE (R/P; %): 1.5/0.2	NNH R1: 9 R2: 10	**Quality Rating:** Fair **Analysis:** ITT; total of 1272 patients (trials 01 & 303); 4 patients out of 1276 did not report any post-randomization CSBMs. Sensitivity analyses including 4 non-reporting patients revealed similar results. Observed-cases approach to missing post-baseline data with last-observation-carried-forward applied. **Overall Attrition:** R1/R2/P (%) 18.8/17.6/11.1 **<u>Risk of Bias</u>** **Internal Validity:** <u>Selection:</u> Low bias; computerized randomization and allocation concealment via offsite IVRS <u>Performance:</u> Low bias, blinding of patients and study monitors; unclear how PK samples at wk 7 were blinded but linaclotide levels were not detectable <u>Attrition:</u> Low bias; Less than 20% overall, with <10% difference between treatment groups. <u>Adherence to IVRS:</u> 86.3% Level of adherence to study medication, crossovers and contamination not discussed **External Validity:** <u>Patient Characteristics:</u> similar between groups; may not reflect general population <u>Setting:</u> geographic region used as a fixed effect term for analysis instead of trial center as some sites had small numbers of patients <u>Outcomes:</u> 200 patients provided 90% power to detect treatment differences in the primary endpoint. 2°outcomes that required pts to recall current symptoms compared to baseline subject to bias (e.g., severity, straining)

3. Rao S, et al.[4] **Trial LIN-MD-31** (IBS-C) DB, PC, PG, MC, RCT Phase III	R: Linaclotide 290 µg P: Placebo Duration: 12 weeks + 4 weeks RW period	Mean age: 43.3/43.7 years Male: 9.4/9.6% White: 77.5/76.2% Age ≥65 yrs: 4.7/6.6% Inclusion Criteria: Men and women ≥ 18 yrs who met modified Rome II criteria fo IBS-C; abdominal pain or discomfort with ≥ 2 of 3 features reported for min o 12 wks in the 12 mo before screening: i) relieved w/defecation, ii) onset assoc w/Δ freq of stool, or iii) onset assoc w/ Δ in form of stool before taking tegaserod or lubiprostone; < 3 SBMs/wk + one or more s/sx during >25% BMs for min of 12 weeks: straining; lumpy/hard stools; sensation of incomplete evacuation; avg score of ≥3 for daily ab pain; avg <3 CSBMs/wk and ≤5 SBMs/wk. Exclusion Criteria: loose or watery stool for >25% BMs in preceeding12 wks; during baseline, a BSFS score of 7 for any SBM, or 6 for >1 SBM; hx cathartic colon, laxative abuse, ischemic colitis, GI surgery, diverticulitis, family hx colorectal ca. Constipating drugs like narcotics excluded; however, patients on stable doses of drugs for IBS for 3(days prior to trial that may cause constipation allowed to continue (e.g. TCAs). Rescue med allowed ~ CIC trials	N= 803 ITT: 800 R: 405 P: 395	1° endpoints (n (%)) a) Responders with ≥30% ↓ ab pain and ↑ ≥ 1 CSBM from baseline in ≥ 6/12 wks (FDA 1°): R: 136 (33.6) P: 83 (21.0) OR (95% CI): 1.9 (1.4,2.7) P<0.0001 b) ≥30% ↓ avg daily worst ab pain (9/12 wks) R: 139 (34.3) P: 107 (27.1) OR (95% CI): 1.4 (1.0,1.9) P=0.0262 c) ≥3 CSBMs & ≥1 CSBM from baseline (≥9/12 weeks) R: 79 (19.5) P: 25 (6.3) OR (95% CI): 3.7 (2.3,5.9) P<0.0001 d) Combined responder (a+b): R: 49 (12.1) P: 20 (5.1) OR (95% CI): 2.6 (1.5,4.5) P=0.0004 2° endpoints a) CSBM Δ from baseline (mean): R: 2.3 P: 0.7 P<0.0001 b) Worst ab pain, Δ from baseline (mean): R: -1.9 P: -1.1 P<0.0001	NNT (1°) a) 8 b) 14 c) 8 d) 14 NNT (2°) N/A	ADEs, any events (%): 56.2/53.0 ADEs with ≥2% incidence (%): Diarrhea: 19.5/3.5 P<0.0001 Abdominal pain: 5.4/2.5; P=0.0462 Flatulence: 4.9/1.5; P=0.0084 Headache: 4.9/3.5; P=0.3825 Abdominal distension: 2.2/0.8; P=0.1434 Mortality: No deaths during treatment SAEs: 2 patients each arm (0.5% both arms) Discontinuation due to ADEs (%): 7.9/2.8 Discontinuation due to diarrhea (%): 5.7/0.3 >50% of patients w/diarrhea experienced in the 1st 2 week No diarrhea graded as severe ADE	NNH R: 6	**Quality Rating:** Fair **Analysis:** ITT; 800 patients met criteria for efficacy analysis & 802 met criteria for safety analysis **Overall Attrition:** (R/P): 23.2%/15.6% **Risk of Bias** **Internal Validity:** Selection: Low bias; computerized randomization and allocation concealment via offsite IVRS Performance: Low bias, blinding of patients and study monitors; unclear how PK samples at baseline and wk 4 were blinded but linaclotide levels were not detectable Attrition (R/P): Potential bias; overall attrition of linaclotide arm >20% due to greater loss to follow-up (4.2/2.5%) & incidence of adverse events (7.9/2.5%). Between group difference <10%. Adherence to IVRS: (R:P; %): 71/73 Level of adherence to study medication, crossovers and contamination not discussed. **External Validity:** Patient Characteristics: significant differences existed at baseline for symptoms of abdominal fullness, stool consistency & straining; may not reflect general population. Setting: geographic region used as a fixed effect term for analysis instead of trial center as some sites had small numbers of patients Outcomes: 400 patients per arm provided >85% power to detect treatment differences. Comorbid conditions such as diverticulitis may be present in the general population; Patients could meet some criteria for primary endpoints but still have dx of constipation according to Rome III guidelines (if <3 BMs/wk).

4. Chey WD, et al.[11] **Trial MCP-103-302** (IBS-C) DB, PC, PG, MC, RCT Phase III	R: Linaclotide 290 µg P: Placebo Duration: 26 weeks 1° and 2° efficacy assessed at 12 weeks Safety data assessed at 26 weeks	Mean age: 44.6/44.0 years Male: 8.2/12.7% White: 78.8/77.2% Age ≥65 yrs: 5.7/4.2% Inclusion Criteria: Men and women ≥ 18 yrs who met modified Rome II criteria for IBS-C; abdominal pain or discomfort with ≥ 2 of 3 features reported for min of 12 wks in the 12 mo before screening: i) relieved w/defecation, ii) onset assoc w/Δ freq of stool, or iii) onset assoc w/ Δ in form of stool before taking tegaserod or lubiprostone; < 3 SBMs/wk + one or more s/sx during >25% BMs for min of 12 weeks: straining; lumpy/hard stools; sensation of incomplete evacuation; avg score of ≥3 for daily ab pain; avg <3 CSBMs/wk and ≤5 SBMs/wk. Exclusion Criteria: loose or watery stool in absence of laxative for >25% BMs in preceding 12 wks; mushy stool for >1 SBM or watery stool for any SBM during baseline; hx GI resection, cholecystectomy 2 mo or ab surgery 6 mo before trial, bariatric surgery; hx diverticulitis. Constipating drugs like narcotics excluded; however, patients on stable doses of drugs for IBS for 30 days prior to trial that may cause constipation allowed to continue (e.g. TCAs).	N=805 ITT= 804 R: 401 P: 403	1° endpoints (P<0.0001 all endpoints) a) % responders with ≥30% ↓ ab pain and ↑ ≥ 1 CSBM from baseline in ≥ 6/12 wks (FDA 1°): R: 33.7% P: 13.9% OR (95% CI): 3.2 (2.2, 4.5) b) ≥30% ↓ avg daily worst ab pain (9/12 wks) R: 38.9% P: 19.6% OR (95% CI): 2.6 (1.9, 3.6) c) ≥3 CSBMs & ≥1 CSBM from baseline (≥9/12 weeks) R: 18% P: 5.0% OR (95% CI): 4.2 (2.5, 7.0) d) Combined responder (a+b): R: 12.7% P: 3.0% OR (95% CI): 4.7 (2.4,8.8) 2° endpoints a) CSBM Δ from baseline (mean): R: 2.2 P: 0.7 b) Worst ab pain, Δ from baseline (mean): R: -1.9 P: -1.1	NNT (1°) a) 5 b) 5 c) 8 d) 10 NNT(2°) N/A	ADEs, any events (%): R: 65.4% P: 56.6% P<0.05 ADEs with ≥2% incidence (%): Diarrhea: 19.7/2.5 P<0.0001 No other statistically significant differences in ADEs between treatment groups Mortality: 0% SAEs: R: 1% P: 1.7% (none related to linaclotide) Discontinuation due to ADEs (%): 10.2%/2.5% Discontinuation due to diarrhea (%): 4.5%/0.2% Onset of diarrhea in linaclotide-treated patients: Within 1 wk: 48.1% Within 4 wks: 75.9% No diarrhea graded as severe ADE	NNH R: 6	**Quality Rating:** Fair **Analysis:** ITT; 804 patients met criteria for analysis. **Risk of Bias** **Internal Validity:** Selection: Low bias; computerized randomization via IVRS Performance: Potential bias; blinding of patients and study monitors; unclear how PK samples at baseline and wk 4 were blinded. Out of 98 patients analyzed, 2 had levels of linaclotide just above threshold of 0.2 ng/ml. Attrition: Potential bias; only reported for 26, not 12 weeks; R=26.9%/P=24.3%; between group differences was 2.6% Adherence: Performed by pill counts at visits up to 12 weeks; 94/95% (R:P) **External Validity:** Patient Characteristics: no significant differences between treatment groups except for sex, with a higher percentage of females in the linaclotide arm (P=0.038); may not reflect general population Setting: geographic region used as a fixed effect term for analysis instead of trial center as some sites had small numbers of patients Outcomes: 400 patients per arm provided >85% power to detect treatment differences. Comorbid conditions such as diverticulitis may be present in the general population; Patients could meet some criteria for primary endpoints but still have a dx of constipation according to Rome III guidelines (if <3 BMs/wk)

5. Johnston JM, et al.[14] Linaclotide Improves Abdominal Pain & Bowel Habits in a Phase IIb Study of Patients with IBS-C DB, PC, MC, RCT Phase IIb dose-range finding study	R1: Linaclotide 75 µg R2: Linaclotide 150 µg R3: Linaclotide 300 µg R4: Linaclotide 600 µg P: Placebo	Mean Age (range): 44.4 (18-72) yrs Male: 8% White: 80% Inclusion Criteria: men and women ≥ 18 yrs who met modified Rome II criteria for IBS reporting <3 SBMs per week & 1 or more of the following Sx for ≥ 12 weeks in the 12 months preceding study entry: 1) straining during ≥ 25% of BMs; 2) lumpy/hard stools during ≥ 25% of BMs; 3) sensation of incomplete evacuation during >25% of BMs. During 2-wk baseline, required to report a mean score of ≥ 2.0 for daily assessment of ab pain or ab discomfort, plus mean of <3 CSBMs and ≤6 SBMs/week. Exclusion criteria: pregnant or breast-feeding patients, presence of loose, mushy, watery stools for >25% BMs OR score of 6 or 7 on BSFS w/o laxative use for previous 24 hrs during 2-wk baseline, Hx of pelvic floor dysfunction, colon surgery, ab surgery in previous 60 days, need for manual maneuvers for BM, or laxative abuse. PO or suppository bisacodyl up to 15 mg/day allowed as rescue medication for severe constipation at 72 hrs after last BM, provided no >2 doses and none used 3 days before first dose study med. Stable, continuous fiber regimen & antidepressants allowed if stable 30 days prior to enrollment.	N = 420 ITT = 419 R1: 79 R2: 82 R3: 84 R4: 89 P: 85	1° endpoint: Mean change from baseline to 12 weeks in weekly CSBM rate: R1: 2.90 (P<0.001) R2: 2.49 (P<0.01) R3: 3.61 (P<0.001) R4: 2.68 (P<0.001) P: 1.01 Additional endpoints: CSBM 75% responder (≥ 3 CSBMs/week and an ↑ of ≥1 CSBM/wk for ≥ 9 out of 12 weeks). for all values except linaclotide 150 µg : R1: 25.3% (P<0.05) R2: 19.5% R3: 32.1% (P<0.01) R4: 23.6% (P<0.05) P: 11.8% Mean change from baseline to 12 weeks in weekly SBM rate: R1: 4.62 (P<0.001) R2: 4.36 (P<0.001) R3: 4.97 (P<0.001) R4: 5.64 (P<0.001) P: 1.68 SBM 75% responder (≥ 3 SBMs/week and an ↑ of ≥1 SBM/wk for ≥ 9 out of 12 weeks) (%): R1: 54.4% (P<0.01) R2: 39.0% R3: 65.5% (P<0.001) R4: 52.8% (P<0.01) P: 29.4% Stool Consistency (BSFS mean change from baseline) R1: 1.91 (P<0.001) R2: 1.80 (P<0.001) R3: 2.28 (P<0.001) R4: 2.20 (P<0.001) P: 0.56	NNT (1°) N/A NNT (2°) R1: 7 R2: 13 R3: 5 R4: 8 N/A R1: 4 R2: 10 R3: 3 R4: 4 N/A	ADEs with ≥3% incidence (%): Diarrhea: 14.6% Abdominal pain: 5.4% UTI: 4.2% Nausea: 3.9% Nasopharyngitis: 3.3% Headache: 3.3% URTI: 3.3% Diarrhea was the only dose-dependent AE: R1:11.4% R2: 12.2% R3: 16.5% R4: 18.0% P: 1.2% Diarrhea graded as severe: R1: 2.3% R2: 2.5% R3: 1.2% R4: 4.5% Discontinuation due to AE (%) R1: 5% R2: 7.3% R3: 3.5% R4: 11.2% P: 2.3% Discontinuation due to diarrhea: R1: 2.5% R2: 4.9% R3: 1.1% R4: 6.7% P: 0% Median no. of days to initial onset of diarrhea: 4 Mortality: none reported	NNH R1: 10 R2: 9 R3: 7 R4:6	**Quality Rating:** Fair **Analysis:** ITT, 419 met criteria for analysis; missing data not imputed; analysis did not include a last observation carried forward approach (patients were considered non-responders for weeks with missing data) **Overall Attrition (R1/R2/R3/R4/P):** 20.2/18.3/16.5/20.2/23.5% Endpoints were not identified as a priori; it is unclear when additional endpoints were assessed P-values and confidence intervals not provided for safety data **Risk of Bias** **Internal Validity:** Selection: Low bias; computerized randomization via a statistician not associated with the trial Performance: Likely low bias; all study personnel blinded but a formal description of dummy placebo design was not provided Attrition: Potential bias; over 20% in 75 µg and 600 µg arms (R1 & R4) and placebo arms, however between group differences are < 10% Adherence: Patients reported time study medication (and any rescue medication) was taken daily via IVRS. Adherence rates not reported. **External Validity:** Patient Characteristics: No baseline P-values are provided; characteristics appear similar between treatment groups. Results may not reflect response in general population w/respect to race. Setting: U.S. geographic region used as a fixed effect term for analysis instead of trial center as some sites had small numbers of patients Outcomes: 80 patients per arm provided 95% power to detect treatment differences. Abdominal pain is a significant component of IBS, however the ordinal scale used to measure patient response to treatment was not validated. It is unclear which additional outcomes were identified a priori, therefore responses to non-validated instruments (mean changes in ab pain, bloating, straining) must be interpreted with caution when considering the general population.

6. Lembo AJ, et al.[13] Efficacy of Linaclotide for Patients with Chronic Constipation DB, PC, PG, MC, RCT Phase IIa dose-range finding study	R1: Linaclotide 75 µg R2: Linaclotide 150 µg R3: Linaclotide 300 µg R4: Linaclotide 600 µg P: Placebo	Mean Age (SD): 47.3 (13.7) yrs Male: 8% White: 84% Inclusion criteria: men and women ≥ 18 yrs who met modified Rome II criteria for CC reporting <3 SBMs per week & 1 or more of th following Sx for ≥ 12 weeks in the 12 months preceding study entry: 1) straining during > 25% of BMs; 2) lumpy/hard stools during > 25% of BMs; 3) sensation o incomplete evacuation during >25% of BMs. During 2-wk baseline, required to report avg <3 CSBMs and ≤ 6 SBMs per week via IVRS. Exclusion criteria: pregnant or breast-feeding patients, meeting Rome II criteria for IBS, hx pelvic floor dysfunction, need for manual maneuvers for BM, hx any colon surgery or ab operations within 60 days o study, hx laxative abuse. Score of 6 or 7 on BSFS excluded. PO or suppository bisacody up to 15 mg/day allowed as rescue medication for severe constipation at 72 hrs after last BM, provided no >2 doses and none used 3 days before first dose study med. Stable, continuous fiber regimen & antidepressants allowed if stable 30 days prior to enrollment.	N=310 ITT=307 R1:59 R2: 56 R3 62 R4: 62 P: 68	1° endpoint: Change in mean weekly SBM frequency from baseline to 4 weeks: R1: 2.6 R2:3.3 R3: 3.6 R4: 4.3 P:1.5 All P-values ≤0.05; test for linear trend was significant P<0.0001 Additional endpoints SBM responder rate (defined as weekly SBM rate ≥3 and a increase ≥1 relative to baseline): R1: 59.3% R2: 55.4% R3: 61.3% R4: 67.7% P: 32.4% All P-values ≤0.01 Change in mean weekly CSBM frequency from baseline to 4 weeks: R1: 1.5 R2: 1.6 R3:1.8 R4: 2.3 P: 0.5 All P-values ≤0.01 Change in overall PAC-QOL score from baseline to 4 weeks: R1: -0.72 (42.4%); P≤0.05 R2: -0.80 (44.6%); P≤0.05 R3: -0.67 (30.6%); P=0.0515 R4: -0.83 (48.4%); P≤0.05 P: -0.41 (26.5%)	NNT (1°) N/A R1: 4 R2: 4 R3: 3 R4: 3 N/A R1: 6 R2: 6 R3: 24 R4: 5	ADEs, patients with at least one event (n(%)): R1: 21 (35.6) R2: 18 (32.1) R3: 18 (29.0) R4:24 (38.1) P: 22 (31.9) Most common ADE was diarrhea (n(%)): R1: 3 (5.1%) R2: 5 (8.9%) R3: 3 (4.8%) R4: 9 (14.3%) P: 2 (2.9%) 2 incidences of diarrhea graded as severe, both in 600 µg arm Discontinuation due to ADE/diarrhea (n): R1: 0 R2: 2/1 R3: 2/2 R4: 3/3 P: 2 Half of reports of diarrhea were within 2 days of starting study medication Mortality: none reported P-values and confidence intervals not provided for safety data	NNH R1: 27 R2: 5 R3:-34 R4: 16 R1: 45 R2: 17 R3: 53 R4: 9	**Quality Rating:** Fair **Analysis:** ITT, 307 met criteria for analysis; observed cases approach to missing data applied (missing values not imputed) **Overall Attrition (R1/R2/R3/R4/P):** 8.5/10.5/6.5/19.0/11.6% Endpoints were not identified as a priori; it is unclear when additional endpoints were assessed **Risk of Bias** **Internal Validity:** Selection: Low bias; computerized randomization via validated computer system Performance: Likely low bias; all study personnel blinded but a formal description of dummy placebo design was not provided Attrition: Potential bias; <20% in all arms, however between group differences are >10% between R1 and placebo arms Adherence: Patients reported time study medication was taken daily via IVRS **External Validity:** Patient Characteristics: No baseline P-values are provided; more patients enrolled in placebo group; characteristics appear similar between treatment groups. Results may not reflect response general population w/respect to race or age. Setting: U.S. geographic region and treatment group used as fixed effect terms for analysis of covariance instead of trial center since trial was conducted at 57 clinical centers Outcomes: 60 patients per arm projected to provide 88% power to detect treatment difference (anticipating 10 patients lost per arm), however R4 600 µg arm lost 12 patients. Additional endpoints relied on non-validated instruments (mean changes in ab pain, constipation severity, bloating, straining and global relief); therefore results must be interpreted with caution. Primary endpoint has become more rigorous for recent phase III trials.

Study design abbreviations: DB = double-blind, RCT = randomized trial, PC = placebo-controlled, PG = parallel-group, MC=multi-center.
Results abbreviations: OR= Odds Ratio, NNT = number needed to treat, NNH = number needed to harm, CI = confidence interval
Quality Rating: Good- likely valid; Fair- likely valid/possibly valid; Poor- fatal flaw-not valid

Appendix 1: Specific Drug Information

CLINICAL PHARMACOLOGY[1]

Linaclotide is structurally related to endogenous guanylin peptides and acts as a guanylate cyclase-C (GC-C) agonist. Guanylate cyclase-C is present on the luminal surface of intestinal epithelium. Linaclotide and its active metabolite bind to GC-C and stimulate increases in intracellular and extracellular cyclic guanosine monophosphate (cGMP). Within intestinal epithelial cells, increases in cGMP initiate a signal-transduction cascade that activates the cystic fibrosis transmembrane conductance regulator (CFTR) ion channel. This results in secretion of chloride and bicarbonate ions into the intestinal lumen, which ultimately results in increased intestinal fluid and accelerated intestinal transit. Linaclotide mediated increase in cGMP is thought to be the mechanism that leads to a reduction in intestinal pain symptoms, since increased cGMP has been shown to decrease the activity of pain-sensing nerves in animal models.

PHARMACOKINETICS[1]

Parameter	Result
Oral Bioavailability	Low systemic bioavailability; below the limit of quantitation with 145 mcg and 290 mcg doses
Protein Binding	Plasma concentrations following PO doses are not measurable, therefore degree of binding cannot be calculated
Elimination	Eliminated in feces. Recovery in stool averages 5% (fasted) and 3% (fed), virtually all as active metabolite.
Half-Life	Standard PK parameters cannot be calculated
Metabolism	Metabolized by the GI tract to active metabolite MM 419447 that lacks the tyrosine moiety. Drug and metabolite are proteolytically degraded in the lumen to smaller peptides and amino acids.

DOSE & AVAILABILITY[1]

STRENGTH	ROUTE	FREQUENCY	DOSAGE:	RENAL ADJ	HEPATIC ADJ	Pediatric Dose	Elderly Dose	OTHER DOSING CONSIDERATIONS
145 mcg 290 mcg	Oral	Once daily	IBS-C: 290 mcg CIC: 145 mcg (capsules)	Not required	Not required	**BBW** Safety & efficacy not established	Insufficient data to determine if dosage changes are warranted	Take on an empty stomach 30 minutes prior to first meal of the c Swallow capsules whole; do not break apart or chew

ALLERGIES/INTERACTIONS[1]

Systemic drug-drug interactions and/or plasma protein binding-mediated drug interactions are not anticipated due to the fact that linaclotide and its active metabolite are not measurable in plasma following oral administration. In vitro analysis indicates that the agent does not interact with the cytochrome P450 system; likewise, linaclotide is neither an inhibitor nor a substrate of P-glycoprotein. No severe allergic reactions occurred in the pooled phase 3 trial dataset however incidences of skin and respiratory symptoms suggestive of hypersensitivity were reported in both linaclotide and placebo treatment arms. The overal incidence of skin manifestations was 1.3% for linaclotide and 1.6% for placebo; the incidence of pulmonary manifestations of hypersensitivity was 0.7% fo linaclotide-treated patients and 0.5% in placebo-treated patients.

DRUG SAFETY[1,12]

Serious (REMS, Black Box Warnings, Contraindications):

- BBW: Contraindicated in pediatric patients up to 6 years of age. Avoid use in pediatric patients 6 through 17 years of age. Linaclotide has caused deaths i young juvenile mice at clinically relevant adult doses. The FDA has waived the requirement to study linaclotide in pediatric populations pending furthe studies to isolate the underlying cause of death in young mice.
- Contraindications: Pediatric patients up to age six; patients with mechanical gastrointestinal obstruction.
- Warnings and Precautions: Hold or stop the agent if severe diarrhea occurs. Suspected adverse reactions should be reported to 1-800-FDA-1088 o www.fda.gov/medwatch.
- REMS: not required as of October, 2012.

The FDA has expressed concern that the greatest safety risk of linaclotide is the theoretical development of anti-linaclotide antibodies and cross-reactio with endogenous peptides. Such cross-reactivity could lead to deficiency syndromes. Reviewers concluded that likely adverse events could includ hypernatremia, volume overload, hypertension, and constipation. The FDA has indicated that anti-drug antibody assays must be developed and a clinica trial must be performed in adults to assess anti-drug antibody responses in patient samples.[12]

112

Look-alike / Sound-alike (LA/SA) Error Risk Potential: none identified.

Pregnancy/Lactation rating: Pregnancy rating of "C". No adequate, well-controlled studies of linaclotide have been performed in pregnant women. Fetal affects have been observed in animal studies at doses much higher than the 290 mcg ceiling dose, but only with maternal toxicity. Therefore, linaclotide should be used in pregnancy only when the benefit outweighs the risk. It is unknown whether linaclotide is excreted in human breast milk, however plasma levels of linaclotide and its metabolite are not measurable at approved doses. Caution is warranted when the agent is administered to nursing women.

Tolerability: Diarrhea was the most common adverse reaction reported in IBS-C and CIC patients. Severe diarrhea occurred at a rate of 2% for patients treated w both the 145 mcg and 290 mcg doses of linaclotide, vs. less than 1% of placebo-treated patients. Overall, 5% of linaclotide-treated patients discontinued due to diarrhea vs. less than 1% of placebo-treated patients. Diarrhea occurred in the first two weeks of treatment for the majority of patients treated with linaclotide. 8% of CIC patients treated with linaclotide and 4% of placebo-treated patients discontinued treatment prematurely due to adverse reactions.

ADVERSE REACTIONS[1]

IBS-C (Trials MCP-103-302 & LIN-MD-31; incidence ≥ 2.0% and greater than placebo)

Adverse Reactions	**Linaclotide 290 mcg [N=807] %**	**Placebo [N=798] %**
Gastrointestinal		
Diarrhea	20	3
Abdominal pain (any region)	7	5
Flatulence	4	2
Abdominal distention	2	1
Infections and Infestations		
Viral Gastroenteritis	3	1
Nervous System Disorders		
Headache	4	3

CIC (Trials LIN-MD-31 and MCP-103-302; incidence ≥ 2.0% and greater than placebo)

Adverse Reactions	Linaclotide 145 mcg [N=430] %	Placebo [N=423] %
Gastrointestinal		
Diarrhea	16	5
Abdominal pain (any region)	7	6
Flatulence	6	5
Abdominal distention	3	2
Infections and Infestations		
Upper respiratory tract infection	5	4
Sinusitis	3	2

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19

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Month/Year of Review: March 2013
PDL Classes: Topical Analgesics/Anesthetics

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

Current Status of PDL Class:

- Preferred Agents: CAPSAICIN CREAM
- Non Preferred Agents: CAPSAICIN PATCH, DICLOFENAC GEL AND SOLUTION, DICLOFENAC TRANSDERMAL PATCH (FLECTOR) LIDOCAINE CREAM, LIDOCAINE TRANSDERMAL PATCH (LIDODERM),

Previous Recommendations:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events
- Efficacy and safety not established in patients under 18
- Consider including capsaicin and lidocaine by PA criteria.

Methods:

A Medline OVID search was conducted with the following search terms: capsaicin, benzocaine, tetracaine, lidocaine, prilocaine, ketorolac, diclofenac, methyl salicylate, menthol, amlexanox, dibucaine, bromfenac, nepafenac, trolamine, aphthous mouth ulcer, acute pain, actinic keratosis, myalgia, osteoarthritis, eye pain, rheumatoid arthritis, corneal abrasion, extraction of cataract eye pain, burn, diabetic neuropathy, local anesthetic, topical analgesic, otitis, skin irritation, stomatitis, toothache, ulcer, dental prosthesis pain, arthritis, musculoskeletal pain, neuropathic pain, postherpetic neuralgia, neuropathy, psoriasis. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to January 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 157 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, four relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Ravishankar[1] et al conducted a small (n=100), fair quality study which compared 4% tetracaine gel with tetracaine-lidocaine (both 7% strength) patches for topical anesthesia prior to venous cannulation. Patients were randomized to receive either the gel or the patch prior to needle insertion. Pain after insertion was measured by a visual analogue scale of 0 (no pain) to 100 (the worst pain imaginable). No significant difference in pain response was found between the median group score for the gel versus the patch (11 versus 10; p = 0.63).

Another comparison of topical anesthetics in venous cannulation by Poonai[2] et al also measured the efficacy of lidocaine versus tetracaine for pain reduction. This small (n=60), fair quality trial randomized children aged 5 to 12 years old to either 4% liposomal lidocaine cream or 4% tetracaine gel prior to IV insertion. Pain was measured on an analogue scale; in this study children picked a face from the Revised Faces Pain Scale that best demonstrated their pain level. The faces corresponded to a numerical value between 0 (no pain) and 10 (very bad pain). Again no difference was found in pain response between the two treatments: mean score for the lidocaine group 3.4, for the tetracaine group 4.3 (p=0.28).

Bourolias[3] et al compared 10% lidocaine spray with 2% tetracaine solution for preventing pain and discomfort during transnasal fiber optic laryngoscopy. Forty-eight patients were randomized prior to the procedure to receive nasal sponges soaked either in lidocaine or tetracaine as an anesthetic. Pain was measured on a visual analogue scale of 0 (no pain) to 10 (intolerable pain). The tetracaine solution group had a lower mean pain score than the lidocaine group (2.29 versus 3.04; $p<0.001$). This was a low quality study with poorly defined methodology; blinding, randomization and allocation concealment were not described.

Lastly, a postoperative pain relief trial by Hardy[4] et al compared 2% viscous lidocaine solution with rectal diclofenac suppositories. This small (n=130) study recruited children 5 to 12 years old and measured pain relief after tonsillectomy through a visual analogue scale designed for children (similar to the one described in the Poonai study). No statistical difference in pain scores was seen between the two treatments ($p=0.474$). This was a low quality trial: blinding, randomization and concealment were not discussed, and results were published without treatment differences.

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
In September 2012[7], the FDA released a safety communication for OTC menthol, methyl salicylate, and capsaicin use. After several instances of serious burns were reported, the FDA advised consumers to stop using all OTC topical muscle and joint pain-relievers and seek medical attention if they experience signs of skin injury where the product was applied, such as pain, swelling, or blistering of the skin.

Also in 2012, a safety communication regarding the use of oral benzocaine was released. In April[8] the FDA issued a warning of rare cases of methemoglobinemia reported with benzocaine use. The majority of cases occurred in children under the age of two; because of this, the FDA recommended not using benzocaine in children under two years old.

New Systematic Reviews:
No new or updated, relevant, head-to-head systematic reviews were identified. A protocol[9] from the Cochrane Collaborative was published in 2010. The authors proposed to conduct a systematic review to measure any difference between topical analgesics to treat acute and chronic pain in adults. No estimated date of completion is listed.

Guidelines:
The 2012 updated guideline for osteoarthritis[10] treatment from the American College of Rheumatology was reviewed. The 2010 guidance[11] on neuropathic pain treatment from the UK's National Institute for Clinical Excellence was also reviewed; as was the 2011 guideline[12] published by the American Academy of Neurology, the American Association of Neuromuscular Medicine and the American Academy of Physical Medicine and Rehabilitation. In 2010, the American Society of Anesthesiologists updated guidelines on chronic pain[13]; they published new guidelines for acute pain[14] in the perioperative setting in 2012. No changes regarding the use of analgesics or anesthetics were found.

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

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4. Rhendra Hardy MZ, Zayuah MS, Baharudin A, et al. The effects of topical viscous lignocaine 2% versus per-rectal diclofenac in early post-tonsillectomy pain in children. *Int. J. Pediatr. Otorhinolaryngol.* 2010;74(4):374–377.

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14. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. *Anesthesiology*. 2012;116(2):248–273.

Appendix 1

Randomized Control Trials

Ravishankar N, Elliot SC, Beardow Z, Mallick A. A comparison of Rapydan® patch and Ametop® gel for venous cannulation. *Anaesthesia*. 2012; 67(4):367–370.
Ametop(®) gel (4% tetracaine) is used to provide topical anaesthesia for venous cannulation. Rapydan(®) patch (7% lidocaine and 7% tetracaine) has been developed to provide topical anaesthesia by a different mechanism, that of heat assisted delivery. We compared the topical anaesthetic effect of these agents for venous cannulation. One hundred healthy adults undergoing day-case surgery were randomly assigned to receive either Rapydan (n = 50) or Ametop (n = 50) before venous cannulation. Pain on insertion was scored on a visual analogue scale between 0 and 100 (where 100 = unbearable pain). Median(IQR[range]) pain scores were not different between groups with 11 (5-20 [0-72]) for Rapydan and 10 (5-24 [0-95]) for Ametop (p = 0.63). Adequate topical anaesthesia was achieved in over 90% of patients in both groups. Rapydan produces topical anaesthesia comparable with Ametop for venous cannulation.

Poonai N, Alawi K, Rieder M, Lynch T, Lim R. A comparison of amethocaine and liposomal lidocaine cream as a pain reliever before venipuncture in children: a randomized control trial. Pediatr Emerg Care. 2012;28(2):104–108.OBJECTIVE: Although the use of anesthetic creams before intravenous (IV) insertion has been shown to be both safe and effective in decreasing pain during IV cannulation, the use of any single agent based on efficacy is not yet considered the standard of care in children. We sought to compare a commonly used preparation, 4% liposomal lidocaine (Maxilene), with 4% amethocaine (Ametop), a newer agent with reportedly good efficacy and an intrinsic vasodilatory effect. METHODS: A total of 60 children aged 5 to 12 years were randomized to receive topically either 4% amethocaine or 4% liposomal lidocaine before IV cannulation. The primary outcome variable was the child's rating of pain using the Faces Pain Scale - Revised. Secondary outcomes included success rate on first IV cannulation attempt, cannulation difficulty ratings by the nurses, and adverse skin reactions. RESULTS: We found no statistically significant differences in self-reported scores in the Faces Pain Scale-Revised with the use of 4% amethocaine versus 4% lidocaine before IV cannulation. There was a trend toward fewer IV cannulation attempts in the 4% amethocaine group. Adverse skin reactions were uncommon, and there were no statistically significant differences between groups. DISCUSSION: This study demonstrates that there is no difference between 4% amethocaine and 4% liposomal lidocaine in reducing pain associated with IV cannulation in children. Amethocaine confers no advantage in improving IV cannulation success rate over lidocaine. Both agents are associated with few local adverse skin reactions.

Bourolias C, Gkotsis A, Kontaxakis A, Tsoukarelis P. Lidocaine spray vs tetracaine solution for transnasal fiber-optic laryngoscopy. *Am J Otolaryngol*. 2010;31(2):114–116.
STATEMENT OF PROBLEM: The aim of this study was to evaluate the efficacy of lidocaine spray 10%, compared with tetracaine 2% solution, as a local anesthetic for patients undergoing transnasal fiber-optic laryngoscopy. METHOD OF STUDY: A prospective study was conducted on patients undergoing transnasal fiber-optic laryngoscopy. Microsurgical sponges were applied in each side of the nose for 10 minutes before laryngoscopy. Patients were randomly classified into group A and group B, in which tetracaine 2% solution and lidocaine spray 10% were used, respectively. Patients were asked to evaluate the severity of pain during the procedure by a visual analog scale. Patients data, pain score, and potential complications were placed in a database and statistically assessed. MAIN RESULTS: Our series consisted of 48 patients. Statistical analysis showed significant lower mean nasal discomfort score in favor of the tetracaine group (2.29 vs 3.04 [P < .001]). No tetracaine complications or side effects occurred. PRINCIPAL CONCLUSION: Neurosurgical sponge application of tetracaine 2% solution is an easy, safe, inexpensive, and effective analgesia for transnasal fiber-optic laryngoscopy.

Rhendra Hardy MZ, Zayuah MS, Baharudin A, et al. The effects of topical viscous lignocaine 2% versus per-rectal diclofenac in early post-tonsillectomy pain in children. Int. J. Pediatr. Otorhinolaryngol. 2010;74(4):374–377.
INTRODUCTION: Tonsillectomy is frequently associated with postoperative pain of considerable duration, which is usually accompanied by the substantial consumption of both opioid and non-opioid analgesic such as NSAIDs and local anaesthetics. OBJECTIVE: The aim of this study was to evaluate the efficacy between 2% viscous lignocaine and sodium diclofenac based upon the visual analogue scores (VASs), consumption of pethidine 0.5mgkg(-1) as the rescue drug postoperatively and time taken to resume feeding. METHODS: 130 patients aged between 5 and 12 years old were randomly allocated into 2 groups to be given either 2% viscous lignocaine 4mgkg(-1) body weight topically post-tonsillectomy or sodium diclofenac 1mgkg(-1) per-rectal post-induction of anaesthesia. Postoperatively visual analogues score was done for 24h, the amount of pethidine given and time when the patient start taking oral feeding of clear fluid, soft diet and normal diet were documented. RESULTS: There was no significant difference in the visual analogue scores in both groups, however the requirement of pethidine as the rescue drug postoperatively was significant 2h post-tonsillectomy (p=0.023) in viscous lignocaine group compared to sodium diclofenac. The time taken to resume oral feeding and soft diet was also significant in viscous lignocaine group (p=0.016 and p=0.007) whereas there was no significant in taking normal diet. CONCLUSION: We concluded that 2% viscous lignocaine applied topically post-tonsillectomy is comparable to sodium diclofenac per-rectal in providing analgesia and faster oral feeding.

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Month/Year of Review: March 2013
PDL Classes: Topical Steroids

Date of Last Review: October 2009
Source Document: Provider Synergies

Current Status of PDL Class:

- Preferred Agents: ALCLOMETASONE CREAM/OINTMENT, BETAMETHASONE CREAM/LOTION/OINTMENT, CLOBETASOL CREAM/OINTMENT, DESONIDE CREAM/OINTMENT, FLUOCINOLONE CREAM/SOLUTION, FLUOCINOLONE ACETONIDE, HYDROCORTISONE CREAM/OINTMENT/SOLUTION, TRIAMCINOLONE CREAM/OINTMENT
- Non Preferred Agents: MOMETASONE, DESOXIMETASONE, HALOBETASOL, PREDNICARBATE (DERMATOP), FLURANDRENOLIDE (CORDAN), CLOCORTOLONE (CLODERM), AMCINONIDE, HALCINONIDE (HALOG)

Previous Recommendations:

- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events
- Consider covering at least one representative from each potency group

Methods:

A Medline OVID search was conducted with the following search terms: alclometasone, desonide, fluocinolone, hydrocortisone, hydrocortisone valerate, hydrocortisone butyrate, betamethasone dipropionate, betamethasone valerate, fluticasone, mometasone, prednicarbate, amcinonide, desoximetasone, diflorasone, triamcinolone, halobetasol, clobetasol, skin disorder, atopic dermatitis, hyperkeratotic dermatosis, eczema, pruritus ani, vitiligo, allergic disorder, skin disease, collagen disease, plaque psoriasis, and scalp psoriasis. The search was limited to English language articles of controlled trials conducted on humans published from 2009 to January 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 American Academy of Dermatology (AAD), and the UK's National Institute of Clinical Excellence (NICE).

New Trials:

A total of 120 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo or not a steroid), or outcome (non-clinical). After a review of titles and abstracts for inclusion, three relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

All three trials compared topical corticosteroids for treating psoriasis. All were small or very small trials of low quality without defined methods (allocation, blinding) and poorly described results.

Queille-Roussel[1] et al conducted a small (n=24), within-subject randomized, intraindividual comparison trial. Five topical treatments (calcipotriol ointment, calcipotriol cream, calcipotriol + betamethasone cream, calcipotriol + betamethasone gel, and calcipotriol + hydrocortisone ointment) and an ointment vehicle control were applied simultaneously to a predetermined site on individuals; each individual had six test sites total on their trunk, legs, or arms. Success was measured by response and scaled from 0 to 5 with clearer skin having lower scores. Calcipotriol + betamethasone ointment and gel were more effective at improving plaques ($p<0.001$) than all other compounds, but were not significantly different from one another ($p= 0.23$). The calcipotriol ointment and hydrocortisone ointment were more

effective than the calcipotriol cream and placebo ($p<0.001$) but had no statistical difference between one another ($p=0.053$).

Lee[2] et al also compared steroids on intraindividual sites. Five psoriasis patients were given fluocinonide, clobetasol, halobetasol cream, and placebo ointment on a site on either the upper or lower extremity for 12 days. All treatments saw improvement, with 80% of treated areas classified as "clear or almost clear" compared with zero for placebo. There was no statistical difference between steroid treatments.

Mentor[3] et al conducted a trial comparing clobetasol spray with betamethasone plus calcipotriene ointment in 93 patients with psoriasis over a four week treatment period. Patients were randomized to either the spray or ointment. Plaque changes were measured by investigators and graded on a scale. After four weeks no statistical difference was seen between the numbers of patients judged to have successful treatment (73% vs. 65%; $p>0.05$).

New drugs:
None

New Formulations/Indications:
None

New FDA safety alerts:
No new safety alerts were found, but safety labeling changes were added to topical flurandrenolide[4] warning of increased absorption when used in pediatric patients and for adult patients when applied to the groin, hands or face.

New Systematic Reviews:
No new or updated, relevant systematic reviews were identified.

Guidelines:
The 2009 updated version for psoriasis[5] treatment from the American Academy of Dermatology was reviewed; as was the psoriasis guidance[6] from the UK's National Institute for Clinical Excellence. No changes regarding the use of steroids were found.

Recommendations:

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

References:

1. Queille-Roussel C, Hoffmann V, Ganslandt C, Hansen KK. Comparison of the Antipsoriatic Effect and Tolerability of Calcipotriol-Containing Products in the Treatment of Psoriasis Vulgaris Using a Modified Psoriasis Plaque Test. *Clinical Drug Investigation*. 2012;32(9):613–619.

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Appendix 1

Randomized Control Trials

Queille-Roussel C, Hoffmann V, Ganslandt C, Hansen KK. Comparison of the Antipsoriatic Effect and Tolerability of Calcipotriol-Containing Products in the Treatment of Psoriasis Vulgaris Using a Modified Psoriasis Plaque Test. *Clinical Drug Investigation*. 2012; 32(9):613–619.

BACKGROUND AND OBJECTIVE: In 1972, Dumas and Scholtz developed the psoriasis plaque test to evaluate the potency of local corticosteroids. Through further modification of this method, the efficacy between antipsoriatic products can be differentiated. This method allowed for the simultaneous application of several products to different test sites in the same psoriasis patient. The objective of this current study was to compare the antipsoriatic effect of six topical products using a modified version of the original psoriasis plaque test with emphasis on the predictive capacity of this model. Validation of the use of immunohistochemical and histological scoring of biopsy material, in conjunction with clinical scoring, in the prediction of antipsoriatic effects was an additional objective. METHODS: This study was a single-centre, investigator-blinded, within-subject randomized, active- and vehicle-controlled, intraindividual comparison of six topical products in patients with psoriasis vulgaris. The products evaluated were calcipotriol ointment (50 μg/g); calcipotriol cream (50 μg/g); two-compound ointment (calcipotriol 50 μg/g; betamethasone dipropionate 0.5 mg/g); two-compound gel (calcipotriol 50 μg/g; betamethasone dipropionate 0.5 mg/g) [all in their marketed formulations]; an investigational ointment (calcipotriol 25 μg/g; hydrocortisone 10 mg/g); and a vehicle control. Psoriasis patients (≥18 years of age; n = 24) received simultaneous topical application of each of the products 6 days a week for a period of 21 days, at different test sites located on psoriasis plaques. Clinical assessment of the test sites was completed twice a week. Test site biopsies were taken at the final visit for histological analysis. The primary endpoint was the absolute change in total clinical score (TCS; erythema, scaling and infiltration) from baseline. RESULTS: For all products, the change in TCS correlated well with changes in histological and immunohistochemical values. The two-compound ointment and the two-compound gel both resulted in a large and significant reduction in TCS. Calcipotriol ointment and the calcipotriol/hydrocortisone ointment were less effective, although they were still more effective than the calcipotriol cream and the ointment vehicle. CONCLUSION: This study has demonstrated that the modified psoriasis plaque test can provide a relatively quick and effective method to evaluate the antipsoriatic effect of several topical treatments in small cohorts and that, by combining clinical scoring and histological assessment, a more accurate prediction of the antipsoriatic effect can be made. The two-compound formulations (ointment and gel) had a comparable antipsoriatic effect, which was superior to the other products tested. Furthermore, these data indicate that the gel formulation could provide an alternative effective treatment option to the well-established two-compound ointment for psoriasis patients.

Lee CS, Koo J. The efficacy of three class I topical synthetic corticosteroids, fluocinonide 0.1% cream, clobetasol 0.05% cream and halobetasol 0.05% cream: a Scholtz-Dumas bioassay comparison. *J Drugs Dermatol*. 2009; 8(8):751–755.

BACKGROUND: This study compared the efficacy of a novel, topical class I synthetic, 0.10% fluocinonide corticosteroid with two other class I corticosteroids and placebo for the treatment of plaque psoriasis. METHODS: A 0.5 gram dose of fluocinonide 0.1% cream, clobetasol propionate 0.05% cream, halobetasol propionate 0.05% cream, and placebo ointment were applied to test sites on one psoriatic plaque per patient (n=5). Test sites were outlined according to the Scholtz-Dumas bioassay. Test sites were assessed by a blinded evaluator (1 = psoriasis worsened to 5 = psoriasis clear or almost clear), cleaned and medications were reapplied on days 3, 5, 7, 10 and 12. RESULTS & CONCLUSION: The three class I corticosteroid products were comparably effective, numerically and statistically, in clearing the psoriatic plaques. Upon completion of treatment, 60-80% of active-treated sites were clear or almost clear of psoriasis compared to zero with the placebo.

Menter A, Abramovits W, Colón LE, Johnson LA, Gottschalk RW. Comparing clobetasol propionate 0.05% spray to calcipotriene 0.005% betamethasone dipropionate 0.064% ointment for the treatment of moderate to severe plaque psoriasis. *J Drugs Dermatol*. 2009; 8(1):52–57.

Topical corticosteroids are widely used in the treatment of psoriasis. This study was conducted to compare the efficacy and safety of clobetasol propionate (CP) 0.005% spray to calcipotriene 0.005%-betamethasome diproprionate 0.064% (C-BD) ointment in patients with moderate to severe plaque psoriasis. Assessments were made at baseline, week 2, week 4 (end of treatment) and week 8 (4 weeks post treatment). An assessment for Overall Disease Severity (ODS) found that 75% of CP spray-treated patients achieved a rating of clear or almost clear after 4 weeks of treatment compared to 45% of C-BD ointment-treated patients (P=.003). Adverse events were reported by less than one-third of patients from each treatment group (31% for CP spray and 33% for C-BD ointment).

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Month/Year of Review: March 2013
PDL Classes: Oral Antifungals

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

- Preferred Agents: CLOTRIMAZOLE TROCHE, FLUCONAZOLE TABLET/SUSPENSION, KETOCONAZOLE, NYSTATIN
- Non Preferred Agents: TERBINAFINE (LAMISIL), GRISEOFULVIN, TERBINAFINE, KETOCONAZOLE, FLUCYTOSINE, ITRACONAZOLE, VORICONAZOLE, POSACONAZOLE (NOXAFIL), AMPHOTERICIN B SUSPENSION (FUNGIZONE)

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 one medication from this group
- Recommend including nystatin for pediatric use

PA Criteria/QL:

- PA for non-preferred antifungals to approve use for only OHP covered diagnoses. Minor fungal infections of the skin are only covered when complicated by an immunocompromised host (Appendix 1).

Methods:

A Medline OVID search was conducted with the following search terms: clotrimazole, fluticasone, flucytosine, itraconazole, ketoconazole, miconazole, posaconazole, nystatin, voriconazole, griseofulvin, terbinafine, tinea unguium, tinea barbae, tinea capitis, tinea corporis, tinea cruris, tinea pedis, lichen planus, pityriasis vesicolor, systemic sclerosis, Candidiasis, cryptococcal meningitis, candidemia, vulvovaginal candida, Trichophytosis, Blastomycosis, Candida endophthalmitis, Candida pyelonephritis, Cryptococcosis, Leishmaniasis, Cutaneous sporotrichosis, mycosis, Histoplasmosis, Onychomycosis, tinea, Candida endophthalmitis, Aspergillosis, Chromoblastomycosis, Coccidioidomycosis, febrile neutropenia, Paracoccidioidomycosis, Sporotrichosis, seborrheic dermatitis, Allescheriosis, Fusarium infection. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to November week 3 2012.

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).

New Trials:

A total of 305 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo or IV antifungals), or outcome (non-clinical). After review of titles and abstracts for inclusion, ten relevant head-to-head clinical trials were identified and are discussed here. Please see Appendix 2 for the full abstracts.

Two trials compared prophylactic fluconazole and nystatin in very low weight neonates. Infants studied by Violaris et al[1] were randomly assigned to fluconazole or nystatin groups and were followed up to 15 months. Study enrollment was stopped early due to several deaths in both treatment groups from infection. The study finished underpowered. In the study by Aydemir et al[2], infants were randomized into one of the two treatments groups or a third placebo group and followed for 12 months. Neither study showed a significant difference between fluconazole and nystatin in preventing fungal infections. Both studies were low quality with multiple flaws in design and methods.

Treatment of vaginal yeast infection was the topic of two trials comparing oral fluconazole and a topical antifungal agent. Consolaro et al[3] showed fluconazole was more effective at eradicating vaginal candidiasis than topical nystatin (87% to 74%; p<0.05). Fluconazole was also more effective than intra-vaginal clotrimazole (80.5% vs. 70%; p<0.001) in the trial conducted by Sekhavat et al[4]. Both trials were fair to low quality. Blinding was an issue for both trials, neither trial discussed treatment allocation, and randomization methods were not clearly explained.

Three recent studies compared antifungal regimens for invasive fungal infections in fragile or immunocompromised populations. For the fair quality SMILES study, Vazquez et al[5] compared buccal miconazole with clotrimazole troches for oropharyngeal candidiasis (OPC) in patients with HIV. Miconazole was found to be noninferior to clotrimazole in resolving the signs and symptoms OPC 61% vs. 65% (a treatment difference of -0.059; 95% CI -0.140-0.022). A small open-label study conducted by Nussbaum et al[6] examined the efficacy of adding flucytosine to fluconazole to treat cryptococcal meningitis in HIV patients. Combination therapy was found to have a more rapid clearance rate of infection than fluconazole alone (treatment difference of 0.17; 95% CI 0.09–0.25) in this low quality trial. The number of deaths at the end of treatment however, was not significantly different between the treatment groups. In a high quality study, Wingard et al[7] compared fluconazole with voriconazole for prevention of invasive fungal infections (IFI) in hematopoietic cell transplantation patients. No statistical difference was found between treatments for any of the primary endpoints including freedom from IFI and death.

Several trials looked at skin and nail fungal infections. A low quality, open-label, cross-sectional study by Grover et al[8] evaluated oral griseofulvin, fluconazole or terbinafine to treat tinea capitis in children under the age of 12. Although griseofulvin was found to be the most effective at resolving infections (90% cure rate vs. 88% for terbinafine and 84% for fluconazole), the differences between the three were not statistically significant. Elewski et al[9] examined several different posaconazole regimens with terbinafine and placebo in a fair quality, phase two trial of adult patients with toenail infections. Compared with placebo, all patients in the posaconazole treatment arms had a significantly (p<0.01) greater proportion of patients with complete cure. Several posaconazole arms also had a higher rate of complete cure than terbinafine, although none were statistically significant.

A low quality study by Dehghan et al[10] compared topical clotrimazole with oral fluconazole for treating adults with tinea versicolor. Patients were treated for twelve weeks; at the end of treatment both groups had high rates of response (92% clotrimazole vs. 81.8% fluconazole, p=0.77) but the difference between the two treatments was not significant.

New drugs:
No new oral antifungal medications were approved.

New Formulations/Indications:
A new buccal formulation of miconazole was approved in April 2010. Oravig™ is indicated for the treatment of oropharyngeal candidiasis for patients over 16 years old.[11]

New FDA safety alerts:
In August 2011, the FDA released a safety alert regarding systemic fluconazole use. The FDA found treatment with chronic, high doses (400-800mg/day) of fluconazole during the first trimester of pregnancy was associated with birth defects in infants. Single low dose fluconazole (i.e. 150 mg) to treat vaginal yeast infection (candidiasis) was not implicated. Based on this information, the pregnancy category for fluconazole indications (other than for vaginal candidiasis) was changed from category C to category D.[12]

Several safety label changes were updated for oral antifungals in the last few years. In September 2010, the FDA added a label warning for increased risk of QT prolongation with posaconazole use.[13] In October 2010, the FDA revised the griseofulvin safety labeling to include a warning for increased risk of severe skin and hepatic adverse events.[14] The FDA also added a label warning for increased risk of hearing impairment with terbinafine use in April 2012.[15]

New Systematic Reviews:

Three new or updated, relevant systematic reviews were identified. None of the reviews' conclusions require altering current practice for oral antifungal use. Please see Appendix 3 for the full abstracts.

Tey et al[16] compared the effectiveness of griseofulvin and terbinafine in treating tinea capitis. Seven studies with 2163 patients were included in the meta analysis. Although patients treated with terbinafine had a higher rate of symptom resolution, it was not statistically significant (OR 1.22; 95% CI 0.975-2.277). Information for individual trial quality was not described.

Wang et al[17] compared the efficacy and safety of using fluconazole or itraconazole to prevent fungal infections in severely neutropenic patients with hematologic malignancies. Nine randomized control trials of mostly fair quality (four had no explanation of allocation concealment; only one trial attempted blinding) were included in the meta analysis for a total of 2254 patients. Itraconazole was more likely to prevent an invasive fungal infection (RR 1.33; 95% CI 1.02-1.73), although there were no statistically significant differences between the two regarding overall mortality (RR 0.95; 95% CI 0.77-1.17) or fungal-related mortality (RR1.28; 95%CI 0.80-2.07).

Wang and Chang et al[18] also looked at immunocompromised patients with hematologic malignancies to determine the comparative safety of various antifungals used to treat or prevent invasive fungal infections. 8745 patients were included from 39 trials of low-to-fair quality (very few trials described allocation concealment; the majority were not blinded); of the oral antifungals examined, itraconazole had the highest percentage of patients to discontinue due to adverse effects (18.8%; 95% CI 14.3-23.2) and discontinued patients due to elevated liver enzymes (1.5%; 95% CI 0-4.0). Fluconazole (adverse event discontinuation rate: 2.2%, 95% CI 0-4.6; discontinuation due to liver enzymes: 0.7%, 95% CI 0-1.4) and voriconazole (adverse event discontinuation rate: 9.5%, 95% CI 2.3-16.8; discontinuation due to liver enzymes: not calculated) were also included.

Guidelines:
The updated guideline[19] for pulmonary infections from the American Thoracic Society was reviewed; as was the updated sexually transmitted disease guideline[20] from the Centers for Disease Control. Updated treatment guidelines for cryptococcal diseases[21], febrile neutropenia[22], and intra-abdominal infections[23] from the Infectious Disease Society of America were also evaluated. No changes regarding the use of antifungals were found.

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

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2. Aydemir C, Oguz SS, Dizdar EA, et al. Randomised controlled trial of prophylactic fluconazole versus nystatin for the prevention of fungal colonisation and invasive fungal infection in very low birth weight infants. *Archives of Disease in Childhood - Fetal and Neonatal Edition*. 2010;96(3):F164–F168.

3. Consolaro M, Martins H, Da Silva M, Paiva L, Svidzinski T. Efficacy of Fluconazole and Nystatin in the Treatment of Vaginal Candida Species. *Acta Dermato Venereologica*. 2012;92(1):78–82.

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13. Safety Information > Noxafil (posaconazole) Oral Suspension. 2010. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm228417.htm. Accessed December 17, 2012.

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15. Safety Information > Lamisil (terbinafine hydrochloride) Tablets and Oral Granules. 2012. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm283119.htm. Accessed December 17, 2012.

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Appendix 1

Randomized Control Trials

Grover C, Arora P, Manchanda V. Comparative evaluation of griseofulvin, terbinafine and fluconazole in the treatment of tinea capitis. *International Journal of Dermatology*. 2012; 51(4):455–458.

Tinea capitis (TC) is a common childhood fungal infection which, if untreated, can cause long-term scarring. A number of antifungal drugs with proven efficacy are available for the treatment of TC. However, varying dosage schedules, changes in epidemiology, and rising drug resistance are factors that hamper treatment in some cases. A prospective, non-blinded, cross-sectional study of three commonly used drugs (terbinafine, griseofulvin, and fluconazole) was undertaken in children aged ≤12 years, presenting to a pediatric superspecialty hospital. The comparative efficacies of these three drugs were evaluated. A total of 75 patients (25 in each treatment group) who completed the designated treatment protocol were included in the final analysis. Of these, 60% had non-inflammatory TC and 56% had an ectothrix pattern on hair microscopy. Trichophyton violaceum was the most commonly isolated fungus. Cure rates of 96%, 88%, and 84% were achieved with griseofulvin, terbinafine, and fluconazole, respectively. Overall, seven patients required prolonged therapy. No side effects to therapy were seen. Griseofulvin remains the drug of choice in the treatment of TC. Terbinafine was the second best agent and offered the advantage of a shorter course of therapy. Fluconazole had comparatively low cure rates but was easier to administer than the other two medications.

Consolaro M, Martins H, Da Silva M, Paiva L, Svidzinski T. Efficacy of Fluconazole and Nystatin in the Treatment of Vaginal Candida Species. *Acta Dermato Venereologica*. 2012; 92(1):78–82.

The aim of this study was to determine and compare the efficacy of treatment with fluconazole and nystatin in Brazilian women with vaginal Candida. In a population of 932 women, vaginal cultures were performed for yeasts, whether or not the women showed signs and symptoms of vulvovaginal candidiasis. Yeasts were isolated from 12.2% of the women (114/932): 53.2% of the yeasts were Candida albicans, 27.0% C. glabrata, 13.5% C. tropicalis and 6.3% C. parapsilosis. Treatment was carried out with both drugs. The overall mean cure rates with fluconazole (87.0%) and nystatin (74.0%) were similar; among women with non-albicans, the cure rate with fluconazole was 100%, whereas that with nystatin was 44.4%. The cure rate for women with C. albicans was high with both fluconazole and nystatin; however, for those with non-albicans species the cure rate was excellent with fluconazole and very low with nystatin, differing from the majority of in vitro studies.

Elewski B, Pollak R, Ashton S, Rich P, Schlessinger J, Tavakkol A. A randomized, placebo- and active-controlled, parallel-group, multicentre, investigator-blinded study of four treatment regimens of posaconazole in adults with toenail onychomycosis. *British Journal of Dermatology*. 2012; 166(2):389–398.

Onychomycosis accounts for up to 50% of all onychopathies. OBJECTIVES: To evaluate the efficacy of four posaconazole regimens compared with placebo in the treatment of toenail onychomycosis, to assess the safety and tolerability of posaconazole, and to estimate the relative efficacy of posaconazole against terbinafine. METHODS: A phase 2B, randomized, placebo- and active-controlled, parallel-group, multicentre, investigator-blinded (double blind for placebo) study (ClinicalTrials.gov identifier: NCT00491764). Onychomycosis patients aged 18-75years (n=218) were randomized equally to one of six treatment regimens: posaconazole (oral suspension) 100, 200 or 400mg once daily (24weeks); posaconazole 400 mg once daily (12weeks); terbinafine (tablets) 250mg once daily (12weeks); or placebo (24weeks). The primary efficacy variable was complete cure (negative mycology and 0% nail involvement) at week 48. RESULTS: All posaconazole treatment arms had a significantly (P<=0.012) greater proportion of patients with complete cure at week 48 compared with placebo. The proportions of patients with complete cure were numerically higher for posaconazole 200mg/24weeks (54.1%) and 400mg/24weeks (45.5%), but lower for 400mg/12weeks (20%) compared with terbinafine (37%; differences were not statistically significant). Posaconazole was well tolerated. Seven patients receiving posaconazole withdrew because of asymptomatic liver enzyme increases, as mandated by protocol discontinuation criteria. CONCLUSIONS: The efficacy and favourable safety profile of posaconazole suggest a potential new treatment for onychomycosis. The availability of low-cost generic terbinafine may limit posaconazole use to second-line treatment of infections refractory to, or patients intolerant of, terbinafine, or nondermatophyte mould infections.

Sekhavat L, Tabatabaii A, Tezerjani FZ. Oral fluconazole 150mg single dose versus intra-vaginal clotrimazole treatment of acute vulvovaginal candidiasis. *Journal of Infection and Public Health*. 2011; 4(4):195–199.

To compare the safety and efficacy of fluconazole 150 mg single dose and intra-vaginal clotrimazole 200mg per day for six days in the treatment of the acute episode of vulvovaginal candidiasis (VVC). METHODS: In a prospective study, 142 patients with acute clinical and mycological confirmed VVC were enrolled and divided randomly in two groups. 70 patients received intra-vaginal tablet (200mg) daily for seven days, whereas 72 patients received single dose oral fluconazole (150 mg). Second and third visits were done for all patients seven days and one month after treatment and the clinical and mycological outcomes evaluated. The analysis performed using SPSS statistical software (version 15). RESULTS: At the second visit, 61 patients (84.7%) were cured clinically (inflammation and discharge) and 58 patients (80.5%) mycologically in fluconazole group and 60 patients (83.3%) were cured clinically and 49 patients (70%) mycologically in clotrimazole group (P=0.01). At the third visit, only one patient in fluconazole group and 17 patients in clotrimazole group had clinical sign of VVC (P=0.001). CONCLUSION: Oral fluconazole single dose seems to be a valid and promising therapy to cure acute signs and symptoms of VVC.

Aydemir C, Oguz SS, Dizdar EA, et al. Randomised controlled trial of prophylactic fluconazole versus nystatin for the prevention of fungal colonisation and invasive fungal infection in very low birth weight infants. *Archives of Disease in Childhood - Fetal and Neonatal Edition*. 2010; 96(3):F164–F168.

Invasive fungal infections are a major cause of morbidity and mortality in preterm infants. The authors conducted the first prospective, randomised controlled trial of nystatin compared with fluconazole for the prevention of fungal colonisation and invasive fungal infection in very low birth weight (VLBW) neonates. METHODS: During a 12-month period, all VLBW neonates were assigned randomly to receive nystatin (1 ml suspension, 100 000 U/ml, every 8 h), fluconazole (3 mg/kg body weight, every third day) or placebo from birth until day 30 of life (day 45 for neonates weighing <1000 g at birth). The authors performed weekly surveillance cultures and systemic fungal susceptibility testing. RESULTS: During the study period, 278 infants (fluconazole group, n=93; nystatin group, n=94; control group, n=91) weighing <1500 g at birth were admitted. There were no differences in birth weight, gestation, gender or risk factors for fungal infection among the groups. Fungal colonisation occurred in 11.7% of the nystatin group and 10.8% of the fluconazole group, as compared with 42.9% of the control group. The incidence of invasive fungal infection was 4.3% in the nystatin group and 3.2% in the fluconazole group, as compared with 16.5% in the control group. There were no differences in fungal colonisation and invasive fungal infection between the nystatin and fluconazole groups. CONCLUSIONS: Prophylactic nystatin and fluconazole reduce the incidence of colonisation and invasive fungal infection in VLBW neonates. The authors believe that nystatin is an alternative to fluconazole, because nystatin is safe, inexpensive, well tolerated and effective.

Wingard JR, Carter SL, Walsh TJ, et al. Randomized, double-blind trial of fluconazole versus voriconazole for prevention of invasive fungal infection after allogeneic hematopoietic cell transplantation. *Blood*. 2010; 116(24):5111–5118.

Invasive fungal infection (IFI) is a serious threat after allogeneic hematopoietic cell transplant (HCT). This multicenter, randomized, double-blind trial compared fluconazole (N = 295) versus voriconazole (N = 305) for the prevention of IFI in the context of a structured fungal screening program. Patients undergoing myeloablative allogeneic HCT were randomized before HCT to receive study drugs for 100 days, or for 180 days in higher-risk patients. Serum galactomannan was assayed twice weekly for 60 days, then at least weekly until day 100. Positive galactomannan or suggestive signs triggered mandatory evaluation for IFI. The primary endpoint was freedom from IFI or death (fungal-free survival; FFS) at 180 days. Despite trends to fewer IFIs (7.3% vs 11.2%; P = .12), Aspergillus infections (9 vs 17; P = .09), and less frequent empiric antifungal therapy (24.1% vs 30.2%, P = .11) with voriconazole, FFS rates (75% vs 78%; P = .49) at 180 days were similar with fluconazole and voriconazole, respectively. Relapse-free and overall survival and the incidence of severe adverse events were also similar. This study demonstrates that in the context of intensive monitoring and structured empiric antifungal therapy, 6-month FFS and overall survival did not differ in allogeneic HCT recipients given prophylactic fluconazole or voriconazole. This trial was registered at www.clinicaltrials.gov as NCT00075803.

Vazquez JA, Patton LL, Epstein JB, et al. Randomized, Comparative, Double-Blind, Double-Dummy, Multicenter Trial of Miconazole Buccal Tablet and Clotrimazole Troches for the Treatment of Oropharyngeal Candidiasis: Study of Miconazole Lauriad® Efficacy and Safety (SMiLES). *HIV Clinical Trials*. 2010; 11(4):186–196

Oropharyngeal candidiasis (OPC) is the most common opportunistic infection among persons infected with human immunodeficiency virus (HIV). Once-daily miconazole 50 mg buccal tablet (MBT) is a novel delivery system using an extended-spectrum azole with potent in vitro activity against many Candida species, including some that may be resistant to other azoles. METHODS: This phase 3, double-blind, double-dummy, multicenter trial evaluated 578 randomized patients with HIV infection and OPC. The study compared the efficacy and safety of MBT once daily with clotrimazole 10 mg troches (CT) 5 times daily for 14 days. The co-primary efficacy endpoints were clinical cure at test of cure (TOC) visit (days 17-22) in the intent-to-treat (ITT) and per protocol (PP) populations. RESULTS: Clinical cure rate at TOC visit for MBT-treated patients was statistically noninferior to CT-treated patients in both the ITT (61% vs 65%) and PP (68% vs 74%) populations. Secondary endpoints, safety, and tolerability were similar between treatment groups. CONCLUSIONS: In this large trial, once-daily MBT was shown to be noninferior to CT 5 times daily in the treatment of OPC in HIV-positive patients. MBT offers an effective, safe, and well-tolerated topical treatment option for OPC administered as a convenient once-daily dose.

Dehghan M, Akbari N, Alborzi N, Sadani S, Keshtkar AA. Single-dose oral fluconazole versus topical clotrimazole in patients with pityriasis versicolor: A double-blind randomized controlled trial. *The Journal of Dermatology*. 2010; 37(8):699–702.

This study was designed to compare the therapeutic effects of topical clotrimazole and systemic fluconazole in pityriasis versicolor. A double-blind randomized controlled trial was carried out in the dermatological clinic of Gorgan, northern Iran, between April 2006 and May 2007. All consecutive patients with pityriasis versicolor were included and randomly divided into two groups. In the first group (G1), patients underwent treatment with a single dose of fluconazole capsule (400 mg) and placebo cream. In the second group (G2), patients underwent treatment with clotrimazole cream (twice daily) and placebo capsule. The course of treatment was 2 weeks. All subjects were re-evaluated 2, 4 and 12 weeks after the end of the therapeutic course. After 2 weeks, the rate of complete resolution of disease was significantly higher in G2 than G1 (49.1% vs 30%). After 4 weeks, 41 patients (81.2%) of G1 and 52 patients (94.9%) of G2 showed complete resolution. After 12 weeks, 46 patients (92%) in G1 and 45 patients (81.8%) in G2 showed complete resolution. Recurrence rate in G1 and G2 were 6% and 18.2%, respectively. No complications were seen in either group. In this study, clinical response at week 4 was greater in the clotrimazole group than the fluconazole group. Recurrence at week 12 after treatment was less with oral fluconazole than clotrimazole cream. So, for better evaluation, more studies need to be done.

Nussbaum JC, Jackson A, Namarika D, et al. Combination Flucytosine and High-Dose Fluconazole Compared with Fluconazole Monotherapy for the Treatment of Cryptococcal Meningitis: A Randomized Trial in Malawi. *Clinical Infectious Diseases*. 2010; 50(3):338–344.

Cryptococcal meningitis is a major cause of human immunodeficiency virus (HIV)-associated morbidity and mortality in Africa. Improved oral treatment regimens are needed because amphotericin B is neither available nor feasible in many centers. Fluconazole at a dosage of 1200 mg per day is more fungicidal than at a dosage of 800 mg per day, but mortality rates remain unacceptably high. Therefore, we examined the effect of adding oral flucytosine to fluconazole. METHODS: From 13 February through 2 December 2008, HIV-seropositive, antiretroviral-naive patients experiencing their first episode of cryptococcal meningitis were randomized to receive (1) 14 days of fluconazole (1200 mg per day) alone or (2) in combination with flucytosine (100 mg/kg per day) followed by fluconazole (800 mg per day), with both groups undergoing 10 weeks of follow-up. The primary end point was early fungicidal activity, derived from quantitative cerebrospinal fluid cultures on days 1, 3, 7, and 14. Secondary end points were safety and 2- and 10-week mortality. RESULTS: Forty-one patients were analyzed. Baseline mental status, cryptococcal burden, opening pressure, CD4 (+) cell count, and HIV load were similar between groups. Combination therapy was more fungicidal than fluconazole alone (mean early fungicidal activity +/- standard deviation -0.28 +/- 0.17 log colony-forming units [CFU]/mL per day vs -0.11 +/- 0.09 log CFU/mL per day; P < .001). The combination arm had fewer deaths by 2 weeks (10% vs 37%) and 10 weeks (43% vs 58%). More patients had grade III or IV neutropenia with combination therapy (5 vs 1, within the first 2 weeks; P = .20), but there was no increase in infection-related adverse events. CONCLUSIONS: The results suggest that optimal oral treatment for cryptococcal meningitis is high-dose fluconazole with flucytosine. Efforts are needed to increase availability of flucytosine in Africa. Clinical trials registration. isrctn.org Identifier: ISRCTN02725351.

Violaris K, Carbone T, Bateman D, Olawepo O, Doraiswamy B, LaCorte M. Comparison of Fluconazole and Nystatin Oral Suspensions for Prophylaxis of Systemic Fungal Infection in Very Low Birthweight Infants. *American Journal of Perinatology*. 2009; 27(01):073–078.

We compared the efficacy and safety of fluconazole and nystatin oral suspensions for the prevention of systemic fungal infection (SFI) in very low birthweight infants. A prospective, randomized clinical trial was conducted over a 15-month period, from May 1997 through September 1998, in 80 preterm infants with birthweights <1500 g. The infants were randomly assigned to receive oral fluconazole or nystatin, beginning within the first week of life. Prophylaxis was continued until full oral feedings were attained. Blood and urine cultures were obtained at enrollment and then weekly thereafter. Thirty-eight infants were randomly assigned to receive oral fluconazole (group I), and 42 infants were assigned to receive nystatin (group II). Birthweight, gestational age, and risk factors for fungal colonization and SFI at the time of randomization and during the hospital course were similar in both groups. SFI developed in two infants (5.3%) in group I and six infants (14.3%) in group II. The difference between these two rates was not statistically significant (relative risk, 0.37; 95% confidence interval, 0.08 to 1.72). There were no deaths in group I and six deaths in group II (P = 0.03). Two infants died of neonatal sepsis, and four deaths were related to necrotizing enterocolitis and/or spontaneous intestinal perforation. No deaths were due to SFI. Enrollment was halted before completion and the study did not attain adequate power to detect a hypothesized drop in SFI rate from 15 to 5%. Although the results cannot justify any conclusion about the relative efficacy of fluconazole versus nystatin in prevention of SFI, the significantly higher mortality rate in the nystatin group raises questions about the relative safety of this medication.

Appendix 2

New Systematic Reviews

Tey HL, Tan ASL, Chan YC. Meta-analysis of randomized, controlled trials comparing griseofulvin and terbinafine in the treatment of tinea capitis. *Journal of the American Academy of Dermatology*. 2011; 64(4):663–670.

BACKGROUND: Griseofulvin has been the standard treatment for tinea capitis but newer antifungal agents, particularly terbinafine, are increasingly being used because of their shorter duration of treatment and more consistent absorption rates. OBJECTIVE: We sought to compare the efficacy of oral griseofulvin and oral terbinafine in the treatment of tinea capitis. METHODS: A search of MEDLINE, EMBASE, Cochrane Central Register of Clinical Trials, and the Cochrane Skin Group Ongoing Skin Trials Register was performed up to January 2010 for randomized controlled trials comparing griseofulvin and terbinafine in the treatment of tinea capitis in immunocompetent patients. The primary outcome measure was the complete cure rate. The mycological and clinical cure rates and adverse effects were secondary outcome measures. Pooling of treatment effect was accomplished using a random effects model and the I (2) test was used to check for heterogeneity among the studies. RESULTS: Seven studies involving 2163 subjects were included. There was no significant difference in efficacy between griseofulvin (mean duration of treatment 8 weeks, range 6-12 weeks) and terbinafine (mean duration of treatment 4 weeks, range 2-6 weeks); odds ratio = 1.22 favoring terbinafine (95% confidence interval [CI] = 0.785-1.919; P = .37). In the pooled analysis of 5 studies in which Trichophyton species were the predominant (>=65%) pathogenic dermatophyte, terbinafine showed a trend toward greater efficacy (odds ratio 1.49; 95% CI = 0.975-2.277; P = .065). Subgroup analysis revealed that terbinafine was more efficacious than griseofulvin in treating Trichophyton species (1.616; 95% CI = 1.274-2.051; P < .001) and griseofulvin was more efficacious than terbinafine in treating Microsporum species (0.408; 95% CI = 0.254-0.656; P < .001). Both griseofulvin and terbinafine demonstrated good safety profiles in the studies. LIMITATIONS: Data on efficacy of griseofulvin and terbinafine for separate groups of Trichophyton and Microsporum species were not available from every study. In the subgroup analysis of Microsporum species, data from only 3 studies were available. CONCLUSION: This meta-analysis suggests that terbinafine is more efficacious than griseofulvin in treating tinea capitis caused by Trichophyton species, whereas griseofulvin is more efficacious than terbinafine in treating tinea capitis caused by Microsporum species.

Wang J, Zhan P, Zhou R, et al. Prophylaxis with itraconazole is more effective than prophylaxis with fluconazole in neutropenic patients with hematological malignancies: a meta-analysis of randomized-controlled trials. *Medical Oncology*. 2009; 27(4):1082–1088.

Antifungal prophylaxis using fluconazole or itraconazole has been studied for many years but still no consensus has been reached regarding their safety and effectiveness. We performed a systematic meta-analysis to assess the efficacy of fluconazole compared to itraconazole in neutropenic patients with hematological malignancies. We gathered the data for our analysis from MEDLINE, EMBASE, Cochrane-controlled trials register, Cochrane Library, and Science Citation Index (1/1990 to 1/2009) searches. Risk ratio (RR) and 95% confidence intervals (CIs) were calculated using the random effect model. Nine RCTs were identified that were published in full text. Significantly, fewer patients were withdrawn from the studies due to the development of adverse effects with fluconazole prophylaxis when compared with itraconazole (RR 0.45, 95% CI 0.27-0.75, P=0.002). There were statistically significant differences regarding fungal infections (RR 1.34, 95% CI 1.08-1.67, P=0.009) and invasive fungal infections (RR 1.33, 95% CI 1.02-1.73, P=0.03) between the two educations. There were no statistically significant differences regarding overall mortality (RR 0.95, 95% CI 0.77-1.17, P=0.64), fungal-related mortality (RR 1.28, 95% CI 0.80-2.07, P=0.31), and proven fungal infections (RR 1.38, 95% CI 0.75-2.53, P=0.30). The analysis of published evidence reveals that itraconazole administration resulted in significantly fewer episodes of fungal infections and invasive fungal infections compared with fluconazole.

Wang JL, Chang CH, Young-Xu Y, Chan KA. Systematic Review and Meta-Analysis of the Tolerability and Hepatotoxicity of Antifungals in Empirical and Definitive Therapy for Invasive Fungal Infection. *Antimicrobial Agents and Chemotherapy*. 2010; 54(6):2409–2419.

To evaluate the tolerability and liver safety profiles of the systemic antifungal agents commonly used for the treatment of invasive fungal infection, we conducted a systematic review and meta-analysis of randomized controlled trials published before 31 August 2009. Two reviewers independently applied selection criteria, performed quality assessment, and extracted data. We used the beta-binomial model to account for variation across studies and the maximum likelihood method to estimate the pooled risks. We identified 39 studies with more than 8,000 enrolled patients for planned comparisons. The incidence rates of treatment discontinuation due to adverse reactions and liver injury associated with antifungal therapy ranged widely. The pooled risks of treatment discontinuation due to adverse reactions were above 10% for amphotericin B formulations and itraconazole, whereas they were 2.5% to 3.8% for fluconazole, caspofungin, and micafungin. We found that 1.5% of the patients stopped itraconazole treatment due to hepatotoxicity. Furthermore, 19.7% of voriconazole users and 17.4% of itraconazole users had elevated serum liver enzyme levels, although they did not require treatment discontinuation, whereas 2.0% or 9.3% of fluconazole and echinocandin users had elevated serum liver enzyme levels but did not require treatment discontinuation. The results were similar when we stratified the data by empirical or definitive antifungal therapy. Possible explanations for antifungal agent-related hepatotoxicity were confounded by antifungal prescription to patients with a high risk of liver injury, the increased chance of detection of hepatotoxicity due to prolonged treatment, or the pharmacological entity.

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Month/Year of Review: March 2013
Date of Last Review: February 2010
PDL Classes: Topical Antifungals
Source Document: Provider Synergies

Current Status of PDL Class:
- Preferred Agents: NYSTATIN CREAM/OINTMENT, MICONAZOLE CREAM
- Non Preferred Agents: TOLNAFTATE, KETOCONAZOLE, CLOTRIMAZOLE, CICLOPIROX, ECONAZOLE, NAFTIFINE, BUTENAFINE, SULCONAZOLE, OXICONAZOLE (OXISTAT),

Previous Recommendations:
- Evidence does not support a difference in efficacy/effectiveness
- Evidence does not support a difference in harm/adverse events

PA Criteria/QL:
- PA required for non-preferred agents covering only for a covered diagnosis and trial of a generic formulation (Appendix 1).

Methods:
A Medline OVID search was conducted with the following search terms: clotrimazole, tolnaftate, naftifine, econazole, butenafine, ciclopirox, sulconazole, sertaconazole, miconazole, nystatin, terbinafine, oxiconazole, tinea unguium, tinea capitis, tinea corporis, tinea cruris, tinea pedis, lichen planus, pityriasis versicolor, Candidiasis, vulvovaginal candida, Blastomycosis, Coccidioidomycosis, Cryptococcosis, mycosis, Histoplasmosis, Onychomycosis, tinea, Chromoblastomycosis, seborrheic dermatitis. The search was limited to English language articles of controlled trials conducted on humans published from 2010 to December week 3 2012.

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).

New Trials:
A total of 210 citations resulted from the initial MEDLINE search. Articles were excluded due to the wrong study design (observational), comparator (placebo or non-antifungal), or outcome (non-clinical). After review of titles and abstracts for inclusion, four relevant head-to-head clinical trials were identified and are discussed below. Please see Appendix 1 for the full abstracts.

Two trials compared oral fluconazole and a topical antifungal agent to treat vaginal yeast infections. Consolaro et al[1] showed fluconazole was more effective at eradicating vaginal candidiasis than topical nystatin (87% to 74%; $p<0.05$). A trial Sekhavat et al[2] also demonstrated fluconazole as superior to intra-vaginal clotrimazole (80.5% vs. 70%; $p<0.001$). Both trials were fair to low quality; blinding was an issue for both trials, neither trial discussed treatment allocation, and randomization methods were not clearly explained.

A low quality study by Dehghan et al[3] compared topical clotrimazole with oral fluconazole for treating adults with tinea versicolor. At the end of twelve weeks both groups had high rates of response (92% clotrimazole vs. 81.8% fluconazole, $p=0.77$) but the difference between the two treatments was not significant.

A low quality small study by Chen et al[4] looked at the adjunctive efficacy of using topical treatment in children with tinea capitis. Patients were randomized to use either 1% selenium sulfide or 1% ciclopirox shampoo with oral griseofulvin for eight weeks. At the end of treatment 91.7% of children using selenium sulfide and 90.4% of children using ciclopirox had a mycological cure; the difference between the shampoos was not statistically significant.

New drugs:
No new topical antifungal medications were approved.

New Formulations/Indications:
A new buccal formulation of miconazole was approved in April 2010. Oravig™ is indicated for the treatment of oropharyngeal candidiasis for patients over 16 years old.[5]

New FDA safety alerts:
No new safety alerts were found for topical antifungals.

New Systematic Reviews:
No new or updated, relevant systematic reviews were identified. A protocol for a future systematic review[6] was published at the Cochrane Collaboration. This review will try to establish any efficacy differences in topical antifungals for tinea cruris and corporis. No date was given for estimated completion.

Guidelines:
The updated sexually transmitted disease guideline[7] from the Centers for Disease Control was reviewed. No changes regarding the use of antifungals were found.

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

References:

1. Consolaro M, Martins H, Da Silva M, Paiva L, Svidzinski T. Efficacy of Fluconazole and Nystatin in the Treatment of Vaginal Candida Species. *Acta Dermato Venereologica*. 2012;92(1):78–82.

2. Sekhavat L, Tabatabaii A, Tezerjani FZ. Oral fluconazole 150mg single dose versus intra-vaginal clotrimazole treatment of acute vulvovaginal candidiasis. *Journal of Infection and Public Health*. 2011;4(4):195–199.

3. Dehghan M, Akbari N, Alborzi N, Sadani S, Keshtkar AA. Single-dose oral fluconazole versus topical clotrimazole in patients with pityriasis versicolor: A double-blind randomized controlled trial. *The Journal of Dermatology*. 2010;37(8):699–702.

4. Chen C, Koch LH, Dice JE, et al. A Randomized, Double-Blind Study Comparing the Efficacy of Selenium Sulfide Shampoo 1% and Ciclopirox Shampoo 1% as Adjunctive Treatments for Tinea Capitis in Children. *Pediatric Dermatology*. 2010;27(5):459–462.

5. Oravig prescribing information. *Strativa Pharmaceuticals, Woodcliff Lake NJ*. 2010. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/022404lbl.pdf. Accessed December 17, 2012.

6. El-Gohary M, Burgess H, Doney L, et al. Topical antifungal treatments for tinea cruris and tinea corporis. In: The Cochrane Collaboration, El-Gohary M, eds. *Cochrane Database of Systematic Reviews*. Chichester, UK: John Wiley & Sons, Ltd; 2012. Available at: http://doi.wiley.com/10.1002/14651858.CD009992. Accessed January 9, 2013.

7. Workowski KA. Sexually Transmitted Diseases Treatment Guidelines, 2010. *CDC.gov*. 2010. Available at: http://www.cdc.gov/MMWr/preview/mmwrhtml/rr5912a1.htm. Accessed December 28, 2012.

Appendix 1

Randomized Control Trials

Consolaro M, Martins H, Da Silva M, Paiva L, Svidzinski T. Efficacy of Fluconazole and Nystatin in the Treatment of Vaginal Candida Species. *Acta Dermato Venereologica*. 2012; 92(1):78–82.

The aim of this study was to determine and compare the efficacy of treatment with fluconazole and nystatin in Brazilian women with vaginal Candida. In a population of 932 women, vaginal cultures were performed for yeasts, whether or not the women showed signs and symptoms of vulvovaginal candidiasis. Yeasts were isolated from 12.2% of the women (114/932): 53.2% of the yeasts were Candida albicans, 27.0% C. glabrata, 13.5% C. tropicalis and 6.3% C. parapsilosis. Treatment was carried out with both drugs. The overall mean cure rates with fluconazole (87.0%) and nystatin (74.0%) were similar; among women with non-albicans, the cure rate with fluconazole was 100%, whereas that with nystatin was 44.4%. The cure rate for women with C. albicans was high with both fluconazole and nystatin; however, for those with non-albicans species the cure rate was excellent with fluconazole and very low with nystatin, differing from the majority of in vitro studies.

Sekhavat L, Tabatabaii A, Tezerjani FZ. Oral fluconazole 150mg single dose versus intra-vaginal clotrimazole treatment of acute vulvovaginal candidiasis. *Journal of Infection and Public Health*. 2011; 4(4):195–199.

To compare the safety and efficacy of fluconazole 150 mg single dose and intra-vaginal clotrimazole 200mg per day for six days in the treatment of the acute episode of vulvovaginal candidiasis (VVC). METHODS: In a prospective study, 142 patients with acute clinical and mycological confirmed VVC were enrolled and divided randomly in two groups. 70 patients received intra-vaginal tablet (200mg) daily for seven days, whereas 72 patients received single dose oral fluconazole (150 mg). Second and third visits were done for all patients seven days and one month after treatment and the clinical and mycological outcomes evaluated. The analysis performed using SPSS statistical software (version 15). RESULTS: At the second visit, 61 patients (84.7%) were cured clinically (inflammation and discharge) and 58 patients (80.5%) mycologically in fluconazole group and 60 patients (83.3%) were cured clinically and 49 patients (70%) mycologically in clotrimazole group (P=0.01). At the third visit, only one patient in fluconazole group and 17 patients in clotrimazole group had clinical sign of VVC (P=0.001). CONCLUSION: Oral fluconazole single dose seems to be a valid and promising therapy to cure acute signs and symptoms of VVC.

Dehghan M, Akbari N, Alborzi N, Sadani S, Keshtkar AA. Single-dose oral fluconazole versus topical clotrimazole in patients with pityriasis versicolor: A double-blind randomized controlled trial. *The Journal of Dermatology*. 2010; 37(8):699–702.

This study was designed to compare the therapeutic effects of topical clotrimazole and systemic fluconazole in pityriasis versicolor. A double-blind randomized controlled trial was carried out in the dermatological clinic of Gorgan, northern Iran, between April 2006 and May 2007. All consecutive patients with pityriasis versicolor were included and randomly divided into two groups. In the first group (G1), patients underwent treatment with a single dose of fluconazole capsule (400 mg) and placebo cream. In the second group (G2), patients underwent treatment with clotrimazole cream (twice daily) and placebo capsule. The course of treatment was 2 weeks. All subjects were re-evaluated 2, 4 and 12 weeks after the end of the therapeutic course. After 2 weeks, the rate of complete resolution of disease was significantly higher in G2 than G1 (49.1% vs 30%). After 4 weeks, 41 patients (81.2%) of G1 and 52 patients (94.9%) of G2 showed complete resolution. After 12 weeks, 46 patients (92%) in G1 and 45 patients (81.8%) in G2 showed complete resolution. Recurrence rate in G1 and G2 were 6% and 18.2%, respectively. No complications were seen in either group. In this study, clinical response at week 4 was greater in the clotrimazole group than the fluconazole group. Recurrence at week 12 after treatment was less with oral fluconazole than clotrimazole cream. So, for better evaluation, more studies need to be done.

Chen C, Koch LH, Dice JE, et al. A Randomized, Double-Blind Study Comparing the Efficacy of Selenium Sulfide Shampoo 1% and Ciclopirox Shampoo 1% as Adjunctive Treatments for Tinea Capitis in Children. *Pediatric Dermatology*. 2010; 27(5):459–462.

Our objective was to compare the efficacy of selenium sulfide shampoo 1% and ciclopirox shampoo 1% as adjunctive treatments for tinea capitis in children. Forty children aged 1–11 years with clinically diagnosed tinea capitis were randomized to receive selenium sulfide shampoo 1% or ciclopirox shampoo 1% twice a week as adjuncts to an 8-week course of ultramicronized griseofulvin dosed at 10–12 mg⁄kg⁄ day. At weeks 2, 4, and 8, subjects returned to the clinic for evaluation and scalp cultures. Subjects then returned for follow-up visits 4 weeks after completing treatment. Overall, by 8 weeks, 30 of 33 (90.9%) treated children demonstrated mycological cure. Selenium sulfide shampoo 1% and ciclopirox shampoo 1% were equally effective as adjunctive treatments for tinea capitis in children in our study.