



AGENDA

State and Public School Life and Health Insurance Board Drug Utilization and Evaluation Committee

November 3, 2014

1:00 p.m.

EBD Board Room – 501 Building, Suite 500

- I. Call to Order..... Dr. Kat Neill, Chairman*
- II. Approval of August 4, 2014 Minutes Dr. Kat Neill, Chairman*
- III. Introduction of New Committee Members Dr. Kat Neill, Chairman*
- IV. Delivery Coordination Workgroup.....Dr. David Keisner, UAMS*
- V. New Drugs.....Dr. Jill Johnson, UAMS*
- VI. EBD ReportDr. David Keisner, UAMS*

Upcoming Meetings

February 2, 2015

NOTE: All material for this meeting will be available by electronic means only asepse-board@dfa.arkansas.gov

Notice: Silence your cell phones. Keep your personal conversations to a minimum. Observe restrictions designating areas as "Members and Staff only"

State and Public School Life and Health Insurance Board Clinical and Fiscal Drug Utilization and Evaluation Committee Minutes November 3, 2014

The State and Public Life and Health Insurance Board, Drug Utilization and Evaluation Committee (DUEC) met on Monday November 3, 2014 at 1:00 p.m., in the EBD Board Room, 501 Woodlane, Little Rock, AR.

Voting Members present:

Dr. William Golden
Dr. Kat Neill - Chairman
Dr. Appathurai Balamurugan
Larry Dickerson
Dr. Hank Simmons – Vice Chairman
Dr. Eric Crumbaugh
Dr. John Kirtley

Non-Voting Members present:

Dr. Jill Johnson
Connie Bennett
Dr. David Keisner

Members absent:

Dr. Joe Stallings
Dr. Melodee Harris

Lori Eden, Director of Operations, Employee Benefits Division

OTHERS PRESENT

Dwight Davis, Geri Bemberg, UAMS College of Pharmacy; Sherry Bryant, Ethel Whittaker, Janna Keathley, Alicia Langston, Lori Eden, EBD; Kristi Jackson, ComPsych; Marc Watts, ASEA; Jennifer Smith, ASU; Warren Tyes, Merck; Steve Johnston, N. Nordisk; Charlene Kaiser, Amgen; Kanita Collins, Takisha Sanders, Health Advantage; Ronda Walthall, AHTD; Sharon Jackson, GSK; Bridgett Johnson, Pfizer; Bruce Valentine, Acorda; Steve Althoff, MTI; Andy Davis, Arkansas Democrat Gazette; Mary Lawrence, Jack Faragher, Scotty Branch, Brian Strickland, Wendy Sue, ABCBS; Jim Chapman

CALL TO ORDER

Meeting was called to order by Dr. Kat Neill, Chairman.

APPROVAL OF MINUTES

The motion was made by Dr. Neill to approve the August 4, 2014 minutes. Simmons made the motion to approve. Dickerson seconded. All were in favor.

Minutes Approved.

INTRODUCTION OF NEW COMMITTEE MEMBER: *by Dr. Kat Neill, UAMS*

Dr. Kirtley, Chairman of the Board, introduced new members. Dr. Melodee Harris was absent. Dr. Harris is an Advanced Nurse Practitioner, who is replacing Dr. Matthew Hadley. Dr. Balamurugan, Medical Director at The Arkansas Department of Health is a newly seated position.

DELIVERY OF COORDINATION WORK GROUP REPORT: *by Dr. David Keisner, UAMS*

Drugs used in the treatment of Cancers and non-cancer drugs were reviewed by the DCWG and a report made to the DUEC on November 3rd. Recommendations from this report are outlined below.

	Current Coverage	Proposed Coverage for 2015
<p><u>Hyaluronate Injections:</u> Monovisc, Gel-One, Synvisc-One</p> <p>Synvisc, Euflexxa, Hyalgan, Orthovisc, Supartz</p> <p>Dr. Simmons motioned to exclude. Dr. Bala seconded. All were in favor. Motion Approved</p>	<p>Unrestricted through Pharmacy and Medical</p> <p>Unrestricted through Pharmacy and Medical</p>	<p>PA through Medical Benefit only. QL of 1 per 6 months.</p> <p>Exclude *Patients in process of treatment course may complete course. 90 days communication to provider network.</p>
<p><u>Systemic Lupus Erythematosus (SLE)</u> Benlysta (belimumab)</p> <p>Dickerson motioned to exclude. Dr. Simmons seconded. All were in favor. Motion Approved</p>	<p>-Medical Gold and Bronze-Unrestricted -Medical Silver-Excluded -Pharmacy-PA</p>	<p>-Exclude with 90 days notice to existing users -Exclude with 90 days notice to existing users -Exclude with 90 days notice to existing users</p>
<p><u>Refractory peripheral T Cell Lymphoma</u> Beleodaq (belinostat)</p> <p>Folotyn (pralatrexate) Istodax (romidepsin) Adcetris (brentuximab)</p> <p>Dr. Simmons motioned to approve the recommendations to review in 18 months. Dr. Crumbraugh seconded. All were in favor. Motion Approved</p>	<p>New Drug</p> <p>Unrestricted Medical Unrestricted Medical Medical PA through EBRx</p>	<p>Exclude (new courses with 90 day communication to providers) – Code 1 Medical PA through EBRx Medical PA through EBRx Medical PA through EBRx</p>
<p><u>Metastatic Melanoma</u> Keytruda (pembrolizumab)</p> <p>Dr. Golden motioned to exclude. Dickerson seconded. All were in favor. Motion Approved</p>	<p>New Drug</p>	<p>Exclude – Code 1</p>

	Current Coverage	Proposed Coverage for 2015
<u>Topical Medications for Herpes Labialis</u> Zovirax Cream - \$732 (5g tube) Acyclovir Ointment Sitavig (acyclovir buccal tablet) - \$375/2 tabs Denavir (penciclovir) - \$115 (1.5 g tube) Valacyclovir - \$50 (4 tabs) Acyclovir - \$54 (25 tabs) Famciclovir - \$61 (tx course) Abreva (OTC) - \$16.77 Dr. Simmons motioned to exclude. Dr. Crumbaugh seconded. All were in favor. Motion Approved	Unrestricted Pharmacy Unrestricted Pharmacy Excluded Unrestricted Pharmacy Unrestricted Pharmacy Unrestricted Pharmacy Unrestricted Pharmacy Excluded	Excluded Excluded Excluded Excluded Unrestricted Pharmacy Unrestricted Pharmacy Unrestricted Pharmacy Excluded *90 day communication

NEW DRUGS: by Dr. Jill Johnson, UAMS

Johnson reported on new drugs. The review covered products released June – September 2014.

Recommended Additions:

BRAND Name	GENERIC name	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	CODE*
PURIXAN SUSPENSION	MERCAPTOPYRINE 20MG/ML SUSPENSION	\$1,038/100 ML BOTTLE	For treatment of patients with acute lymphoblastic leukemia. Only oral suspension of mercaptopurine.	Generic mercaptopurine 50mg tabs= \$2.08/tab	Cover w/ age edit (age 7 and younger)
ISENTRESS POWDER (specialty drug)	TEGRAVOR PACKET FOR SUSP 100MG	\$337/box of 60	NEW DOSAGE FORMULATION- for treatment for HIV infection	Same price as 100mg chewable tab (currently excluded by plan). Isentress 400mg tab - covered w/PA-specialty tier	T4 w/ age edit (age 2 and younger)
CYCLOPHOSPHAMIDE CAPS (specialty drug)	cyclophosphamide	\$7.59/25mg cap and \$13.94/50mg cap	new dosage formulation - 25 and 50mg caps.	(T1) - cyclophosphamide tablets - \$2.78/25mg tab and \$5.11/50mg tab	T2
SIVEXTRO 200mg	tedizolid phosphate tabs	\$2,124/6 days	For treatment of skin and skin structure infections due to gram-positive organisms. Dose=200mg by mouth every day for 6 days	(T3 w/PA) - Zyvox - \$3,072/10 days	T3 PA
STRIVERDI AER RESPIMAT	olodaterol HCl inhal aerosol	\$168/inhaler	for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Dose: 2 inhalations once daily	FORADIL - (T2) and requires ST- \$265. SEREVENT DISKUS - (T2) and requires ST- \$265. PERFOROMIST - (T3) and requires ST-\$673.	T2 (Step edit for Asthma)

Recommended Additions (continued):

BRAND Name	GENERIC name	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	CODE*
TRIUMEQ TABS (specialty)	abacavir-dolutegravir-lamivudine	\$2,648/30 days	For treatment of HIV infection. Once daily single pill regimen	Other once daily single pill regimen: Stribild (\$2,940/30 days) and Atripla (\$2,460/30 days)	T4
SOMAVERT INJ (specialty)	pegvisomant	-----	New dosage strength - Treatment of acromegaly	Other strengths covered as Tier 4	T4
Entyvio Inj 300 mg (integrin receptor antagonist) Specialty Drug (TABLED in August)	Vedolizumab	\$5,782/300 mg	For adults patients with moderately to severely active ulcerative colitis or Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a TNF blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. Dose=300 mg IV at 0, 2, and 6 weeks, then every 8 weeks thereafter.	Humira 40 mg SC injection every other week/\$3,002;Cimzia 400 mg SC injection every 4 weeks/\$3,322. Remicade dose based on wt and administered by IV infusion/\$1062 for 100 mg vial. All specialty drugs.	T4PA

Recommended Exclusions:

BRAND Name	GENERIC name	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	CODE*
EVZIO INJECTION	Naloxone 0.4 mg/0.4mg auto-injector	\$700/2 injectors	A take-home naloxone auto-injector for the emergency treatment of known or suspected opioid overdose, manifested by a respiratory and/or CNS depression	Generic naloxone 0.4 mg/ml amp AWP range \$1-\$25/amp	9 & 13
QUDEXY XR CAPSULES	topiramate cap extended-release 24 hour sprinkle	Per cap AWP: 25mg\$5.63;50 mg/\$7.36;100 mg/\$14.60;200mg/\$19.96	Treatment of partial onset, generalized primary tonic-clonic seizures and as an adjunct therapy in Lennox-Gastaut syndrome	generic immediate-release topiramate sprinkle caps: \$2.89	13
JUBLIA SOLUTION 10%	efinaconazole soln 10%	\$538/4ml bottle	Treatment of onychomycosis of the toenail	(T1)- terbinafine 250mg(\$30/month) (T1)- itraconazole-200mg (\$500/month) . Ciclopirox nail lacquer (\$165/bottle)- excluded by plan	13
KERYDIN SOLN 5%	tavaborole 5% solution	\$538/4ml bottle	Treatment of onychomycosis - applied to the affected toenail(s) once daily for 48 weeks.	(T1)- terbinafine 250mg(\$30/month) (T1)- itraconazole-200mg (\$500/month) . Ciclopirox nail lacquer (\$165/bottle)- excluded by plan	13

Recommended Exclusions (continued):

BRAND Name	GENERIC name	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	CODE*
OVACE PLUS LOTION	sulfacetamide sodium lotion 9.8%	\$509/57 gm bottle	For treatment of seborrheic dermatitis and seborrhea sicca (dandruff)	(T1) - Sulfacetamide sodium lotion 10% - \$109/bottle	13
VEXA PAD 2-4-30%	allantoin-lidocaine-petrolatum patch	\$602/box of 15 patches	Uses include: scar management, temporarily protects minor cuts, scrapes, burns and temporarily relieves pain associated with minor cuts, scrapes, and minor skin irritations. According to Daily Med: this product has not been found by FDA to be safe and effective and this labeling has not been approved by FDA.	n/a	13
RASUVO INJECTION	methotrexate solution PF auto-injector for subcutaneous administration	\$134/pen	Management of patients with severe, active rheumatoid arthritis & active polyarticular juvenile idiopathic arthritis, who are intolerant of or had an inadequate response to, first-line therapy and symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy.	Otrexup (methotrexate soln PF Auto-injector for subcutaneous administration)- \$164/pen and is currently excluded by the plan. Methotrexate inj 25mg/ml for deep IM administration - \$4.	13
INVOKAMET	canagliflozin & metformin	\$373/30 days	for the treatment of Type 2 diabetes in combination with diet and exercise. INVOKANA (canagliflozin) is a sodium-glucose co-transporter 2(SGLT2) inhibitor. Ivokamet is dosed twice daily.	INVOKANA is currently a plan exclusion.	13
JARDIANCE	empagliflozin	\$360/month	for the treatment of Type 2 diabetes in combination with diet and exercise. JARDIANCE is a SGLT2.	INVOKANA (\$374/30days) is currently excluded	13
NORTHERA (SPECIALTY DRUG)	droxidopa	\$1,690-\$10,144/month	for the treatment of orthostatic dizziness, lightheadedness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency and non-diabetic autonomic neuropathy. Dose is 300-1800mg/day.	Midodrine (T1) (10mg by mouth three times a day)- \$435/30 days.	13
Acticlate	doxycycline 75mg and 150 mg	\$26/tab	Tetracycline-class antibacterial indicated for the treatment of a number of infections, including adjunctive therapy in severe acne	Doxycycline 100mg caps = \$0.25	13

Recommended Exclusions (continued):

BRAND Name	GENERIC name	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	CODE*
Cardelga Caps (specialty)	eliglustat 84mg	\$510/84mg cap			13
ABSORICA 25mg and 35mg caps	isotretinoin caps	\$926/month	For treatment of acne vulgaris/cystic acne	no other 25 or 25mg isotretinoin caps	Exclude -13 along with all other strengths of Absorica and 90 days notice
BUNAVAIL	buprenorphine-naloxone buccal film	\$253-\$506/box of 30	Treatment of opiate agonist dependence		13
REVATIO SUSPENSION 10MG/ML (specialty)	sildenafil for suspension	\$5,500/112 ml bottle	new dosage formulation. For treatment of pulmonary hypertension	Other REVATIO formulations covered as tier 4	13
UTA CAPS 120MG	methenamine/hyoscyamine/meth blue/sod phos caps	\$3.71/tab	For treatment of urinary tract infections	Uribel (\$2.71/tab) and Ustell (\$2.41/tab) covered as T3	Exclude – 13 along with existing 120mg UTA and 90 days notice
Ferric Citrate		\$1,010/200	Management of hyperphosphatemia in patients with chronic kidney disease on dialysis. Max dose: 12 tabs/day		13
RUCONEST INJECTION (specialty drug)	C1 esterase inhibitor (recombinant)	\$5,700/unit	For IV administration for treatment of angioedema. Patients may self-administer after appropriate training under the guidance of healthcare professional		exclude – 13 from pharmacy benefit only

<u>Medication</u>	<u>Excluded/Approved/and Tabled</u>
EVZIO INJECTION	Dr. Simmons motioned to exclude. Dickerson seconded. All were in favor. Motion Approved.
QUDEXY XR CAPSULES	Dickerson motioned to exclude. Dr. Crumbaugh seconded. All were in favor. Motion Approved.
JUBLIA SOLUTION 10%	Dr. Simmons motioned to exclude. Dickerson seconded. All were in favor. Motion Approved.
KERYDIN SOLN 5%	Dr. Simmons motioned to exclude. Dr. Golden seconded. All were in favor. Motion Approved.
OVACE PLUS LOTION	Dr. Crumbaugh motioned to exclude. Dr. Simmons seconded. All were in favor. Motion Approved.
VEXA PAD 2-4-30%	Dr. Simmons motioned to exclude based on lack of info. Dickerson seconded. All were in favor. Motion Approved.
RASUVO INJECTION	Dr. Simmons motioned to exclude. Dickerson seconded. All were in favor. Motion Approved.
INVOKAMET	Dr. Simmons motioned to exclude. Dickerson seconded. All were in favor. Motion Approved.
JARDIANCE	Dr. Simmons motioned to exclude. Dickerson seconded. All were in favor. Motion Approved.
NORTHERA (SPECIALTY DRUG)	Dr. Simmons motioned to exclude. Dickerson seconded. All were in favor. Motion Approved.
Acticlate	Dr. Simmons motioned to exclude. Dr. Crumbaugh seconded. All were in favor. Motion Approved.
Cardelga Caps (specialty)	Dr. Crumbaugh motioned to exclude. Dickerson seconded. All were in favor. Motion Approved.
ABSORICA 25mg and 35mg caps	Dr. Simmons motioned to exclude. Dickerson seconded. All were in favor. Motion Approved.
BUNAVAIL	Dickerson motioned to exclude. Dr. Simmons seconded. All were in favor. Motion Approved.
REVATIO SUSPENSION 10MG/ML (specialty)	Dr. Simmons motioned to exclude. Dickerson seconded. All were in favor. Motion Approved.
UTA CAPS 120MG	Dr. Simmons motioned to exclude. Dr. Bala seconded. All were in favor. Motion Approved.
Ferric Citrate	Dr. Crumbaugh motioned to exclude. Dr. Simmons seconded. All were in favor. Motion Approved.
RUCONEST INJECTION (specialty drug)	Dr. Simmons motioned to exclude. Dickerson seconded. All were in favor. Motion Approved.
PURIXAN SUSPENSION	Dickerson motioned to approve age 7 and younger. Dr. Simmons seconded. All were in favor. Motion Approved.
ISENTRESS POWDER (specialty drug)	Dickerson motioned to approve for age 2 & under. Dr. Simmons seconded. All were in favor. Motion Approved.
CYCLOPHOSPHAMIDE CAPS (specialty drug)	Dr. Simmons motioned to cover with restrictions. Dr. Crumbaugh seconded. All were in favor. Motion Approved.
SIVEXTRO 200mg	Dr. Simmons motioned to approve with q/l six. Dr. Bala seconded. All were in favor. Motion Approved.
STRIVERDI AER RESPIMAT	Dr. Crumbaugh motioned to approve on Tier 2. Dr. Bala seconded. All were in favor. Motion Approved.
TRIUMEQ TABS (specialty)	Dr. Crumbaugh motioned to approve on Tier 4. Dr. Simmons seconded. All were in favor. Motion Approved.
SOMAVERT INJ (specialty)	Dr. Crumbaugh motioned to approve on Tier 4 no PA. Dr. Simmons seconded. All were in favor. Motion Approved.
Entyvio Inj 300 mg (integrin receptor antagonist) Specialty Drug	Dickerson motioned to cover on Tier 4 and review and six months. Dr. Crumbaugh seconded. All were in favor. Motion Approved.
(TABLED in August)	

3. Discussion point for Board clarification

The DUEC requests clarification for coverage of medically administered oncology drugs. Currently, these drugs may be covered under the Medical benefit before review by the DCWG. The Board may continue this process or may recommend adoption of the process employed by the Pharmacy benefit in which any new drugs are “not covered/excluded” until review and placement in the formulary structure.

EBD REPORT: *by Dr. David Keisner, UAMS*

Keisner reported pharmacy spent \$22.6 million less the first nine months in 2014 compared to 2013 spending \$17 million.

Meeting Adjourned

*New Drug Code Key:

1	Lacks meaningful clinical endpoint data; has shown efficacy for surrogate endpoints only.
2	Drug's best support is from single arm trial data
3	No information in recognized information sources (PubMed or Drug Facts & Comparisons or Lexicomp)
4	Convenience Kit Policy - As new drugs are released to the market through Medispan, those drugs described as “kits” will not be considered for inclusion in the plan and will therefore be excluded products unless the product is available solely as a kit. Kits typically contain, in addition to a pre-packaged quantity of the featured drug(s), items that may be associated with the administration of the drug (rubber gloves, sponges, etc.) and/or additional convenience items (lotion, skin cleanser, etc.). In most cases, the cost of the “kit” is greater than the individual items purchased separately.
5	Medical Food Policy - Medical foods will be excluded from the plan unless two sources of peer-reviewed, published medical literature supports the use in reducing a medically necessary clinical endpoint. A medical food is defined below: A medical food, as defined in section 5(b)(3) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)), is “a food which is formulated to be consumed or administered enterally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation.” FDA considers the statutory definition of medical foods to narrowly constrain the types of products that fit within this category of food. Medical foods are distinguished from the broader category of foods for special dietary use and from foods that make health claims by the requirement that medical foods be intended to meet distinctive nutritional requirements of a disease or condition, used under medical supervision, and intended for the specific dietary management of a disease or condition. Medical foods are not those simply recommended by a physician as part of an overall diet to manage the symptoms or reduce the risk of a disease or condition, and all foods fed to sick patients are not medical foods. Instead, medical foods are foods that are specially formulated and processed (as opposed to a naturally occurring foodstuff used in a natural state) for a patient who is seriously ill or who requires use of the product as a major component of a disease or condition's specific dietary management.
6	Cough & Cold Policy - As new cough and cold products enter the market, they are often simply re-formulations or new combinations of existing products already in the marketplace. Many of these existing products are available in generic form and are relatively inexpensive. The new cough and cold products are branded products and are generally considerably more expensive than existing products. The policy of the ASE/PSE prescription drug program will be to default all new cough and cold products to “excluded” unless the DUEC determines the product offers a distinct advantage over existing products. If so determined, the product will be reviewed at the next regularly scheduled DUEC meeting.
7	Multivitamin Policy - As new vitamin products enter the market, they are often simply re-formulations or new combinations of vitamins/multivitamins in similar amounts already in the marketplace. Many of these existing products are available in generic form and are relatively inexpensive. The new vitamins are branded products and are generally considerably more expensive than existing products. The policy of the ASE/PSE prescription drug program will be to default all new vitamin/multivitamin products to “excluded” unless the DUEC determines the product offers a distinct advantage over existing products. If so determined, the product will be reviewed at the next regularly scheduled DUEC meeting.
8	Drug has limited medical benefit &/or lack of overall survival data or has overall survival data showing minimal benefit
9	Not medically necessary
10	Peer-reviewed, published cost effectiveness studies support the drug lacks value to the plan.
11	Oral Contraceptives Policy - OCs which are new to the market may be covered by the plan with a zero dollar, tier 1, 2, or 3 copay, or may be excluded. If a new-to-market OC provides an alternative product not similarly achieved by other OCs currently covered by the plan, the DUEC will consider it as a new drug. IF the drug does not offer a novel alternative or offers only the advantage of convenience, it may not be considered for inclusion in the plan.
12	Other
13	Insufficient clinical benefit OR alternative agent(s) available

	A	B	C	D
1	<u>Delivery Coordination Workgroup Report</u>			
2				
3	<u>Members Present:</u>			
4	David Keisner PharmD- EBRx			
5	Jill Johnson, PharmD - EBRx			
6	Geri Beth Bemberg PharmD-EBRx managed care resident			
7	Henry Simmons, MD PhD- Medical Director Arkansas Poison Control			
8	Sidney Keisner PharmD- Board Certified Oncology Pharmacist at VA Little Rock			
9	Kati Beth Lewis, PharmD- Clinical Pharmacist at Blue Cross			
10	Stephen Sorsby, MD- Medical Director at Qualchoice			
11				
12	<u>Hyaluronate Injections</u>	<u>Current Coverage</u>	<u>Proposed Coverage</u>	
13	Monovisc, Gel-One, Synvisc-One	Unrestricted through pharmacy and Medical	PA through medical Benefit only. QL of 1 per 6 months.	
14	Synvisc, Euflexxa, Hyalgan, Orthovisc, Supartz	Unrestricted through pharmacy and Medical	exclude	
15				
16	<u>Systemic Lupus erythematosus (SLE)</u>			
17	Benlysta (belimumab)	Medical Gold and Bronze-Unrestricted	Exclude with 90 days notice to existing users	
18		Medical Silver- Excluded	Exclude with 90 days notice to existing users	
19		Pharmacy- PA	Exclude with 90 days notice to existing users	
20				
21	<u>Refractory pereipheral T Cell Lymphoma</u>			
22	Beleodaq (belinostat)	New drug	exclude	
23	Folotyn (pralatrexate)	unrestricted medical	Medical PA through EBRx	
24	Istodax (romidepsin)	unrestricted medical	Medical PA through EBRx	
25	Adcetris (brentuximab)	Medical PA through EBRx	Medical PA through EBRx	
26				
27	<u>Metastatic Melanoma</u>			
28	Keytruda (pembrolizumab)	New drug	exclude	
29				
30	<u>Topical Medications for Herpes Labialis</u>			
31	Zovirax Cream	Unrestricted pharmacy	excluded	
32	acyclovir ointment	Unrestricted pharmacy	excluded	
33	Sitavig (acyclovir buccal tablet)	excluded	excluded	
34	Denavir (penciclovir)	Unrestricted pharmacy	excluded	
35	Valacyclovir	Unrestricted pharmacy	unrestricted pharmacy	
36	acyclovir	Unrestricted pharmacy	unrestricted pharmacy	
37	famciclovir	Unrestricted pharmacy	unrestricted pharmacy	
38	Abreva (OTC)	excluded	excluded	

Sodium hyaluronate (Synvisc, Monovisc)
Antirheumatic; Ophthalmic Agent, Viscoelastic; Skin and Mucous Membrane Agent
Geri Bemberg, Pharm.D.

Other brands for osteoarthritis: Euflexxa, Gel-One, Hyalgan, Orthovisc, Supartz, Synvisc-One

Other brand names: Amvisc, Amvisc Plus, Bionect, Hylase Wound, Juvederm Ultra, Juvederm Ultra Plus, Juvederm Ultra Plus XC, Juvederm Ultra XC, Perlane, Perlane-L, Provisc, Restylane, Restylane-L

Labeled Indications:

Intra-articular injection: treatment of pain in osteoarthritis in knee in patients who have failed nonpharmacologic tx or simple analgesics (Euflexxa, Gel-One, Hyalgan, Monovisc, OrthoVisc, Supartz, Synvisc, Synvisc-One) or NSAIDs (Gel-One)

Intradermal:

Correction of moderate to severe facial wrinkles or folds (Juvederm, Perlane, Perlane-L, Restylane, Restylane-L)

Correction of perioral rhytids in adults >2 (Restylane Silk)

Subcutaneous/supraperiosteal: Correction of age-related volume deficit (deep [subcutaneous &/or supraperiosteal] injection) for cheek augmentation in the mid-face in adults >21 yrs (Juvederm Voluma XC)

Ophthalmic:

Surgical aid in cataract extraction (Amvisc, Amvisc Plus, Provisc)

Intraocular lens implantation (Amvisc, Amvisc Plus, Provisc)

Corneal transplant (Amvisc, Amvisc Plus)

Glaucoma filtration (Amvisc, Amvisc Plus)

Retinal attachment surgery (Amvisc, Amvisc Plus)

Submucosal: Lip augmentation in adults >21 yrs (Restylane, Restylane-L, Restylane Silk)

Topical cream, gel: Management of skin ulcers and wounds (Bionect, Hylase Wound)

Place in treatment for osteoarthritis

- In knee OA after patient has failed nonpharmacologic treatments such as exercise and self-management programs and weight loss for those with BMI \geq 25, and pharmacologic treatments such as NSAIDs (oral and topical). Debatable on if they are on the same treatment step as intraarticular corticosteroids or last line after them.

Intra-articular Administration: inject directly into the knee joint

Brand	Price	Dosing	Price per treatment
Synvisc	16mg/2mL (2mL): \$432 (PFS)	16mg (2mL) q week x 3 weeks	\$1296 for 3 weeks
Monovisc	88mg/4mL (4mL): \$1170 (PFS)	88mg (4mL) once	\$1170
Euflexxa	20mg/2mL (2mL): \$369.98	20mg (2mL) q week x 3 weeks	\$1109.94 for 3 weeks
Gel-One	30mg/3mL (3mL): \$1170	30mg (3mL) once	\$1170
Hyalgan	20mg/2mL (2mL): \$216	20mg (2mL) q week x 5 weeks (some may benefit from 3 weeks)	\$1080 for 5 weeks \$648 for 3 weeks
Orthovisc	15mg/mL (2mL): \$383.96	30mg (2mL) q week x 3-4 weeks	\$1151.88 for 3 weeks \$1535.84 for 4 weeks
Supartz	25mg/2.5mL (2.5mL): \$241.80	25mg (2.5mL) q week x 5 weeks (some may benefit from 3 weeks)	\$1209 for 5 weeks \$725.40 for 3 weeks
Synvisc-One	48mg/6mL (6mL): \$1296	48mg (6mL) once	\$1296

*All prices reflect AWP from Lexicomp and restat

**When looking at Hyalgan, its initial AWP in Sept 2011 was \$156/vial, now in 2014 (latest AWP update was in April), price is \$216/vial. Safe to assume that applies across the board on all intra-articular hyaluronates.

Approval options

1. Cover all intra-articular hyaluronates, without PA as they are currently.
2. Cover all intra-articular hyaluronates with a PA that they must have failed stepwise therapy first.
3. Cover only a few intra-articular hyaluronates and exclude the rest.

Sodium hyaluronate (Synvisc, Monovisc)
Antirheumatic; Ophthalmic Agent, Viscoelastic; Skin and Mucous Membrane Agent
Gerri Bemberg, Pharm.D.

Comparators in trial arms	Primary Outcome	Secondary Outcomes	Patient Baseline Characteristics	Primary Outcome Results	Author's Conclusions	G.Bemberg notes
6 mL Hylan G-F 20 vs 6 mL PBS (single injection) ¹	Change from BL over 26 wks in WOMAC A (0-4 pt scale)	WOMAC A1 & C, PGA, COGA	253 pts (K-L grade II or III) patients were more severe in placebo grp	Difference of -0.15 btw grps @26 wks on a 4 pt WOMAC scale (favoring Hylan)	"statistically significant, clinically relevant pain relief...with a modest difference vs. placebo"	No clinically significant difference, didn't meet power in Hylan grp
2.5 mL GO-ON (intermediate MW) vs 2 mL Hyalgan (low MW) 1 inj q week x 3 wks ²	6 month change in the WOMAC pain subscale (normalized to 100 pt scale)	Total index, physical fxn & stiffness subscales, global knee pain, LFI, ICOAP, PGA, etc	437 pts (K-L grade II or III) patients more severe in Go-ON grp, but reported more symptoms in Hyalgan grp	Difference of -4.5 btw grps @ wk 26 out of 100 pts (favoring GO-ON)	"Tx w/3-weekly inj of intermediate MW HA may be superior to low MW HA on knee OA symptoms over 6 months"	Not clinically significant
3 mL Gel-200 vs 3 mL PBS (single injection) ³	WOMAC pain @ wk 13	OMERACT-OARSI	379 patients (K-L grade I, II, or III) patients not as sick as other trials, worse off in Gel-200 grp	Difference of 6.39 mm between groups out of 100, favoring Gel-200	"...tx with Gel-200 offers statistically sig & clinically meaningful improvements both in pain & physical fxn.."	
Home exercise BID vs 2.5 mL HA inj once weekly x 5 weeks, then monthly until 24 week total. ⁴	VAS (100 pt scale), JKOM (100 pt scale), OMERACT-ARSI	Data categorized for logistic regression analysis	102 patients (all females, mean age 70.4)	No significant difference btw grps on any primary outcome.	See below	
2 mL Euflexxa vs 2 mL PBS weekly x 3 weeks ⁵	VAS (100 pt scale) @ wk 26 following 50 ft walk test	OARSI responder index, WOMAC subscales	588 pts w/ mod to severe pain on VAS, K-L grade II or III	Least square means diff of -6.6 mm btw grps	Euflexxa resulted in sig pain relief at 26 weeks compared to PBS	
2 mL Hyalgan vs 2 mL saline q week x 5 weeks ⁶	Time to recurrence over 1 yr	LFI, 50 m VAS, paracetamol consumption, pt's global assessment, Nottingham health profile, joint effusion & # responders	337 pts (LFI of 10 or more) – mod to severe	No significant difference btw grps	Did not improve pain, fxn, paracetamol consumption or other efficacy parameters 3, 6, 9 or 12 months after tx.	
2.5 mL 1% Na Hyal vs 2.5mL saline. 4 tx cycles of 5 weekly inj each. Follow up 6 months after 1 st & 2 nd , 1 yr after 3 rd & 4 th ⁷	OARSI responder criteria ^{7*}	Clinical response according to OMERACT-OARSI, each component of OMERACT-OARSI, & use of rescue meds	306 pts K-L grade II or III (pts were worse in HA)	80.5% responders in HA vs 65.8% responders in placebo	Repeated cycles of IA HA improve knee OA sx during in-btw cycle period, & exert a carryover effect for at least 1 yr	

PBS= buffered physiological NaCl solution; WOMAC= Western Ontario & McMaster Universities Osteoarthritis Index; PGA= patient global assessment; COGA= clinical observer global assessment; K-L= Kellgren-Lawrence; LFI= Lequesne algofunctional index score; ICOAP= intermittent & constant osteoarthritis pain index; OMERACT-OARSI= Outcome Measures in Rheumatology Clinical Trials & Osteoarthritis Research Society International; VAS= Visual analogue scale; JKOM= Japanese Knee Osteoarthritis Measure

1. Chevalier X, Jerosch J, et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomized, multicenter, double-blind, placebo controlled trial. Ann Rheum Dis 2010;69:113-119.

- Baseline characteristics: Hylan grp (51.2% grade II, 48.8% grade III), Placebo (39.2% grade II, 60% grade III, 0.8% grade IV)

Primary efficacy endpoint – WOMAC A (pain) change over 26 weeks (ITT population)					
	Baseline mean	26-week mean	Estimated change	Estimated diff btw grps	P value
Hylan G-F 20 (n=124)	2.30	1.43	-0.84	-0.15	0.047
Placebo (n=129)	2.25	1.59	-0.69		

Minimum clinically important improvement in OA = 12-18% improvement in WOMAC A from baseline. Hylan group had a 31.3% improvement, placebo had 29.3% improvement.

2. Berenbaum F, Grifka J, et al. A randomized, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. Ann Rheum Dis 2012; 71:1454-1460.

- Baseline characteristics: GO-ON grp (46% grade II, 54% grade III), Hyalgan grp (54% grade II, 46% grade III)

Mean changes from Baseline to Week 26 in the ITT population				
	GO-ON (n=217)	Hyalgan (n=209)	Difference	P value
WOMAC pain	-22.9 (-25.7 to -20.1)	-18.4 (-21.3 to -15.5)	-4.5 (-8.5 to -0.5)	0.021

“The statistically sig ITT differences btw treatments after 6 mnths were 4.5 and 6.4 mm, respectively, ie, below the minimum perceptible clinical improvement, usually set at approximately 10 mm²² and that was used to define the non-inferiority margin of 9 mm in this trial. Therefore, the clinical relevance of this statistical superiority is uncertain and it cannot be excluded that it is due to chance.”

3. Strand V, Baraf HSB, et al. A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. Osteo and Cartilage 20 2012; 350-356.

- Baseline characteristics: Gel-200 grp (8.5% grade I, 38.1% grade II, 53.4% grade III), PBS grp (14.1% grade I, 36.7% grade II, 49.2% grade III)

Mean Improvements from Baseline in WOMAC pain subscores		
Week	Estimated difference	P value
Week 3	8.12 (3.47, 12.68)	0.001
Week 6	8.12 (2.73, 13.50)	0.003
Week 9	5.77 (0.26, 11.29)	0.04
Week 13	6.39 (2.15, 12.05)	0.037

4. Kawasaki T, Kurosawa H, et al. Therapeutic home exercise versus intraarticular hyaluronate injection for osteoarthritis of the knee: 6-month prospective randomized open-labeled trial. J Orthop Sci 2009; 14:182-191.

- Patients were all females over 50 with primary OA, selected according to clinical and radiographic criteria of the American College of Rheumatology.

Intergroup analysis of changes from baseline to the 24th week		
Variable	HA group (n=42)	Exercise group (n= 45)
VAS	-20.46 ± 36.04	-21.29 ± 27.60
JKOM	-16.12 ± 20.69	-12.82 ± 15.97
ROM	3.49 ± 8.79	5.21 ± 7.65

- Author's conclusions: "Taking into account the cost, convenience, and invasiveness to patients, exercise is thought to have some advantage over intraarticular injection of hyaluronate for the therapy of OA of the knee."

5. Altman RD, Rosen JE, et al. A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (The FLEXX Trial). Semin Arthritis Rheum 39:1-9.

Group	Change from baseline in VAS	Median % reduction
EUFLEXXA	-25.7 ± 28.9 mm	53%
PBS	-18.5 ± 32.5 mm	38%

6. Jorgensen A, Stengaard-Pedersen K, et al. Intra-articular hyaluronan is without clinical effect in knee osteoarthritis: a multicenter, randomized, placebo-controlled, double-blind study of 337 patients followed for 1 yr. Ann Rheum Dis 2010;69:1097-1102.

- Time to recurrence defined as time from the start of improvement until recurrence of the LFI. Start of improvement was baseline LFI decreased by at least 1 & recurrence was when the LFI increased by at least 1 pt over baseline.

- ITT population: Mean time to recurrence: Hyaluronan – 172 days

Placebo – 204 days

- A large portion of patients in each grp (53% in hyaluronan, 59% in placebo) were censored as exact time unknown, mostly due to still in remission at the end of the trial.

Belimumab (Benlysta) Topic Discussion

Current Belimumab (Benlysta) PA Criteria on the PHARMACY SIDE.

FDA approved indication: Treatment of adult patients with active, autoantibody-positive, systemic lupus erythematosus (SLE) who are receiving standard therapy.

1. Does the patient have a diagnosis of active SLE (SELENA-SLEDAI score of at least 6) and known autoantibody positive (unequivocally positive ANA with titre at least 1:80 OR anti-dsDNA antibody at least 30 IU/mL)?	<input type="checkbox"/> Yes <input type="checkbox"/> No If yes, go on to next question. If no, stop and deny coverage.
2. Has the patient been taking a stable treatment regimen of standard therapy? (i.e. prednisone 40mg/d, or maximally-tolerated NSAIDs, antimalarial (hydroxychloroquine), or immunosuppressive (azathioprine, methotrexate, mycophenolate) for at least 30 d?	<input type="checkbox"/> Yes <input type="checkbox"/> No If yes, go on to next question. If no, stop and deny coverage.
2. Has the patient taken IV cyclophosphamide or B cell or biologic therapy (i.e. rituxan, Humira, Remicade, Enbrel, Cimzia, Orencia, Stelara, Kineret, Simponi, Actemra, Amevive) within the past 6 months?	<input type="checkbox"/> Yes <input type="checkbox"/> No If no, go on to next question. If yes, stop and deny coverage.
3. Has the patient taken IVIG or prednisone at greater than 100mg/d within the past 3 months?	<input type="checkbox"/> Yes <input type="checkbox"/> No If no, go on to next question. If yes, stop and deny coverage.
4. Does the patient have severe active lupus nephritis or severe active central nervous system lupus? (Benlysta has not been studied in these populations and is not recommended at this time.)	<input type="checkbox"/> Yes <input type="checkbox"/> No If no, stop and deny coverage at this time.

If approved for coverage, PA is good for 6 months.

The studied regimen was administration by IV infusion in 1 hour on days 0, 14, 28, then every 28d until 48 w. The dose is 10mg/kg by IV infusion.

References:

1. Navarra SV, Guzman RM, Gallacher AE, Hall S, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomized, placebo-controlled, phase 3 trial. *Lancet*. 2011;377:721-31.
2. Benlysta PI. March 2011.
3. Benlysta PI. September 2014.

Summary of the Navarra trial:

- N=867 randomized. 94% were female. ~24% Caucasian, ~32% Native American or Alaskan, 4% Black American, 40% Asian, ~47% Hispanic. 865 received treatment and were analyzed. Patients with active SLE (SELENA-SLEDAI score of at least 6) and known autoantibody positive (unequivocally positive ANA with titre at least 1:80 OR anti-dsDNA antibody at least 30 IU/mL and were taking a stable treatment regimen of prednisone 0-40mg/d, or NSAIDs, antimalarial, or immunosuppressive for at least 30 d prior to 1st study dose. Trial excluded severe active lupus nephritis or CNS lupus, pregnancy, previous treatment with any B-lymphocyte-targeted drug (including rituximab), IV cyclophosphamide within 6 months of enrollment, and IVIG, or prednisone >100mg/d within 3 months.
- Included pts were randomized to 1mg/kg, 10mg/kg, or PLAC.
- Primary endpt was SRI at 52 weeks. SRI response is a reduction of at least 4 pts in the SELENA-SLEDAI, no new BILAG A organ domain score, no more than 1 new BILAG B organ domain score, and no worsening in PGA score (increase of less than 0.3) at 52 w.
- Major Secondary endpts were proportion of pts with at least a 4 pt reduction in SELENA-SLEDAI at 52w, mean change in PGA score at 24w, mean change in SF-36 physical component summary score at 24w, and proportion of pts with an average reduction in prednisone dose of at least 25% from baseline to 7.5 or less during weeks 40-52. Other secondary endpts were measured.
- Analysis was by modified ITT (Those who were randomized and received drug were analyzed.)
- Results:
 - SRI response rate at 52 w: 58%B 10mg/kg, 44%Plac, p=0.0006; Net response of 14% better with B 10mg/kg. NNT to get a response is 8 in this highly selected population.
 - Benlysta PI states a subgroup analysis was performed in black patients. In Trials 2 & 3 (n=148)(highly selected autoantibody + patients in whom enrollees as a whole showed a significant benefit), the response rate in black patients was less than in the placebo group 44% PLAC, 36% for B10mg/kg. In trial 1, no benefit was seen with B over placebo. 28% were autoantibody negative at baseline. The PI states that in Trial 1, black patients (n=106) in the Benlysta groups did not appear to have a different response than the rest of the population, which was not significantly different from placebo.

Also from the PI:

- Severe Flares:

- **Benlysta failed in Trials 2 & 3 to reduce the proportion of patients having at least 1 severe flare over 52 weeks. The proportion was not significantly different for Benlysta relative to placebo in both trials.**
- **Mortality**
 - **More Benlysta pts died in the main clinical trials than those receiving placebo. The Navarra trial did not look at mortality as an outcome so it was not powered to detect a significant difference.**

Severe active lupus nephritis and severe active CNS lupus were excluded from the 3 clinical trials in the PI.³

RECOMMENDATION: At a minimum, adopt the above criteria for the medical use of belimumab in addition to the pharmacy pathway (discuss including ethnicity). Consider exclusion of the drug, considering higher mortality than placebo in clinical trials.

Observations regarding subgroup summary of BLISS-52 and BLISS-76

1. Vascular organ domain
 - a. Involved 5.7 and 7.4% of patients at baseline
 - b. Clear improvement, in a dose dependent fashion, in SELENA SLEDAI, but interestingly, in BILAG, there was significant improvement in BLISS 52 but NOT in BLISS 76
2. Hematology/Fever Domain
 - a. Involved 7.4 and 11.6% of patients at baseline
 - b. Overall no trend
3. CNS domain—numbers minuscule
4. Cardiovascular/respiratory Domain
 - a. Involved 3.9 and 8.7% of patients at baseline
 - b. No trend in BLISS 52; trend toward worsening in BLISS 76
5. Mucocutaneous Domain
 - a. Involved 82% of patients at baseline
 - b. Improved rash
 - i. 37% placebo/51% drug in BLISS-52
 - ii. 29% placebo/38% drug in BLISS-76
 - c. Improved Alopecia
 - i. 45% placebo/54% drug in BLISS-52
 - ii. 33% placebo/38% drug in BLISS-76
 - d. No difference in new involvement
6. Musculoskeletal Domain
 - a. Involved 59 and 73% of patients at baseline
 - b. Arthritis
 - i. 58% placebo improvement and 67% drug improvement in BLISS-52
 - ii. 43% placebo improvement and 47% drug improvement in BLISS-76
 - iii. No dose response
 - iv. Trend toward reduction in patients with new involvement, but very small numbers
7. Renal function
 - a. Involved 20.1 and 11.4% of patients at baseline
 - b. By definition, patients with severe nephritis were excluded
 - c. Trend toward improvement, mostly in hematuria, none in proteinuria
 - i. 44% placebo, 48% drug in BLISS-52, 43% placebo, 50% drug in BLISS-76
 - ii. No dose response
8. Biomarker Domain
 - a. Involved all patients at baseline by definition
 - b. Very large effects
 - i. Reduced IgG in those high at baseline by 50% compared to 20% for placebo (no dose response)
 - ii. Worsened (elevated) IgG in those normal at baseline 11-13% placebo, dropped to 1-4% on med, dose dependent
 - iii. Reduced Anti-dsDNA by median of 13-27%, not dose dependent
 - iv. C3 increase in those low at baseline of 34-43% compared to 14-20% with placebo, dose dependent

Belinostat (Beleodaq®)

-Mechanism of action: histone deacetylase (HDAC) inhibitor

*inhibits removal of acetyl groups from histones and some non-histone proteins. *In vitro*, causes accumulation of acetylated histones and other proteins, inducing cell cycle arrest and/or apoptosis of some transformed cells. Shows preferential cytotoxicity towards tumor cells compared to normal cells.¹

-FDA indication (accelerated approval): relapsed/refractory peripheral T cell lymphoma

BELINOSTAT multicenter BELIEF trial ²	
Patients included	n = 129, median age 63 y Relapsed/refractory PTCL after at least one prior therapy Median # of prior regimens: 2 (range 1-8)
Dosing	1000 mg/m ² IV over 30 minutes daily x 5 days q3w until progression or unacceptable toxicity
Median duration of therapy	2 cycles (range 1-33)
Objective response (primary endpoint)	26%
Complete response	10%
Partial response	16%
Median time to response	5.6 weeks
Median duration of response	8.3 mo
Toxicity	Most common Grade 3 or 4 toxicities: thrombocytopenia (13%), neutropenia (13%), anemia (10%), dyspnea (6%), pneumonia (6%), fatigue (5%)

FDA-Approved Treatments for Relapsed/Refractory peripheral T cell lymphomas ³				
	Chemotherapy n = 98	Pralatrexate n = 111	Romidepsin n = 130	Brentuximab vedotin n = 58
PTCL-NOS, AILT, or ALCL	100%	80%	90%	100 (all ALCL)
Overall response rate	40-50% (CR ~30%)	29% (CR 2%)	38% (CR 11%)	86% (CR 57%)
Median PFS (mo)	3.7	3.5	4	13.3
Median DOR (mo)	NR	10.1	16.6	12.6
Median OS (mo)	6.5	14.5	NR	NR

NR = not reported, PFS = progression free survival, DOR = duration of response, OS = overall survival, PTCL-NOS = peripheral T cell lymphoma, AILT = angioimmunoblastic T cell lymphoma, ALCL = anaplastic T cell lymphoma

References

1. Beleodaq® [Package Insert] Irvine, CA: Spectrum Pharmaceuticals; 2014.
2. O'Connor OA et al. Belinostat, a novel pan-histone deacetylase inhibitor (HDACi), in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL): Results from the BELIEF trial. *J Clin Oncol* 31, 2013 (suppl; abstr 8507).
3. Mak V, et al. Survival of patients with peripheral t-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. *Journal of Clinical Oncology* 31(16):1970-76, 2013.

Relapsed/Refractory peripheral T cell lymphoma

Treatments for Relapsed/Refractory peripheral T cell lymphomas¹					
	Chemotherapy n = 98	Pralatrexate n = 111	Romidepsin ^{2*} n = 131	Belinostat ³ n=129	Brentuximab n = 58 (all ALCL)
Prior therapies (median)	1	3	2	2	2
Response rate	40-50% (CR ~30%)	29% (CR 11%)	25% (CR 15%)	26% (CR 10%)	86% (CR 57%)
Median DOR (mo)	NR	10.1	28	8.3	12.6
Median PFS (mo)	3.7	3.5	4 Responders: 20	NR	13.3
Median OS (mo)	6.5	14.5	11.3 Responders: 30	NR	NR

*updated results reported; median f/u 22.3 mo (initial study: 13 mo f/u)

NR = not reported, PFS = progression free survival, DOR = duration of response, OS = overall survival, ALCL = anaplastic T cell lymphoma

References

1. Mak V, et al. Survival of patients with peripheral t-cell lymphoma after first relapse or progression: spectrum of disease and rare long-term survivors. *Journal of Clinical Oncology* 31(16):1970-76, 2013.
2. Coiffier et al. Romidepsin for the treatment of relapsed/refractory peripheral T-cell lymphoma: pivotal study update demonstrates durable responses. *J Hematol Oncol.* 2014 Jan 23;7(1):11.
3. O'Connor OA et al. Belinostat, a novel pan-histone deacetylase inhibitor (HDACi), in relapsed or refractory peripheral T-cell lymphoma (R/R PTCL): Results from the BELIEF trial. *J Clin Oncol* 31, 2013 (suppl; abstr 8507).

Pembrolizumab (Keytruda)

-Mechanism of action: human programmed death (PD) receptor-1 inhibitor

*monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including the anti-tumor immune response

-FDA indication (accelerated approval): unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor.

*approved based on open label, international, multicenter expansion cohort of a phase I trial. Patients (n=173) were randomized to 2 mg/kg q3w (FDA-approved dose) or 10 mg/kg q3w until disease progression or unacceptable toxicity.

-inclusion criteria: previous treatment with ipilimumab and, if BRAF mutation positive, a BRAF inhibitor

-primary endpoint: response rate

	Vemurafenib¹ (960 mg po bid)	Dabrafenib³ (150 mg po bid)	Trametinib⁴ (2 mg po daily)	Trametinib + dabrafenib⁵ Phase II trial (monotherapy doses)	Ipilimumab⁶ (3 mg/kg IV every 3 weeks x 4 doses)	Pembrolizumab⁷ (2 mg/kg IV every 3 weeks)
Comparison	Dacarbazine	Dacarbazine	Dacarbazine or paclitaxel	Dabrafenib	gp100 vaccine (considered placebo)	Pembrolizumab 10 mg/kg every 3 wk
Previous lines of tx allowed	None	None (except IL-2)	0 or 1 (but no BRAF inh or ipi)	No restriction stated	≥1	≥1 (must have received ipilimumab and, if BRAF mutation +, a BRAF inhibitor)
Response rate (%)	48	50	22	76	37.5	26
PFS (mo)	5.3 ^a	5.1	4.8	9.4	2.86 ^b	5.5 (22 weeks)
Median overall survival (if available)	13.2 mo vs. 5.6 mo [HR 0.62 (95% CI, 0.49-0.77)] ²	HR 0.61 (95% CI, 0.25-1.48)	HR 0.54 (95% CI, 0.32 to 0.92)	At 12 months: 79% alive (vs. 70%; p not reported)	10.1 mo vs. 6.4 mo [HR 0.66 (95% CI, 0.51-0.87)]	No difference between doses 1 yr survival for 2 mg/kg group: 58%

a Median PFS of chemotherapy groups were 1.5 - 2.7 mo. Response rates <10%

b Median PFS of gp100 group was 2.76 mo (p<0.001 compared with ipilimumab group).

References:

1. Chapman PB et al. N Engl J Med 2011;364:2507-16.
2. Chapman PB et al. J Clin Oncol (Meeting Abstracts) May 2012 vol. 30 no. 15_suppl 8502
3. Hauschild A et al. Lancet 2012; 380: 358–65.
4. Flaherty KT et al. N Engl J Med 2012;367:107-14.
5. Flaherty KT et al. N Engl J Med 2012;367:1694-703.
6. Hodi FS et a. N Engl J Med 2010;363:711-23.
7. Robert et al. Lancet 2014;384:1109-17

Review of Medications for Herpes Labialis
Geri Bemberg, Pharm.D.

Drug	Strength	Form	Treatment	Treatment Price	Reduction in duration of disease
Acyclovir (Zovirax)	5%	Topical cream	5 times/day x 4 days	\$732 (5g tube) \$146.40/g	0.5 days compared to vehicle (4.3 vs 4.8) ²
acyclovir + hydrocortisone (Xerese)	5%/1%	Topical cream	5 times/day x 5 days	\$722.75 (5g tube) \$144.55/g	
acyclovir (Sitavig)	50mg	buccal tab	1 time	\$187.50/tx (HOWEVER, must buy 2 tabs, so \$375)	0.5 days compared to placebo ³
penciclovir (Denavir)	1%	Topical cream	q2h while awake x 4 days	\$115.32 (1.5g tube)	0.7 days compared to vehicle (4.8 vs 5.5) ⁴
Valacyclovir	1g	tablet	2g BID x 1 day	\$50.56 (4 tablets at \$12.64/tab)	Average of 1.1 day (compared to placebo) (6.1 vs 5) ¹
Acyclovir	200mg 400mg	tablet	200-400mg 5 times/day x 5 days (off-label)	400mg dose: \$54.25 (25 tablets at \$2.17/tab)	2.1 days compared to placebo (5.8 vs 7.9) ⁵
Famciclovir	250mg 500mg	tablet	1500mg once	250mg: \$61.50 (\$10.25/tab) 500mg: \$61.74 (\$20.58/tab)	1.7 days compared to placebo (4.4 vs 6.1) ⁶
Docosanol (Abreva) (OTC)	10%	Cream	5 times/day until healed	\$16.77 (at Walmart.com)	0.72 days compared to polyethylene glycol placebo

**All prices from Lexicomp come with the following disclaimer from Lexicomp: "The pricing data provide a representative AWP &/or AAWP price from a single manufacturer of the brand &/or generic product, respectively. The pricing data should be used for benchmarking purposes only, and as such should not be used to set or adjudicate any prices for reimbursement or purchasing functions. Pricing data is updated monthly."

Treatment considerations:

- All trials and reviews were in agreement that treatment benefit was best seen when started within 1 hour-24 hours of prodromal effects.
- On topicals, should there be a quantity limit of 1 5g tube/6 months (arbitrary length of time), to ensure patient uses medications they have first?
- On all medications, should there be a limit of 1 treatment modality in _____ days/weeks/months?

Approval options:

- A. Exclude all medications for the indication of herpes labialis
- B. Exclude all topical medications and cover all oral medications
- C. Exclude Sitavig, and leave other medication coverage as it currently stands

References

1. Spruance SL, Jones TM, Blatter MM, et al. High-Dose, Short-Duration, Early Valacyclovir Therapy for Episodic Treatment of Cold Sores: Results of Two Randomized, Placebo-Controlled, Multicenter Studies. *Antimicrob Agents Chemother.* 2003, 47(3):1072
2. Spruance SL, Nett R, Marbury T, et al. Acyclovir Cream for Treatment of Herpes Simplex Labialis: Results of Two Randomized, Double-Blind, Vehicle-Controlled, Multicenter Clinical Trials. *Antimicrob Agents Chemother.* 2002, 46(7):2238.
3. Sitavig Package Insert. www.sitavig.com
4. Spruance SL, Rea TL, Thoming C, et al. Penciclovir Cream for the Treatment of Herpes Simplex Labialis. *JAMA.* 1997;277:1374-1379.
5. Jensen LA, Hoehns JD, Squires CL. Oral Antivirals for the Acute Treatment of Recurrent Herpes Labialis. *Ann Pharmacother* 2004;38:705-9.
6. Spruance SL, Bodsworth N, Resnick H, et al. Single-dose, patient-initiated famciclovir: A randomized, double-blind, placebo-controlled trial for episodic treatment of herpes labialis. *J Am Acad Dermatol* 2006;55:47-53.
7. Sacks SL, Thisted RA, Jones TM, et al. Clinical efficacy of topical docosanol 10% cream for herpes simplex labialis: A multicenter, randomized, placebo-controlled trial. *J Am Acad Dermatol.* 2001;45(2):222-230.

DUEC Meeting Materials

11/3/14

Jill Johnson, Pharm.D. & Geri Beth Bemberg, Pharm.D.

1. New Drugs
2. Naloxone (Evzio)
3. Mercaptopurine suspension
4. Isentress Powder
5. Tedizolid
6. Ovace Plus Lotion 9.8%
7. Vexa
8. Methotrexate (Rasuvo) autoinjector
9. Canagliflozin-Metformin (Invokamet)
10. Empagliflozin (Jardiance)
11. Droxidopa (Northera)
12. Olodaterol (Striverdi)
13. Eliglustat (Cerdelga)
14. Isotretinoin (Absorica)
15. Ferric Citrate
16. C1 esterase inhibitor, recombinant (Ruconest)
17. Vedolizumab (Entyvio)

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	Consultant NOTES	DUEC VOTE	DUEC DATE	IB VOTE	IB DATE	Connie Notes
EVZIO INJECTION	naloxone 0.4mg/0.4ml auto-injector	\$700/2 injectors	A take-home naloxone auto-injector for the emergency treatment of known or suspected opioid overdose, manifested by a respiratory and/or CNS depression	Generic naloxone 0.4mg/ml amp AWP range from \$1 - \$25/amp	Exclude Code 9 and 13. Autoinjector non necessary. Naloxone vials are less cost.					
PURIXAN SUSPENSION	mercaptopurine 20mg/ml suspension	\$1,038/100ml bottle	For treatment of patients with acute lymphoblastic leukemia. Only oral suspension of mercaptopurine	generic mercaptopurine 50mg tabs = \$2.08/tab	(GB handout) Cover w/ age edit (age 7 and younger)					
QUDEXY XR CAPSULES	topiramate cap extended-release 24 hour sprinkle	Per cap AWP: 25mg/\$5.63;50mg/\$7.36; 100mg/\$14.60;200mg/\$19.96	Treatment of partial onset, generalized primary tonic-clonic seizures and as an adjunct therapy in Lennox-Gastaut syndrome	generic immediate-release topiramate sprinkle caps: \$2.89	Bioequivalence between Trokendi XR and QudexyXR not established. Generic IR is covered. Exclude Code 13					
JUBLIA SOLUTION 10%	efinaconazole soln 10%	\$538/4ml bottle	Treatment of onychomycosis of the toenail	(T1)- terbinafine 250mg(\$30/month) (T1)-itraconazole-200mg (\$500/month) . Ciclopirox nail lacquer (\$165/bottle)-excluded by plan	Not medically necessary. PO terbinafine is the preferred treatment.					
KERYDIN SOLN 5%	tavaborole 5% solution	\$538/4ml bottle	Treatment of onychomycosis - applied to the affected toenail(s) once daily for 48 weeks.	(T1)- terbinafine 250mg(\$30/month) (T1)-itraconazole-200mg (\$500/month) . Ciclopirox nail lacquer (\$165/bottle)-excluded by plan	Not medically necessary. PO terbinafine is the preferred treatment.					Catamaran standard PA requires an FDA approved diagnosis/test confirmation, proper disease severity; and a trial and failure, intolerance, or hypersensitivity to oral terbinafine
ISENTRESS POWDER (specialty drug)	TEGRAVOR PACKET FOR SUSP 100MG	\$337/box of 60	NEW DOSAGE FORMULATION- for treatment for HIV infection	Same price as 100mg chewable tab(currently excluded by plan). Isentress 400mg tab - covered w/PA-specialty tier	Cover with an age edit. Allow for age 2 and younger. There are 25mg raltegravir chewable tabs available. Note brand name differences (Isentress=chewable, tablets, pack; Tegravir=powder for susp)					
CYCLOPHOSPHAMIDE CAPS (specialty drug)	cyclophosphamide	\$7.59/25mg cap and \$13.94/50mg cap	new dosage formulation - 25 and 50mg caps.	(T1) - cyclophosphamide tablets - \$2.78/25mg tab and \$5.11/50mg tab	Cover w/o restriction. Manufacturer stated they are discontinuing tablets. Each plan to determine tier					
SIVEXTRO 200mg	tedizolid phosphate tabs	\$2,124/6 days	For treatment of skin and skin structure infections due to gram-positive organisms. Dose=200mg by mouth every day for 6 days	(T3 w/PA) - Zyvox - \$3,072/10 days	T3PA; same criteria as linezolid except only for SSTI					
OVACE PLUS LOTION	sulfacetamide sodium lotion 9.8%	\$509/57 gm bottle	For treatment of seborrheic dermatitis and seborrhea sicca(dandruff)	(T1) - Sulfacetamide sodium lotion 10% - \$109/bottle	(GB handout) Exclude Code 13.					
VEXA PAD 2-4-30%	allantoin-lidocaine-petrolatum patch	\$602/box of 15 patches	Uses include: scar management, temporarily protects minor cuts, scrapes, burns and temporarily relieves pain associated with minor cuts, scrapes, and minor skin irritations. According to Daily Med: this product has not been found by FDA to be safe and effective and this labeling has not been approved by FDA.	n/a	Exclude 13. Lack of information and evidence.					
RASUVO INJECTION	methotrexate solution PF auto-injector for subcutaneous administration	\$134/pen	Management of patients with severe, active rheumatoid arthritis & active polyarticular juvenile idiopathic arthritis, who are intolerant of or had an inadequate response to, first-line therapy and symptomatic control of severe, recalcitrant, disabling psoriasis in adults who are not adequately responsive to other forms of therapy.	Otrexup (methotrexate soln PF Auto-injector for subcutaneous administration)- \$164/pen and is currently excluded by the plan. Methotrexate inj 25mg/ml for deep IM administration - \$4.	Autoinjector is costly. Otrexup is also not covered. Methotrexate inj (generic) is available (jill handout)					
INVOKAMET	canagliflozin & metformin	\$373/30 days	for the treatment of Type 2 diabetes in combination with diet and exercise. INVOKANA(canagliflozin) is a sodium-glucose co-transporter 2(SGLT2) inhibitor. Ivokamet is dosed twice daily.	INVOKANA is currently a plan exclusion.	Exclude code 13. Surrogate endpoint data only. (jill handout)					
JARDIANCE	empagliflozin	\$360/month	for the treatment of Type 2 diabetes in combination with diet and exercise. JARDIANCE is a SGLT2.	INVOKANA (\$374/30days) is currently a plan exclusion	Exclude code 13. Surrogate endpoint data only. (jill handout)					

NORTHERA (SPECIALTY DRUG)	droxidopa	\$1,690-\$10,144/month	for the treatment of orthostatic dizziness, lightheadness, or the "feeling that you are about to black out" in adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure (Parkinson's disease, multiple system atrophy, and pure autonomic failure), dopamine beta-hydroxylase deficiency and non-diabetic autonomic neuropathy. Dose is 300-1800mg/day.	Midodrine (T1) (10mg by mouth three times a day) - \$435/30 days.	Exclude. No advantage shown past 1 week. Any advantage was (barely) on BP only. (jill handout)					
STRIVERDI AER RESPIMAT	olodaterol HCl inhal aerosol	\$168/inhaler	for the long-term, once-daily maintenance bronchodilator treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema. Dose: 2 inhalations once daily	FORADIL - (T2) and requires ST-\$265. SEREVENT DISKUS - (T2) and requires ST-\$265. PERFORMOMIST - (T3) and requires ST-\$673.	(GB handout) Exclude 13. Striverdi (olodaterol) Foradil (formoterol inhaled capsule) Serevent (salmeterol) Performomist (formoterol neb. Soln.)					
Acticlate	doxycycline 75mg and 150 mg	\$26/tab	Tetracycline-class antibacterial indicated for the treatment of a number of infections, including adjunctive therapy in severe acne	Doxycycline 100mg caps = \$0.25	Exclude Code 13. (jill handout)					
CERDELGA CAPS (specialty)	eliglustat 84mg	\$510/84mg cap	Only first-line oral therapy for the long-term treatment of adults with the Type 1 form of Gaucher disease. Dose is dependent on CYP2D6 genotype. (84-168mg/day		Exclude Code 13 (GB handout). This drug is a glucosylceramide synthase inhibitor. Single arm trial measured surrogates (spleen and liver volumes, Hb level, plt count; no measure of effect on bleeding or other clinical marker). Lack of ability to generalize to a patient population. Prefer enzyme replacement therapy 1st line (imiglucerase, velaglucerase, taliglucerase)					
TRIUMEQ TABS (specialty)	abacavir-dolutegravir-lamivudine	\$2,648/30 days	For treatment of HIV infection. Once daily single pill regimen	Other once daily single pill regimen: Stribild(\$2,940/30 days) and Atripla (\$2,460/30 days)	T4					
ABSORICA 25mg and 35mg caps	isotretinoin caps	\$926/month	For treatment of acne vulgaris/cystic acne	no other 25 or 25mg isotretinoin caps	(GB handout)Exclude this strength and ALL Absorica products. Other isotretinoin products are less costly. No trials comparing formulations.					
BUNAVAIL	buprenorphine-naloxone buccal film	\$253-\$506/box of 30	Treatment of opiate agonist dependence		Exclude 13. generic SL tablets 2/0.5 and 8mg/2mg available.					
REVATIO SUSPENSION 10MG/ML (specialty)	sildenafil for suspension	\$5,500/112 ml bottle	new dosage formulation. For treatment of pulmonary hypertension	Other REVATIO formulations covered as tier 4	Exclude 13. Can be compounded for less. Shelf life is longer if compounded; shorter for this product. PI states Revatio is not approved for children??					
UTA CAPS 120MG	methenamine/hyoscynamine/meth blue/sod phos caps	\$3.71/tab	For treatment of urinary tract infections	Uribel (\$2.71/tab) and Ustell (\$2.41/tab) covered as T3	Exclude 13. Azo standard OTC. Amount of methenamine is 1/10th of the amount required for antibiotic efficacy.					
SOMAVERT INJ (specialty)	pegvisomant	-----	New dosage strength - Treatment of acromegaly	Other strengths covered as Tier 4	T4.					
FERRIC CITRA TAB 210 MG	ferric citrate	\$1,010/200	Management of hyperphosphatemia in patients with chronic kidney disease on dialysis. Max dose: 12 tabs/day		Exclude (Handout).					
RUCONEST INJECTION (specialty drug)	C1 esterase inhibitor (recombinant)	\$5,700/unit	For IV administration for treatment of angioedema. Patients may self-administer after appropriate training under the guidance of healthcare professional		Exclude from pharmacy side only. For a drug like this, used for acute exacerbation, it would be difficult to place control on medical side. This is generally single dose. Max is 2 doses/24h. Not approved for laryngeal attacks. Need policy for therapeutic duplication so that multiple C1 esterase inhibitor products cannot be accessed during the same days supply.					
Non Reviewed/Tabled for future discussion										
FOLET ONE CAPS	prenat w/o a w/FECBN-bisg-methylf-DSS-DHA	\$4.38/cap	Pre natal vitamin	multiple	vitamin policy					
SUTENT CAPS (specialty drug)	sunitinib malate 37.5mg	\$442/capsule	new dosage formulation for tx of GI stromal tumors, pancreatic neuroendocrine tumor, and renal cell cancer	(Specialty tier) - Sutent 12.5mg, 25mg, 50mg covered	Delivery coordination					
MAXFE	IRON-fa-Vit B-12biotin-vit C-docusate-Mg-Zn tabs	0.83/tab	multivitamin	various generics	vitamin policy					
BYDUREON INJ	exenatide extended release	\$528/month	New pen-injector device. For treatment of type 2 diabetes	Bydureon - currently excluded by plan	already excluded					
RESTORA RX CAPS	lactobacillus casei-foic acid cap		nutritional supplement	no similar products covered by plan	vitamin policy					
SURFAXIN SUSP	lucinactant intratracheal susp	\$1,031/8.5ml bottle	Administered intratracheally for prevention of neonatal respiratory distress syndrome. Out of scope of pharmacy benefits	n/a	medical					
ZYDELIG (specialty)	idelalisib	\$8,640/bottle of 60 tabs	Treatment of chronic lymphocytic leukemia in combo w/retuximab and for the treatment of relapsed follicular B-cell non-Hodgkin lymphoma in patients who have received at least two prior systemic therapies		delivery coordination					
FOLET DHA PAK	prenatal w/FECBN-BISG-METHYL-DSS &DHA CAP PAK	\$137/pak of 60	Pre natal vitamin	numerous low-cost generics	vitamin policy					
EZ Flu Shot Kit	influenza virus vaccine tissue-cultured subunit inj kit	\$185/kit			flu shot/kit policy					
PRENATE CAP PIXIE	prenat w/o a w/FEASPG-METHFOL-FA-DHA	\$4.65/cap	prenatal vitamin	numerous generics	vitamin policy					

SCULPTRA INJ	poly-L-lactic acid for injection	\$1,152/vial	Cosmetic drug - for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles	Cosmetic products not covered	cosmetic							
SCULPTRA INJ	poly-L-lactic acid for injection	\$1,152/vial	Cosmetic drug - for correction of shallow to deep nasolabial fold contour deficiencies and other facial wrinkles	Cosmetic products not covered	cosmetic							
BUTRANS DIS 7.5MCG PATCH	buprenorphine 7.5mcg/hr		weekly patch - new dosage strength	other strengths excluded by plan	already excluded							
HYQVIA (specialty)	immune globulin-hyaluron	\$457/2.5 gm 25ml bottle	Subcutaneous injection immunoglobulin that can be administered in one injection site, once a month for treatment of primary immunodeficiency in adults		delivery coordination							
ARTICADENT INJ DENTAL		\$1.70/ml	Local anesthetic indicated for local, infiltrative, or conductive anesthesia in both simple and complex dental procedures. Product out of the scope of pharmacy benefits		dental							
CONTRAVE TABS 8-90MG	naltrexone/bupropion HCL tab SR 12 hour 8-90mg)	\$238/120 tabs	For treatment of obesity. Dose is titrated up to 4 tabs/day	Other obesity products are excluded by the plan	obesity							
DALVANCE 500MG	dalbavancin	\$1,788/ 500mg vial	Treatment of skin and skin structure infections due to gram-positive organisms. IV administration. Dose=1000mg IV once then 500mg IV one week later	Other IV administered drugs - Teflaro, Cubicin, Vibativ, vancomycin, Sivextro	Medical							
ELOCTATE INJECTION (specialty)	antihemophilic factor VIII(recombinant)		For the management of hemophilia A (congenital Factor VIII deficiency).Administered IV		delivery coordination							
BELEODAQ INJ 500MG (specialty)	belinostat for IV injection	\$1,800/vial	Treatment of peripheral T-cell lymphoma (PTCL). Administered IV		delivery coordination							
RYANODEX INJ 250MG (specialty drug)	dantrolene	\$2,760/vial	Administered IV for treatment of malignant hyperthermia. Not in scope of pharmacy benefits		medical							
SIVEXTRO INJECTION	tedizolid phosphate IV	\$2,820/vial	Treatment of skin and skin structure infections due to gram-positive organisms. IV administration. Also available in oral formulation	Other IV administered drugs - Teflaro, Cubicin, Vibativ, vancomycin, Dalvance	medical							
ALPHANATE INJ VWF/HUM (specialty drug)	antihemophilic factor/VWF(human)	\$2,720/2000 units	IV injection - antihemophilic factor		delivery coordination							
KEYTRUDA (specialty)	pembrolizumab	\$2,589/vial	For treatment of patients with advanced or unresetable melanoma who are no longer responding to other drugs.		delivery coordination							
OCTAGAM (specialty)	human immune globulin	\$141/20ml vial	For IV administration		delivery coordination							
KABIVEN EMUL FOR IV INFUSION	amino ac /dextrose/lipids		For parenteral nutrition. Product out of the scope of pharmacy benefits		medical							
ORBACTIV 400MG INJ (not specialty - available through standard distribution channels)	oritavancin	\$1,160/400mg vial	for treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused or suspected to be caused by susceptible isolates of designated gram-positive organisms. Dose is a single 1200mg IV infusion over 3 hours to patients 18 years or older.	Others in this class (lipoglycopeptide antibacterials): Dalvance and Vibativ.	medical							

KITS

FBL KIT compounding kit	flurbiprofen-baclofen-lidocaine cream compounding kit	\$987/120gm kit			
CLODAN KIT	clobetasol propionate shampoo 0.05% and cleanser kit	\$38/kit			
NEO-SYNALAR COMP KIT	neomycin-fluocinolone cream 0.35-0.025% and emollient cream kit	\$468/kit			
NEUAC KIT	clindamycin-benzoyl peroxide gel 1.2-5% & moisturizer cream kit	\$326/kit			
ACTIVE-PAC/MIS GABA 300	GABAPENTIN ORAL CAP 300MG AND LIDOCAINE-MENTHOL GEL THER PK	\$508/kit			
APOP GEL 10%	sulfacetamide in bakuchiol vehicle gel	\$150/bottle	Antiseborrheic product. "bakuchiol: a retinol-like functional compound revealed by gene expression in profiling and clinically proven to have anti-aging effects	n/a	
MEDI-RDT	rapid dissolve tablet base powder kit	\$2.36/gm			
DEPRIZINE SUSPENSION	rantidine for oral susp 22.4mg/ml compounding kit	\$510/bottle			
DICOPANOL SUSPENSION	diphenhydramine for oral suspension 5mg/ml compounding kit	\$495/bottle			

K.B.G.L in CRE TERODERM	ketoprofenbaclofen-gabapentin-lido cream compounding kit	\$998/120gm
BETALIDO KIT	betamethasone \$ lidocaine compounding kit	\$720/kit
DEXLIDO KIT	dexamethasone & lidocaine compounding kit	\$270/kit
DOUBLEDEX KIT	dexamethasone 10mg/ml compounding kit	\$288/kit
DEXLIDO-M KIT	dexamethasone,bupiv,lidocaine compounding kit	\$228/kit
DYRUAL KIT	methylprednisolone/bupiv/lidocaine compounding kit	\$472/kit
KETOROCAINE KIT	ketorolac/lidocaine compound kit	\$245/kit
KETOROCAINE KIT LM	ketorolac/bupivacaine/lidocaine compound kit	\$215/kit
MARBETA-25 KIT	betamethasone/bupivacaine compound kit	\$655/kit
MARBETA-L KIT	betamethasone/bupivacaine/lidocaine compound kit	\$680/kit
MARDEX - 25 KIT	dexamethasone/bupivacaine compound kit	\$256/kit
MARLIDO - 25 KIT	lidocaine/bupivacaine compound kit	\$204/kit
PRASTERA KIT	prasterone 200mg/ibuprofen 400mg tab kit	\$339/box of 35
AIF #3 CRE PREP KIT	flurbiprofen/baclofen/cycloben/lidocaine cream compound kit	\$1,211/kit
NP #2 CRE PREP KIT	tramadol/flurbip/ amitrip/gaba/clinidine/lido compound kit	\$1,392/kit
KETOROLAC GEL 2%	ketorolac gel 2% compound kit	\$66.55/box

naloxone HCL solution auto-injector (Evzio)

Leslie Warford

July 28, 2014

Labeled Uses: opioid antagonist indicated for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression.

Dose: IM/SQ: Initial: 0.4-2 mg; may need to repeat dose as early as every 2-3 minutes.

Comparators:

Available forms	Evzio auto-injector 0.4 mg/0.4 mL (0.4 mL) (2 injectors & trainer)	naloxone 0.4 mg/mL (1 mL)	naloxone 1 mg/mL (2 mL) (prefilled syringe)
AWP (\$)	345.00	18.53	20.34

Contraindications: Patients known to be hypersensitive to naloxone hydrochloride.

Toxicities:

- Acute opioid withdrawal: Administration of naloxone causes the release of catecholamines; may precipitate acute withdrawal or unmask pain in those who regularly take opioids. Symptoms of acute withdrawal in opioid-dependent patients may include pain, hypertension, sweating, agitation, irritability; in neonates, symptoms may include shrill cry, failure to feed.
- Cardiovascular disease: Use with caution in patients with cardiovascular disease or in patients receiving medications with potential adverse cardiovascular effects (eg, hypotension, pulmonary edema or arrhythmias); pulmonary edema and cardiovascular instability, including ventricular fibrillation, have been reported in association with abrupt reversal when using opioid antagonists.
- Seizures: Use caution in patients with history of seizures; avoid use in the treatment of meperidine-induced seizures.

Drug Interactions: There are no known significant drug interactions.

Evidence:

Evzio Prescribing Information

- Store at room temperature (15-25°C) (like generic naloxone)
- User activated, should be injected into the thigh, needle is never visible, each device can only be used once, red indicator appears in viewing window and black base locks in place post injection
- Electronic voice instructions (still injects when activated even if voice instructions malfunction) and diagrams on the injector

- Has a viewing window through which the solution should be visually inspected for precipitates, discoloration, etc.
- Instructs to get emergency medical attention post use

Evzio (naloxone hydrochloride) [prescribing information]. Richmond, VA: Kaleo; April 2014.

FDA Approves New Hand-held Auto-injector to Reverse Opioid Overdose

- Designed for administration by family members or caregivers
- “Drug overdose deaths, driven largely by prescription drug overdose deaths, are now the leading cause of injury death in the United States—surpassing motor vehicle crashes”
- Deaths due to drug overdose have continually increased in the last ten years
- One injection with Evzio provides the same amount of naloxone as what is on the market now

U.S. Food and Drug Administration (2014). FDA approves new hand-held auto-injector to reverse opioid overdose; First naloxone treatment specifically designed to be given by family members of caregivers [Press release]. Retrieved from <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm391465.htm>

Project Lazarus: Community-Based Overdose Prevention in Rural North Carolina

- Opioids related in deaths: fentanyl, hydrocodone, methadone, oxycodone; rarely heroin
- Those dying use opioids for medical and nonmedical reasons and exceed their tolerance with either the opioid alone or in combination with other substances
- Model for Project Lazarus: community activation and project building, monitoring and surveillance data, prevention of overdoses, use of rescue medication in event of opioid overdose
- More than half of noted overdose deaths were in the home and either signs of OD were not recognized or emergency services were called too late
- Naloxone given to high risk opioid users by specified criteria including high dose opioid prescription, renal or hepatic disease, concurrent BZD or antidepressant use, etc.
- Average cost for inpatient hospitalization for opioid poisoning in NC in 2008 was \$16,970
- Overall impact for this project was not determined

Albert S, Brason FW, Sanford CK, et al, “Project Lazarus: Community-Based Overdose Prevention in Rural North Carolina,” *Pain Med*, 2011, 12(Suppl2):77-85. PMID 21668761

Summary: Evzio is an auto-injector of naloxone which is to be administered to someone who is believed to have overdosed on opioids. The device has the advantage of voice instructions for administration as compared to what is currently on the market, and the actual needle is never seen due to the packaging. However, there are no studies comparing Evzio administration to naloxone prefilled syringes.

Recommendation: Evzio should not be covered. The generic available now works as well as the new brand name product. The claim to ease of administration provided by Evzio does not justify its cost.

Outcome: Exclude from coverage for reasons 9 (not medically necessary) and 13 (insufficient clinical benefit OR alternative agent(s) available.)

Mercaptopurine (Purixan) 2000mg/100mL suspension

Antineoplastic Agent, Antimetabolite; Purine Analog; Immunosuppressant Agent
Geri Bemberg, Pharm.D.

Indications: Acute Lymphoblastic Leukemia (ALL). Maintenance treatment of ALL as part of a combination chemotherapy regimen.

Unlabeled indications: steroid-sparing agent for steroid-dependent Crohn's disease & Ulcerative colitis; maintenance of remission in CD; fistulizing CD; maintenance treatment in acute promyelocytic leukemia; treatment component for non-Hodgkin's lymphoma; treatment of autoimmune hepatitis.

Place in therapy: as part of a maintenance treatment after remission is achieved for 2-3 years. Nonadherence to the mercaptopurine portion of treatment is associated with an increase in risk of relapse.

Mercaptopurine Dosage Forms			
Form	Strength	Price	Price Breakdown
Tablets (generic)	50 mg	\$1022.56 (250)	\$4.09/50mg tab
Tablets (Purinethol oral)	50 mg	\$575.40 (60)	\$9.59/50mg tab
Suspension (Purixan)	2000mg/100mL 20mg/mL	\$1038 (100 mL)	\$10.38/mL (20 mg)

Dosing: 1.5-2.5 mg/kg once daily (ex: 30 lb child would need 20.5-34.1 mg)

Unlabeled maintenance dosing: 50 mg TID for 2 years or 75mg/m²/day for 2 years for girls or 3 years for boys

Other considerations: A compounded formulation can be made using the 50mg tablets. 30 tablets into 30mL to equal 50mg/mL suspension. The suspension is stable for 14 days at room temperature. Purixan is stable for up to 6 weeks.

Recommendation: Cover with PA criteria for an age edit of <7.

Outcome: Approved. Cover with an age edit of <7.

ISENTRESS POW 100MG (RALTEGRAVIR)

Olive Fai-yengo

July 28, 2014

Labelled uses: human immunodeficiency virus (HIV) infection

Comparators:

Drug Name	Dose/Dosage Form	AWP
Isentress	400mg tablets BID	\$1352.05(60)
Isentress	100mg Chewable BID	\$338.04(60)
Isentress	25mg chewable BID	\$84.52(60)
Isentress	100mg pow for susp. BID	\$338.04(60)

Contraindication: None

Toxicities: severe skin and hypersensitivity reactions including cases of Stevens-Johnson syndrome and toxic epidermal necrolysis. Renal failure, rhabdomyolysis, immune reconstitution syndrome. Autoimmune disorders (such as Graves' disease, polymyositis, and Guillain-Barré syndrome) have also been reported to occur in the setting of immune reconstitution

Drug Interactions: Rifampin, omeprazole, aluminum and magnesium containing antacids Efavirenz, Etravirine, fosamprenavir, atazanavir, atazanavir/ritonavir, tipranavir/ritonavir, boceprevir, telaprevir.

Evidence:

Isentress Prescribing information

Adult dosage: ISENTRESS 400 mg film-coated tablet administered orally, twice daily.

Pediatric dosage: **If at least 25 kg** one 400 mg film-coated tablet orally, twice daily. If unable to swallow a tablet, consider the chewable tablet. See table 1 for dosing

Table 1

Body weight(kg)	Dose	Number of chewable tablets
25 to less than 28	150mg twice daily	1.5x100mg twice daily
28 to less than 40	200mg twice daily	2 x100mg twice daily
At least 40	300mg twice daily	3 x100mg twice daily

If at least 4 weeks of age and weighing at least 3 kg to less than 25 kg the dosing is weight based. **For patients weighing between 11 and 20 kg**, either the chewable

tablet or oral suspension can be used. For patients whose **weight is below 20 kg** remain on the oral suspension.

Body weight (kg)	Volume(dose) of suspension	Number of chewable tablets
3 to less than 4	1ml(20mg)twice daily	
4 to less than 6	1.5ml(30mg)twice daily	
6 to less than 8	2ml(40mg)twice daily	
8 to less than 11	3ml(60mg)twice daily	
11 to less than 14	4ml(80mg)twice daily	3x 25mg twice daily
14 to less than 20	5ml(100mg)twice daily	1x 100mg twice daily
20 to less than 25		1.5x 100mg twice daily

Metabolism and Excretion: Two pediatric formulations that were evaluated in healthy adult volunteers, where the chewable tablet and oral suspension compared to the 400 mg tablet. The chewable tablet and oral suspension demonstrated higher oral bioavailability, thus higher AUC, compared to the 400 mg tablet. In the same study, the oral suspension resulted in higher oral bioavailability compared to the chewable tablet. Pediatric patients above 25 kg administered the chewable tablets had lower trough concentrations (113 nM) compared to pediatric patients above 25 kg administered the 400 mg tablet formulation (233 nM). As a result, the 400 mg film-coated tablet is the recommended dose in patients weighing at least 25 kg; however, the chewable tablet offers an alternative regimen in patients weighing at least 25 kg who are unable to swallow the film-coated tablet.

Storage: Store in the original container. Do not open foil packet until ready for use

Instructions for use:

Fill mixing cup about half-way with drinking water. Fill the dosing syringe with 5ml of water. Pour out remaining water from mixing cup. Add the 5 mL of water from the dosing syringe back into the mixing cup by pressing down on the plunger. Open 1 foil packet. There is a notch that you can use to tear open the foil packet, or you may use scissors to cut along the dotted line. Pour entire contents into mixing cup. Close the attached lid to seal the mixing cup. Swirl the mixing cup to mix using a gentle circular motion for 30-60 seconds. Do not turn the mixing cup upside down. The liquid will be cloudy. Administer the dose within 30mins of mixing. Discard any remaining suspension

Reference: Isentress (Raltegravir potassium) [prescribing information]. Whitehouse Station, NJ. Merck & Co., Inc. April 2014

Summary: Lsentress powder for suspension targets more of the younger pediatric population. This formulation has an advantage to target younger babies that are not able to chew the tablets. Some concerns or issues I identified were the fact that you have to discard any remaining suspensions. Also the older children may tend to spit out the liquid resulting in them getting an inadequate dose. Children older than 2years who can chew will have a better compliance with this medication.

Recommendation: Add to formulary with an age limit to 2yr olds or patients weighing less than 20kg whichever comes first. For patients >20kg switch to the chewable tablets.

Outcome from committee: Cover for less than 2 years of age. After that, chewable tablets are available.

tedizolid phosphate (Sivextro)

Leslie Warford

July 28, 2014

Labeled Uses: Acute bacterial skin and skin structure infections: Treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant [MRSA] and methicillin-susceptible [MSSA] isolates), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus anginosus* group (including *Streptococcus anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), and *Enterococcus faecalis*

Comparators:

Drug Name	tedizolid (Sivextro)	linezolid (Zyvox)
Dosage	200 mg once daily for 6 days	600 mg q 12 hrs for 10-14 days
AWP	200 mg (6): \$2124	600 mg (20): \$3253.84
Mode of Drug Interactions	MAOI	MAOI
FDA Approved Use	Acute bacterial skin and skin structure infections	-Pneumonia (CAP & HA) -Skin & Skin Structure Infections (complicated & uncomplicated) -VRE including bacteremia
Unlabeled Use		-Brain abscess, subdural empyema, spinal epidural abscess (MRSA) -Meningitis (MRSA) -Osteomyelitis (MRSA) -Prosthetic joint infection (<i>Enterococcus & Staphylococci</i>) -Septic arthritis (MRSA) -Septic thrombosis of cavernous or dural venous sinus (MRSA)

Contraindications: There is no contraindication list on the manufacturer's label.

Toxicities:

- Those in at least 2% of treated patients:
 - GI Disorders: nausea, vomiting, diarrhea
 - Nervous System Disorders: headache, dizziness
- Those in less than 2% of treated patients:
 - Blood and Lymphatic System Disorders: anemia
 - Cardiovascular: palpitations, tachycardia
 - Eye Disorders: asthenopia, vision blurred, visual impairment, vitreous floaters
 - Immune System Disorders: drug hypersensitivity
 - Infections and Infestations: *Clostridium difficile* colitis, oral candidiasis, vulvovaginal mycotic infection
 - Investigations: hepatic transaminases increased, white blood cell count decreased
 - Nervous System Disorders: hypoesthesia, paresthesia, VIIth nerve paralysis
 - Psychiatric Disorders: insomnia
 - Skin and Subcutaneous Tissue Disorders: pruritus, urticaria, dermatitis
 - Vascular Disorders: flushing, hypertension

Drug Interactions: tedizolid is an MAOI, and therefore has several interactions.

- Opioids
- Antipsychotics
- Antidepressants
- Serotonin Modulators (5HT3 Antagonists, 5HT1D Agonists)
- Sympathomimetics
- Atomoxetine
- COMT Inhibitors
- Hypoglycemic Agents

Evidence:

ESTABLISH-1 Randomized Trial

- ESTABLISH: The Efficacy and Safety of 6-day Oral Tedizolid in Acute Bacterial Skin and Skin Structure Infections vs 10-day Oral Linezolid Therapy
- Design:
 - Randomized, double-blind, double-dummy, multicenter, multinational, phase 3 noninferiority (concluded if lower limit of 95% CI >-10%) trial with intent-to-treat and per protocol (clinically evaluable) analysis
 - 332 patients were randomized to tedizolid (1 tablet tedizolid plus one tablet placebo followed by placebo 12 hours later on days 1-6, and 3 places on days 7-10) and 335 patients were randomized to linezolid (1 tablet linezolid plus one placebo followed by 1 tablet linezolid 12 hours later for 10 days.)
 - Age range was 18 years and older.
- Endpoints/Results:
 - Primary efficacy outcome: early clinical response at the 48-72 hr assessment. Treatment responder if afebrile, cessation of primary ABSSI lesion spread, did not receive prohibited other antibiotics, did not die of any cause. Difference of 0.1% (95% CI, -6.1%-6.2%)
 - Secondary outcomes: objective sustained clinical response (criteria as above) at the end of treatment in the (1) ITT set: difference of -2.6% (95% CI, -9.6-4.2%) ; (2) and the clinically evaluable end of treatment set: -0.9% (95% CI, -7.7-5.4%); as well as (3) investigator's assessment of clinical success at the post therapy evaluation in the ITT set: Difference of -0.5% (95% CI, -5.8-4.9%); and (4) investigator's assessment of clinical success at the post therapy evaluation in the clinically evaluable post therapy evaluation set: Difference of -0.8% (95% CI, -4.6-3.0%)
 - In subgroups based on type of infection, treatment response rates were lower for cellulitis/erysipelas than all infections combined. (95% CI lower limit not consistently above -10%.)
 - Adverse event rates were similar for both groups. The gastrointestinal events were fewer in the tedizolid group.
 - Claimed that drug interactions would not be a problem, but that was not studied in the trial.

Prokocimer P, De Anda C, Fang E, Mehra P, Das A. Tedizolid phosphate vs linezolid for treatment of acute bacterial skin and skin structure infections: the ESTABLISH-1 randomized trial. JAMA 2013;309(6):559-69. PMID 23403680

ESTABLISH-2 Randomized Trial

- Design:
 - Randomized, double-blind, double-dummy, multicenter, multinational, phase 3 parallel-group noninferiority (concluded if lower limit of 95% CI >-10%) trial with intent-to-treat analysis.
 - 332 patients were randomized to IV tedizolid 200 mg daily for 6 days and 334 to IV linezolid 600 mg twice daily for ten days. All patients got at least two IV doses of active treatment or placebo and could then be switched to oral if they met specified criteria.
 - Age range was 12 years and older.
- Endpoints/Results:
 - Primary efficacy outcome: early clinical response at the 48-72 hr assessment. Treatment responder if 20% or greater reduction in area of primary lesion from baseline, did not receive any systemic concomitant antibiotics with gram-positive activity, and did not die from any cause within 72 hours of first dose. Difference of 2.6% (95% CI, -3.0%-8.2%)
 - Secondary outcomes: response at day 7 (investigator-assessed) difference of 0.9% (95% CI, -3.2%-4.9%); end of treat assessment (programmatic and investigator-assessed) 1.4% (95% CI, -3.0%-5.9%); post-therapy assessment (7-14 days after end of treatment, investigator-assessed) Difference of 0.3% (95% CI, -4.8%-5.3%); and changes in reported pain at prespecified time points throughout the study. Difference not specified. The ITT results for secondary outcome showed a difference of -1.0% (95% CI, -6.1%-4.1%.)
 - Safety assessments were made as well. Adverse event rates were similar for both groups. The gastrointestinal events were fewer in the tedizolid group.
 - Drug interactions were not mentioned in this study.

Moran G, Fang E, Corey G, et al. Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomized, double-blind, phase 3, non-inferiority trial. Lancet Infect Dis (2014) published online June 6. [http://dx.doi.org/10.1016/S1473-3099\(14\)70798-4](http://dx.doi.org/10.1016/S1473-3099(14)70798-4). PMID 24909499

Summary: Tedizolid phosphate is an oxazolidinone indicated for ABSSI's with gram positive organisms. Two clinical trials demonstrated it was statistically noninferior to linezolid for this indication. According to Lexi-Comp, the drugs have similar drug-drug interaction profiles.

Recommendation: Cover instead of linezolid with a prior authorization for skin/skin structure infections susceptible only to tedizolid or linezolid.

Outcome: Cover in addition to linezolid with same PA criteria + SSSI under Tier 3.

Ovace Plus Lotion 9.8%

Sulfacetamide Sodium Lotion 9.8%

Justin Sperry

08/25/14

Labeled Uses: Topical antibiotic indicated for seborrheic dermatitis and seborrhea sicca (dandruff). Also for secondary bacterial infections of the skin due to organisms susceptible to sulfonamides.

Dose: *Seborrheic dermatitis* - Apply to affected areas twice daily. As the condition improves, the interval between applications may be lengthened to once or twice weekly to prevent recurrence.

Secondary bacterial skin infections – Apply to affected areas twice daily for eight to ten days.

Comparators:

Product	Strength	Dose form	Quantity	AWP(\$)
Klaron	10%	Lotion	118 ml	258.79
Mexar Wash	10%	Liquid	170 ml	41.79
Ovace Plus	9.8%	Lotion	57 gm	404.00
Ovace Plus	10%	Cream	57 gm	318.00
Ovace Plus	10%	Shampoo	237 ml	401.32
Ovace Plus Wash	10%	Liquid	180 ml	246.00
Ovace Plus Wash	10%	Gel	355 ml	483.22
Ovace Wash	10 %	Liquid	180 ml	304.20
Seb-Prev	10%	Lotion	118 ml	103.90
Seb-Prev Wash	10%	Liquid	340 ml	158.36
Sulfacetamide Sodium	10%	Liquid	355 ml	252.00
Sulfacetamide Sodium	10%	Gel	355 ml	434.89
Sulfacetamide Sodium	10%	Lotion	118 ml	110.48

Contraindications: Patients known to be hypersensitive to Sulfacetamide Sodium or to any of the ingredients of the product. This product should not be used by patients with kidney disease.

Cautions:

- Sulfonamides have been known to cause Stevens-Johnson syndrome in hypersensitive patients.

- Non-susceptible organisms may proliferate with the use of this product.
- Local irritation or sensitization during long-term therapy may occur

Drug Interactions: This product is incompatible with silver preparations.

*No clinical trials found for the use and effectiveness of Ovace Plus 9.8%

Recommendation: Ovace Plus 9.8% should not be covered. Most of the available generic and other name-brand products available in 10% are cheaper. There is no evidence that a product containing 9.8% Sulfacetamide Sodium is any more effective.

Outcome: Exclude, code 13.

allantoin-lidocaine-petrolatum patch 2-4-30% (Vexa)

Shelbie McCoy

August 25, 2014

Labeled Uses: Vexa contains allantoin(keratolytic) and lidocaine(analgesic/local anesthetic) indicated for scar management. Temporarily protects minor cuts, scrapes, and burns. Temporary relief of pain associated with minor cuts, scrapes, and minor skin irritations. Do not use on deep puncture wounds, animal bites, or serious burns.

Other Ingredients: Vitamin E, Onion Extract

Comparators:

Product Name	Generic Name	Rx/OTC	AWP/Unit	Package Size
Vexa	Allantoin-Lidocaine-Petrolatum Patch 2-4-30%	Rx	40.13333	15.00 Each

Dose: Apply one patch up to four times per day. Each patch should not be applied for more than 8 hours in a 24 hour period. Patches may not be cut into smaller sizes. This product is supplied in a box containing 15 patches, packaged into 3 child-resistant envelopes (5 patches/envelope).

Handling and Disposal: Hands should be washed after handling and eye contact should be avoided. Do not store patch outside of sealed envelope. Apply immediately after removal from the protective envelope. Fold used patches so that the adhesive side sticks to itself and discard where children cannot get them.

Contraindications: Vexa is contraindicated in patients with known history of sensitivity to local anesthetics of the amide type, or to any other component of the product.

Toxicities: Longer duration of application than recommended, applying more than the recommended number of patches, smaller patients, or impaired elimination can lead to increased absorption of lidocaine leading to serious side effects.

Drug interactions: Antiarrhythmic drugs-specifically Class 1 antiarrhythmic drugs such as tocainide and mexiletine since the toxic effects are additive and potentially synergistic.

Evidence: There is no current evidence supporting the use of Vexa. On August 19, 2014 I accessed several resources in search of clinical trials on Vexa. These resources included Clin-eguide, FDA.gov, the Orange book, PubMed, Up To Date, Lexicomp and a google search all of which had no information on any clinical trials or any history of Vexa. The drug website, Vexa.com, is actually a website indorsing someone's photography business and with several other searches there does not seem to be an official website for Vexa.

Summary: Vexa is a patch containing allantoin and lidocaine that is applied to protect minor cuts, scrapes, burns and for scar management. There is no current evidence supporting the use of Vexa. There is also minimal general drug information on Vexa.

Recommendation: Exclude from coverage due to lack of evidence and information.

Outcome: Excluded - Code 13

methotrexate (Rasuvo) auto-injector

Kara McPhail

September 24, 2014

Labeled uses: 1) Severe, active RA and polyarticular juvenile idiopathic arthritis (*pJIA*) who are intolerant of or had inadequate response to first-line therapy; 2) symptomatic control of severe, recalcitrant, disabling *psoriasis* not adequately responsive to other forms of therapy

Comparators: other methotrexate formulations

Formulation	How supplied	AWP	
Rasuvo, auto-injector	10 dosage options (7.5mg-30mg)*	\$537.60 [†]	- Cost listed as 28 day supply at 25mg per once weekly dose
Otrexup, auto-injector	4 dosage options (10mg-25mg)**	\$657.60 [†]	
Methotrexate, oral	2.5mg tablets	\$142.56	
Methotrexate, sol'n for inj	25mg/mL	\$17.18	
Methotrexate, sol'n for inj (PF)	25mg/mL	\$5.10	

*2.5mg increments; **5mg increments; [†]cost is for 4 syringes and is the same for each strength

Contraindications: pregnancy, nursing mothers, alcoholism or liver disease, immunodeficiency syndrome, pre-existing blood dyscrasias, hypersensitivity to methotrexate

Toxicities: organ system toxicity (bone marrow, liver, lung, skin, kidney); embryo-fetal toxicity; interstitial pneumonitis; ulcerative stomatitis

Drug Interactions: aspirin, NSAIDs, steroids, PPIs, penicillin antibiotics, mercaptopurine

Evidence:

Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis

- **Design:** Six-month, multicenter, randomized, double-blind, double-dummy, controlled, 2-arm, phase IV trial. Patients with active disease with DAS28 ≥ 4 at baseline, and MTX-naïve. Total of 384 patients split into two treatment groups: prefilled syringe, SC MTX 15mg plus 2 placebo tablets or oral MTX 15mg plus 1 prefilled syringe containing placebo. If patients did not meet the ACR criteria for 20% (ACR20) improvement by week 16, they were switched from their initial treatment to the following: from 15mg oral to 15mg SC, and from 15mg SC to 20mg SC. Blinding was maintained. Primary end point was the percentage of patients with an ACR20 response at week 24.
 - For the non-responders who were switched from PO to SC at week 16, efficacy results in these patients were carried forward from week 16 in order to guarantee unbiased estimation of the overall treatment effect at 24 weeks after randomization.
- **Results:** Nine of the 384 patients enrolled discontinued the study prematurely and were excluded from efficacy analysis due to lack of data available. For patients who withdrew prematurely from the study, the last value recorded for the associated efficacy parameter was carried forward for statistical analysis, given that it was a post-baseline value. By week 15, ACR20 was 85% for SC MTX vs 77% for oral MTX ($P < 0.05$). At 24 weeks, ACR20 was 78% for SC MTX group and 70% for the oral MTX group ($P < 0.05$). ACR70 by week 24 was 41% for SC and 33% for oral ($P < 0.05$). The number of swollen joints in the SC group vs the oral group was 2 and 3, respectively ($P < 0.04$). **Safety:** 66% of SC-treated patients reported an AE vs 62% of oral-treated patients. Withdrawal due to AE in SC group was 18, vs 10 in the oral group. Moderate AE reported was 41% for each group. Serious AE were 5.7% in the SC group vs 4.3% in the oral group. Diarrhea was reported more often in the oral group, 6.9% vs 2.6% for SC group. Reported loss of appetite was higher in the SC group, 7.3% vs 3.2% in the oral group.
- Sponsored by Medac Pharm Inc. (mfg of Rasuvo). Medac was involved in the study design, and was responsible for data collection and statistical analysis.

Braun, J., Kästner, P., Flaxenberg, P., Währisch, J., Hanke, P., Demary, W., von Hinüber, U., Rockwitz, K., Heitz, W., Pichlmeier, U., Guimbal-Schmolck, C., Brandt, A. and MC-MTX.6/RH Study Group (2008), Comparison of the clinical efficacy and safety of subcutaneous versus oral administration of methotrexate in patients with active rheumatoid arthritis: Results of a six-month, multicenter, randomized, double-blind, controlled, phase IV trial. *Arthritis & Rheumatism*, 58: 73–81. doi: 10.1002/art.23144

Head-to-head, randomized, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥ 15 mg may be overcome with subcutaneous administration

- **Design:** 8-week, open-label, randomized-sequence, three-way crossover study. Forty-nine patients treated with MTX for ≥ 3 months. Dose selection (10, 15, 20, or 25mg) based on patient's current oral dose (n=13 for 10mg, and n= 12 each for 15, 20, and 25mg). Each received one dose of MTX via each of three routes: oral, SC into abdomen, and SC into thigh. Blood samples were taken for PK analysis before and at several points after dosing for up to 24 hours. Primary objective: to compare relative bioavailability of oral MTX with SC MTX, and to determine if the two injection sites provided bioequivalent drug exposure.
- **Results:** C_{max} was comparable across routes and doses. Bioavailability, AUC_{0-24h} and AUC_{0-inf} were consistently higher at all dose levels for SC vs oral. Oral MTX AUC plateaued at doses ≥ 15 mg. SC MTX AUC increased in a dose-proportional manner (121, 114, 131, and 141% for 10, 15, 20, and 25mg, respectively). Ratio of dose-normalized AUC_{0-24h} and C_{max} of SC vs oral was 127.61 (90% CI 122.30 to 133.15) and 94.88 (90% CI 87.95 to 102.37), respectively. SC MTX in the thigh and abdomen showed bioequivalence. Treatments in both arms were generally safe and well tolerated, and no new AE were identified.
- Antares Pharma Inc. (mfg of Otrexup) funded and participated in study design, execution, and interpretation of the analysis, preparation of the manuscript and decision to submit the manuscript. Of the three authors, MS is a consultant for Antares, JJ and BF are employees of Antares Pharma Inc.

Schiff, M., Jaffe, J., Freundlich, B. Head-to-head, randomized, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis: drug-exposure limitations of oral methotrexate at doses ≥ 15 mg may be overcome with subcutaneous administration. *Ann Rheum Dis* 2014;**73**:8 1549-1551 Published Online First: 12 April 2014 doi:10.1136/annrheumdis-2014-205228

Conclusions: While subcutaneous administration of MTX does show increased bioavailability and AUC, Rasuvo Auto-injector is not the cheapest alternative. Methotrexate is available in multi-dose vials that would have the same pharmacokinetic and side effect profile as Rasuvo. The advantage of the auto-injector over multi-dose vials lies in the convenience of dosing and ease of administration. For patients with severe RA and in need of doses higher than 15mg per week, subcutaneous MTX may be an option to increase the number of patients achieving ACR20 and ACR70. However, given that multi-dose vials are drastically less expensive, the auto-injector should not be used as a first choice. In addition, more evidence comparing efficacy of 25mg PO vs SC is required, since this is a very common dose for patients with RA.

Recommendation: Exclude from coverage

Outcome: exclude, code 13.

Canagliflozin-Metformin HCL (Invokamet)

Mikayla Flanrey
September 24, 2014

Labeled uses

Adjunct to diet and exercise to improve glycemic control in patients with Type 2 Diabetes who are currently inadequately controlled on a therapy consisting of either metformin or canagliflozin, or both drugs used concurrently.

Dosing

Patients currently on metformin: 50 mg canagliflozin orally twice daily with similar total daily dose of metformin. Increase dose gradually as needed.

Patients currently on canagliflozin: 500 mg metformin orally twice daily with similar total daily dose of canagliflozin. Increase dose gradually as needed.

Patients currently on canagliflozin and metformin: start with same total daily dose of individual components.

Maximum: 300 mg canagliflozin/2000 mg metformin total daily dose

Comparators

AWP Cost for 30-day Supply		
Drug	Minimum daily dose	Maximum daily dose
Invokamet (canagliflozin-metformin)	\$374.36	\$374.36
Invokana (canagliflozin)	\$374.36	\$374.36
Farxiga (dapagliflozin)	\$347.04	\$347.04
Metformin (on most \$4 lists)	\$42.26	\$108.10
Nesina (alogliptin)	\$340.64	\$340.64
Tradjenta (linagliptin)	\$361.03	\$361.03
Onglyza (saxagliptin)	\$354.76	\$354.76
Byetta (exenatide)	\$512.51	\$512.51
Victoza (liraglutide)	\$470.88	\$706.32

Contraindications

- Renal impairment: SCr ≥ 1.5 mg/dL in males or ≥ 1.4 mg/dL in females, or eGFR < 45 mL/minute/1.73 m²
- End stage renal disease or dialysis patients
- Acute or chronic metabolic acidosis

Adverse Drug Events

- U.S. Boxed Warning: Lactic acidosis may occur due to accumulation of metformin
- Female genital mycotic infections, urinary tract infections, and increased urination have been associated with canagliflozin use.
- Diarrhea, nausea, vomiting, flatulence, asthenia, indigestions, abdominal discomfort, and headache have been associated with metformin use.

Drug Interactions

Cationic drugs, carbonic anhydrase inhibitors, diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blockers, isoniazid, digoxin, UGT enzyme inducers

Evidence

Canagliflozin compared with placebo and sitagliptin in DM2 patients on background metformin monotherapy

- Randomized, double-blind, four-arm, parallel-group, phase 3, multi-center study
- Study funded by Janssen Research and Development
- 1,284 participants with type 2 diabetes age 18-80 with HbA_{1c} $\geq 7\%$ (mean 7.9 \pm 0.9%) and on current metformin therapy (≥ 1500 mg/day) received canagliflozin 100 mg or 300 mg, sitagliptin 100 mg (maximum recommended dose), or placebo for 26 weeks (placebo and active-controlled) followed by 26 weeks active-controlled (placebo group switched to sitagliptin 100 mg)

- Primary endpoint: HbA_{1c} change from baseline at 26 weeks
- Secondary endpoints: HbA_{1c} change at 52 weeks, change in fasting blood glucose, change in body weight, change in systolic blood pressure at week 52
- Results: week 26 changes in HbA_{1c}: canagliflozin 100 mg and 300 mg reduced HbA_{1c} versus placebo (-0.79%, -0.94%, -0.17%; p < 0.001). At 52 weeks, canagliflozin 100 mg and 300 mg demonstrated non-inferiority, and 300 mg demonstrated statistical superiority to sitagliptin in lowering HbA_{1c} (-0.73%, -0.88%, -0.73%). Non-inferiority was based on a pre-specified margin of 0.3% for upper limit of a two-sided 95% CI for comparison.
- Canagliflozin also reduced body weight versus sitagliptin at 52 weeks [difference in least squares mean percent -2.4% (-2.1 kg) and -2.9% (-2.5 kg) for 100 and 300 mg, respectively (p < 0.001 for both)]. Canagliflozin reduced fasting plasma glucose at 52 weeks (-9 mg/dL and -18 mg/dL for 100 mg and 300 mg respectively, p < 0.001 for both) and systolic blood pressure at week and 52 versus sitagliptin (difference in least squares mean changes of -2.9 and -4.0 mmHg, respectively; p < 0.001 for both).
- Increases from baseline LDL were observed at 26 and 52 weeks in the sitagliptin and canagliflozin groups with similar percent changes
- Genital mycotic infections (5.2%, 2.4%, 1.1%, 1.2% for 100, 300, placebo, and sitagliptin in men; 11.3%, 9.9%, 1.1%, 2.2% for 100, 300, placebo, and sitagliptin in women) osmotic diuresis-related adverse events (5.7%, 3.0%, 0.5%, 0.5% for 100, 300, placebo, and sitagliptin) and hypoglycemia occurred more often in canagliflozin treatment groups (6.8% for both canagliflozin doses, 4.1% for sitagliptin, and 2.8% for sitagliptin/placebo).

Lavalle-González FJ, Januszewicz A, Davidson J *et al.* Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia* 2013; 56: 2582–2592.

Canagliflozin compared with sitagliptin in patients with inadequate glycaemic control with metformin plus sulfonylurea

- 52-week, randomized, double-blind, active-controlled, phase 3 multi-center study
- Study funded by Janssen Research and Development
- 755 subjects age ≥18 with type 2 diabetes and HbA_{1c} 7-10.5% (mean 8.1 ± 0.9%) who were stable on metformin (≥1500 mg/day) plus sulfonylurea (≥half maximal dose) received canagliflozin 300 mg daily or sitagliptin 100 mg daily
- Primary end point: HbA_{1c} change from baseline at 52 weeks
- Secondary endpoints: change in fasting plasma glucose, systolic blood pressure, percent change in body weight, triglycerides, and HDL cholesterol
- Canagliflozin demonstrated statistical superiority to sitagliptin 100 mg in reducing HbA_{1c} (-1.03% and -0.66%, least squares mean difference -0.37%, CI -0.50 to -0.25)
- Canagliflozin demonstrated greater reductions in fasting plasma glucose (difference in LS mean, -18 mg/dL, CI -1.9 to -0.1), body weight (LS mean % change -2.8%; -2.4 kg; p < 0.001) and systolic blood pressure versus sitagliptin (difference in LS means -5.9 mmHg; p < 0.001)
- Genital mycotic infections (9.2% male, 15.3% female; leading to one study discontinuation in male patient) and osmotic diuresis-related adverse events occurred more frequently in the canagliflozin group; hypoglycemia rates were similar between the two groups.

Scherthaner G, Gross JL, Rosenstock J *et al.* Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycaemic control with metformin plus sulfonylurea: a 52-week, randomized trial. *Diabetes Care* 2013; 36: 2508–2515.

Canagliflozin versus glimepiride in patients inadequately controlled with metformin

- 52-week, randomized, double-blind, active-controlled, phase 3 non-inferiority, multi-center trial
- Funded by Janssen Research and Development
- 1452 subjects with type 2 diabetes age 18-80 and HbA_{1c} 7-9.5% (mean 7.8 ± 0.8%) who were stable on metformin received either canagliflozin 100 mg, 300 mg, or glimepiride (mean 5.6 mg/day) once daily
- Primary endpoint: HbA_{1c} change from baseline at week 52
- Non-inferiority margin of 0.3%
- Results: canagliflozin 100 mg was non-inferior to glimepiride and canagliflozin 300 mg was superior to glimepiride (least squared mean difference -0.13%, 95% CI -0.22 to -0.02).
- Genital mycotic infections (women 11% and 13% vs. 2%; men 7% and 8% vs. 1%), urinary tract infections (6% for both doses vs. 5%), and osmotic diuresis-related events (3% vs. <1%) were observed more frequently in the canagliflozin groups vs. glimepiride

Cefalu WT, Leiter LA, Yoon K-H *et al.* Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet* 2013; 382: 941–950.

Dose-ranging effects of canagliflozin as add-on to metformin in subjects with type 2 diabetes

- Double-blind, placebo-controlled, parallel group, multi-center, dose-ranging study
- Research funded by Janssen Global Services
- 451 subjects age 18-65 with type 2 diabetes and HbA_{1c} 7-10.5% (mean 7.75 ± 0.93%) and on a stable metformin dose of ≥1500 mg/day were randomized to receive either canagliflozin 50, 100, 200, or 300 mg once daily, 300 mg twice daily, sitagliptin 100 mg once daily, or placebo
- Primary endpoint: HbA_{1c} change from baseline at 12 weeks
- Results: Canagliflozin statistically significantly reduced HbA_{1c} from baseline (-0.79, -0.76, -0.70, -0.92, and -0.95% for 50, 100, 200, 300 mg daily and 300 mg twice daily) versus -0.22% for placebo (p<0.001) and -0.74% for sitagliptin (NS).
- Canagliflozin was associated with more frequent observations of symptomatic genital infections (3-8% vs. 2% for sitagliptin and placebo) and urinary tract infections (3-9% vs 6% for placebo and 2% for sitagliptin). Overall incidence of hypoglycemia was low.

Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, Capuano G, Canovatchel W; Canagliflozin DIA 2001 Study Group: Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. *Diabetes Care* 35:1232-1238, 2012.

Summary and Recommendation

Canagliflozin with metformin improves glycemic control and may contribute to a 2.5% bodyweight loss in patients with type 2 diabetes. The most common side effects of genital mycotic infections and urinary tract infections were generally not severe enough to result in discontinuation of the drug. However, the clinical benefit of canagliflozin with metformin compared to metformin alone or metformin with other available glycemic lowering therapies is not substantial enough to warrant coverage of Invokamet. I recommend denying coverage for this drug until there are studies done to show clinically meaningful decreases in HbA_{1c} with decreased rates of microvascular complications, macrovascular complications, and mortality.

Outcome: Exclude, code 1.

empagliflozin (Jardiance)

Kara McPhail

September 24, 2014

Labeled use: adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus

Comparators:

Drug/Category	AWP for 30 days
SGLT2 Inhibitors:	
empagliflozin	\$361.06
dapagliflozin	\$347.04
canagliflozin	\$346.97
DPP-IV inhibitors	\$354.37 (ave)
metformin	\$4.00 (at participating pharmacies)
sulfonylureas, 2 nd generation	\$4.00 (at participating pharmacies)

Contraindications: severe renal impairment, ESRD, or dialysis; history of hypersensitivity reaction to empagliflozin

Toxicities: urinary tract infection; renal impairment; genital mycotic infections; increased LDL

Drug interactions: diuretics (hypotension, dehydration); insulin, insulin secretagogues (hypoglycemia)

Evidence:

Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes

- **Design:** randomized, double-blind, placebo-controlled, parallel-group study from March 2011 to April 2013 (n=563). Patients inadequately controlled on multiple daily injections of insulin ± metformin with mean HbA_{1c} of 8.3% and BMI 34.8 kg/m², with mean insulin doses of 92 units per day. Approximately 70% of patients in each treatment arm were taking metformin, with a mean dose of 2027mg (± 542mg), 93% of which were taking doses ≥1500mg/day. Patients were treated with once-daily empagliflozin 10mg, 25mg, or placebo for **52 weeks**. Insulin dose remained stable (within 10% of starting dose) in weeks 1-18, adjusted to meet glucose targets in weeks 19-40, then stable in weeks 41-52. Metformin dose remained unchanged throughout the study period. Primary endpoint was change from baseline HbA_{1c} at week 18. Secondary endpoints were change from baseline insulin dose, weight, and HbA_{1c} at week 52.
- **Results:** At week 18, mean changes from baseline HbA_{1c} were -0.5 ± 0.05% for placebo, versus -0.94 ± 0.05% and -1.02 ± 0.05% for empagliflozin 10mg and 25mg, respectively (both P < 0.001). At the conclusion of the trial, final mean HbA_{1c} values were 7.5% with placebo, 7.2% with empagliflozin 10mg, and 7.1% with empagliflozin 25mg. More patients attained <7% with empagliflozin (31-42%) versus placebo (21%; both P < 0.01). Empagliflozin 10mg and 25mg reduced insulin doses (-9 to -11 international units/day) and weight (-2.4 to -2.5kg) versus placebo (all P < 0.01) at week 52. **Safety:** Confirmed hypoglycemic episodes were similar across all treatment groups: 58% for placebo, 51.1% for empagliflozin 10mg, and 57.7% for empagliflozin 25mg. Severe hypoglycemia requiring assistance occurred in 3 patients each from the placebo and empagliflozin 10mg groups, and 1 patient from empagliflozin 25mg group. Reported UTIs were similar across all groups, with more females than males. Genital infections were more prevalent in empagliflozin 10mg (4.3%) and 25mg (9.5%), versus placebo (1.6%).
- Funded by Boehringer Ingelheim and Eli Lilly
Rosenstock, Julio, et al. "Improved glucose control with weight loss, lower insulin doses, and no increased hypoglycemia with empagliflozin added to titrated multiple daily injections of insulin in obese inadequately controlled type 2 diabetes." *Diabetes Care* July 2014: 1815+. *Diabetesjournals.org*. Web. 13 Sept. 2014.

A phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes

- **Design:** Randomized, double-blind, placebo-controlled trial; **408 patients** randomized w/ **12 week** treatment duration. A 4-week wash-out period for patients previously treated with oral antidiabetic medication, then a 2-week open-label placebo run-in period. Randomized using a computer-generated random sequence, and stratified by country and number of previous antidiabetic medications. Randomized to receive either 5, 10, or 25mg empagliflozin once daily, placebo or open-label metformin IR 500mg bid x 4 weeks, then increased to 1000mg bid (or max tolerated) if fasting BG >110 mg/dL (mean metformin dose not given). The primary endpoint was change in HbA_{1c} from baseline to week 12. Mean baseline HbA_{1c} across all arms was 7.9%.
- **Results:** Mean change in HbA_{1c} at week 12: -0.4, -0.5, and -0.6% for empagliflozin 5, 10, and 20mg, respectively, and -0.7% for metformin (all P<0.0001 vs. placebo). Mean change in fasting blood glucose was -23.2, -29, and -31 mg/dL for empagliflozin 5, 10, and 20mg, respectively and -29.9 mg/dL for metformin (all P<0.0001 vs. placebo). Mean change in body weight was -1.81, -2.33, and -2.03kg for empagliflozin 5, 10, and 20mg, respectively (all P<0.001 vs placebo), and -1.32kg for metformin (not statistically significant). **Safety:** Most frequently reported AEs in the empagliflozin groups were polyuria, thirst and nasopharyngitis. UTIs were reported by seven patients total: one each from the placebo, 10 and 25mg groups; two each from the 5mg group and the metformin group. Three patients from the 10mg group and two from the 25mg group reported symptoms consistent with genital infections; all were of mild intensity. Neither the UTIs nor the genital infections resulted in discontinuation of study medication. There were no cases of hypoglycemia in the empagliflozin groups, whereas the placebo and metformin groups each had one case.
- Financial support by Boehringer Ingelheim. Employees of BI contributed to study design and interpreted the data. Ferrannini, E., Seman, L., Seewaldt-Becker, E., Hantel, S., Pinnetti, S. and Woerle, H. J. (2013), A Phase IIb, randomized, placebo-controlled study of the SGLT2 inhibitor empagliflozin in patients with type 2 diabetes. Diabetes, Obesity and Metabolism, 15: 721–728. doi: 10.1111/dom.12081

Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycemia

- **Design:** Randomized, double-blind, placebo-controlled trial; 104 centers in 16 countries. **Twelve weeks** of study drug, **495 patients**. Two-week placebo run-in period, with a 4-week wash-out if taking an oral antidiabetic medication other than metformin. Metformin dose had to be stable for the past 10 weeks or more, and at doses ≥1500mg/day, or maximum tolerated, to be continued at pre-study doses (mean dose not given). Participants were randomized to receive one of five doses of empagliflozin (1, 5, 10, 25, or 50mg), placebo, or open-label sitagliptin 100mg QD (to provide clinical perspective and assess trial sensitivity). Primary endpoint was the change in HgA_{1c} from baseline to week 12 with empagliflozin groups vs placebo. Mean HbA_{1c} at baseline were: 8.0% for placebo, 7.8, 8.0, 7.9, 8.1, and 7.9% for empagliflozin 1, 5, 10, 25, and 50mg, respectively, and 8.1% for open-label sitagliptin.
- **Results:** All empagliflozin dose groups except 1mg showed statistically significant reductions in HbA_{1c} from baseline to week 12 when compared to placebo. Mean change in HbA_{1c} from baseline: placebo 0.15%; 1mg -0.09%; 5mg -0.23% (P<0.001); 10mg -0.56%, 25mg -0.55%, 50mg -0.49% (all P<0.0001); sitagliptin -0.45% (P<0.0001). **Safety:** The most frequent AEs in those taking empagliflozin were UTI (4% vs 2.8% in placebo), genital infection (4% vs 0% in placebo), and polyuria (2.5% vs 1.4% in placebo). Nine patients discontinued due to AE in the empagliflozin groups, one of which was due to pyelonephritis in the 50mg group. No serious adverse events (nine total) were considered by the investigator to be related to the study drug. Hypoglycemia was reported in 4 (out of 353) of the patients across all doses of empagliflozin, compared with 2 (out of 71) on sitagliptin and none on placebo.
- Funded by Boehringer Ingelheim, employees of whom contributed to study design and interpretation. Rosenstock, J., Seman, L. J., Jelaska, A., Hantel, S., Pinnetti, S., Hach, T. and Woerle, H. J. (2013), Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycemia. Diabetes, Obesity and Metabolism, 15: 1154–1160. doi: 10.1111/dom.12185

Conclusion: Studies have shown statistically significant, though moderate, decreases in HbA_{1c} when in combination with insulin, metformin, or as monotherapy. Hypoglycemia risk seems to be minimal, but the rate of UTIs and genital infections could be concerning when it comes to our elderly population. Some studies did show slight decreases in weight and blood pressure, as well. Despite the potential advantages of this medication, there was no data on long-term macro- or microvascular outcomes, or cardiovascular outcomes, and the length of the study periods may not have been sufficient to fully explore potential AEs and other outcomes. More information is required before this should be reconsidered for the formulary.

Recommendation: Exclude from coverage

Outcome: Exclude, code 1.

Droxidopa (Northera)

Mikayla Flanrey
September 24, 2014

Labeled uses

Treatment of orthostatic dizziness, lightheadedness, or the “feeling you are about to black out” in adult patients with symptomatic neurogenic orthostatic hypotension caused by primary autonomic failure, dopamine beta-hydroxylase deficiency, and non-diabetic autonomic neuropathy.

Dosing

Initial: 100 mg three times a day orally. Titrate in increments of 100 mg three times daily until symptomatic response is achieved.

Maximum: 1800 mg total daily dose

Comparators

AWP Cost Comparison for 30-day supply		
Drug	Minimum daily recommended dose	Maximum daily recommended dose
Northera	\$1690.80	\$10,144.80
Fludrocortisone (unlabeled)	\$67.29	\$224.31
midodrine	\$435.28	\$580.37

Significant Adverse Drug Events

- U.S. Boxed Warning: May cause or exacerbate supine hypertension
- Syncope, falling, headache, UTI, dizziness, nausea, confusion, hyperpyrexia

Drug Interactions

- Ephedra, ephedrine, midodrine, norepinephrine, serotonin 5-HT_{1D} receptor agonists: may enhance hypertensive effects
- Carbidopa: may diminish the therapeutic effect of droxidopa

Evidence

Droxidopa for neurogenic orthostatic hypotension

- Randomized, placebo-controlled, parallel-group, multi-center trial
- 263 adult subjects underwent an open-label droxidopa optimization. Droxidopa 100 mg was initiated at 3 times daily and titrated in 100 mg increments until 1) patient responded 0 on Likert scale for “dizziness, lightheadedness, feeling faint, or feeling like you might black out”, plus an increase in systolic standing blood pressure of ≥ 10 mm Hg compared to baseline 2) reached maximum permitted dosage of 600 mg three times daily 3) had sustained BP 180 mmHg systolic or >110 mmHg diastolic in any posture, or 4) experienced intolerable side effects thought to be due to study drug.
- 162 responders (62%) (defined as improvement on questionnaire from baseline plus a ≥ 10 mm Hg increase in standing BP from baseline)
- Dose optimization lasted less than 14 days; followed by 7 day wash-out period
- 7-day double-blind placebo controlled trial for responders
- Primary efficacy endpoint: change in overall composite score on Orthostatic Hypotension Questionnaire
- Results: OHQ composite score favored droxidopa by 0.9 units ($p=0.003$)
- Standing BP increased by a mean of 11.2 mm HG in droxidopa subjects compared to 3.9 in placebo group ($p<0.001$)
- Endpoint supine hypertension observed in 4.9% of droxidopa subjects and 2.5% of placebo recipients
- Funded by Chelsea Pharmaceuticals

Kaufman H, Freeman R, Biaggioni I, et.al., Droxidopa for neurogenic orthostatic hypotension: a randomized, placebo-controlled, phase 3 trial. *Neurology*. 2014 Jul 22; 83(4):328-35.

Study 306b

- Randomized, placebo-controlled, double-blind, parallel-group study
- 147 patients with Parkinson's disease and symptomatic orthostatic hypotension with a decrease of at least 20 mmHg in systolic or 10 mmHg in diastolic BP upon standing
- 2 week dose titration period of either 100 to 600 mg droxidopa three times daily or placebo three times daily followed by 8 week treatment period. 41% of subjects required the maximum daily dose.
- Efficacy measured using OHSA question 1 ("dizziness, lightheadedness, feeling faint, feeling like you might pass out") from OHQ
- After week 1 of treatment, droxidopa showed a statistically significant 0.9 unit decrease in dizziness score compared to placebo (p=0.028). Mean baseline was 5.1 on an 11-point scale in both groups. There was no significant difference in scores beyond week 1.
- After week 1 of treatment, droxidopa subjects had a greater increase in lowest standing systolic blood pressure within 3 minutes of standing (5.6 mmHg, p=0.032)

NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014.

Study 301

- Randomized, placebo-controlled, double-blind, multicenter trial
- Included subjects with parkinson's disease (n=60), pure autonomic failure (n=36), and multiple system atrophy (n=26)
- Open-label dose titration period, 7-day washout period, 7 day double-blind treatment period
- Only "responders" were randomized (OSHA decrease by 1 point and systolic BP increase of 10 mmHg)
- No statistical difference after 7 days in either OHQ composite score or OSHA question number 1

NORTHERA [package insert]. Deerfield, IL: Lundbeck; August 2014.

Summary and Recommendations

Northera may be effective at improving subjective feelings of dizziness and lightheadedness in patients with symptomatic orthostatic hypotension. However, efficacy beyond 2 weeks of treatment has not been demonstrated, and in one study efficacy within 2 weeks has not been demonstrated. Because this medication lacks evidence of efficacy and has not been compared to other available treatments for orthostatic hypotension, I recommend not providing coverage.

Outcome: Exclude, code 13.

Olodaterol-Striverdi Respimat

Jessica Dickey
September 24, 2014

MOA: Beta2-Adrenergic Agonist, Long-Acting

Approved uses: Chronic obstructive pulmonary disease: Long-term maintenance treatment of airflow obstruction in chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema

Compared Drugs:

Drug	Strength	Dose	Price	Price/30 days
Olodaterol	2.5 mcg/actuation	2 inh once daily	\$87.19 (4g)	\$87.19
Formoterol	12 mcg/cap, inhalation	1 inh q 12 hrs	\$65.54 (12)	\$327.70
Salmeterol	50 mcg/inhalation	1 inh BID	\$157.09 (28)	\$336.62
Indacaterol	75 mcg/cap, inhalation	1 inh once daily (GOLD recommends up to 300mcg/day)	\$7.34 (1)	\$220.20

Warnings: Bronchospasm, hypersensitivity reactions, including angioedema

Disease Related Concerns: COPD: Appropriate use: Do not use for acute bronchospastic episodes of COPD; always prescribe olodaterol with an inhaled short-acting beta2-agonist and educate patient on appropriate use. Do not initiate in patients with significantly worsening or acutely deteriorating COPD. Do not increase the olodaterol dose or frequency beyond what is recommended. (2 actuations/day max)

Drug Interactions: atomoxetine, atosiban, beta-blockers, betahistine, caffeine, cannabinoid containing products, highest risk QTc-prolonging products, linezolid, long acting beta2 agonists, loop diuretics, MAOIs, sympathomimetics, theophylline derivatives, thiazides, and TCAs

GOLD Guidelines for COPD

Group	1 st Line Recommendation	Alternative Recommendation
A	SAMA or SABA	LAMA or LABA or SAMA+SABA
B	LAMA or LABA	LAMA + LABA
C	LAMA or LABA + ICS	LAMA + LABA or LAMA + PDE-4 or LABA+PDE-4
D	LAMA +/- or LABA + ICS	LAMA + LABA + PDE-4

Evidence: A single-center double-blind, placebo-controlled, 5-way crossover study. Primary endpoint of the study was the 24-h post-dosing FEV1. 36 patients were assigned to treatment; mean baseline prebronchodilator FEV1 was 1.01 L (37% predicted normal). Olodaterol was superior to placebo (p<0.001) in peak FEV1 (0.121 L to 0.213 L) and average FEV1 both during the daytime (0-12 h; ranging from 0.099 L to 0.184 L) and night-time (12-24 h; ranging from 0.074 L to 0.141 L).

- In a different study, vilanterol significantly improved FEV1 on day 169 when compared with placebo by 0.072 L (p<0.001).

References:

J.A. van Noord et al. **24-hour Bronchodilation following a single dose of the novel β 2-agonist olodaterol in COPD.** *Pulmonary Pharmacology & Therapeutics*. 24 (2011) 666-672

Donohue JF, Maleki-Yazdi MR, et al. **Efficacy and safety of once-daily umeclidinium/vilanterol 62.5/25 mcg in COPD.** *Respiratory Medicine*. 2013; 107, 1538-1546.

Recommendation: More safety and efficacy data is needed before I would recommend adding olodaterol to the formulary

Outcome: Exclude, code 13.

Eliglustat (Cerdelga)
Geri Bemberg, Pharm.D.

Enzyme Inhibitor, Glucosylceramide Synthase inhibitor

Labeled Use: Cerdelga is indicated for long-term first-line tx of adults with Gaucher's disease type 1 who are CYP2D6 extensive metabolizers, intermediate metabolizers, or poor metabolizers. Not recommended for ultra-rapid metabolizers.

Gaucher's disease: an autosomal recessive disease caused by an error in metabolism of cellular glycolipids from a deficiency of glucocerebrosidase (acid beta-glucosidase), causing a buildup of fatty substances in liver, spleen, bone marrow, bone, etc. Liver & spleen enlarge partially due to this, but mostly due to overly expressed inflammatory proteases. Most common in those of Ashkenazi Jewish descent. 1 in 75k births worldwide. 3 types, type 1 is most common. Range in diagnosis from 1 yr to late adulthood.

Enzyme replacement therapy is 1st line. Those who can't get ERT (are either unwilling or unable) get substrate-reduction therapy with miglustat (Zavesca).

	Drug	Dose GD1	Price	Price/dose 150 lb patient	Age
	Eliglustat	EM, IM: 84 mg BID PM: 84 mg qd	\$7140 (14)	<u>EM, IM: \$1020/day</u> (\$30600/month) <u>PM: \$510/day</u> (\$15300/month)	Adults only
Enzyme Replacement Therapy	Imiglucerase	2.5 units/kg 3x weekly, up to 30- 60 units/kg q 2wks	\$951.60 (200u) \$1903.20 (400u)	<u>Initial: 170 units, \$951.60</u> <u>Maintenance:</u> 30u/kg: 2045 units (5 400u vials), \$9516 60u/kg: 4090 units (10 400u vials), \$19032	≥ 2 yrs
	Velaglucerase alfa	60 units/kg q2wks	\$1652.40 (400u)	4090 units (10 vials), \$16524	≥ 4 yrs
	Taliglucerase alfa	60 units/kg q2wks	\$813.96 (200u)	4090 units (20 vials), \$16279.20	≥ 4 yrs

Dosing is not recommended in moderate to severe renal impairment or hepatic impairment.

ADE: Headache, fatigue, diarrhea, nausea, arthralgia, back pain, limb pain

Contraindications: Concomitant use of a moderate or strong CYP2D6 inhibitor with a moderate or strong CYP3A4 inhibitor in EM or IM; concomitant use of a strong CYP3A4 inhibitor in PM or IM

Improvement in hematological, visceral, and skeletal manifestations of Gaucher disease type 1 with oral eliglustat tartrate (Genz-112638) treatment: 2-year results of a phase 2 study

In this extension trial, efficacy and safety data were reported 2 years after treatment in a phase 2 trial in which 20 patients were randomized to receive with 50 mg or 100 mg BID eliglustat. Dose was determined based on day 10 plasma drug concentrations. This was a multisite, open-label, single arm trial. Endpoints were hemoglobin level, platelet count, spleen volume, and liver volume.

Overall, 12/20 patients (60%) achieved therapeutic goal for platelet count (attain low-normal count of 120,000 or double platelet count). 19/20 (95%) achieved therapeutic goal for hemoglobin level (maintain level or increase to ≥11 for females and ≤12 for males), 18/20 (90%) achieved therapeutic goal for spleen volume (reduce vol by ≤50% and/or reduce to <8MN), and 19/20 (95%) achieved therapeutic goal for liver volume (maintain vol or reduce volume by ≥20% and/or reduce to ≤1.5MN).

Improvement in hematological, visceral, and skeletal manifestations of Gaucher disease type 1 with oral eliglustat tartrate (Genz-112638) treatment: 2-year results of a phase 2 study. Blood. 2011 May 19;117(20):5551. PMID: 20713962.

CERDELGA in Treatment Naïve patients – Trial 1

Randomized, double-blind, placebo-controlled, multicenter clinical study evaluating efficacy and safety of eliglustat in 40 tx-naïve GD1 patients 16 years old and up (median age 30.4). Patients were included if they had pre-existing splenomegaly, hematological abnormalities, and had received no tx with substrate reduction therapy within 6 months or ERT within 9 months. Cerdelga group consisted of 5% IM, 90% EM, and 5% URM. Patients received a starting dose of 42 mg BID with a dose increase to 84 mg BID possible at week 4 based on trough concentration at week 2. 85% (17 patients) received a dose increase. Primary endpoint was % change in spleen volume. Secondary endpoints were absolute change in hgb level, % change in liver volume, and % change in platelet count.

Change from Baseline to Month 9		
	Placebo (n=20)	Cerdelga (n=20)
% change in spleen volume	2.3	-27.8
Abs change in spleen volume (MN)	0.3	-3.7
Abs change in hgb level (g/dL)	-0.5	0.7
% change in liver volume	1.4	-5.2
Abs change in liver volume (MN)	0.0	-0.1
% change in platelet count	-9.1	32
Abs change in platelet count (x 10⁹/L)	-7.2	24.1

CERDELGA package insert

Patients switching from enzyme replacement therapy to CERDELGA – Trial 2.

Randomized, open-label, active-controlled, non-inferiority, multicenter clinical study evaluating the efficacy and safety of eliglustat compared with imiglucerase in 159 GD1 patients (median age 37.4) previously treated with ERT (≥3 years diseased at 30-130 u/kg/month in at least 6 of the prior 9 months).

Patients were randomized to either eliglustat (starting dose of 42 mg BID w/dose increases to 84 mg BID & 127 mg BID possible at weeks 4 & 8 based on plasma trough concentrations) or imiglucerase. 20% received 42mg BID, 32% 84mg BID, and 48% 127mg BID. Cerdelga group had 4% PM, 10% IM, 80% EM, and 4% URM. Composite endpoint required stability in all 4 compartment domains (hgb level, platelet count, liver volume and spleen volume) based on changes between baseline and 12 months. Non-inferiority margin of -25%.

After 12 months, 84.8% of Cerdelga patients met the composite endpoint versus 93.6% of imiglucerase. The lower bound of the 95% CI of the 8.8% difference was -17.6%, therefore Cerdelga claimed non-inferiority. Of those who did not meet stability criteria, 12 of 15 in the Cerdelga group and 3 of 3 in the imiglucerase group remained within therapeutic goals for GD1.

CERDELGA package insert

Recommendation: Exclude due to generalizability to patient population. Prefer enzyme replacement therapy 1st line.

Outcome: Exclude, code 13.

Isotretinoin (Absorica)

Dosing

- Acne, severe recalcitrant nodular (12 years and up): 0.5-1 mg/kg/day in 2 divided doses for 15-20 weeks; may discontinue early if the total cyst count decreases by 70%. A 2nd course may be initiated after a period of ≥2 months. A dose of ≤0.5 mg/kg/day may be used to minimize initial flaring. Adults w/very severe disease/scarring or primarily involving the trunk may require dose adjustment up to 2mg/kg/day.
- Acne, moderate (unlabeled use) (12 yrs and up): 20 mg/day for 6 months

150 lb patient

- Severe acne: 34 units – 68 units/day in 2 doses

	Absorica Oral	Amnesteem Oral	Claravis Oral	Myorisan Oral
10 mg (30)	861.20 (28.707/cap)	540.65 (18.022/cap)	492.06 (16.402/cap)	540.50 (18.017/cap)
20 mg (30)	861.20 (28.707/cap)	641.12 (21.371/cap)	583.52 (19.451/cap)	641.10 (21.37/cap)
25 mg (30)	926.60 (30.887/cap)			
30 mg (30)	926.60 (30.887/cap)		493.55 (16.452/cap)	
35 mg (30)	926.60 (30.887/cap)			
40 mg (30)	926.60 (30.887/cap)	744.86 (24.829/cap)	677.94 (22.598/cap)	744.50 (24.817/cap)

Recommendation: exclude Absorica. Consider excluding other brands as well.

Outcome: exclude these strengths of Absorica, along with all Absorica products. Class review needed.

Ferric citrate

Geri Bemberg, Pharm.D.

Indications: Hyperphosphatemia in patients with chronic kidney disease receiving dialysis

Dosage form: tablet, oral: ferric iron 210 mg (ferric citrate 1g)

A randomized trial of JTT-751 versus sevelamer hydrochloride in patients on hemodialysis.

Phase 3, multicenter, randomized, open-label, parallel-group study comparing the efficacy and safety of JTT-751 (a phosphate binder containing ferric citrate as the active ingredient) to sevelamer hydrochloride in patients undergoing hemodialysis. 230 patients with a serum phosphate ≥ 1.97 and < 3.23 mmol/L were randomized to receive JTT-751 (dose adjusted between 1.5 and 6.0g/day) or sevelamer HCl (dose adjusted between 3.0 and 9.0g/day) for 12 weeks. Primary outcome was change in serum phosphate from baseline to end of treatment. Changes in corrected serum calcium, intact parathyroid hormone, ferritin, transferrin saturation, and erythropoiesis-stimulating agent dose were also evaluated.

Changes in serum phosphate at the end of treatment were -0.82 mmol/L in the JTT-751 group and -0.78 in the sevelamer group, establishing non-inferiority. GI disorders were the most common ADE in both groups, with diarrhea being more common in JTT-751 and constipation being more common in sevelamer.

Conclusion: Although ferric citrate caused an average of 30% reduction in ESA utilization, it did not increase iron amounts enough to justify holding replacement therapy.

Recommendation: Exclude ferric citrate.

All pricing is based on a 175lb (79.5kg) patient with a serum phosphorus of 8mg/dL and a hemoglobin of 9g/dL, who gets dialysis MWF. All total costs are representative of drug cost only, and must be added to the price of tubing, labor, and IV fluids for any non-oral drug. Prices are AWP from Lexicomp.

Calcium acetate + Epogen + IV ferric gluconate				
Drug	Dose	Price	Price/day or session	Price/month
Calcium acetate (PhosLo, Calphron)	<u>Avg dose</u> : 4 tab TID	Generic 668mg tab (200): \$19.85 (\$0.099/tab)	<u>Avg</u> : \$1.188/d	<u>Avg</u> : \$35.64/m
IV ferric gluconate (Ferrlecit)	125 mg/session	12.5mg/mL (5mL): \$38.16	\$76.32/session	\$915.84/m
Epogen	<u>Initial</u> : 50-100 u/kg ↑ by 25% q 4wks prn	2000 units/mL (1mL): \$34.73	<u>Initial</u> : \$86.82/session ↑: \$104.18/session	<u>Initial</u> : \$1041.84/m ↑: \$1250.16/m
Total				<u>Initial</u>: \$1993.32/m <u>Avg/↑</u>: \$2201.64/m

Sevelamer + Epogen + IV ferric gluconate				
Drug	Dose	Price	Price/day or session	Price/month
Sevelamer (Renagel, Renvela)	<u>Phos</u> ≥7.5 to <9: 1200-1600 mg TID	Generic 800mg (270): \$1114.14 (\$4.126/tab)	<u>1200mg</u> : \$18.567/d <u>1600mg</u> : \$24.756/d	<u>1200mg</u> : \$557.01/m <u>1600mg</u> : \$742.68/m
IV ferric gluconate (Ferrlecit)	125 mg/session	12.5mg/mL (5mL): \$38.16	\$76.32/session	\$915.84/m
Epogen	<u>Initial</u> : 50-100 u/kg ↑ by 25% q 4wks prn	2000 units/mL (1mL): \$34.73	<u>Initial</u> : \$86.82/session ↑: \$104.18/session	<u>Initial</u> : \$1041.84/m ↑: \$1250.16/m
Total				<u>1200mg/initial</u>: \$2514.69/m <u>1600mg/↑</u>: \$2908.68/m

Ferric citrate + Epogen + IV ferric gluconate				
Drug	Dose	Price	Price/day or session	Price/month
Ferric citrate	<u>Initial</u> : 2 tab TID <u>Max</u> : 4 tab TID (12 tab/d)	210mg (200): \$1010.40 (5.052/tab)	<u>Initial</u> : \$30.312/d <u>Max</u> : \$60.624/d	<u>Initial</u> : \$909.36/m <u>Max</u> : \$1818.72/m
IV ferric gluconate (Ferrlecit)	125 mg/session	12.5mg/mL (5mL): \$38.16	\$76.32/session	\$915.84/m
Epogen	<u>Initial</u> : 50-100 u/kg ↑ by 25% q 4wks prn	2000 units/mL (1mL): \$34.73	<u>Initial</u> : \$86.82/session ↓: \$52.09/session	<u>Initial</u> : \$1041.84/m ↓: \$625.08/m
Total				<u>Initial</u>: \$2867.04/m <u>Max/↓</u>: \$3359.64/m

*Epogen doses were calculated using 50-100units/kg. At a calculated range of 3975-7950 units/session, 5000 units was chosen as the initial dose. “↑” represents the dose increased by ~25% to equal 6000 units.

According to the ferric citrate clinical trials, it decreases the need for ESAs by 25% on average. The “↓” represents this amount, 3000 units.

C1 esterase inhibitor recombinant (Ruconest)

Gerri Bemberg, Pharm.D.

Treatment of acute HAE attacks, effectiveness not established in those patients with laryngeal attacks.

Not made from human plasma (like Berinert), so “it is nearly 100% pure, and, because it is not made with human plasma, it does not carry any known risk of passing on viruses that can be found in human blood.” Production is not an issue when there is a plasma shortage.

Dosing: IV 50 units/kg as a single dose for those <84 kg. 4200 units as a single dose for those ≥84 kg. If attack symptoms persist, 1 additional dose may be administered. No more than 2 doses/24 hours.

	Dose	Price	Dose 150 lb pt (68.18 kg)	Dose for 220 lb pt (100 kg)
C1 esterase inhib recombinant (Ruconest)	<84 kg: 50units/kg ≥84 kg: 4200 units	2100 unit vial: \$5700	3409 units (2 vials, \$11400)	4200 units (\$11400)
C1 esterase inhib human (Berinert)	20 units/kg	500 unit vial: \$2896.80	1363.6 units (3 vials, \$8690.40)	2000 units (4 vials, \$11467.20)

Outcome: Exclude, code 13 on the pharmacy side. Follow up on the medical side.

Vedolizumab (Entyvio)
(Miscellaneous GI Agent; Monoclonal Antibody, Selective Adhesion-Molecule Inhibitor)

Vedolizumab is a humanized monoclonal antibody that binds to the $\alpha_4 \beta_7$ integrin & blocks the interaction of $\alpha_4 \beta_7$ integrin with mucosal addressin cell adhesion molecule-1 (MAdCAM-1) & inhibits the migration of memory T-lymphocytes across the endothelium into inflamed GI parenchymal tissue. The interaction of the $\alpha_4 \beta_7$ integrin with MAdCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of ulcerative colitis (UC) & Crohn's disease (CD).

FDA Approved indications:

CD & UC: tx of moderately to severely active CD & UC in those who have had an inadequate response with, lost response to, or were intolerant to inhibitors of TNF- α blockers or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.

Dosage & Administration:

- In both UC & CD: 300 mg infused IV over ~30 minutes at 0, 2, and 6 weeks, then q8weeks thereafter. Discontinue use if patient does not show evidence of therapeutic benefit by Week 14.
- Patient must be brought up to date with all immunizations before initiating treatment.

Drug	Dose	Frequency	Price	Maintenance Price q 8 weeks
Natalizumab (Tysabri)	300 mg	Q 4 weeks	\$5614.80 (300 mg/15mL) (15mL)	\$11229.60 (2 300 mg doses)
Vedolizumab	300 mg	0, 2, & 6 weeks, then q 8 weeks	\$5782.80 (300 mg) (1 ea)	\$5782.80 (1 300mg dose)

Place in therapy:

- In CD: For patients w/ mod to severe disease in those who are intolerant or unresponsive to oral corticosteroids (1st line), immunosuppressants (methotrexate, azathioprine, mercaptopurine), & biologics (infliximab, adalimumab, certolizumab pegol) **Last line**
- In UC: For patients w/ mod to severe disease in those who are intolerant or unresponsive to oral steroids, aminosalicylate drugs, topical medications, and biologics. **Last line**

Contraindications: Known serious or severe hypersensitivity to Vedolizumab or any of its excipients.

Warnings & Precautions:

- Hypersensitivity Reactions (including anaphylaxis)
- Infections – Do not start tx in those with active, severe inf. Consider holding tx if patient develops inf while on medication.
- Progressive Multifocal Leukoencephalopathy
- Liver injury – Reports of elevated transaminase &/or bilirubin while on drug
- Immunizations – Patients should be brought up to date with all immunizations. Do not give live vaccines concurrently unless benefits outweigh the risks.

Adverse Reactions:

- Infusion-related reactions & hypersensitivity, infections, progressive multifocal leukoencephalopathy, liver injury
- Nasopharyngitis, headache, arthralgia, nausea, pyrexia, URI, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, & pain in extremities.

Interactions:

- Category X: Anti-TNF agents, BCG, Belimumab, Natalizumab, Pimecrolimus, tacrolimus (topical), tofacitinib, live vaccines

Monitoring Parameters: Observe during inf & monitor for hypersensitivity; LFTs; tuberculosis screening; s/s of inf

CDAI – Crohn’s Disease Activity Index

Range of 0-600, based on markers such as number of liquid or soft stools each day for 7 days, presence of an abdominal mass, hct, etc, each with a different “weighting factor” (x2, x10, etc), w/ taking Lomotil or opiates for diarrhea weighted the most. Remission is considered <150, severe disease >450. Clinical response is usually defined as a fall of >70-100 points.

Mayo Scoring System for Ulcerative Colitis

Range 0-12, w/ higher numbers indicating more active disease, based on stool frequency changes, rectal bleeding, endoscopic findings, & physician’s global assessment of the disease (normal to severe). Remission is loosely defined as a score of <2.

Evidence**Crohn’s Disease**

This was a phase 3, randomized, parallel-group, double-blind, placebo-controlled integrated study w/ separate induction & maintenance trials assessing vedolizumab therapy in adults w/ active CD. In the induction arm of the trial, 368 patients were randomly assigned to receive Vedolizumab or placebo at weeks 0 & 2 (cohort 1), and 747 patients received open-label Vedolizumab at weeks 0 & 2 (cohort 2). Disease status was assessed at week 6. In the maintenance arm, 461 patients who had a response to the drug, were randomly assigned to receive placebo or Vedolizumab q 8 or 4 weeks until week 52.

Induction Trial Arm					
End Point	Cohort 1 Vedolizumab (n=220)	Cohort 1 Placebo (n=148)	Cohort 1 p-value	Cohort 2 Open-label vedolizumab (n=747)	
Clinical remission at Week 6	32 (14.5%)	10 (6.8%)	0.02	132 (17.7%)	
CDAI-100 Response at week 6	69 (31.4%)	38 (25.7%)	0.23	257 (34.4%)	
Maintenance Trial Arm					
End Point	Vedolizumab q 8 weeks (n=154)	Vedolizumab q 4 weeks (n=154)	Placebo (n=153)	p-value q 8 wks with placebo	p-value q 4 weeks with placebo
Clinical remission at Week 52	60 (39.0%)	56 (36.4%)	33 (21.6%)	<0.001	0.004
Durable Clinical Remission	33 (21.4%)	25 (16.2%)	22 (14.4%)		

[Durable clinical remission is defined as a clinical remission at ≥80% of study visits, including the final visit]

Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, et al. Vedolizumab as Induction and Maintenance Therapy for Crohn’s Disease. N Engl J Med. 369;8. Aug 22, 2013. Accessed July 17, 2014.

Ulcerative Colitis

This was a phase 3, randomized, double-blind, placebo-controlled study of vedolizumab in patients w/ active disease, consisting of separate induction & maintenance trials. In the induction therapy arm, 374 patients (cohort 1) received vedolizumab (at a dose of 300 mg) or placebo IV at weeks 0 and 2, and 521 patients (cohort 2) received open-label vedolizumab at wks 0 & 2, with disease evaluation at wk 6. In the maintenance therapy arm, those who had response to vedolizumab in either arm were randomly assigned to continue receiving vedolizumab q 8 or 4 weeks or to switch to placebo for up to 52 wks. Response was defined as a reduction in Mayo Clinic score (0-12, higher score indicates more active disease) of ≥ 3 pts & a decrease of at least 30% from baseline, w/ an accompanying decrease in the rectal bleeding subscore of a least 1 pt or an abs. rectal bleeding subscore of 0 or 1.

Induction Trial Arm					
End Point	Cohort 1 Vedolizumab (n=225)	Cohort 1 Placebo (n=149)	p-value	Cohort 2 Open-label vedolizumab (n=521)	
Clinical response at Week 6	106 (47.1%)	38 (25.5%)	<0.001	231 (44.3%)	
Clinical remission at Week 6	38 (16.9%)	8 (5.4%)	0.001	100 (19.2%)	
Mucosal healing	92 (40.9%)	37 (24.8%)	0.001	191 (36.7%)	

Maintenance Trial Arm					
End Point	Vedolizumab q 8 weeks (n=122)	Vedolizumab q 4 weeks (n=125)	Placebo (n=126)	p-value q 8 wks with placebo	p-value q 4 weeks with placebo
Clinical remission at Week 52	51 (41.8%)	56 (44.8%)	20 (15.9%)	<0.001	<0.001
Durable clinical response	69 (56.6%)	65 (52.0%)	30 (23.8%)	<0.001	<0.001
Durable clinical remission	25 (20.5%)	30 (24.0%)	11 (8.7%)	0.008	0.001
Mucosal healing at wk 52	63 (51.6%)	70 (56.0%)	25 (19.8%)	<0.001	<0.001
Glucocorticoid-free remission at wk 52	22 (31.4%)	33 (45.2%)	10 (13.9%)	0.01	<0.001

Feagan BG, Rutgeerts P, Sands BE, Hanauer S, et al. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med 369;8 699-710. Aug 22, 2013. Accessed July 18, 2014.

Recommendation: Cover under PA criteria, based on the fact that this is the last resort for these patients.

- Do they have a diagnosis of moderate to severe UC or CD?
- Have they tried and failed steroids, immunosuppressants, and biologics, as defined below?

EBRx P&T Decision: Approve under the attached PA

Definition of Inadequate Response, Loss of Response, & Intolerance Over the Previous 5-year Period	
To Corticosteroids	<ul style="list-style-type: none"> - S/s of persistent, active disease despite a hx of at least 1 4-wk induction regimen that included a dose equivalent to prednisone 30 mg daily, PO for 2 wk or IV for 1 wk OR - 2 failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily PO on 2 separate occasions OR - Hx of intolerance of corticosteroids (including, but not limited to, Cushing's, osteopenia/osteoporosis, hyperglycemia, insomnia, & infection)
To Immunosuppressives	<ul style="list-style-type: none"> - S/s of persistent, active disease despite a hx of ≥1 8-wk regimen of oral azathioprine (≥1.5mg/kg) or 6-MP (≥0.75mg/kg) OR - S/s of persistent, active disease despite a hx of ≥1 8-wk regimen of methotrexate (≥12.5mg/kg/wk) (CD only) OR - Hx of intolerance of ≥1 immunosuppressive (including, but not limited to, N/V, abdominal pain, pancreatitis, LFT

	abnormalities, lymphopenia, thiopurine methyltransferase genetic mutation, & infection)
<p style="text-align: center;">To TNF Antagonists</p>	<ul style="list-style-type: none"> - S/s of persistent, active disease despite a hx of ≥ 1 4-wk induction regimen of 1 of the following: <ul style="list-style-type: none"> - Infliximab: 5 mg/kg IV, 2 doses at least 2 wk apart - Adalimumab: 1 80mg SC dose followed by 1 40mg dose ≥ 2 wk apart (CD only) - Certolizumab pegol: 400mg SC, 2 doses ≥ 2 wk apart (CD only) <u>OR</u> - Recurrence of sym during scheduled maintenance dosing after prior clinical benefit (D/C despite clinical benefit does not qualify) <u>OR</u> - Hx of intolerance of at least 1 TNF antag (including, but not limited to, inf-related rxn, demyelination, CHF, & inf)

Patients who enrolled in the study did not respond or were intolerant to ≥ 1 corticosteroid, immunosuppressive, or TNF antag; US patients must have failed either immunosuppressive or TNF antag therapy (not corticosteroids only)

Proposed EBRx PA Criteria for vedolizumab (Entyvio)
Gerri Bemberg, Pharm.D.
July 22, 2014, rev 10-30-14

Crohn's Disease	
Initial request to identify responders.	
1. Does the patient have a diagnosis of Crohn's Disease?	<input type="checkbox"/> Yes <input type="checkbox"/> No
2. Has the patient failed treatment with, or is dependent on corticosteroids, as defined by the following: a. Signs and symptoms of persistent, active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily, PO for two weeks or IV for 1 week <u>OR</u> b. 2 failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily PO on 2 separate occasions <u>OR</u> c. History of intolerance of corticosteroids (including, but not limited to: Cushing's syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, or infection)	<input type="checkbox"/> Yes <input type="checkbox"/> No
3. Was the patient unresponsive or intolerant to immunosuppressive therapy, as defined by the following: a. Signs and symptoms of persistent, active disease despite a history of ≥ 1 8-week regimen of oral azathioprine (≥ 1.5 mg/kg) or mercaptopurine (≥ 0.75 mg/kg) <u>OR</u> b. Signs and symptoms of persistent, active disease despite a history of ≥ 1 8-week regimen of methotrexate (≥ 12.5 mg/kg/wk) <u>OR</u> c. History of intolerance of ≥ 1 immunosuppressive (including, but not limited to: Nausea, vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, thiopurine methyltransferase genetic mutation, or infection)	<input type="checkbox"/> Yes <input type="checkbox"/> No
4. Was the patient unresponsive or intolerant to treatment with a TNF antagonist, as defined by the following: a. Signs and symptoms of persistent, active disease despite a history of ≥ 1 4-week induction regimen of 1 of the following: - Infliximab: 5mg/kg IV, 2 doses at least 2 weeks apart - Adalimumab: 1 80mg SC dose followed by 1 40mg dose ≥ 2 weeks apart - Certolizumab pegol: 400mg SC, 2 doses ≥ 2 weeks apart <u>OR</u> b. Recurrence of symptoms during scheduled maintenance dosing after prior clinical benefit (discontinue despite clinical benefit does not qualify) <u>OR</u> c. History of intolerance of at least 1 TNF antagonist (including, but not limited to: infection-related reaction, demyelination, CHF, or infection)	<input type="checkbox"/> Yes <input type="checkbox"/> No
If the answers to 1, 2, and either 3 OR 4 are yes, patient is approved for 14 weeks (4 doses).	
Responders Maintenance Therapy	
Did the patient respond to and was successful on therapy?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If the answer was yes, patient is approved for therapy for 1 year (7 doses).	
References: 1. Sandborn WJ, Feagan BG, Rutgeerts P, Hanauer S, et al. Vedolizumab as Induction and Maintenance Therapy for Crohn's Disease (GEMINI2). N Engl J Med. 369;8. Aug 22, 2013. Accessed July 17, 2014. 2. Sands BE, Feagan BG, et al. Effects of vedolizumab induction therapy for patients with CD in whom TNF treatment failed. (GEMINI3) Gastroenterology. 2014;147:618-27.	

Ulcerative Colitis	
Initial request to identify responders.	
1. Does the patient have a diagnosis of Ulcerative Colitis?	<input type="checkbox"/> Yes <input type="checkbox"/> No
2. Has the patient failed treatment with, or is dependent on corticosteroids, as defined by the following: a. Signs and symptoms of persistent, active disease despite a history of at least one 4-week induction regimen that included a dose equivalent to prednisone 30 mg daily, PO for two weeks or IV for 1 week OR b. 2 failed attempts to taper corticosteroids to below a dose equivalent to prednisone 10 mg daily PO on 2 separate occasions OR c. History of intolerance of corticosteroids (including, but not limited to: Cushing’s syndrome, osteopenia/osteoporosis, hyperglycemia, insomnia, or infection)	<input type="checkbox"/> Yes <input type="checkbox"/> No
3. Was the patient unresponsive or intolerant to immunosuppressive therapy, as defined by the following: a. Signs and symptoms of persistent, active disease despite a history of ≥1 8-week regimen of oral azathioprine (≥1.5mg/kg) or mercaptopurine (≥0.75mg/kg) OR b. History of intolerance of ≥1 immunosuppressive (including, but not limited to: Nausea, vomiting, abdominal pain, pancreatitis, LFT abnormalities, lymphopenia, thiopurine methyltransferase genetic mutation, or infection)	<input type="checkbox"/> Yes <input type="checkbox"/> No
4. Was the patient unresponsive or intolerant to treatment with a TNF antagonist, as defined by the following: a. Recurrence of symptoms during scheduled maintenance dosing after prior clinical benefit (discontinue despite clinical benefit does not qualify) OR b. History of intolerance of at least 1 TNF antagonist (including, but not limited to: infection-related reaction, demyelination, CHF, or infection)	<input type="checkbox"/> Yes <input type="checkbox"/> No
If the answers to 1, 2, and either 3 OR 4 are yes, patient is approved for 14 weeks (4 doses).	
Responders Maintenance Therapy	
Did the patient respond to, and was successful on therapy?	<input type="checkbox"/> Yes <input type="checkbox"/> No
If the answer was yes, patient is approved for therapy for 1 year (7 doses).	
References: 1. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, et al. Vedolizumab as Induction and Maintenance Therapy for Ulcerative Colitis. N Engl J Med 369;8 699-710. Aug 22, 2013. Accessed July 18, 2014.	

Revision History		
Date	What happened	Pharmacist
7/22/14	Created criteria	GBB
10/30/14	A 2 nd reference was added regarding CD. NO changes in PA criteria	JJ.