



AGENDA

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

February 01, 2016

1:00 p.m.

EBD Board Room – 501 Building, Suite 500

- I. *Call to Order..... Dr. Hank Simmons, Chairman*
- II. *Approval of December 14, 2015 Minutes Dr. Hank Simmons, Chairman*
- III. *Delivery Coordination Workgroup..... Dr. Geri Bemberg, UAMS*
- IV. *Clarifications from Oct Meeting.....Dr. Geri Bemberg, Dr. Jill Johnson, UAMS*
- V. *DESI Drug ReviewDr. David Keisner, UAMS*
- VI. *Topical Local Anesthetics..... Dr. Geri Bemberg, UAMS*
- VII. *2nd Review of Drugs.....Dr. Jill Johnson, UAMS*
- VIII. *New Drugs.....Dr. Jill Johnson, UAMS*
- IX. *EBD Report Dr. Geri Bemberg, UAMS*

Upcoming Meetings

April 4, 2016

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
February 1, 2016**

The State and Public Life and Health Insurance Board, Drug Utilization and Evaluation Committee (DUEC) met on Monday February 1, 2016 at 1:00 p.m., in the EBD Board Room, 501 Woodlane, Little Rock, AR.

Voting Members present:

Dr. Scott Pace
Dr. Kat Neill – Vice-Chairman
Dr. Geri Bemberg
Dr. Hank Simmons Chairman
Dr. Appathurai Balamurugan
Dr. William Golden
Dr. John Kirtley
Larry Dickerson

Non-Voting Members present:

Dr. Jill Johnson
Connie Bennett

Members absent:

Dr. Melodee Harris

Lori Eden, Deputy Executive Director, Employee Benefits Division

OTHERS PRESENT

David Keisner, UAMS College of Pharmacy; Sherry Bryant, Ethel Whittaker, Janis Harrison, Shay Burleson, EBD; Marc Watts, ASEA; Charlene Kaiser, Amgen; Takisha Sanders, Health Advantage; Mary Abels, AHTD; Jennifer Smith, ASU; Arlene Chan-Mouton, Leah Ramirez, ACHI; Jon McGuire, Eric Brumleve, Cameron James, GSK; Bridgett Johnson, Pfizer; Takisha Sanders, Jessica Akins, Health Advantage; Jim Chapman, ABBVIE; Connie Bennett, Optum Rx; Marck Adkison, Allcare Specialty; Treg Long, ACS; Karyn Langley. Qualchoice; Kelli Heathman, Biogen; Janie Huff, Takeda; Frances Bauman, Nova Nordisk; Sean Teague, Merck; Dr. Creshelle Nash, ABCBS

CALL TO ORDER

Meeting was called to order by Dr. Hank Simmons, Chairman.

APPROVAL OF MINUTES

The request was made by Dr. Simmons to approve the December 14, 2015 minutes. Dr. Pace made the motion to approve. Dr. Neill seconded. All were in favor.

Minutes Approved.

DELIVERY OF COORDINATION WORK GROUP REPORT: *by Dr. Geri Bemberg, UAMS*

Delivery Coordination Workgroup Report: *by Dr. Geri Bemberg, 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 February 1st. Recommendations from this report are outlined below.

Metastatic Melanoma	Current Coverage	Proposed Coverage for 2016
Cobimetinib (Cotellic) with/ Vemurafenib (Zelboraf)	Cobimetinib – Exclude Vemurafenib – T4PA	Cobimetinib – T4PA Vemurafenib – T4PA
<u>Squamous-Cell NSCLC</u> Nivolumab (Opdivo)	Covered, Medical PA	<u>For this indication:</u> 1) Continue covering OR 2) Exclude for this indication due to drug being deemed “clinically effective, but not cost effective” by NICE.

A. Dr. Simmons reported the Delivery Coordination Workgroup recommended cover Cotellic and Zelboraf at T4 with a PA. In addition, continue covering Opdivo as it is currently covered, until the Board has more information on the clinical and cost effectiveness.

Dr. Golden motioned to (1) Table the drug to the next meeting, (2) Request the Board to review the concepts regarding cost effectiveness and it’s role in the decision making about coverage. Dr. Pace seconded. All were in favor.

Motion approved.

B. Clarifications from October Meeting: *by Dr. Geri Bemberg, UAMS*

Dr. Bemberg reported on a previous discussion of covering **Zetia (ezetimibe)**, a cholesterol absorption inhibitor, on Tier 3, PA. Should **Vytorin (ezetimibe/simvastatin)** be covered? Dr. Pace reported Zetia will become generic in 2016 and that Vytorin will not. **There will be no changes. The Committee recommends revisiting the discussion when Zetia becomes generic and requests the Board’s decision.**

C. DESI Drug Review: *by Dr. David Keisner, UAMS*

Dr. Keisner reported that a DESI drugs is “one that the FDA has determined to be safe, but not effective.” Drug Efficacy Study Implementation (DESI) classifies all pre-1962 drugs as effective, ineffective, or needing further study. The Kefauver-Harris Drug Control Act requires all drugs to be efficacious in addition to being safe. There are 42 DESI drugs currently covered under the plan. However, the plan has obtained a new pharmacy vendor, MedImpact. The new vendor has DESI drugs classified as excluded. Dr. Keisner would like a recommendation from the committee to cover or exclude.

Dr. Golden motioned to exclude with a 90-day notice to current users. Dr. Neill seconded. All were in favor.

Motion Approved.

D. Topical Local Anesthetics: *by Dr. Geri Bemberg, UAMS*

Dr. Bemberg reported on the topical anesthetics. A single GPI or Generic Product Identifier number covers all lidocaine topical local anesthetics. At this time, all new GPIs are reviewed as new drugs. However, beginning in early 2015 new products began to be released under existing, generic GPIs. Such drugs are really new brands or “branded generics” that sometimes have new indications. Thus, they enter the market under a GPI already usually assigned to a brand that has either been discontinued or is a current generic. As such, they have not been identified to the Plan as new drugs and have thereby slipped through the cracks. Almost every time these new brands lack significant evidence and would not have originally been covered by the Plan. The GPIs associated with Lidocaine/Menthol Patch 4 -1% and Capsaicin/Menthol Patch 0.0375-5% are the main repeat offenders. Fortunately, there were only two users in the 4th quarter of 2015.

Dr. Kirtley motioned to exclude. Pace seconded. All were in favor.

Motion approved.

E. 2nd Review of Drugs: *by Dr. Jill Johnson, UAMS*

- 1) Envarus XR – tacrolimus extended-release tablets – Recommendation: Value proposition for the product is convenience of daily dosing and potential for decreased adverse events related to kinetics of BID dosing. However, discontinuation secondary to adverse events does not support this proposition. **Dr. Pace motioned to exclude alongside Astagraf XL.. Dr. Neill seconded. All were in favor. Motion Approved.**
- 2) Empagliflozin (Jardiance) – Used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (noninsulin dependent) as monotherapy or combination therapy. **Proposal: Cover empagliflozin by covering; Jardiance- (empagliflozin 10mg or 25mg daily), Synjardy- (empagliflozin 5mg/metformin 500mg, 5/1000, 12.5/500, 12.5/1000, given BID), continue to exclude Glyxambi (empagliflozin and linagliptin) with PA criteria. Dr. Pace motioned to approve with PA criteria that will be developed. Dickerson seconded. All were in favor. Motion Approved.**
- 3) Evolocumab (Repatha) and Alirocumab (Praluent) – The Insurance Board voted 11/17/2015 to exclude the drugs as recommended by DUEC. At the request of Dr. Andrew Kumpuris, DUEC re-evaluated the class. Again, it remains without clinical outcome data from current trials that are not due to be complete until 2017. **The Committee recommends continuation of the current policy and reevaluation when new data becomes available. Dr. Golden motined to cover as approved by the FDA. Dr. Pace seconded. Dickerson & Kirtley voted no. All remaining were in favor. Motion Approved.**

Dr. Simmons inquired if the committee would like a reconsideration of the previous vote?

Dr. Neill motioned to reconsider the previous vote. Dr. Golden seconded.

Dr. Pace motioned to reconsider the class upon further data and continue with the same policy review and evaluate new data when it becomes available. Dr. Golden seconded. All were in favor.

Motion Approved.

NEW DRUGS: by Dr. Jill Johnson, UAMS

Johnson reported on new drugs. The review covered products released October 12, 2015– January 4, 2016.

A. Recommended Additions

1. Nonspecialty medications-proposed additions

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	DUEC VOTE
Spiriva Aer Respimat 1.25mg	Tiotropium inhal aerosol	\$378/inhaler	Asthma in patients 12 & older	Other Spiriva strengths at T2	Tier 2
Tolak	Fluorouracil Cream 4%	\$180/40mg tube	For actinic keratosis	Fluorouracil cream 5% = \$247/40gm	Cover, tier TBD.
Varubi tabs 50mg	Rolapitant 90mg tab	\$636/2-90mg t	Chemotherapy induced nausea	Cover as same tier as Emend (T2)	Tier 2
Narcan Spray	Nalozone HCl nasal spray 4mg/0.1ml	\$150/box of 2 spray bottles of 4mg/0.1ml	For opiate agonist overdose and opiate agonist induced respiratory depression		Tier 3,QL 1/31d
Pradaxa cap 110mg	Dabigatran 110mg	\$6.67/cap	Line extension. Anticoagulant.	Pradaxa currently T2	Tier 2

2.Specialty medications-proposed additions

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	DUEC VOTE
Genvoya	Elvitegra V-cobic-emtricitab-tenofov AF tab	\$3,090/30 tabs	HIV infection		Tier 4
Nucala Injection	Mepolizumab inj	\$3,000/100mg	Add-on maintenance treatment of patients w/severe asthma. 100mg SQ injection every 4 weeks.		Tier 4 same as omalizumab
Gleostine caps 5mg	Lomustine 5mg	\$125/5mg	Line-extension. For treatment of Hodgkin's disease, malignant glioma		T3QL of 1/qGW
Empliciti	Elotizumab IV solution	\$2,841/400mg cap-dose varies	Treatment of multiple myeloma		T4 PA
Adynovate inj	Antihemophilic factor recom pegylated	\$2.38/unit	Antihemophilic factor		T4PA Dx of Hemophilla
Coagadex	Coagulation Factor X human	\$9.29/unit	Coagulation factor		T4PA (handout)

B. Recommended Exclusions

1. Nonspecialty Medications-proposed exclusion

BRAND NAME	GENERIC NAME	PRICING	INDICATION	SIMILAR THERAPIES ON	EXCLUSION
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		(AWP)		FORMULARY/AWP	CODE
Durlaza Cap 162mg	Aspirin SR 24hr	\$216/30	24 our extended release aspirin for the prevention of stroke/acute cardiac events	Aspirin covered at 100%	Exclude code 13
Keveyis tabs 50mg	Dichlorphenamide 50mg tab	\$163.80/tab dose=100-200mg/day	Primary hyperkalemic periodic paralysis, and related variants. Max dose=200mg/day		Exclude code 13
Hygel Gel 2.5%	Hyaluronate sodium gel 2.5%	\$45/10 gm	Protects skin ulcers, burns or wounds from irritation		Exclude. Alternate is Bionect
Restora Spri Pak	Lactobacillus-folic acid	\$28.84/28 packets	Antidiarrheal (line extension)		Exclude code 13
Tresiba Flex	Insullin degludec pen injector	\$106/3ml pen 100u/ml. \$213/3ml pen 200u/ml	Long acting basal Insulin – Type 1 and Type 2 diabetes		Exclude code 13
Seebri neoha Cap	Glycopyrrolate inhal cap	\$357/1 inhaler 60 caps	Long-term, maintenance treatment of airflow obstruction inpatients w/COPD		Exclude & negotiate for lowest net cost
Utibron Cap Neohaler	Indacaterol-glycopyrrolate inhal caps	\$357/1 inhaler 60 caps	Dual Combination bronchodilator for patients w/COPD		Exclude code 13
Belbuca	Buprenorphine HCl buccal film	\$306-\$758/box of 60	Treatment of moderate-severe pain, opiate dependence/withdrawal		Exclude code 13
Vivlodex Caps	Meloxicam 5 7 10mg caps	\$23.76/cap	Treatment of Osteoarthritis pain	Generic meloxicam available in 7.5 & 15mg tabs	Exclude code 13
Veltasa Powder	Patiromer sorbitex calcium for suspension packet	\$714/box of 30-25.2g	Treatment of hyperkalemia		Exclude code 13
Renovo Lido5 Cream	Capsaicin-lidociane-menthol cream	\$720/60gm tube	Topical anesthetic and analgesic indicated for the relief of pain related to minor cuts, grazes, and irritation	Capsaicin 0.25% cream= \$18/45gm AWP Lidociane 5% cream=\$43/30gm AWP	Exclude, OTC Alternative.
2. Specialty Medications-proposed exclusions					
BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	EXCLUSION CODE
Aristada	Aripiprazole IM ER prefilled syringe	\$1265/441mg; \$898/662mg; \$2528/882mg	Abilify Maintena (monthly extended release IM)-Invega Sustenna, Invega Irinz-T4		Exclude code 13
Odomzo caps	Sonidegib phosphate cap 200mg	\$12,060/30 daps. Dose=200mg/day	Treatment of adult patients with locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or those		Exclude code 1

			who are not a candidate for surgery or datiation therapy. Dose=200mg/day	
Lonsurg	Trifluridine-tipiracil tabs	\$9,840/60-20mg	Treatment of colorectal cancer. Dose=160mg	Exclude code 1
Onivyde	Irinotecan liposome IV inj	NA	For pancreatic cancer-out of scope of PBM services	Exclude
Yondelis inj	Trabectedin for inj	NA	For soft tissue sarcoma-out of scope of PBM services	Exclude code 1
Stranxiq Inj	Asfotase alfa	\$6720/mg-dose varies	Subcutaneous injection for treatment of hypophosphatasia	Exclude, reevaluate after 04/16
Imlygix Injection	Talimogene laheparepvec intralesional inj	\$5,280/vial-out of schpe of pharmacy benefits	Malignant melanoma	Exclude
Darzalex	Daratumumab IV soln	\$2,160/400mg Dose varies. Out of scope of pharmacy benefits	FDA designated orphan drug for treatment of multiple myeloma in patients who have received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent	Exclude code 1
Tagrisso	Osimertinib tabs	\$15,300/30-80mg tabs	Treatment of metastatic EGFR T790M mutation positive non-small cell lung cancer, after progression on or after EGFR tyrosine kinase inhibitor therapy	Exclude code 1
Ninlaro Caps	Ixazomib	\$3,468/4mg cap-dose varies	Treatment of multiple myeloma	Exclude. FDA to work out issues wit statistical discrepancies.
Ferriprox Soln	Deferiprone solution	\$5,435/500ml bottle	Transfusional iron overload	Exclude code 13
Alecensa 150mg capse	Alectinib 150mg caps	\$14,791/240-150mg caps. Dose=600mg	Treatment of non-small cell lung cancer	Exclude code 1
Bendeka Inj	Bendamustine IV soln	\$2,788/100mg vial. Out of scope of pharmacy benefits	Treatment of chronic lymphocytic leukemia & non-Hodgkin's lymphoma	NA for pharmacy benefit. Medical
Kanuma Inj	Sebelipase Alfa IV soln	\$12,200/20mg vial. Out of scope of pharmacy	Treatment of lysosomal acid lipase deficiency	Exclude code 1

		benefits.		
Portrazza Inj	Necitumamab IV soln	\$4,800/800mg vial. Out of scope of Pharmacy benefits	Treatment of advance squamous non-small cell lung cancer	Exclude code 1

C. New Drugs Tabled for April, 2016 DUEC

Viberzi Tabs	Eluxadoline	\$1,152/60-100mg tabs. Dose=200mg/day	Treatment of irritable bowel syndrome wit diarrhea	Table. Not yet reviewed by EBRx.
Uptravi Tabs	Selexipag Tabs	\$17,400/#60-1600mcg tabs	Treatment of pulmonary hypertension to delay disease progression and reduced risk of hospitalization.	Table. EBRx has not yet evaluated.

Dr. Golden motioned to approve Section A, Non-Specialty and Specialty additions. Dickerson seconded. All were in favor.

Motion Approved.

Dickerson motioned to accept Section B, Non-Specialty and Specialty exclusions. Neill seconded. All were in favor.

Motion Approved.

***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 eternally 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

EBD REPORT: *by Dr. Geri Bemberg, UAMS*

Dr. Bemberg reported on the Top 10 Drug Categories by Plan Cost, The Top Drugs by Plan Spend and The Top 10 Drugs by Average Ingredient Cost. The Plan driver is antidiabetics, which cost the plan in 2015 \$18,067,719.00 for 122,062 prescriptions. Due to inflation the cost was \$1.8 million more than the previous year.

Connie Bennett of Optum reported that the 2015 trend was 8% per member per month. The generic dispense rate 89.6%, and the member share was 26.6%.

Meeting Adjourned

Delivery Coordination Workgroup Report

Members

- Geri Bemberg, PharmD – EBRx
- David Keisner, PharmD – EBRx
- Jill Johnson, PharmD – EBRx
- Andrew Mullings-Lewis, PharmD – EBRx Managed Care Resident
- Henry Simmons, MD, PhD – Medical Director Arkansas Poison Control
- Sidney Keisner, PharmD – Board Certified Oncology Pharmacist, VA Little Rock
- Kati Beth Lewis, PharmD – Clinical Pharmacist BCBS/Wendy See, PharmD
- Stephen Sorsby, MD – Medical Director, Qualchoice/Barry Fielder, PharmD

	<u>Current Coverage</u>	<u>Proposed Coverage</u>
<u>Metastatic Melanoma</u>		
Cobimetinib (Cotellic) w/ Vemurafenib (Zelboraf)	Cobimetinib - Excluded Vemurafenib – T4PA	Cobimetinib – T4PA Vemurafenib – T4PA
<u>Squamous-Cell NSCLC</u>		
Nivolumab (Opdivo)	Covered, Medical PA	<u>For this indication:</u> 1) Continue covering OR 2) Exclude for this indication due to drug being deemed “clinically effective, but not cost effective” by NICE.

Topical Local Anesthetics
GPI 9085*****

9085***** GPI covers all topical local anesthetics from topical lidocaine cream to combination patches. At this time, all new GPIs are reviewed as new drugs. However, beginning in early 2015, new products began to be released under existing generic GPIs. These new drugs are new brands or “branded generics,” sometimes with new indications, that enter the market under a GPI already usually assigned to a brand that has been discontinued and a current generic. As such, they have not been identified to the plan to be new drugs, and have slipped through the cracks. When this happens in this category, almost every time, the new brands have zero evidence associated with them and would not have originally been covered by the plan.

There are two main GPIs with repeat offenders in this area. The information concerning them follows.

GPI	908599028859** (Lidocaine/menthol patch)					
	Brand	Rx/OTC	AWP/unit	Date Added	Info in Daily Med/Lexi/drug sources	Current Tier
90859902885930 Lidocaine/menthol patch 4-1%	Avalin Pad	OTC	39.00	2/23/15	Human OTC Drug	
	Avalin-Rx Pad	Rx	40.38667	4/9/15		1
	Endoxcin Pad	OTC	40.25	5/19/14	Human OTC Drug	
	Lenzapatch	OTC	42.00	4/9/13	Human OTC Drug	
	Puroxcin Pad	OTC	40.25	7/23/14		
	Elenzapatch	Rx	40.25	11/11/13		1
	Lidodextrapine Pad	Rx	46.554	9/16/14		1
	Reciphexamine Dis	Rx	46.554	9/8/14		
	Prolida Pad	OTC	46.33333	2/17/15	Human OTC Drug	
	Zeruvia	Rx	82.964	11/19/14		1
	Lidenza Patch	Rx	36.66667	3/11/15	Unapproved drug other	1
	Releevia ML Pad	Rx	40.00	3/11/15	Unapproved drug other	1
	Synvexia Pad	Rx	98.664	12/4/14	Unapproved drug other	1
	Provenza pad	Rx	82.04	12/22/14	Unapproved drug other	1
	Lorenza Pad	Rx	52.75533	1/26/15	Unapproved drug other	1
	Pain Relief Pad Patch	OTC	45.00	1/29/15		
Aflexeryl-LC Pad	OTC	35.00	2/5/15	Human OTC Drug		

90859902685940 Capsaicin/menthol patch 0.0375-5%	Medrox Pad	OTC	25.52	7/24/12	Human OTC Drug	
	Aleveer Dis	OTC	38.24	11/11/13	DSC, Obsolete Date 12/30/16	
	Qroxin Pad	Rx	46.53733	10/8/14		2
	Neuvaxin Pad	Rx	58.13333	2/5/15		2
	Capsiderm Pad	OTC	46.33333	2/17/15	Human OTC Drug	
	Captracin Pad	Rx	38.24	12/29/14	DSC, Obsolete Date 10/15/17	2
	Renovo Pad	Rx	78.72667	10/13/14	Unapproved drug other	2
	Sinelee Pad	Rx	45.888	12/1/14		2
	Releevia Pad	Rx	36.33333	11/19/14	Unapproved drug other	2
	Releevia MC Pad	Rx	40.00	3/11/15	Unapproved drug other	2
	Pain Relief Pad Patch	Rx	43.33	1/29/15		2
	MAC Patch Pad	Rx	38.22667	1/26/15		2
	Aflexeryl-MC Pad	OTC	35.00	2/5/15	Human OTC Drug	
	Flexin Pad	Rx (RxClaim)	60.00	7/7/15	Human OTC Drug (Dailymed)	2

None of these were reviewed by DUEC at any point. For 2015, these drugs cost the plan a little over \$250,000.

Current Utilization

2 utilizers Q4 2015

Other options:

Capsaicin/menthol: Salon-pas pain relieving gel packs: \$9.49 at Walgreens for 6.

Lidocaine patches are available T1PA.

There is no evidence comparing topical lidocaine to topical lidocaine combined with menthol. Lidocaine patches are current covered with PA.

Recommendation:

Exclude all drugs under these 2 GPs.

2015 EBD DESI DRUGS

ANUCORT-HC
ESTERIFIED ESTROGENS/METHYLTESTOSTERONE
ESTERIFIED ESTROGENS/METHYLTESTOSTERONE HS
ESTERIFIED ESTROGENS/METHYLTESTOSTERONE
HYDROCORTISONE ACETATE
COVARYX HS
CHLORDIAZEPOXIDE HCL/CLIDINIUM BROMIDE
ISOMETHEPTENE/DICHLORALPHENAZONE/ACETAMINOPHEN
HYDROCORTISONE ACETATE/PRAMOXINE
COVARYX
CORTANE-B-OTIC
EEMT
PRODRIN
PRAMOSONE
ANUSOL-HC
RECTACORT-HC
DERMAZENE
EEMT HS
GUAIFENESIN DAC
NODOLOR
DONNATAL
PRAMOSONE E
OTO-END 10
XENADERM
CORTANE-B AQUEOUS
VASOLEX
REVINA
VYtone
ALCORTIN A
AERO OTIC HC
GRX HICORT 25
HYDROCORTISONE/IODOQUINOL
CORTIC
HYDROCORTISONE ACETATE/PRAMOXINE HCL
LIBRAX
PROCTOCORT
ANALPRAM-HC
ISOMETHEPTENE MUCATE/CAFFEINE/ACETAMINOPHEN
TRIMO-SAN
ANALPRAM-HC SINGLES
ANALPRAM E
NOVACORT
CORTANE-B

Second Review of Drugs

1. Envarsus
2. Empagliflozin
Jardiance & Synjardy
3. PCSK9 inhibitors
Praluent & Repatha

tacrolimus extended-release tablets
Envarsus XR

AGENT	PRICE (MONTH SUPPLY)
TACROLIMUS 5MG DAILY (#3 1MG QAM AND #2 1MG QPM)	\$233.10*
ASTAGRAF XL 5MG DAILY	\$713.52
ENVARUSUS XR 4MG MG DAILY	\$560.16

*MAC PRICE

Evidence

The conversion study was a R, DB, open-label, multinational study evaluating daily tacrolimus extended-release vs. tacrolimus BID for maintenance immunosuppression to prevent reject in stable adult kidney transplants patients (n=324). Study population was an average of 50 years of age, Caucasian (73%), 65% grafts for deceased donors. **Incidence of BPAR, graft loss, death or loss to f/u at 12 months was similar between groups with 0% treatment difference.** Discontinuation was higher in the tacrolimus extended-release compared to the IR group (13% vs 6%). **Discontinuation due to adverse reaction was higher in the tacrolimus extended-release group compared to the placebo group (7.4% vs 1.2%).**¹

A phase III non-inferiority randomized trial examined efficacy and safety of daily tacrolimus extended-release vs. tacrolimus BID. **Extended release tacrolimus demonstrated noninferiority to tacrolimus twice daily in efficacy failure rates. The total daily doses of tacrolimus between tacrolimus extended-release and tacrolimus BID were 4.9mg and 4.7mg in the trial, respectively at the trial's conclusion.** Both formulations showed a statistically significant decreased in mean tacrolimus daily dose between baseline and month 12.²

Of note, a separate study 2-sequence, open-label, multicenter trial evaluated kidney transplant patients who were stable on BID tacrolimus but complained of hand tremors who were then switched to tacrolimus extended-release. Switching from to daily tacrolimus extended-release improved tremors (based on FTM score), tremor amplitude, and quality of life.³

Recommendation: Value proposition for the product is convenience of daily dosing and potential for decreased adverse events related to kinetics of BID dosing. However, discontinuation secondary to adverse events does not support this proposition. Recommend exclusion alongside Astagraf XL.

1. ENVARUSUS XR package insert.
2. Bunnapradist S, et al. Conversion from twice-daily tacrolimus to once-daily extended release tacrolimus (LCPT): the phase III randomized MELT trial. Am J Transplant. 2013 Mar;13(3):760-9. doi: 10.1111/ajt.12035. Epub 2012 Dec 21. PubMed PMID: 23279614; PubMed Central PMCID: PMC3613750
3. Langone A, Steinberg SM, Gedaly R, Chan LK, Shah T, Sethi KD, Nigro V, Morgan JC. Switching Study of Kidney Transplant Patients with Tremor to LCP-TacR0 (STRATO): an open-label, multicenter, prospective phase 3b study.

Empagliflozin (Jardiance)

Jill Johnson, Pharm.D., BCPS

1/27/2016

Labeled use: As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (noninsulin dependent) as monotherapy or combination therapy.

Comparators:

Drug/Category	AWP for 30 ds
SGLT2 Inhibitors: Empagliflozin (Jardiance) 10mg, 25mg	\$435.66, 435.66
Dapagliflozin (Farxiga) 5mg, 10mg	\$435.68, 411.53
Canagliflozin (Invokana) 100mg, 300mg	\$435.67, 435.67
Empagliflozin/metformin (Synjardy) empagliflozin 5mg/metformin 500mg, 5/12.5/500, 12.5/1000, given BID	\$435.66 (#60)
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

Evidence:

Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in T2DM. N Engl J Med. 2015;373:2117-28. (noninferiority and superiority)

N=7020 T2DM pts AND CV disease and either no BG lowering drugs for 12 weeks before randomization and with HbA1C 7-9% OR DID receive BG lowering drugs for at least 12 w before R and HbA1C 7-10%. Also had high risk CV disease.

Results:

Outcome	Placebo (N=2333)		Empagliflozin (N=4687)		Hazard Ratio (95% CI)	P Value
	no. (%)	rate/1000 patient-yr	no. (%)	rate/1000 patient-yr		
Death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke: primary outcome*	282 (12.1)	43.9	490 (10.5)	37.4	0.86 (0.74-0.99)	
Noninferiority						<0.001†
Superiority						0.04†
Death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina: key secondary outcome*	333 (14.3)	52.5	599 (12.8)	46.4	0.89 (0.78-1.01)	
Noninferiority						<0.001†
Superiority						0.03†
Death						
From any cause	194 (8.3)	28.6	269 (5.7)	19.4	0.68 (0.57-0.82)	<0.001
From cardiovascular causes	137 (5.9)	20.2	172 (3.7)	12.4	0.62 (0.49-0.77)	<0.001
Fatal or nonfatal myocardial infarction excluding silent myocardial infarction	126 (5.4)	19.3	223 (4.8)	16.8	0.87 (0.70-1.09)	0.23
Nonfatal myocardial infarction excluding silent myocardial infarction	121 (5.2)	18.5	213 (4.5)	16.0	0.87 (0.70-1.09)	0.22
Silent myocardial infarction‡	15 (1.2)	5.4	38 (1.6)	7.0	1.28 (0.70-2.33)	0.42
Hospitalization for unstable angina	66 (2.8)	10.0	133 (2.8)	10.0	0.99 (0.74-1.34)	0.97
Coronary revascularization procedure	186 (8.0)	29.1	329 (7.0)	25.1	0.86 (0.72-1.04)	0.11
Fatal or nonfatal stroke	69 (3.0)	10.5	164 (3.5)	12.3	1.18 (0.89-1.56)	0.26
Nonfatal stroke	60 (2.6)	9.1	150 (3.2)	11.2	1.24 (0.92-1.67)	0.16
Transient ischemic attack	23 (1.0)	3.5	39 (0.8)	2.9	0.85 (0.51-1.42)	0.54
Hospitalization for heart failure	95 (4.1)	14.5	126 (2.7)	9.4	0.65 (0.50-0.85)	0.002
Hospitalization for heart failure or death from cardiovascular causes excluding fatal stroke	198 (8.5)	30.1	265 (5.7)	19.7	0.66 (0.55-0.79)	<0.001

Whether the mortality benefit is a class effect has not been determined. The Canagliflozin CV Assessment Study (CANVAS) and the DECLARE-TIMI58 trial with dapagliflozin will be completed in 2017.

It is unknown which dose of empagliflozin should be used as the 10mg&25mg groups were pooled.

It is also unknown how a CV mortality benefit can be seen without a reduction in MI or stroke; possibly the reduction in hosp for HF.

Troubling is the nonsignificant INCREASE in fatal/NF stroke with empagliflozin. If the CV mortality effect was mediated by BP reduction, stroke should NOT be numerically increased.

NICE:

Empagliflozin in a dual therapy regimen in combination with metformin is recommended as an option for treating T2DM, only if:

- a sulfonylurea is contraindicated or not tolerated, or
- the person is at significant risk of hypoglycaemia or its consequences.

Empagliflozin in a triple therapy regimen is recommended as an option for treating type 2 diabetes in combination w/:

- metformin and a sulfonylurea or
- metformin and a thiazolidinedione.

Empagliflozin in combination with insulin with or without other antidiabetic drugs is recommended as an option for treating type 2 diabetes.

PROPOSAL:

Cover empagliflozin by covering:

Jardiance (empagliflozin 10mg or 25mg daily)

Synjardy (empagliflozin 5mg/metformin 500mg, 5/1000, 12.5/500, 12.5/1000, given BID)

Continue to exclude Glyxambi (empagliflozin and linagliptin)

Cover empagliflozin in a dual therapy regimen in combination with metformin only if a sulfonylurea is contraindicated or not tolerated or the person is at significant risk of hypoglycemia.

Cover empagliflozin in a triple therapy regimen in combination with metformin + sulfonylurea or metformin + thiazolidinedione.

Cover empagliflozin in combination with insulin with or without other antidiabetic drugs.

All patients must be secondary prevention CAD patients.

CVD, defined by ≥1 of the following:

MI >2 mo prior

Multivessel CAD

Single vessel CAD with positive stress test or UA hospitalization in prior year

UA >2 mo prior and evidence of CAD

Stroke >2 mo prior

Occlusive PAD

All patients must have HbA1C below 10% before receiving empagliflozin.(as they were in the trial; those >8.5% did not benefit as much and on average had numerically a 14% increased risk of CV death in the empagliflozin group.

PCSK9 Inhibitors
Evolocumab (Repatha) and Alirocumab (Praluent)
Jill Johnson, Pharm.D., BCPS
1/29/2016

The Insurance Board voted 11/17/2015 to exclude the drugs as recommended by DUEC. Dr. Drew Kumpuris requested EBRx reevaluate the class because he believes the drugs are effective despite there being any clinical outcome reductions yet shown in clinical trials. Trials evaluating clinical outcomes are in progress, however, are not due to be complete until 2017.

The New England Comparative Effectiveness Public Advisory Council (CEPAC) evaluated the topic and published their findings 11/24/15. Their findings are summarized below:

Summary and Comment

The results of ICER's cost-effectiveness analysis suggest that the use of PCSK9 inhibitors may produce substantial reductions in non-fatal MIs, non-fatal strokes, and cardiovascular deaths over 20 years. The NNTs (number of patients that would be needed to be treated for 5 years to avoid one major adverse cardiovascular event) for PCSK9 inhibitors appears to be very favorable; however, treatment with PCSK9 inhibitors generates cost-effectiveness ratios that exceed commonly accepted thresholds such as \$100,000/QALY. Achieving cost-effectiveness at a threshold of \$100,000/QALY would require price reductions of 63% to 82% compared with current prices. And the results of our analysis of potential budget impact suggest that even deeper reductions may be required to avoid excessive cost burdens to the health care system. Our value-based price benchmark for each PCSK9 inhibitor is \$2,177 annually, which represents an 85% reduction from the list price of \$14,600.

Details

- Multiple randomized clinical trials have demonstrated that lowering LDL-C with statin therapy reduces the risk of MI, stroke, and death from CVD.
- Several drugs that lower LDL-C – including hormone therapy, niacin, and torcetrapib – have not decreased cardiovascular disease events when evaluated in randomized trials despite lowering LDL-C.
- The recently published IMPROVE-IT trial demonstrated that the LDL-lowering ability of ezetimibe added to statin therapy significantly reduced cardiovascular event rates in pts recently discharged for ACS by 6% (95% CI 1 to 11%) after a median follow-up of approximately 5 years.
- 2013 ACC/AHA updated guidelines include:
 - “strong” recommendation for high intensity statin therapy to treat individuals with cardiovascular disease who are ≤ 75 years of age; moderate intensity statin use in individuals with diabetes mellitus and LDL-C levels between 70 and 189 mg/dL who are ages 40-75 years of age; and high intensity statin use in individuals aged 40-75 with a 10-year risk for cardiovascular disease ≥ 7.5% and LDL-C levels between 70 and 189 mg/dL. The guideline also make a “moderate” recommendation for high intensity statin therapy to treat all individuals with LDL-C levels ≥ 190 mg/dL who are ≥ 21 years of age.
- Earlier NCEP III guidelines:
 - Statin therapy was recommended to reach a target LDL-C level of < 100 mg/dL for individuals with cardiovascular disease and those with a 10-year risk ≥ 20%. For individuals with multiple risk factors and a 10-year risk < 20%, the target LDL-C level was < 130 mg/dL.
- Unmet clinical need in:
 - Familial hypercholesterolemia; HoFH have LDL-C >500 (affects ~1 case/1million people), HeFH have LDL-C levels about 2-3Xs normal 250-300mg/dL(affects ~1/500)
 - Statin intolerance 2` to muscle symptoms; Mild CK (<4XULN), Frank myositis (CK>4XULN)
 - Precise measurements are difficult because muscle symptoms arising form other causes are common, particularly in older individuals.
 - 2 studies examined statin intolerance: 10% mild-mod symptoms on high intensity statin (PRIMO study); 9.4% incidence of muscle symptoms w/ atorva 80mg vs 4.6% placebo (STOMP study)

- The more recent IMPROVE-IT trial randomized 18,144 patients hospitalized for an acute coronary syndrome in the prior 10 days to the combination of simvastatin and ezetimibe or simvastatin and placebo and followed them for a median of approximately 5 years. The estimated cumulative event rate at 7 years was 32.7% in the ezetimibe group and 34.7% in the placebo group (p=0.016).
- No head to head trials with PCSK9 inhibitors exist
- A high-quality meta-analysis by Navarese and colleagues was also identified and provided the basis for many of the findings in this review.¹ Most of the clinical trials were of relatively short duration. Seventeen trials had follow-up of <1 year, two trials had one year of follow-up, and five trials had follow-up longer than one year. Fourteen trials involved comparisons of PCSK9 inhibitors to placebo, seven compared PCSK9 inhibitors to ezetimibe, and three involved both comparisons
- The Navarese meta-analysis demonstrated the LDL reduction is very similar between the two drugs.
- There are 5-year large outcome studies ongoing for both alirocumab and evolocumab that should present initial results in 2017.
- Individual studies completed to date were not powered to evaluate outcomes such as mortality or CVD adverse events. However, the meta-analysis by Navarese combined data from existing studies to examine these outcomes. The most important clinical outcomes for lipid lowering therapy include death from cardiovascular disease, myocardial infarction (MI), stroke, and unstable angina requiring hospitalization. Navarese and colleagues did not report the stroke outcomes, so we meta-analyzed these using the same technical approach.

Table 7: Meta-analysis results for patient-oriented outcomes

Outcome	OR (95% CI)	P	I ²	N	Events PCSK9 group (%)	Events control group (%)
All-cause mortality	0.45 (0.23-0.86)	0.015	0%	10,159	19 (0.3%)	21 (0.5%)
CVD Mortality	0.50 (0.23-1.10)	0.084	0%	10,159	12 (0.2%)	13 (0.3%)
MI	0.49 (0.26-0.93)	0.030	0%	5,195	19 (0.6%)	19 (1.0%)
Stroke	1.97 (0.69-5.65)	0.206	0%	4,683	14 (0.5%)	3 (0.2%)
Unstable angina	0.61 (0.06-6.14)	0.676	0%	3,894	1 (0.05%)	1 (0.08%)

- As shown in the table above, the findings of the meta-analysis suggest that the PCSK9 inhibitors reduce the odds of all-cause and cardiovascular mortality by about 50%, but the total number of events is low and the confidence intervals are wide.
- The odds ratio for stroke in the meta-analysis was twice as high in the PCSK9 group, but the confidence interval is very wide and not statistically significant.
- Harms:
 - Nearly all studies have less than 6 months of follow-up data, but results from individual studies and from the Navarese meta-analysis have found that PCSK9 drugs are very well-tolerated; there have been no findings suggestive of significant increases in adverse event rates. There are more injection site reactions, which may lead to slightly higher rates of drug discontinuation compared to the control group. There is a slight excess of neurocognitive events with PCSK9 inhibitors, but the results are not statistically significant. There is also a trend towards more myalgias in the PCSK9 treated participants, but this is balanced by a statistically significant reduction in the number of participants with elevations in the muscle enzyme creatine kinase (CK).
- The promising evidence on patient-centered outcomes from the published meta-analysis is limited in several ways. First, the 95% confidence intervals for the odds ratios estimating clinical benefit either include 1.0 or approach 1.0. Second, the evidence in this meta-analysis combines data from trials of two different PCSK9 inhibitors, each with two different dosing schedules, with too few events in the evidence base to attempt subgroup analyses. Another limitation of the meta-analysis is that the populations studied were also quite different: young adults with homozygous FH and very high LDL-C; older adults with LDL-C < 100, but not at goal; and older adults who have already had a heart attack or stroke. A last reason for caution about the findings of the meta-analysis is that the PCSK9 inhibitors were compared to two different control arms: placebo and ezetimibe. The percentage LDL-C reduction consistently favored PCSK9 inhibitors, but the magnitude varied slightly by population and significantly by control group. It is likely that the clinical benefits will vary by dose, drug, background drug therapy, and population studied.

- The evidence base provides high certainty that PCSK9 inhibitors lead to superior reductions in LDL-C levels compared to both placebo and ezetimibe. The percent reduction in LDL-C with PCSK9 treatment is approximately 55-60% and appears not to differ substantially across different patient subpopulations.
- Pharmacoeconomics:
 - **Secondary Prevention Among Patients with a Prior History of CVD and LDL-C \geq 70mg/dL on Statin Therapy**
Compared with the control arm, treatment with ezetimibe improved outcomes at an ICER of \$372,000/QALY while PCSK9 inhibitors averted 2,235,100 MACE over twenty years and produced 3,581,200 additional QALYs at an ICER of \$557,000/QALY.
 - As shown in table ES 6 below, we also evaluated the drug costs at which PCSK9 inhibitors would be considered cost-effective under conventional willingness-to-pay thresholds of \$50,000/QALY, \$100,000/QALY, and \$150,000/QALY. Across all subpopulations and thresholds of interest, these prices **represented discounts of 6-86% from the full wholesale acquisition cost of \$14,600**. When all patient subpopulations are merged to reflect the entire eligible population, prices were \$2,412, \$3,615, and \$4,811 to achieve thresholds of \$50,000, \$100,000, and \$150,000 per QALY respectively.

Patient Subpopulation	WTP threshold		
	\$50,000/QALY	\$100,000/QALY	\$150,000/QALY
FH on statin (as treated) + statin-intolerant †	\$2,100	\$3,100	\$4,000
Pre-existing CVD, LDL-C \geq 70 mg/dL and statin-intolerant ††	\$2,600	\$3,900	\$5,200
Pre-existing CVD, LDL-C \geq 70 mg/dL on maximally tolerated statin dose †††	\$2,400	\$3,600	\$4,800
ALL SUBPOPULATIONS	\$2,412	\$3,615	\$4,811

- Results from the budget impact model showed that if both the FH and CVD populations are treated with the uptake pattern assumptions described in the report, 527,000 individuals in the United States would receive PCSK9 therapy in the first year. After one year of PCSK9 treatment, cost offsets due to reduced cardiovascular adverse events range from \$593 for per patient with FH to \$1,010 per patient for patients with CVD who are statin-intolerant. Including this cost offset, one-year budget impact is still estimated to be quite high: approximately \$7.2 billion for all patient populations combined.
- As uptake of new PCSK9 inhibitors is estimated to increase over the entire 5-y time horizon, we estimate that approximately 2.6 million persons would receive PCSK9 inhibitor therapy for \geq 1 years by the end of that period. Total budgetary impact over 5 years is estimated at approximately \$19 billion, \$15 billion, and \$74 billion for the FH, CVD statin-intolerant, and CVD not at LDL-C target subpopulations, respectfully. When these 5-y budget impact figures are annualized, they equal \$21.6 billion in net health care cost growth/y for the US. This annualized potential budget impact is well above the budget impact threshold of \$1.8 billion (for the two drugs combined). In order to not exceed this budget impact threshold, less than 0.5%, or 1 in 200 eligible patients, could be treated at the list price of \$14,600 per year.
- Even at a drug cost of \$2,412 per year, the cost at which the cost/QALY = \$50,000, if 50% of all eligible patients are ultimately treated over a 5-year time period the annualized budget impact is approximately \$4 billion per year. At the list price of \$14,600 used for this report, if only 25% of eligible patients receive treatment, the annualized budget impact is approximately \$19 billion, meaning that over the 5-year period a total of almost \$100 billion would have been added to health care costs in the United States.

Recommendation by EBRx: Await the evidence from randomized clinical trials to see whether clinical even reduction is achieved.

New Drugs

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	JIT'S NOTES	DUEC DATE	DUEC VOTE	IB DATE	IB VOTE
NON-SPECIALTY DRUGS									
Spiriva Aer Respinat 1.25mg	tiotropium inhal aerosol	\$378/inhaler	For asthma in patients 12 & older	Other Spiriva strengths at T2	T2, consider class a rebate opportunity (handout)	2016 02 01			
Durlaza Cap 162mg	aspirin SR 24hr	\$216/30	24 hour extended release aspirin for the prevention of stroke/acute cardiac events	aspirin covered at 100%	Exclude, code 13 (handout)	2016 02 01			
Tolak	fluorouracil Cream 4%	\$180/40gm tube	For actinic keratosis	Fluorouracil cream 5% = \$247/40gm	Cover, tier TBD. Generic 5%cream 40g is \$257.39AWP. This is \$180/40gAWP. For now. Exclude, code 13 (handout)	2016 02 01			
Kevevis tabs 50mg	dichlorophenamide 50mg tab	\$163.80/tab. Dose= 100-200mg/day	Primary hyperkalemic periodic paralysis, primary hypokalemic periodic paralysis, and related variants. Max dose= 200mg/day		Options (see handout)	2016 02 01			
Varubi tabs 90mg	rolapitant 90mg tab	\$636/2-90mg tabs	Chemotherapy induced nausea/vomiting prophylaxis. Dose=180mg PO as a single dose on day 1 of chemotherapy		Exclude. Alternate is Bionect.	2016 02 01			
Hygel Gel 2.5%	hyaluronate sodium gel 2.5%	\$45/10 gm	Protects skin ulcers, burns, or wounds from irritation		Exclude, code 13, code 4, code 7	2016 02 01			
Restora Spr Pak	Lactobacillus-fohic acid	\$28.84/28 packets	antidiarrheal (line extension)		Exclude, code 13. (handout)	2016 02 01			
Tresiba Flex	insulin degludec pen injector	\$106/3ml pen 100U/ml, \$213/3ml pen 200U/ml	long acting basal insulin - Type 1 and Type 2 diabetes		Exclude for now, code 13. Negotiate for lowest net cost.	2016 02 01			
Seebri Neohta Cap	glycopyrrolate inhal cap	\$357/1 inhaler 60 caps	Long-term, maintenance treatment o airflow obstruction in patients w/COPD		Exclude, code 13. (handout)	2016 02 01			
Udron Cap Neohaler	indacaterol-glycopyrrolate inhal caps	\$357/1 inhaler 60 caps	Dual Combination bronchodilatorfor patients w/COPD		Exclude, code 13	2016 02 01			
Belbuca	buprenorphine HCl buccal film	\$306-\$758/box of 60	Treatment of moderate-severe pain, opiate dependence/withdrawal		Exclude, code 13	2016 02 01			
Vivlodex Caps	meloxicam 5 & 10mg caps	\$23.76/cap	Treatment of osteoarthritis pain.	Generic meloxicam available in 7.5 and 15mg tabs	Exclude, code 13. Many generic alternatives. Also meloxicam 7.5&15mg.	2016 02 01			
Valtassa Powder	patronom sorbitex calcium for suspension packet	\$74.4/box of 30-25.2g	Treatment of hyperkalemia		Exclude, code 13. Kayexalate is an alternative.	2016 02 01			
Narcain Spray	naloxone HCl nasal spray	\$150/box of 2 spray bottles of 4mg/0.1ml	For opiate agonist overdose and opiate agonist induced respiratory depression		13, OI, 131d	2016 02 01			
Renovo Lidos Cream	capsaicin-lidocaine-menthol cream	\$720/60gm tube	Topical anesthetic and analgesic indicated for the relief of pain related to minor cuts, grazes, and irritation	Capsaicin 0.25% cream = \$18/45gm AWP Lidocaine 5% cream = \$43/30gm AWP	Exclude, OTC alternative. Exclude entire GPI due to low cost OTC alternatives.	2016 02 01			
Pradaxa cap 110mg	debigatran 110mg	\$6.67/cap	line extension. Anticoagulant.	Pradaxa currently T2	T2	2016 02 01			
SPECIALTY DRUGS									
Arstada	aripiprazole IM ER pre-filled syringe	\$1,265/441mg;\$1.89/8/662mg;\$2,528/882mg	Extended release injection to treat adults with schizophrenia administered by a HCP every 4-6 weeks	Abilify Maintena (monthly extended release IM)- \$1,265/441mg;\$1,898/662mg;\$2,525/882mg. Invega Sustenna, Invega Trinz - T4	Exclude, code 13. handout	2016 02 01			
Odonto caps	sonideglo phosphate cap 200mg	\$12,060/30 caps. Dose=200mg/day	Treatment of adult patients with locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or those who are not a candidate for surgery or radiation therapy. Dose = 200mg/day		Exclude, code 1. Handout	2016 02 01			
Lonsurf	trifluridine-tpiracil tabs	\$9,840/60-20mg	Treatment of colorectal cancer. Dose=160mg on days 1,2,3,4,5 and 8,9,10,11,12, repeated every 28 days		Exclude, code 1.	2016 02 01			
Onivyde	irinotecan liposome IV inj	NA	for pancreatic cancer - out of scope of PBM SERVICES		Exclude or T4	2016 02 01			

Yondelis inj	trabectedin for inj	NA	For soft tissue sarcoma - out of scope of PBM services		Exclude, code 1	2016 02 01			
Strengid inj	asfotase alfa	\$6,720/80mg - dose varies	Subcutaneous injection for treatment of hypophosphatasia		Exclude, reevaluate after 4/2016.	2016 02 01			
Genvoya	eltregra V-Cobic-entricitab-tenofovir AF tab	\$3,090/30 tabs	HIV infection		T4	2016 02 01			
Imlygic Injection	talinogene laherparepvec intraleosomal inj	\$5,280/vial - out of scope of pharmacy benefits	Malignant melanoma		Exclude, code - Issue with informative censoring	2016 02 01			
Nucala Injection	mepolizumab inj	\$3,000/100mg	Add-on maintenance treatment of patients w/severe asthma. 100mg SQ injection every 4 weeks		Exclude, or T4PA same as omalizumab	2016 02 01			
Gleostine caps 5mg	lomustine 5mg	\$125/5mg	line-extension. For treatment of Hodgkin's disease, malignant glioma		T3QL of 1/46w.	2016 02 01			
Darzalex	daratumumab IV soln	\$2,160/400mg. Dose varies. Out of scope of pharmacy benefits	multiple myeloma in patients who have received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent		Exclude, code 1	2016 02 01			
Corellis tabs	cobimetinib fumarate	\$7,273/63 20mg tabs. Dose=60mg x 21 of 28 days, repeat	Treatment of unresectable or metastatic melanoma in patients with a BRAF V600E or V600K mutation, in combination with vemurafenib		T4PA	2016 02 01			
Tagrisso	osimertinib tabs	\$15,300/30-80mg tabs. Dose=80mg PO daily	Treatment of metastatic EGFR T790M mutation positive non-small cell lung cancer, after progression on or after EGFR tyrosine kinase inhibitor therapy		Exclude, code 1	2016 02 01			
Viberzi tabs	eluxadoline	\$1,152/60-100mg tabs. Dose=200mg/day	Treatment of irritable bowel syndrome with diarrhea		Table. Not yet reviewed by EBRx.	2016 02 01			
Empliciti	elotuzumab IV solution	\$2,841/400mg vial. Out of scope of pharmacy benefits	Treatment of multiple myeloma		T4PA. See handout and criteria.	2016 02 01			
Niltlaro Caps	ixazomib	\$3,468/4mg cap - dose varies	Treatment of multiple myeloma		Exclude: FDA to work out issues with statistical discrepancies.	2016 02 01			
Adynovate inj	antihemophilic factor recom pegylated	\$2,387/unit	Antihemophilic factor		T4PA. Dk of Hemophilia A	2016 02 01			
Coagadex	coagulation Factor X human	\$9,29/unit	coagulation factor		T4PA (handout)	2016 02 01			
Ferriprox Soln	deferiprone solution	\$5,435/500ml bottle	Transfusional iron overload		Exclude, code T3. Alternatives deferroxamine, Exlade & Jademu.	2016 02 01			
Alecensa 150mg caps	alecicrpb 150mg caps	\$14,791/240-150mg caps. Dose=600mg po bid	Treatment of non-small cell lung cancer		Exclude, code 1	2016 02 01			
Bendeka inj	benzamustine IV soln	\$2,788/100mg vial. Out of scope of pharmacy benefits	Treatment of chronic lymphocytic leukemia & non-Hodgkin's lymphoma		NA for pharmacy benefit. Medical.	2016 02 01			
Kanuma inj	sebelipase alfa IV soln	\$12,000/20mg vial. Out of scope of pharmacy benefits	Treatment of lysosomal acid lipase deficiency		Exclude, code 1	2016 02 01			
Portazac inj	neclumumab IV soln	\$4,800/800mg vial. Out of scope of pharmacy benefits	Treatment of advanced squamous non-small cell lung cancer		Exclude, code 1	2016 02 01			
Uptravi tabs	selisipape tabs	\$17,400/860-1600mcg tabs	Treatment of pulmonary hypertension to delay disease progression and reduce risk of hospitalization.		Table. EBRx has not yet evaluated.	2016 02 01			

Tiotropium-Spiriva Respimat 1.25 mcg / actuation
 Andrew Mullings, Pharm.D.
 11/16/2015

Product Summary: Tiotropium Respimat 2.5 mcg/actuation is currently approved for COPD maintenance therapy. Tiotropium Respimat 1.25 mcg/actuation is currently indicated for long-term treatment of asthma in adults and adolescents 12 years or older

<u>Drug</u>	<u>Strength</u>	<u>Dose</u>	<u>Price/30 days</u>
Tiotropium Respimat—SMI (4 gm Aerosol solution)	1.25 mcg/actuation	Once daily, 2 puffs	\$378.84
Tiotropium HandiHaler—DPI	18 mcg/capsule	Once daily, 1 capsule	\$378.84
Acclidinium	400 mcg/actuation	1 inhalation BID	\$337.68
Salmeterol	50 mcg/actuation	1 BID	\$350

Evidence

Kerstjens, HAM, Engel, M, Dahl, R et al. Tiotropium in asthma poorly controlled with standard combination therapy. N Engl J Med. 2012; 367: 1198–1207

Design: Two replicate, randomized, DB, parallel group design controlled trials in patients (n=912) with asthma receiving inhaled glucocorticoids and LABAs randomized to tiotropium (5 mcg/day) or placebo, both delivered by a soft-mist inhaler for 48 weeks. All patients were symptomatic, had a post bronchodilator FEV1 of <80% predicted (mean of 62%), and had a history of at least one severe exacerbation in the previous year. Those diagnosed with COPD or who had recently smoked were excluded.

Results: At 24 weeks, the mean (±SE) change in the peak FEV1 from baseline was greater with tiotropium than with placebo in the two trials: a difference of 86±34 ml in trial 1 (P=0.01) and 154±32 ml in trial 2 (P<0.001). The addition of tiotropium increased the time to the first severe exacerbation, (deterioration needing initiation or doubling of oral corticosteroids for at least 3 days), (282 days vs. 226 days), with an overall reduction of 21% in the risk of a severe exacerbation (hazard ratio, 0.79; P=0.03). Drug related adverse events were 5.7% in the tiotropium group vs. 4.6% in the placebo group.

Kerstjens, HAM, Casale T, Bleecker E et al. Tiotropium or salmeterol as add-on therapy to inhaled corticosteroids for patients with moderate symptomatic asthma: two replicate, double-blind, placebo-controlled, parallel-group, active-comparator, randomised trials Lancet Resp Med. 2015; 367-376

Design: Two replicate, randomized, DB, parallel group, active-comparator and placebo controlled trials in patients (n=2103) with asthma receiving medium-dose inhaled glucocorticoids randomized to tiotropium (2.5 or 5 mcg/day), salmeterol 50 mcg BID, or placebo.

Results: Peak and trough FEV1 responses were significantly greater with tiotropium and salmeterol than with placebo and were similar in both studies. Time to first exacerbation was unable to be assessed.

Paggiaro P, Halpin D, Buhl R, et al. The Effect of Tiotropium in Symptomatic Asthma Despite Low- to Medium-Dose Inhaled Corticosteroids: A Randomized Controlled Trial. J Allergy Clin Immunol Pract. 2015 Nov 7. pii: S2213-2198

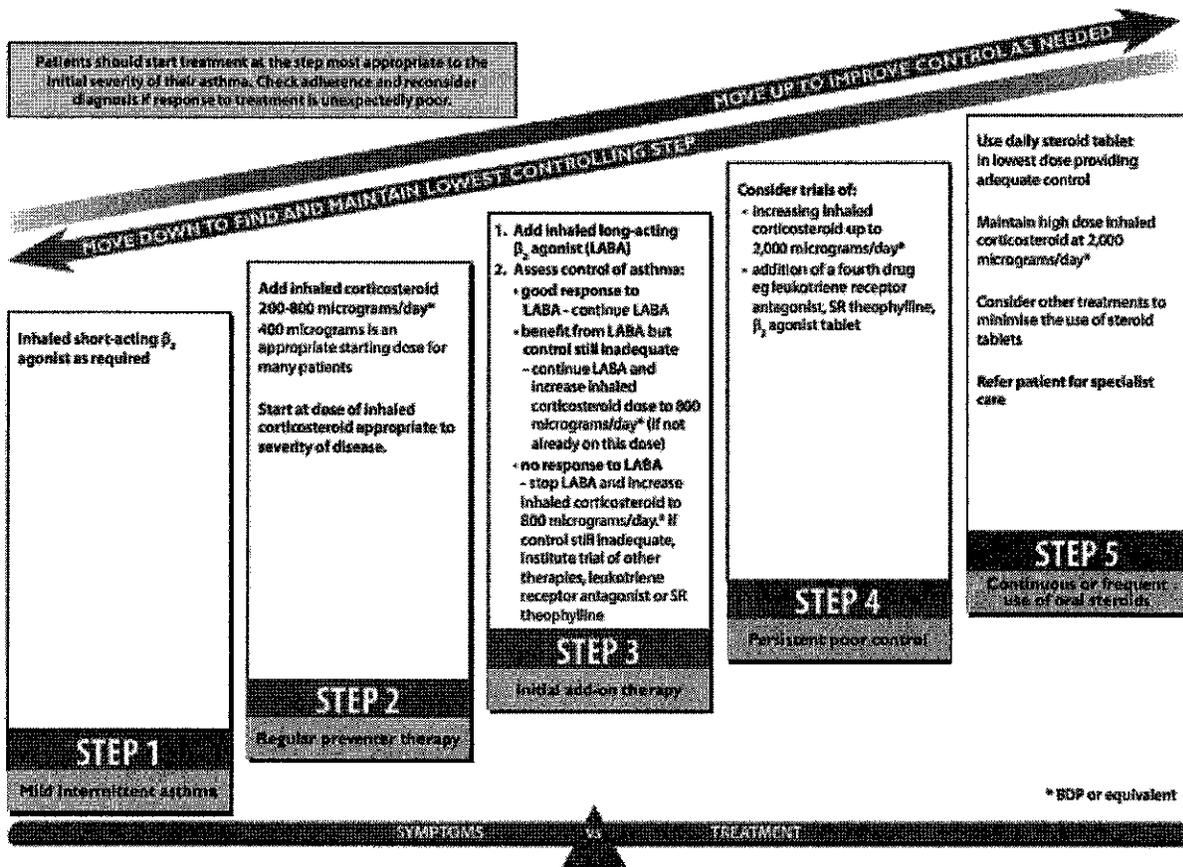
Design: A DB, placebo controlled trial in patients (n=464) with symptomatic asthma receiving medium-dose ICS (200-400 mcg budesonide or equivalent) randomized to tiotropium (2.5 mcg or 5

mcg/day) or placebo. Patient characteristics were 61% female; mean age 43 years; mean baseline FEV₁ 78% of predicted normal).

Results: Both doses of tiotropium respimat superior to placebo (adjusted mean difference from placebo: 5 mcg, 128 mL; 2.5 mcg, 159 mL; both P < .001). Adverse events were comparable.

Recommendation: Continue to cover tier 2, monitor prices increases and consider opportunities for rebates. Consider prior authorization of the 1.25 mcg/actuation strength due requiring both tobacco abstinence and concomitant ICS use.

British Thoracic Society Guidelines 2014



Aspirin (Durlaza) 162.5mg capsules

Brooklyn Pruett, P4

November 2015

Labeled Uses: Nonsteroidal anti-inflammatory drug (NSAIDs) indicated to reduce the risk of death and myocardial infarction in patients with chronic coronary artery disease, such as patients with a history of myocardial infarction or unstable angina pectoris or with chronic stable angina and to reduce the risk of death and recurrent stroke in patients who have had an ischemia stroke or transient ischemic attack.

Comparator Drugs:

	Dose for Antiplatelet Therapy	Cost
Durlaza ® (aspirin)	162.5mg	\$7.20/tablet x 30 = \$216/month
Aspirin	81mg	\$0.07/tablet x 30 = \$2.10/month
Clopidogrel Bisulfate	75mg	\$6.96/tablet x 30 = \$208.80/month (AWP) \$0.20-\$0.50/tablet x 30 = \$6-\$15/month (WAC)

Dosage and Administration: po 162.5mg capsule once daily

Mechanism of Action: Irreversibly inhibits cyclooxygenase-1 and 2 enzymes, via acetylation, which results in decreased formation of prostaglandin precursors resulting in inhibition of platelet aggregation for their lifespan of about 7-10 days.

Contraindications: Pts with a hypersensitivity to NSAIDs and pts who have asthma, rhinitis, and nasal polyps.

Adverse Reactions: Agitation, cerebral edema, coma, confusion, dizziness, headache, lethargy, seizure, hyperkalemia, metabolic acidosis, respiratory alkalosis, dyspepsia, hepatic enzyme elevation, hepatitis, Reye's Syndrome, interstitial nephritis, papillary necrosis, proteinuria, and renal insufficiency and failure.

Interactions: Alcohol, renin-angiotensin system inhibitors, anticoagulants, antiplatelets, phenytoin, valproic acid, methotrexate, and NSAIDs.

Evidence: No trials have been conducted to determine clinical safety or efficacy of Durlaza.

Pharmacodynamics package insert: The dose-response relationship for Durlaza and immediate release (IR) aspirin towards COX-1 inhibition was characterized by examining the inhibition of serum TXB₂ and urine 11-dehydro-TXB₂ at 24h following a single dose. Doses over the range of 20mg to 325mg for Durlaza and 5mg to 81mg for IR aspirin respectively were studied. Half-maximal inhibition of serum TXB₂ and urine 11-dehydro-TXB₂ occurred with doses of Durlaza about 2-fold the dose of IR aspirin. Based on this relationship, the pharmacodynamic effect of Durlaza 162.5mg is similar to that attained with IR aspirin 81mg. The mean inhibition of TXB₂ following Durlaza (82%) is lower when compared to IR aspirin 81mg (93%) following the first dose. However, upon repeat administration, near maximal inhibition of serum TXB₂ is achieved, similar to what is achieved following repeated daily doses of IR aspirin.

Pharmacokinetics package insert: Following administration of Durlaza, the time to reach peak plasma concentration of aspirin is slightly longer compared to IR aspirin. Median T_{max} for Durlaza is about 2h when compared to 1h following IR aspirin 81mg. The mean C_{max} for Durlaza is approximately 35% of that following IR aspirin 81mg. Aspirin is rapidly hydrolyzed in the plasma to salicylic acid such that plasma levels of aspirin following Durlaza administration are essentially undetectable 4-8h after dosing. In contrast to IR aspirin, measurable levels of salicylic acid at 24 hours following a single dose of Durlaza were observed.

Henry, et al. (abstract only available), conducted a study that assessed the 24 hour biological efficacy of daily low-dose aspirin in coronary artery disease (CAD) pts. The study consisted of 150 stable CAD pts who received once daily aspirin. Two hrs after aspirin ingestion 4.7% of pts had significant platelet aggregation and 24 hrs after ingestion 24.7% of pts had significant platelet aggregation (p<0.0001). 47 pts were included in additional test that were conducted at 6, 12, 16, and 20 hrs after aspirin administration. The results showed that significant platelet aggregation appeared with time after aspirin ingestion 2h- 4% of pts, 6h- 4%, 12h- 11%, 16h- 16%, 20h- 19% and 24h- 28%. The study concluded that once daily low dose aspirin does not provide stable 24 hr antiplatelet protection.

Student Recommendation: Although Durlaza exhibited 24 hr antiplatelet inhibition, there is no evidence to demonstrate the number of reduced cardiac events. Until clinical trials are performed, I do not recommend including Durlaza in formulary.

Outcome of EBRx Committee: Exclude, code 13.

References:

Henry, P, A. Vermillet, B. Boval, C. Guyetand, T. Petroni, J. Dillinger, G. Sideris, C. Bal Dit Sollier, & L. Drouet. "24-hr Time-dependent ASA Efficacy in Pts w/ Stable CAD" *Thromb Haemost Thrombosis & Haemostasis* 105.2 (2010):336-44.
Durlaza ® [package insert]. North Haven, CT: New Haven Pharmaceuticals Inc; 2015.

Dichlorphenamide tab 50 mg (Keveyis)

Andrew Mullings, Pharm.D.

11/16/2015

Background: Periodic paralyses is a group of muscle disorders characterized by episodic muscle weakness at irregular intervals. These conditions are generally hereditary, are associated with alteration in serum potassium level, and sometimes coexists with myotonia.

Product Summary: Dichlorphenamide is the first and only prescription medication approved for the treatment of primary hypokalemic and hypokalemic periodic paralysis and has been shown to reduce the number of attacks of muscle weakness in people with these conditions.

Dichlorphenamide tab 50 mg	50mg BID initially with a maximum of 200mg/day	\$9828
Acetazolamide	250mg BID	\$197.70

Evidence:

Study 1

Design: 9-week, double blind, placebo-controlled multi-center study evaluating dichlorphenamide tab 50 mg vs placebo. Study 1 consisted of two substudies: a substudy in patients with hypokalemic periodic paralysis (n=44), and a substudy in patients with hyperkalemic periodic paralysis (n=21). The primary efficacy endpoint in both substudies was the average number of self-reported attacks of muscle weakness per week over the final 8 weeks of the trial.

Results: In the hypokalemic group, patients treated with dichlorphenamide had 2.2 fewer attacks per week than treated with placebo. In the hyperkalemic group, the patients treated with dichlorphenamide tab 50 mg had 2.9 fewer attacks per week compared to placebo.

Study 2

Design: 35-week, double blind, placebo-controlled, multi-center, two-period crossover study evaluating dichlorphenamide tab 50 mg vs placebo. Study 2 also consisted of two substudies: a substudy in patients with hypokalemic periodic paralysis (n=42), and a substudy in patients with hyperkalemic periodic paralysis (n=31), including patients with Paramyotonia Congenita. a. The primary endpoint in the hypokalemic periodic paralysis substudy was the incidence of acute intolerable worsening (based on attack frequency or severity) necessitating withdrawal. The primary endpoint in the hyperkalemic periodic paralysis substudy was the average number of self-reported attacks of muscle weakness per week.

Results: In the hypokalemic periodic paralysis substudy, mean age of patients was 38 years and 79% of patients were male. Acute intolerable worsening was observed in 2 patients on dichlorphenamide vs. 11 patients on placebo (p=0.02). In the hyperkalemic periodic paralysis substudy, mean age of patients was 37 years and 79% of patients were male. Patients treated had 2.3 fewer attacks per week on dichlorphenamide than on placebo (p=0.006).

Cochrane Review

“The largest included study that met our inclusion criteria suggested that DCP was effective in the prevention of episodic weakness in both hypokalemic and hyperkalemic periodic paralyses. The other two studies provide some evidence that either acetazolamide or pinacidil may improve muscle strength. However we still lack sufficient evidence to provide full guidelines for the treatment of people with periodic paralysis.”

Recommendation: Exclude

Rolapitant Hydrochloride (Varubi)
90mg capsules

Brooklyn Pruett, P4, addendum Jill Johnson, Pharm.D, & Andrew Mullings, Pharm.D.
November 2015, rev 12/2015, rev 1/2016

Labeled Uses: Prevention of delayed nausea and vomiting associated with initial and repeat courses of emetogenic cancer chemotherapy when used in combination with other antiemetic agents.

Comparator Drugs:

	Dose for Nausea/ Vomiting Prevention	Regimen	Cost for Treatment	Current coverage
Varubi® (rolapitant)	180mg	single oral dose	\$318/tablet x 2 = \$636	
Emend® (aprepitant)	Day 1: 125mg Day2/3: 80mg	three day oral dose	\$647.52	PA'd
Emend ® (fosaprepitant)	150mg	single intravenous infusion	\$308.35	NA Medical
Akynzeo ® (netupitant & palonosetron)	300-0.5mg	single oral dose	\$599.76	Excluded, code 13

*dosing for highly emetogenic chemotherapy

Dosage and Administration: 180mg rolapitant, administered approximately 1-2 h before the start of CTX, in combination with dexamethasone and a 5-HT₃ Receptor Antagonist

Mechanism of Action: Selectively and competitively inhibits the substance P/Neurokinin 1 (NK₁) receptor.

Contraindications/Warnings: Contraindicated in patients receiving thioridazine, a CYP2D6 substrate. Recommended to avoid use in patients receiving CYP2D6 substrate with a narrow therapeutic index.

Adverse Reactions: Neutropenia, hiccups, abdominal pain, decreased appetite, dizziness, dyspepsia, urinary tract infection, stomatitis, and anemia

Interactions:

- Moderate CYP2D6 inhibitor- inhibition last at least 7 days and may last longer
- Breast-Cancer-Resistance Protein (BCRP) inhibitor
- P-glycoprotein inhibitor
- Strong CYP3A4 Inducers, there is a significant reduction in plasma concentrations of rolapitant. Avoid use of Varubi in patients who require chronic administration of such drugs (e.g. rifampin)
 - Rolapitant is **NOT** an inhibitor or inducer of CYP3A4. Therefore, no dosage adjustment for dexamethasone (CYP3A4 substrate)

Evidence for Moderately Emetogenic Chemotherapy:

Schwartzberg, Lee S., Manuel R. Modiano, et al. "Safety and Efficacy of Rolapitant for Prevention of Chemotherapy-induced Nausea and Vomiting after Administration of Moderately Emetogenic Chemotherapy or Anthracycline and Cyclophosphamide Regimens in Patients with Cancer: A Randomised, Active-controlled, Double-blind, Phase 3 Trial." *The Lancet Oncology* 16.9 (2015): 1071-078.

Design: A global, R, DB, active-controlled, phase 3 study at 170 cancer centers in 23 countries. Inclusion criteria included cancer patients ≥18y, pts who had not previously received moderately or highly emetogenic chemotherapy, had a Karnofsky performance score of ≥60 (100: no evidence of disease, 60: require occasional assistance, 30: severely disabled, 0: dead), and a predicted life expectancy of ≥4 m. 1369 pts were randomized to either oral rolapitant (one 180mg dose) or placebo 1-2 hrs before administration of moderately (anthracycline plus cyclophosphamide, carboplatin, ifosfamide, irinotecan, & IV cytarabine) emetogenic chemotherapy. Pts also received granisetron (2mg po) & dexamethasone (20mg po) on day 1 & granisetron (2mg po) on days 2 & 3.

Results: The 1` endpoint was the proportion of pts who had no emesis or use of rescue medication in the delayed phase (>24- 120 hr after initiation of chemotherapy). Pt recorded events of vomiting and use of rescue medication were the primary assessment of efficacy. The 2` endpoint included pts with no emesis or use of

rescue medication in the acute phase (0-24 hr) and overall (0-120 hr) phase. There was a statistically significant difference in complete response to rolapitant in the **delayed** phase (**71% rolapitant vs 62% placebo**; $p=0.0002$). There **was not** a statistically significant difference in the **acute** phase. There was a significant difference in complete response to rolapitant in the overall phase (**69% rolapitant vs 58%**; $p<0.0001$). Adverse effects were similar for both treatment groups. Most common were constipation, fatigue, dizziness, & headache. **Summary:** Pts who received a combination of one 180mg oral dose of rolapitant administered on day 1 of chemotherapy, granisetron, and dexamethasone experienced less chemotherapy-induced nausea and vomiting associated with the administration of moderately emetogenic chemotherapy. Data confirmed that rolapitant's protective effect began in the acute phase, was significant in the delayed phase, and continued to be significant in protection throughout all phases. Rolapitant was well tolerated and adverse events were similar to placebo controlled pts.

Evidence for Highly Emetogenic Chemotherapy:

Rapoport, Bernardo L., Martin R. Chasen, et al. "Safety and Efficacy of Rolapitant for Prevention of Chemotherapy-induced Nausea and Vomiting after Administration of Cisplatin-based Highly Emetogenic Chemotherapy in Patients with Cancer: Two Randomised, Active-controlled, Double-blind, Phase 3 Trials." *The Lancet Oncology* 16.9 (2015): 1079-089.

Design: A global, R, DB, active-controlled, phase 3 trial at 155 cancer centers. Inclusion criteria included cancer pts ≥ 18 y, pts who had not previously been treated with cisplatin, had a Karnofsky performance score of 60 or higher, and a predicted life expectancy of 4 months or longer. Pts were randomized to receive either oral rolapitant (one 180mg dose) or a placebo 1-2 hrs before administration of moderately emetogenic chemotherapy. Patients also received granisetron (10ug/kg IV) and dexamethasone (20mg po) on day 1 and dexamethasone (8mg po) twice daily on days 2-4.

Results: The 1' endpoint was the percent of pts who experienced no emesis or use of rescue medication in the delayed phase (>24h-120h after initiation of chemotherapy). Pt recorded events of vomiting and use of rescue medication were the primary assessment of efficacy. The 2' endpoint included pts with no emesis or use of rescue medication in the acute phase (0-24 hrs) and overall (0-120 hrs) phase. Two different arms of the study were conducted (HEC-1 and HEC-2). There was a **statistically significant** difference in the number of pts who experienced nausea and vomiting in the **delayed phase** (HEC-1 **73% rolapitant vs 58% placebo**; $p=0.0006$; HEC-2 **70% rolapitant vs 62% placebo**; $p=0.0426$). When observing data for the secondary endpoint there was a statistically significant difference in one arm and not a statistically significant difference the second arm. When data was pooled together it was statistically significant for a complete response in the acute phase (**84% rolapitant vs 77% placebo**; $p=0.0045$) and in the overall phase (**69% rolapitant vs 59% placebo**; $p=0.0005$).

Summary: Pts receiving cisplatin-based highly emetogenic chemotherapy that also received an oral dose of 180mg rolapitant with granisetron and dexamethasone experienced less chemotherapy-induced nausea and vomiting. There was statistically significant response to rolapitant in both the acute, delayed, and overall phases. Rolapitant was well tolerated with adverse events similar to those reported in the placebo control groups.

Student Recommendations: Rolapitant displayed statistically and clinically significant results in the reduction of chemotherapy induced nausea and vomiting. Rolapitant is a highly selective, long acting Substance P/NK₁ Antagonist that does not induce nor inhibit CYP3A4 and offers a 5 day protection in a single oral dose. Include in formulary with PA criteria. PA criteria should be: **1.** Receiving cisplatin or a moderately emetogenic CTX (anthracycline plus cyclophosphamide, carboplatin, ifosfamide, irinotecan, and IV cytarabine), **2.** granisetron (or other 5HT₃ antagonist), and **3.** dexamethasone.

Outcome of EBRx Committee: Table and discuss with Emend and Akynzeo.

Additional References:

1. Varubi ® [package insert], accessed 11/11/15.

ADDENDUM: Emend has low utilization and will be generic 2016. There are no meta-analyses published for a class review to help determine each agent's place in therapy. Each of the drugs is effective.

OTHER ISSUES:

There was no updated sheet. The discussion points made at the meeting were as follows:

- AWP price of Varubi and Akyzeo may appear cheaper than Emend, although price of these is likely to change
- No head to head data exists. Indirect comparisons may be made but must be taken with a large grain of salt 2'2 differences in patient populations and steroids/5-HT3 antagonists. Hopefully awaiting a meta-analysis in the future
- Large body of evidence for Emend in multiple types of highly emetogenic chemotherapy regimens
- Generic emend is expected this end of 2016
- The potential cost savings of requiring patients to use Varubi or Akynzeo over Emend would create issues in care
- Potential for temporary inclusion in formulary although would open up the door for utilization and create issues if excluded later

Currently Emend has very low utilization in EBD

Recommendation to DUEC 2/1/16: 1. Exclude, code 13. OR 2. Cover all at T3 or T4.

Insulin Degludec Injection- Tresiba FlexTouch®

Micah Sukany, P4

11/17/2015

FDA Indication:

Insulin degludec (IDeg) is a long-acting human insulin analog indicated to improve glycemic control in adults, elderly, and pediatric patients with diabetes mellitus.³

Description:

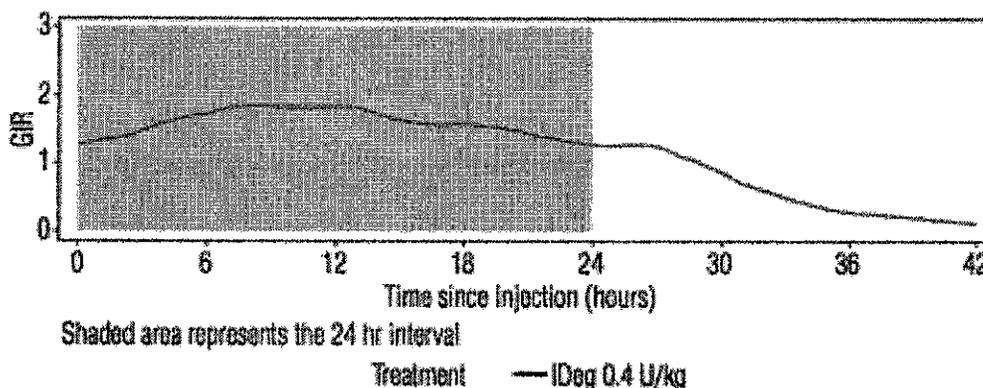
IDeg is a long-acting basal human insulin analog for subcutaneous injection. The molecular structure of IDeg is similar to that of the human insulin amino acid sequence except for a modified beta chain, i.e. the deletion of threonine at position 30 and addition of a 16-carbon fatty diacid to lysine at position 29.¹

Brand	How Supplied	AWP	Price/100Units
Lantus* Subcutaneous	100 units/mL (10 mL)	\$298.21	\$29.82
Lantus* SoloStar Subcutaneous	100 units/mL (3 mL)	\$89.46	\$29.82
Levemir (insulin detemir) Subcutaneous	100 units/mL (10 mL)	\$298.21	\$29.82
Levemir FlexTouch Subcutaneous	100 units/mL (3 mL)	\$89.46	\$29.82
Toujeo SoloStar Subcutaneous	300 units/mL (1.5 mL)	\$134.19	\$29.82
Tresiba FlexTouch Subcutaneous	100 units/mL (3mL)	\$106.52	\$35.51
Tresiba FlexTouch Subcutaneous	200 units/mL (3mL)	\$213.05	\$35.51

*Patent ends February 2016

Mechanism of Action:

The ultra-long action profile of this insulin is mainly attributable to formation of soluble multihexamers at the injection site, from which monomers gradually separate and are absorbed into the circulation, resulting in a flat and stable pharmacokinetic profile at steady state. The addition of the 16-carbon diacid to lysine at position 29 increases binding affinity to albumin further stabilizing pharmacokinetic profile.²



The mean maximum glucose lowering effect (GIRmax) of a 0.4 U/kg dose of IDeg was 2.0 mg/kg/min, which was observed at a median of 12 hours post-dose. The glucose lowering effect of IDeg lasted at least 42 hours after the last of 8 once-daily injections³

Adverse Drug Events: Hypoglycemia, allergic reactions, injection site reactions, lipodystrophy, pruritus, rash, peripheral edema, and weight gain.³

Drug Interactions:

Drugs that may increase risk of hypoglycemia.³

Drugs that may blunt signs and symptoms of hypoglycemia.³

Additional References

1. Wakil, A, et. al. "Efficacy and Safety of ultra-long-acting IDeg." *Therapeutic Advances in Endocrinology and Metabolism* (2012) 3, 55-59.
2. Jonassen, I, et. al "IDeg is a new generation ultra-long acting basal insulin with a unique mechanism of protraction based on multi-hexamer formation." *Diabetes* (2010) 59 (suppl 1): A11.
3. IDeg PI.

Meta-analysis: IDeg resulted in lower rates of nocturnal hypoglycemia and fasting plasma glucose than IGLar in patients with T1DM.

Data were included from seven phase 3a, randomized, open-label, treat-to-target clinical trials in which once-daily IDeg was compared with once-daily IGLar. Two trials included a total of 957 patients with T1DM and five trials included a total of 3360 patients with T2DM; all trials were 26 or 52 weeks in duration. Confirmed hypoglycemia was defined as plasma glucose <3.1 mmol/L or severe episodes requiring assistance, and nocturnal hypoglycemia occurred between 00:01 and 05:59. In all trials, the mean end-of-trial FPG was lower for IDeg than IGLar, reaching statistical significance in three trials. Similarly, IDeg was associated with a lower rate of nocturnal confirmed hypoglycemia vs. IGLar, which was statistically significant in three trials, regardless of type of diabetes or background therapy.

D. Russell-Jones, et. al. "Insulin degludec results in lower rates of nocturnal hypoglycemia and fasting plasma glucose vs. insulin glargline: A meta-analysis of seven clinical trials." *Nutrition, Metabolism & Cardiovascular Diseases* (2015) 25, 898-905.

Clinical Trial: IDeg dose once daily, three times weekly and IGLar resulted in similar mean HbA1C levels after 16-week trial in patients with T2DM.

In this 16-week, randomized, open-label, parallel-group phase 2 trial, participants aged 18–75 years with type 2 diabetes and glycosylated hemoglobin (HbA_{1c}) of 7.0–11.0% were enrolled and treated at 28 clinical sites in 1CCanada, India, South Africa, and the USA. Participants were randomly allocated in a 1:1:1:1 ratio by computer-generated block randomization to receive IDeg either once a day or three times a week or IGLar once a day, all in combination with metformin. The primary outcome was HbA_{1c} after 16 weeks of treatment. Analyses were done by intention to treat. Of 367 patients screened, 245 were eligible for inclusion. 62 participants were randomly allocated to receive IDeg three times a week (starting dose 20 U per injection [1 U=9 nmol]), 60 to receive IDeg once a day (starting dose 10 U [1 U=6 nmol]; group A), 61 to receive IDeg once a day (starting dose 10 U [1 U=9 nmol]; group B), and 62 to receive IGLar (starting dose 10 U [1 U=6 nmol]) once a day. At study end, mean HbA_{1c} levels were much the same across treatment groups, at 7.3% (SD 1.1), 7.4% (1.0), 7.5% (1.1), and 7.2% (0.9), respectively. Estimated mean HbA_{1c} treatment differences from IDeg by comparison with IGLar were 0.08% (95% CI –0.23 to 0.40) for the three dose per week schedule, 0.17% (–0.15 to 0.48) for group A, and 0.28% (–0.04 to 0.59) for group B. Few participants had hypoglycemia and the number of adverse events was much the same across groups with no apparent treatment-specific pattern.

Zinman, Bernard, et. al. "IDeg, an ultra-long-acting basal insulin, once a day or three times a week versus IGLar once a day in patients with type 2 diabetes: a 16-week, randomised, open-label, phase 2 trial." *Lancet* (2011) 377, 924-31.

Clinical Trial: The BEGIN program found similar rates of HbA1c reduction between IDeg and IGLar arms in insulin-naïve patients and non-insulin-naïve patients with T2DM. Additionally, reductions in prebreakfast glycemia was noted in all groups studied.

The BEGIN program studies were multicenter, controlled, open-label, randomized, and conducted in a "treat to target" design. The BEGIN Once Long T2 study¹³ investigated insulin-naïve patients who had previously been treated only with oral antidiabetic agents. This 1-year study was extended giving 2 years of follow-up, and showed a similar HbA_{1c} reduction in the IDeg arm (1.06%) and IGLa arm (1.19%), with an estimated treatment difference

(ETD) of 95% CI (–0.04, 0.22) between the two groups after 52 weeks of treatment. The fasting prebreakfast glycemia reduction was greater in the IDeg arm than in the IGLa arm (ETD IGLa-IDeg 0.43 mmol/L [0.74, 0.13], *P*0.005). The BEGIN Basal-Bolus T2 study included T2DM patients who had been treated with insulin for more than 3 months prior to enrollment. There was a similar statistically significant HbA_{1c} reduction in the IDeg group (1.10%) and the IGLa group (1.18%) with an ETD of 0.08% (0.05, 0.21). However, there was a greater (albeit not statistically significant) reduction of fasting plasma glucose (ETD IGLa – IDeg, 0.29 [0.65, 0.06], *P*0.1075) in the IDeg group.

4. Thuillier, Phillipe, et. a. "Long-term safety and efficacy of IDeg in the management of type 2 diabetes" *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* (2015) 8,483-93.

Future Trials: In 2018, the DEVOTE trial is expected to report findings on increased cardiovascular risk among patient with T2DM using IDeg.

The DEVOTE (NCT 01959529) trial is in progress, and is aiming to enroll 7,500 T2DM subjects at high cardiovascular risk (age 50 years with a history of cardiovascular disease or diabetic nephropathy or age 60 years with cardiovascular risk factors) in order to evaluate such a hypothesis.

4. Thuillier, Phillipe, et. a. "Long-term safety and efficacy of IDeg in the management of type 2 diabetes" *Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy* (2015) 8,483-93.

Summary:

- **As effective in the reduction of HbA1C as IGLa or IDet.**
- **Lower rates of nocturnal hypoglycemia and fasting plasma glucose than IGLa or IDet**
- **Potential for three times weekly dosing.**
- **Uncertainty of safety in patients with increased cardiovascular risk.**

Recommendation: Exclude from coverage until further evidence establishes its efficacy and safety.

Glycopyrrolate inhalation powder (Seebri Neohaler)

Jill Johnson, Pharm.D.

12/1/15

FDA indication: for the long-term, maintenance treatment of airflow obstruction in COPD patients.

Dose: 15.6mcg BID Capsules for inhalation

How supplied: Box of 60 (10 blister cards w/ 6 orange transparent capsules each) + neohaler device

Generic (Brand)	Dose (DPI)	Frequency of Administration	AWP for 30 ds (as of 12/1/15)	UA utilizers 2015 Q3	Current coverage	Proposal
Glycopyrrolate (Seebri Neohaler)	1-15.6mcg cap inhalation	BID	\$357		Not covered	Negotiate for the lowest net cost. If not Spiriva, good communication with members.
Umeclidinium (Incruse Ellipta)	One 62.5 mcg inhalation	QD	\$324.04	0	T3	
Acidinium (Tudorza Pressair)	One 400 mcg inhalation	BID	\$338	2	T2	
Tiotropium (Spiriva Handihaler)	2 inh QD one 18 mcg capsule	QD	\$378	40	T2?	
Tiotropium (Spiriva Respimat)	2 inh QD (5mcg total dose)	QD	\$378	0	?	

Network metaanalysis:

Maintenance treatment w/ acclidinium 400 ug BID is expected to produce similar improvements in lung function, HRQOL, and dyspnea compared to tiotropium 5 QD, tio 18QD, and glycopyrronium 50ug QD.

Karabis, et al. International Journal of COPD. 2013;8:405-423.

Indacaterol-Glycopyrrolate Inhalation capsules 27.5-15.6mcg (Utibron Cap Neohaler)
 Jill Johnson, Pharm.D., BCPS
 12/28/15

FDA indication: maintenance of COPD.
 Dose: Contents of 1 capsule (indacaterol 27.5mcg/glycopyrronium 15.6mcg) twice daily
 How supplied: indacaterol/glycopyrrolate, (27.5mcg, 15.6mcg) inhalation powder in a capsule; box of 60 (10 blister cards w/ 6 yellow capsules each)

	Drug	Strength	How Supplied	Usual Dose	Cost/Unit	Cost/30 Days
	Combined LABA/LAMA					
Utibron Neohaler	indacaterol /glycopyrrolate	27.5/15.6mcg	60-capsule device	1 inhalation BID	AWP = \$5.96/blister	\$358
	Utibron Neohaler (indacaterol maleate/glycopyrrolate)					
	Stiolto RespiNat (tiotropium bromide/olodaterol)	2.5/2.5mcg	4g mist inhaler(60 inhalations)	2 inhalations daily	AWP=\$94.71/gram	\$379
	Anoro Ellipta (umeclidinium/vilanterol)	62.5/25mcg	60-bliстер device	1 inhalation daily	AWP = \$5.96/blister	\$358
	LAMA					
	Spiriva Respimat (tiotropium)	2.5mcg	4 gram canister(60 inhalations)	2 inhalations daily	AWP = \$94.71/gm	\$379
	Seebri Neohaler (glycopyrrolate)	15.6mcg	60-capsule device	1 inhalation BID	AWP = \$5.96/blister	\$358
	Incruse Ellipta (umeclidinium)	62.5mcg	30-bliстер device	1 inhalation daily	AWP = \$9.53/blister	\$286
	Tudorza Pressair (aclidinium bromide)	400mcg	Canister containing 60 metered doses	1 inhalation BID	AWP = \$338/canister	\$338
	LABA					
	Serevent Diskus (salmeterol)	50mcg	60-bliстер device	1 inhalation BID	AWP = \$5.61/blister	\$337
	Foradil Aerolizer (formoterol fumarate)	12mcg	60-capsule device	1 inhalation BID	AWP = \$4.85/capsule	\$292
	Arcapta Neohaler (indacaterol)	75mcg	30-bliстер device	1 inhalation daily	AWP = \$8.06/blister	\$242
	Striverdi Respimat (olodaterol)	2.5mcg	4 gram canister (60 metered doses)	2 inhalations daily	AWP = \$46.71/gm	\$187
Specific pricing detail is not shown for the Spiriva Handihaler; however, the 30 day cost is the same as the RespiNat.						

Evidence:

- Kew KM, Dias S, Cates CJ. Long-acting inhaled therapy (beta-agonists, anticholinergics and steroids) for COPD: a network meta-analysis. *Cochrane Database of Systematic Reviews* 2014, Issue 3. Art. No.: CD010844. DOI: 10.1002/14651858.CD010844.pub2.
Conclusion Quality of life and lung function were improved most on combination inhalers (LABA and ICS) and least on ICS alone at 6 and 12 months. Overall LAMA and LABA inhalers had similar effects, particularly at 12 months. The network has demonstrated the benefit of ICS when added to LABA for these outcomes in participants who largely had an FEV1 that was less than 50% predicted, but the additional expense of combination inhalers and any potential for increased adverse events (which has been shown by other reviews) require consideration. Our findings are in keeping with current National Institute for Health and Care Excellence (NICE) guidelines.
- Buhl R, Gessner C, Schuermann W, et al. *Thorax* 2015;70:311-319.
Indaca 26w MC< R, B, triple dummy, noninferiority design randomized to either indacaterol 110ug+glycopyrronium 50ug qd via Breezhaler device or TIO 18ug QD via HandiHaler+FOR 12ug BID via Aerolizer. Inda/Glyco was NI to TIO/FORM, **however, the inda/glycol dose was 4X higher than what is marketed.**

Proposal:

1. Inda/Glyc is non-inferior to TIO+FOR in improving HRQL. Should negotiate for lowest net cost among combination LABA/LAMAs. Consider step therapy requiring double bronchodilator use prior to ICS in COPD.

OUTCOME of committee discussion: Exclude, code 13.

Buprenorphine HCL Film (Belbuca)

Andrew Mullings, PharmD

1/27/2016

Product Summary: This is a novel buprenorphine delivery system, dosed Q12hrs, indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate

Agent	Current AWP Price for 30 day Supply
Buprenorphine HCL Film 75mcg	\$306.72
Buprenorphine HCL Film 150mcg	\$306.72
Buprenorphine HCL Film 300mcg	\$481.68
Buprenorphine HCL Film 450mcg	\$654.48
Buprenorphine HCL Film 600mcg	\$698.40
Buprenorphine HCL Film 750mcg	\$734.40
Buprenorphine HCL Film 900mcg	\$756.00
Morphine ER 60mg	\$91.98*
*MAC price	

12-Week Study in Opioid-Naïve Patients with Chronic Low Back Pain

An open labeled, dose titration period began for 12 weeks in **749 patients with chronic low back pain 61% of the patients who entered the open-label dose titration period were able to titrate to a tolerable and effective dose and were randomized into a 12-week, double-blind treatment period.** Of the patients who were randomized, the mean pain (SD) scores on a 0 to 10 numeric rating scale (NRS) were 7.1 (1.06) and 7.2 (1.05) prior to open-label titration and 2.8 (1.01) and 2.8 (1.12) at the beginning of the double-blind period for buprenorphine and placebo, respectively. **The change from double-blind baseline to week 12 in mean pain (SD) NRS score was statistically significant favoring patients treated with buprenorphine, compared with patients treated with placebo.**

12-Week Study in Opioid-Experienced Patients with Chronic Low Back Pain

810 patients on chronic opioid therapy (TDD 30-160 mg in MSE for at least 4 weeks) entered an open-label, dose-titration period with buprenorphine for up to 8 weeks, following taper of their prior opioids to 30 mg oral MSE daily. Initiation dose was dependent on baseline MSE. After a dose was reached with adequate analgesia and tolerable adverse effects for a period of 2 weeks, patients were randomized to continue their titrated dose of buprenorphine or matching placebo.

63% of the patients who entered the open-label titration period were able to titrate to a tolerable and effective dose and were randomized into a 12-week double-blind treatment phase. 83% of patients treated with buprenorphine and 57% of patients treated with placebo buccal film completed the 12-week treatment period. **The change from baseline to week 12 in mean pain (SD) NRS score was statistically significant in favor of patients treated with buprenorphine compared with patients treated with placebo.**

Recommendation: Exclude due to lack of comparative efficacy

EBRx Vote: Exclude

Belbuca Package Insert. Endo Pharmaceuticals. 2015.

Patiromer (Veltassa)
Brett Bailey, Pharm.D. Candidate

FDA-approved indication: Treatment of hyperkalemia (Note: this is not for emergent hyperkalemia)

MOA: a non-absorbed, cation exchange polymer that contains a calcium-sorbitol counter ion. Veltassa increases fecal K⁺ excretion through binding of potassium in the lumen of the gastrointestinal tract. Reducing serum potassium levels

Dosage Form and Dosing: Veltassa is an off-white to light-brown powder for oral suspension packaged in single-use packets containing 8.4, 16.8, or 25.2 grams patiromer. The recommended starting dose of Veltassa is 8.4 g patiromer QD w/ food. Doses are adjusted based on serum K⁺ qw or longer in increments of 8.4 grams up to a max dose of 25.2 g QD.

Dosing in Special Populations:

Pregnant/Lactating: not absorbed systemically so maternal use is not expected to harm the fetus or expose risk to an infant through breast milk.

Pediatric Patients: not evaluated

Geriatric: Of the 666 patients treated with Veltassa in clinical studies, 59.8% were age 65 and over, and 19.8% were age 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. Patients age 65 and older reported more gastrointestinal adverse reactions than younger patients.

Renal Dosing: Of the 666 patients treated with Veltassa in clinical studies, 93% had chronic kidney disease (CKD). No dosing adjustments are needed.

Drug Interactions: No formal interaction panel was done but 50% oral drugs were bound. Advise patients who are taking other oral medication to separate the dosing of Veltassa by at least 6 hours. **(Black Box Warning)**

Storage: should be stored in the refrigerator at 2°C to 8°C (36°F to 46°F). If stored at room temp (25°C ± 2°C [77°F ± 4°F]), it must be used w/in 3 m of being taken out of the refrigerator.

Adverse Effects: Constipation, hypomagnesemia, hypokalemia, diarrhea, nausea, abdominal discomfort, and flatulence.

Price:

Medication	AWP (30 days)	AWP (Single-Dose)
Patiromer (Veltassa)	\$595	\$19.83
Sodium Polystyrene (Kayexalate)	-	\$11.25

Clinical Trials:

OPAL-HK: The efficacy was demonstrated in a two-part, single-blind randomized withdrawal study that evaluated Veltassa in hyperkalemic pts w/ CKD on stable doses of ≥1 renin-angiotensin-aldosterone system inhibitor (i.e., ACEi or ARB, or aldosterone antagonist). ~ 97% of pts had HTN, 57% had T2DM, and 42% had CHF.

In Part A, 243 pts were treated with Veltassa for 4 w. Pts w/ a baseline serum K⁺ of 5.1 mEq/L to < 5.5 mEq/L received a starting Veltassa dose of 8.4 grams patiromer/d and pts w/ a baseline serum K⁺ potassium of >5.5 mEq/L to < 6.5 mEq/L received 16.8 grams patiromer/day. The dose of Veltassa was titrated based on the serum K⁺ level, assessed starting on Day 3 and then at weekly visits (Weeks 1, 2 and 3) to the end of the 4-w treatment period. The change was found to be statistically significant. (p<0.001).

	Baseline Potassium (mEq/L)		Overall Population (n=237)
	5.1 to < 5.5 mEq/L (n=90)	5.5 to < 6.5 mEq/L	
Baseline, mean (SD)	5.31 (0.57)	5.74 (0.40)	5.58 (0.51)
Week 4 Change from Baseline, Mean ± SE (95% CI)	-0.65 ± 0.05 (-0.74, -0.55)	-1.23 ± 0.04 (-1.31, -1.16)	-1.01 ± 0.03 (-1.07, -0.95)

In Part B, 107 patients with a Part A baseline serum potassium of 5.5 mEq/L to < 6.5 mEq/L and whose serum potassium was in the target range (3.8 mEq/L to < 5.1 mEq/L) at Part A Week 4 and still receiving RAAS inhibitor medication were randomized to continue Veltassa or to receive placebo to evaluate the effect of withdrawing Veltassa on serum potassium. Results showed a median change of 0.72 and 0.00 for the placebo vs Veltassa, respectively. The difference was statistically significant. (p<0.001)

AMETHYST-DN: The effect of treatment with Veltassa for up to 52 w was evaluated in an open-label study of 304 hyperkalemic pts w CKD and T2DM on RAAS inhibitor therapy. Patiromer consistently maintained normal serum K⁺ levels over 52 w, with few patients requiring dose titration.

Conclusion: Veltassa seems to have efficacy in reducing potassium levels, but has not been compared to its main competitors and is more expensive.

Recommendation: Exclude. It hasn't been compared to other drugs known to lower K⁺.

EBRx Vote Result: Exclude code 13. Kayexalate is the alternative.

References:

Bakris, George L., et al. "Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial." *JAMA* 314.2 (2015): 151-161.

Federal Food and Drug Administration. "Veltassa: Package Insert." October 2015. Accessed online at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/205739s000lbl.pdf

Weir, Matthew R., et al. "Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors." *New England Journal of Medicine* 372.3 (2015): 211-221.

Naloxone nasal spray 4 mg/0.1ml (Narcan Nasal Spray)

Andrew Mullings, PharmD

1/25/2016

Product Summary: Approved for opioid overdose (initial treatment of an opioid-associated life-threatening emergency)

Agent	Dose	Price
Narcan Nasal Spray	4mg/spray	\$75.00
Naloxone Injection Solution	0.4 mg/mL (1 mL)	\$18.71
Evzio Auto Injector 0.4mg	0.4 mg/0.4 mL (0.4 mL)	\$345.00

The package insert contains reference to one PK study in 30 health adult subjects comparing 1 nasal spray in one nostril (4mg total dose) and 2 nasal sprays administered as one nasal spray in each nostril (8 mg total dose), 0.1 mL of 40 mg/mL naloxone hydrochloride solution in each nostril), and 0.4 mg naloxone hydrochloride IM. The results are presented in the table below. **The median naloxone tmax after intranasal administration of NARCAN Nasal Spray (one nasal spray in one nostril or two nasal sprays as one spray in each nostril) was not significantly different compared to the 0.4 mg dose of naloxone hydrochloride intramuscular injection.**

Mean Pharmacokinetic Parameters (CV%) for Naloxone Following Naloxone Nasal Spray and IM of Naloxone to Healthy Subjects			
Parameter	4 mg – One Nasal Spray in one nostril (N=29)	8 mg –Two Nasal Sprays, one in each nostril (N=29)	0.4 mg Intramuscular Injection (N=29)
tmax (h)†	0.50 (0.17, 1.00)	0.33 (0.17, 1.00)	0.38 (0.08, 2.05)
Cmax (ng/mL)	4.83 (43.1)	9.70 (36.0)	0.88 (30.5)
AUCt (hr.ng/mL)	7.87 (37.4)	15.3 (23.0)	1.72 (22.9)
AUC0-inf (h*ng/mL)	7.95 (37.3)	15.5 (22.7)	1.76 (22.6)
t½ (h)	2.08 (29.5)	2.10 (32.4)	1.24 (25.9)
Dose normalized Relative BA (%) vs. IM	46.7 (31.4)	43.9 (23.8)	100

Additionally, a prospective, randomised, unblinded trial (n=155) of evaluated 2 mg naloxone IM vs 2 mg naloxone delivered IN with a mucosal atomizer in treatment of respiratory depression due to suspected opiate overdose in the prehospital setting. Participants were those requiring treatment for suspected opiate overdose and attended by paramedics. Response time was time to regain a respiratory rate greater than 10 per minute. **The mean response time was 6 min [95% CI, 5–7 min] for IM group vs mean of 8 min [95% CI, 7–8 min] for IN group; P = 0.006, log rank).** The IM group had more rapid response than the IN group, and were more likely to have more than 10 spontaneous respirations per minute within 8 minutes (82% v 63%; P = 0.0173).²

Recommendation: Evizo is currently excluded, consider exclusion but discuss moral and ethnical considerations with the committee.

EBRx: Tier 3 QL1

1. Narcan® Nasal Spray Package Insert. Adapt Pharma. 11/2015. Accessed 1/26/2016
2. Kelly AM et al . Randomised trial of intranasal versus intramuscular naloxone in prehospital treatment for suspected opioid overdose. Med J Aust. 2005 Jan 3;182(1):24-7. PubMed PMID: 15651944.

Pradaxa® (dabigatran) 110mg capsule

Rachael McCaleb, PharmD

January 28, 2016

Labeled Indication: Prophylaxis of VTE (DVT and PE) following hip replacement surgery

Pricing: \$6.67/capsule (AWP)

Dosing and Administration¹:

Renal Function	Recommendation
CrCl ≥30 mL/min	110mg taken orally 1-4 hours following surgery ^a , the 220mg taken once daily for 28-35 days
CrCl <30 mL/min	Dosing recommendations are not established
Dialysis	Dosing recommendations are not established

^a If dabigatran is not started on the day of surgery, the starting dose should be 220mg once daily

Contraindications: Patients with known hypersensitivity to dabigatran, active bleed, or mechanical prosthetic heart valve(s).

Evidence:

Efficacy/Safety

	AFib	Total Knee Arthroplasty	Total Hip Arthroplasty
<i>Warfarin daily</i>	RE-LY³: Dabigatran 110mg NI to warfarin for prevention of stroke or systemic embolism: 1.53% per year versus 1.69% per year (p < 0.001)		
<i>Enoxaparin 40 mg daily</i>		RE-MODEL⁴: Dabigatran 220mg NI to enoxaparin for prevention of total VTE and death (p = 0.0003) <i>Safety:</i> Similar safety profiles	RE-NOVATE⁶: Dabigatran 220mg NI to enoxaparin for prevention of total VTE and death (p < 0.0001) <i>Safety:</i> Similar safety profiles RE-NOVATE II⁷: Dabigatran 220mg NI to enoxaparin for prevention of total VTE and death (p < 0.0001) <i>Safety:</i> Similar safety profiles
<i>Enoxaparin 30 mg BID</i>		RE-MOBLIZE⁵: Dabigatran 220mg failed to show NI to enoxaparin or prevention of total VTE and death <i>Safety:</i> Similar safety profiles	

Recommendations:

Approve for coverage.

EBRx P&T outcome: Approve at the same tier as other strengths.

References:

1. Pradaxa (dabigatran) [prescribing information]. Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals Inc; November 2015.
2. Falck-Ytter, Y., Francis, C.W., Johanson, N.A., et al. (2012). Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 141(2 Suppl):e278S-325S.
3. Connolly, S.J., Ezekowitz, M.D., Yusuf, S., et al. (2009). Dabigatran versus warfarin in patients with atrial fibrillation (RE-LY). *N Engl J Med*. 361(12):1139-51
4. Eriksson, B.I., Dahl, O.E., Rosencher, N., et al. (2007). Oral dabigatran etexilate vs. subcutaneous enoxaparin for the prevention of venous thromboembolism after total knee replacement: the RE-MODEL randomized trial. *J Thromb Haemost*. 5:2178-85.
5. The RE-MOBLIZE Writing Committee. (2009). Oral thrombin inhibitor dabigatran etexilate vs North American enoxaparin regimen for prevention of venous thromboembolism after knee arthroplasty surgery. *J Arthroplasty*. 24:1-9.
6. Eriksson, B.I., Dahl, O.E., Rosencher, N., et al. (2007). Dabigatran etexilate versus enoxaparin for prevention of venous thromboembolism after total hip replacement: a randomised, double-blind, non-inferiority trial. *Lancet*. 370(9591):949-56.
7. Eriksson, B.I., Dahl, O.E., Huo, M.H., et al. (2011). Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial. *Thromb Haemost*. 105(4):721-9.

Aripiprazole lauroxil (Aristada)
Amy Brotherton, Pharm.D.
November 17, 2015

Labeled Indication: Treatment of schizophrenia after establishing tolerability to oral aripiprazole

Dosing: Intramuscular injection in the deltoid (441 mg only) or gluteal (441 mg, 662 mg, or 882 mg) muscle by a healthcare professional monthly (or every 6 weeks with 882 mg). With first injection, administer with oral aripiprazole for 21 consecutive days (441 mg, 662 mg, and 882 mg correspond with 300 mg, 450 mg, and 600 mg of aripiprazole, respectively).

Comparators:

Drug	Strengths	Monthly Cost (AWP)	7/22/15 Meeting Decision	Jill's 7/23/15 Proposal	11/17/15 Proposal	>15 point or 34% change in PANSS from baseline value ^c
Aristada (aripiprazole lauroxil ER 1-month injection) ^a	441 mg/1.6 mL 662 mg/ 2.4 mL 882 mg/ 3.2 mL	791.25 791.50 790.88				N
Abilify Maintena IM (ER 1- month injection separated by at least 26 days)	400 mg	1901.35	Exclude	T3PA, require Haldol decanoate or intolerance to it. Require Risperdal Consta after Haldol dec.		Y (-15.1)
Invega ER (oral tab)	1.5 mg 3 mg 6 mg 9 mg 12 mg (3 mg + 9 mg)	1019.87 1019.87 1019.87 1529.80 2549.67	T2PA	Exclude		Y (>-30)
Invega Sustenna (ER 1-month injection)	39 mg 78 mg 117 mg 156 mg 234 mg	401.87 803.80 1205.69 1607.65 2411.42	T3PA, grandfather current users	Exclude, GF current users		N
Invega Trinza (ER 3-month injection)	273 mg 410 mg 546 mg 819 mg	803.80 1205.69 1607.65 2411.42	T3PA	Exclude		N/A
Risperdal Consta (ER 2-week injection)	12.5 mg 25 mg 37.5 mg 50 mg	409.70 819.36 1231.02 1638.72	T3PA	T3PA, require Haldol decanoate or treatment-resistant EPS		N
Haloperidol decanoate (ER 4-week injection) ^b normal dose 10-20Xs daily oral dose	50 mg/mL 100 mg/mL	95.08 181.25	T1	T1		N/A
Fluphenazine decanoate	25 mg/mL	161				N/A

^a882 mg strength can be administered every 4 weeks or every 6 weeks

^bConversion of ER tab to ER 1-month injection: 12 mg=234 mg; 6 mg=117 mg; 3 mg=39-78 mg

^bConversion of ER 1-month injection to 3-month injection: 78 mg=273 mg; 117 mg=410 mg; 156 mg=546 mg; 234 mg = 819 mg

^cHermes et al defines the minimally clinically important difference in the PANSS as >15 point or 34 % change from baseline

Contraindications: Known hypersensitivity to aripiprazole

Black Box Warning: Increased mortality in elderly patients with dementia-related psychosis

Adverse Reactions/Toxicities: The most commonly observed adverse reaction (incidence ≥5% and at least twice that for placebo) was akathisia. Other adverse reactions include: injection site pain; weight gain; increased blood creatine phosphokinase; headache; insomnia; restlessness; cerebrovascular adverse reactions (including stroke); neuroleptic malignant syndrome; tardive dyskinesia; metabolic changes; orthostatic hypotension; leukopenia, neutropenia, and agranulocytosis; seizures; cognitive and motor impairment; disruption of body temperature regulation; and dysphagia.

Drug Interactions: Strong CYP3A4 inhibitors (itraconazole, clarithromycin), strong CYP2D6 inhibitors (quinidine, fluoxetine, paroxetine), strong CYP3A4 inducers (carbamazepine, rifampin), antihypertensive medications, and benzodiazepines (increased sedation and orthostatic hypotension).

Evidence:

Study 1: A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia

- **Design:** An international multicenter, randomized, double-blind, placebo controlled trial with a total of 623 patients aged 18 to 70 years. Qualification criteria included: DSM-IV-TR criteria diagnosed schizophrenia, treatment in the outpatient setting >3 months, and experiencing acute exacerbation with a Positive and Negative Syndrome Scale (PANSS) score of 70 to 120 and a Clinical Global Impressions-Severity of Illness scale (CGI-S) score of ≥ 4 . Patients were randomized in a 1:1:1 ratio to receive gluteal intramuscular injection of aripiprazole lauroxil 441 mg, aripiprazole lauroxil 882 mg, or matching placebo once monthly for 12 weeks. The primary endpoint was change in PANSS total score from baseline to day 85. The secondary endpoint was the change in Clinical Global Impressions-Improvement scale (CGI-I) score at day 85.
- **Results:** Of the 623 randomized patients, 360 completed the study (n=130, 135, and 95 for the 441 mg, 882 mg, and placebo groups, respectively). The mean PANSS total score improved significantly from baseline to day 85 in the aripiprazole lauroxil 441 mg and 882 mg groups, with placebo-adjusted differences of -10.9 ± 1.8 ($P < .001$) and -11.9 ± 1.8 ($P < .001$), respectively. Significant improvements in both treatment groups were demonstrated as early as day 8 and continued throughout the treatment period. The proportion of patients who had significant improvements in CGI-I scores was significantly greater with aripiprazole lauroxil 441 mg and 882 mg treatment versus placebo ($P < .001$). The most common adverse event ($\geq 5\%$) was akathisia (11% versus 4% for placebo).

Study 2: Effect of aripiprazole lauroxil on agitation and hostility in patients with schizophrenia (POST HOC Analysis)

- **Design:** This post-hoc analysis of the previously reported study (study 1) was conducted to determine the effects of aripiprazole lauroxil on the signs and symptoms of hostility and aggressive behavior. Hostility and aggression were assessed by the PANSS Hostility item (P7) and by adjusting for positive symptoms of schizophrenia, somnolence, and akathisia. The PANSS excited component score [P4 (Excitement), P7 (Hostility), G4 (Tension), G8 (Uncooperativeness), and G14 (Poor impulse control)], and the Personal and Social Performance scale disturbing and aggressive behavior domain were also assessed.
- **Results:** Of the 147 patients who received aripiprazole lauroxil 882 mg with a baseline PANSS Hostility item P7 more than 1, there was a significant ($P < 0.05$) improvement versus placebo on the PANSS Hostility item P7 score, which remained significant when PANSS-positive symptoms and somnolence or akathisia were included as additional covariates. The proportion of patients with a PANSS Hostility item P7 more than 1 at endpoint was significantly ($P < 0.05$) lower with aripiprazole lauroxil versus placebo (53.6, 46.1, and 66.3% for 441, 882 mg, and placebo, respectively). A significant improvement ($P < 0.05$) was found for change from baseline in the PANSS excited component score and the proportion of patients with aggressive behavior on the Personal and Social Performance scale.

Conclusion: Aripiprazole lauroxil demonstrated a safety and tolerability profile similar to oral aripiprazole. When compared to Abilify Maintena®, aripiprazole lauroxil ER injectable suspension offers benefits including: availability in multiple effective doses, ability to be administered in the deltoid muscle (for the 441-mg dose only), ability to be administered every 6-weeks (for the 882-mg dose only), and a lower AWP. Since there is no available evidence comparing aripiprazole lauroxil injectable suspension to any other LAI first generation or second generation antipsychotics, haloperidol decanoate and fluphenazine decanoate are still much more cost effective options. Among the second generation LAI antipsychotics, the lowest doses of Risperdal Consta (12.5 mg) and Invega Sustenna (39 mg) appear to be the cheapest options for this class; however, for all other strengths, aripiprazole lauroxil is the cheaper option.

Recommendation: Cover with PA Tier 3 with criteria of: adequate trial with oral formulation aripiprazole, FDA indication only, diagnosis of schizophrenia or psychosis, intolerable EPS that is treatment resistant (previous use of bupropion, benzodiazepines, or propranolol) while on haloperidol decanoate or fluphenazine decanoate.

COMMITTEE OUTCOME: Exclude Code 13

1. Aristada [package insert]. Waltham, MA: Alkermes, Inc; 2015.
2. Meltzer HY, Risinger R, Nasrallah HA et al. A randomized, double-blind, placebo-controlled trial of aripiprazole lauroxil in acute exacerbation of schizophrenia. *J Clin Psychiatry*. 2015; 76(8): 1085-90.
3. Citrome L, Du Y, Risinger R, et al. Effect of aripiprazole on agitation and hostility in patients with schizophrenia. *Int Clin Psychopharmacol*. 2015 Oct 29. [Epub ahead of print].
4. Hermes ED, Sokoloff D, Stroup TS et al. Minimum clinically important difference in the PANSS with data from the CATIE. *J Clin Psychiatry*. 2012;74(4):526-32.

Sonidegib Phosphate (Odomzo)

200mg capsules

Lindsey Alvarez

November 2015

Indications: Adult patients with locally advanced basal cell carcinoma (laBCC) or metastatic BCC (mBCC) that has recurred following surgery or radiation therapy—or those who are not candidates for surgery or radiation therapy.

Recommended dose: 200mg taken po QD OES, at least 1h before or 2h after a meal, until disease progression or unacceptable toxicity

Contraindications: none; no renal or hepatic doing required

DDI: CYP3A; Concomitant admin of a PPI or H2-blocker ↓ steady-state AUC0-24h by 34%.

Alternative Treatments: vismodegib PO once daily (topical for superficial BCC < 3cm only)

Adverse Reactions: The most common adverse reactions occurring in ≥10% of patients are muscle spasms (54%), alopecia (53%), dysgeusia (46%), fatigue, nausea, musculoskeletal pain, diarrhea, decreased weight, decreased appetite, myalgia, abdominal pain, headache, pain, vomiting, and pruritus.

Black Box Warning: Embryo-fetal toxicity. Verify the pregnancy status of females of reproductive potential prior to initiating. Must use 2 methods of contraception during tx and ≥20 months after d/c.

Phase II, Randomized Double-blind Study of Efficacy and Safety of Two Dose Levels of LDE225 in Patients With Locally Advanced or Metastatic Basal Cell Carcinoma (BOLT)²

Drug	Cost per Month (AWP)	Route	Dose
Sonidegib	\$12,070	PO	1 QD
Vismodegib	\$12,070	PO	1 QD
Imiquimob	\$650	Topical	5/wk x6wk
5-fluorouracil	\$260	Topical	BID x3-6wk

Methods: BOLT is a MC, R, DB, phase 2 trial. Eligible patients had laBCC (not amenable to curative surgery or radiation) or mBCC, in addition to adequate bone marrow, liver, and renal fxn.⁴ Pts were randomized via an automated system in a 1:2 ratio to receive 200 mg or 800 mg oral sonidegib daily, stratified by disease, histological subtype, and geographical region. The 1st endpt was the proportion of pts who achieved an objective response (ORR) by 6m after starting sonidegib. Tumor assessments were done at baseline and at weeks 5 and 9 after tx start; then q8wk during year 1, q12wk thereafter, and at d/c. A responder was defined as a confirmed partial response (PR) or confirmed complete response (CR) at 6m. ORR is based on central (radiological) review of tumor assessments as per modified RECIST (mRECIST) criteria for laBCC and RECIST 1.1 criteria for mBCC.

Results: N=229 received sonidegib QD at either 200mg (n=79) or 800mg (n=150). In the 1st efficacy analysis population, 36% of pts in the 200mg group achieved an ORR (20/55 = 36%, 95% CI 24-50). Of those, 43% had laBCC and 15% mBCC. (laBCC: 18/42 = 43%, 95% CI 28-59) (mBCC: 2/13 = 15%, 2-45). AEs were reported in 95% of the 200mg arm, with the most common being muscle spasms (54%), alopecia (53%), and dysgeusia (46%). Serious adverse reactions occurred in 14% of pts in the 200mg arm. Sonidegib was permanently DC'd in 34% of pts or temporarily interrupted in 20% of pts for AEs. Of note, 63% of the pts who d/c due to AE experienced only grade 1 – 2 events.

- The study is still ongoing. Not all pts enrolled are included in the "primary efficacy analysis population". (n=55 for the 200mg group at this time)

Recommendation by student to committee:

Interpretation from PI: "The benefit-to-risk profile of 200mg sonidegib might offer a new treatment option for patients with advanced basal cell carcinoma, a population that is difficult to treat."

- Sonidegib costs the same as vismodegib. I recommend applying the same criteria that exists for vismodegib to sonidegib.
- Additionally, pt must meet all eligibility criteria mentioned above. (>18yo, dx of laBCC or mBCC that can't be surgically removed or irradiated, and adequate bone marrow, liver, and renal fxn)

Outcome of EBRx Committee: Excluded, code 1. Unknown whether it makes life longer or better.

A *Erivedge™ (vismodegib)* was approved by the FDA in 2012 for extraordinarily rare cases of metastatic BCC or locally advanced BCC that become dangerous and even life-threatening. The first medicine ever for advanced BCC, it works by blocking the "Hedgehog" signaling pathway, which is a key step in the development of BCC. It is approved only for very limited circumstances where the nature of the cancer precludes other treatment options (such as surgery or radiation). Several other targeted Hedgehog inhibitors are also being investigated as potential treatments for locally advanced and metastatic BCC. Due to a risk of birth defects, vismodegib should not be used by women who are pregnant or may become pregnant. Birth control must be used by couples if the woman is capable of becoming pregnant.

R

- An 18-month update was presented at the American Society of Clinical Oncology (ASCO) meeting in Chicago in 2013. Data showed an objective response rate of 48.5 and 60.3% for mBCC and laBCC, respectively.
- The most frequent adverse effects were grade 1 and grade 2 events and included muscle spasms (71%), alopecia (65%) and dysgeusia (53%), weight loss (50%) and fatigue (40%).
- In a Phase I clinical trial (n = 33), von Hoff et al. investigated the safety and pharmacokinetics of vismodegib. Based on this data, a pivotal Phase II clinical trial was initiated in 104 patients with mBCC or laBCC. The investigators observed an ORR of 33.3 and 47.6% in mBCC and laBCC patients, respectively.
 - In Phase I: 18 of 33 patients, an objective tumor response including two complete remissions were observed.

V *Imiquimod* is FDA-approved only for superficial BCCs, with cure rates generally between 80 and 90 percent. The cream is rubbed gently into the tumor five times a week for up to six weeks or longer. The first in a new class of drugs that work by stimulating the immune system, it causes the body to produce interferon, a chemical that attacks cancer.

E *5-Fluorouracil (5-FU)*, a chemotherapy drug approved to treat internal cancers, also has been FDA-approved for superficial BCCs, with similar cure rates to imiquimod. The liquid or cream is gently rubbed into the tumor twice a day for three to six weeks. Side effects are variable, and some patients do not experience any discomfort, but redness, irritation, and inflammation usually occur.

Tx

References:

1. Odomzo [Package Insert]. Novartis Pharmaceuticals Corporation. July 2015.
2. Migden MR, et al. Phase II, Randomized Double-blind Study of Efficacy and Safety of Two Dose Levels of LDE225 in Patients With Locally Advanced or Metastatic Basal Cell Carcinoma. *Lancet Oncol.* 2015 Jun;16(6):716-28.
3. Jil Dreier, Reinhard Dummer, Lea Felderer, Mirjam Nägeli, Sharon Gobbi & Rainer Kunstfeld (2014) Emerging drugs and combination strategies for basal cell carcinoma, *Expert Opinion on Emerging Drugs*, 19:3, 353-365.
4. Novartis Pharmaceuticals. A Phase II Study of Efficacy and Safety in Patients With Locally Advanced or Metastatic Basal Cell Carcinoma (BOLT). In: *ClinicalTrials.gov*. *ClinicalTrials.gov* Identifier: NCT01327053 (Accessed on November 11, 2015)
5. E.A. Eisenhauer, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *European Journal of Cancer* 45 (2009) 228 – 247. (see section 4)

<u>Adequate Labs for Inclusion</u>	
Bone Marrow	
	• \geq ANC 1.5×10^9 cells/L
	• Hgb \geq 90 g/L
	• Plt \geq 100×10^9 cells/L
Liver Function	
	• Tbill \leq 1.5 xULN
	• AST and ALT \leq 2.5 xULN
	o \leq 5 xULN if liver mets
Renal Function	
	• CK \leq 1.5 ULN
	• SCr \leq 1.5 xULN
	• 24h CrCl \geq 0.84mL/s/m ²

<u>RESIST OBJECTIVE RESPONSE CRITERIA</u>
Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.
Partial Response (PR): At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Product Summary: Trifluridine-tipiracil (TAS-102) is an oral cytotoxic agent of a combination nucleoside analog and thymidine phosphorylase inhibitor approved treatment of metastatic colorectal cancer previously treated w/fluoropyrimidines, oxaliplatin, and irinotecan-based chemotherapy, an antiangiogenic biologic product, and an anti-EGFR monoclonal antibody, if RAS wild-type.

Available As: Trifluridine-tipiracil (20mg-8.19mg) at \$218.45/tab; (15mg-6.14mg) at \$164.22/tab

35 mg/m ² (based on the trifluridine component) twice daily on days 1 to 5 and days 8 to 12 of a 28-day cycle (maximum per dose: trifluridine 80 mg); round to the nearest 5mg		
Day 1-5	(2 tabs of 15-6.14 and 2 tabs of 20-8.19) X 2	\$7613.40
Day 8-12	(2 tabs of 15-6.14 and 2 tabs of 20-8.19) X 2	\$7613.40
Cost Per Month	\$15226.8	
Cost Per Patient	\$25504.89 - \$48345.09	
Dosing assumes a BSA of 1.88m ² given data in the US		

Evidence

1. Mayer RJ, Cutsem EV, Falcone A, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer. *N Engl J Med* 2015;372:1909-19.

Design: A DB, PC, Phase 3 trial in pts (n=800) with biopsy-documented adenocarcinoma of the colon or rectum who had received ≥2 prior regimens of standard chemotherapy comparing TAS-102 vs. placebo. Patients were required to have received a fluoropyrimidine, oxaliplatin, irinotecan, bevacizumab, and — for patients with KRAS wild-type tumors — cetuximab or panitumumab. ECOG status of 0 or 1 was required.

Results: Pts in the TAS-102 group received the study drug for a mean (±SD) of 12.7±12.0 w (median, 6.7; range, 0.1 to 78.0). The median OS was 7.1 m (95% confidence interval [CI], 6.5 to 7.8) in the TAS-102 group and 5.3 m (95% CI, 4.6-6.0) in the placebo group. The HR for death (TAS-102 vs. placebo) was 0.68 (95% CI, 0.58 to 0.81; P<0.001).

1.8 m improvement in OS

Safety: In the TAS-102 group, a total of 73 pts (14%) required dose reductions. Among the 533 pts who received TAS-102, 38% had grade 3 or higher neutropenia, 4% had febrile neutropenia, and 9% received GCSF; one treatment-related death resulting from septic shock was reported. The incidence of grade 3 or 4 anemia was greater in the TAS-102 group than in the placebo group (18% vs. 3% of the patients), as was the incidence of thrombocytopenia of grade 3 or higher (5% vs. <1%).

2. Yoshino T, Mizunuma N, Yamazaki K, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: a DB, R, PC phase 2 trial. *Lancet Oncol* 2012;13:993-1001. (in Japan)

N=169, at least 20yo, confirmed colorectal adenocarcinoma, >2 regimens std ctx and refractory or intolerant to fluoropyrimidine, irinotecan, and oxaliplatin. Had to be able to take po drugs, ECOG 0-2. Randomized to TAS102 (35mg/m² BID in a 28d cycle [2w cycle of 5 days of treatment, followed by 2d rest, then 14 day rest period] or placebo. Concealed allocation, triple blinded. 1` endpt was OS.

Results: Median f/u 11.3m. Med OS 9.0m (95%CI 7.3-11.3) in TAS102 vs 6.6m (4.9-9.0) placebo. HR for death 0.56, 80% CI 0.44-0.71. 50% TAS102 had grade 3 or 4 neutropenia, 28% leukopenia, 17% anemia. 0% placebo had grade 3 or worse neutropenia or leukopenia; 5% had anemia grade 3 or worse. SAEs 19% in TAS102 vs 9% in placebo. No treatment related deaths.

2.4 m improvement in OS

Recommendation: Exclude due to lack of clinically meaningful difference with a survival benefit of 1.8 months.

The Journal of Clinical Oncology states the improvement over current OS that would be clinically meaningful would be 3-5m or a HR for death of 0.67, or a 1 year survival rate improvement from 25-35% or improvement in PFS of 3-5m, in colon cancer pts with disease progression with all prior therapies (or not a candidate for standard second- or third-line options). *J Clin Onc.* 2014;32(12):1277-80.

Irinotecan Liposome IV (Onivyde) 43mg/10ml (10ml single dose vials)

Andrew Mullings, PharmD, Jill Johnson, Pharm.D.

Revised 11/30/15

Product Summary: Onivyde is a liposomal irinotecan formulation (MM-398) indicated for the treatment of metastatic pancreatic cancer in combination with 5-FU and leucovorin, following a prior gemcitabine based regimen.

NOTE: 1st line therapy for ECOG 0-1 is either FOLFIRINOX or Gemcitabine+albumin-bound paclitaxel (both Category 1 by NCCN). In reference 2 below, the data

Dosing and Cost:

Drug	Dose	Cost/dose	Cost/28d
(Onivyde) Lipo-irinotecan IV 70 mg/m ² Q2w	126 mg	3 vials, \$5832	\$11,664
5FU 2,400 mg/m ² Q2w	4320 mg	\$27	
Racemic LV 200 mg/m ² Q2w	360 mg	\$22.74	
Total Cost Per Cycle (Q2w)		\$5881.74	\$11,763

1.80m² BSA Assumed; Cost (11/30/15) is \$1944/vial.

Evidence:

1. Chen L-T, Von Hoff DD, Li C-P, et al: Expanded analyses of Napoli-1: Phase 3 study of MM-398 (nal-IRI), with or without 5-fluorouracil and leucovorin, versus 5-fluorouracil and leucovorin in metastatic pancreatic cancer previously treated with gemcitabine-based therapy. 2015 Gastrointestinal Cancers Symposium. Abstract 234. Presented January 15, 2015.

N=417 pts w/ metastatic pancreatic adenocarcinoma which progressed after receiving gemcitabine or gem-based therapy.

Drug regimen	OS (95% CI)
Lipo-irinotecan + 5FU+L	6.1 months [4.8 – 8.9]
5FU+L	4.2 months [3.3 – 5.3]
Lipo-irinotecan	NS vs 5FU+L

Major grade ≥3 AEs in the MM-398 + 5-FU/LV, MM-398 and 5-FU/LV arms were neutrophil count decreased (23.1%, 15.3%, 3%), fatigue (13.7%, 6.1%, 3.7%), diarrhea (12.8%, 21.1%, 4.5%), and vomiting (11.1%, 13.6%, 3.0%), respectively.

2. Oettle H et al. Second-line oxaliplatin, folinic acid, and fluorouracil versus folinic acid and fluorouracil alone for gemcitabine-refractory pancreatic cancer: outcomes from the CONKO-003 trial. J Clin Oncol. 2014 Aug 10;32(23):2423-9. doi: 10.1200/JCO.2013.53.6995. Epub 2014 Jun 30. PubMed PMID: 24982456.

N=168 pts w/ advanced pancreatic cancer who progressed while receiving gemcitabine monotherapy.

	Dose	Cost/dose	Cost/28d
Oxaliplatin 85 mg/m ² Q2w	153 mg	100mg/20mL, use 2 vials \$240ea or \$480	\$960
5FU 2,000 mg/m ² Qw	3600 mg	\$24	96
Racemic LV 200 mg/m ² Qw	360 mg	\$22.74	90.96
Total Cost Per Cycle			\$1146.96

1.80m² BSA Assumed

Drug regimen	OS (95% CI)	HR for death (95%CI)
Folinic acid + 5FU	3.3m (2.7-4.0)	
Oxaliplatin + 5FU + Folinic acid¥ (OFF)	5.9m (4.1-7.4)	0.66; 0.48-0.91

Rates of adverse events were similar between treatment arms, with the exception of grades 1 to 2 neurotoxicity, which were reported in 29 pts (38.2%) and 6 patients (7.1%) in the OFF and FF groups, respectively (P .001).

¥Folinic acid is leucovorin calcium.

Comments:

- One small open RCT (n=46) comparing OFF (oxaliplatin, leucovorin, and 5-FU) with BSC was halted due to lack of accrual (lack of acceptance of BSC by patients and physicians). However, the trial did demonstrate a significant median overall advantage of 4.82 months (4.29-5.35) for OFF vs 2.30 months (1.76-2.83) months with BSC in patients who experienced disease progression during first-line gemcitabine.

Options:

1. Highest covered tier. Although OFF therapy is an alternative to Lipo-irinotecan+5FU+L and provides an OS benefit, there is a substantial increase in the rate of grade 1 or 2 neurotoxicity with oxaliplatin. This could be an AE tradeoff. No HTH trials between Lipo-irinotecan+5FU+L vs OFF exist to date.
2. Exclude due to alternative also prolongs OS similarly.

Andrew Addendum:

	ONIVYDE/ 5-FU/LV		5-FU/LV	
	Grades 1 -4 (%)	Grade 3-4 (%)	Grades 1 -4 (%)	Grade 3-4 (%)
Gastrointestinal disorders				
Diarrhea	59	13	26	4
Vomiting	52	11	26	3
Nausea	51	8	34	4
Stomatitis	32	4	12	1
Infections and infestations	38	17	15	10
Sepsis	4	3	2	1
Neutropenic fever/neutropenic sepsis	3	3	1	0
Gastroenteritis	3	3	0	0
IV catheter-related infection	3	3	0	0
General disorders and administration site conditions				
Fatigue	56	21	43	10
Pyrexia	23	2	11	1

	OFF		5-FU/LV	
	Grades 1 -4 (%)	Grade 3-4 (%)	Grades 1 -4 (%)	Grade 3-4 (%)
Gastrointestinal disorders				
Diarrhea	20	1	23	0
Nausea/Emesis	58	1	43	4
Other				
Paresthesia*	46	4	7	0
Pain	77	31	86	40

An important limitation concerning OFF is that the trial it was performed before FOLFIRINOX and nab-paclitaxel in combination with gemcitabine became first-line treatment options for patients with advanced pancreatic cancer. However, it important to consideration only a fraction (21%) of the patients in the Onivyde trial received previous therapy with a platinum agent.

Given the indirect comparative safety and tolerability profile, increased tolerability or safety with Onivyde is questionable.

Trabectedin (Yondelis)
Andrew Mullings, Pharm.D.
12/27/2015

Product Summary: Trabectedin is a novel alkaloid indicated for the treatment of metastatic or unresectable soft tissue sarcoma (STS). It is also currently approved in the EU and Canada for the treatment of relapsed ovarian cancer in combination with PLDH (pegylated liposomal doxorubicin hydrochloride), although the FDA denied that indication in 2009.

Dosing:

- *Soft Tissue Sarcoma:* 1.5mg/m² continuous IV over 24hrs Q3weeks
- *Relapsed ovarian cancer:* 1.1 mg/m² over 3hrs after 90 minute IV infusion of 30mg/m² of PLDH Q4weeks

Supplied as: 1mg at \$2700

Relapsed Ovarian Cancer			
Drug	Trial Dosing	Cost Per Cycle	Average Treatment Cost
Trabectedin	1.1mg/m ² Q4weeks	\$5400	\$27,000
PLDH	30 mg/m ² Q4weeks	\$3,488.40	\$17,442
Trabectedin + PLDH		\$8888.40	\$44,442
Dosing assumes a BMI of 28.1 corresponding to a height of 65 in and weight of 169lbs giving a BSA of 1.84 m ²			

Soft Tissue Sarcoma			
Drug	Trial Dosing	Cost Per Cycle	Average Treatment Cost
Trabectedin	1.5mg/m ² continuous IV over 24hrs Q3weeks	\$8100	\$32,400
Dacarbazine	1 g/m ² Q3weeks	\$215.46	\$430.92
Dosing assumes a BMI of 28.1 corresponding to a height of 65 in and weight of 164lbs giving a BSA of 1.84 m ²			

Evidence

Demetri GD, von Mehren M, Jones RL, et al. Efficacy and Safety of Trabectedin or Dacarbazine for Metastatic Liposarcoma or Leiomyosarcoma After Failure of Conventional Chemotherapy: Results of a Phase III Randomized Multicenter Clinical Trial [Published online before print September 14, 2015]. J Clin Oncol.

Design: Phase III, randomized, open-label, active-controlled, parallel group trial evaluating trabectedin vs. dacarbazine in patients (n=518) with unresectable, locally advanced or metastatic liposarcoma or leiomyosarcomas; and who were previously treated with at least either a combination of an anthracycline and ifosfamide or an anthracycline plus one or more additional cytotoxic chemotherapy regimen(s). The primary study end point was overall survival (OS).

Results: The final analysis of OS was performed at the clinical cut-off date of January 5, 2015, after 381 deaths had occurred, with a median survival follow up of 21 months. **The median number of cycles received was 4 in trabectedin group vs. 2 in dacarbazine group**, with twice the proportion of patients receiving ≥6 cycles in the T group (42% vs 21%). **The median OS was 13.7 months for the trabectedin group vs. 13.1 months for the dacarbazine group.**

Adverse events were increased in the trabectin group with respect to nausea (73% vs 49%), fatigue (67% vs 51%), neutropenia (49% vs 29%), and vomiting (44% vs 21%). Overall toxicities, including grades 3 and 4 were increased with trabectedin.

Of note, it is suggested that the lack of OS benefit may be secondary to subsequent therapy in STS, which were administered to the trabectedin arm at 47% compared to 56% in the dacarbazine arm. Additionally, 18% of patients in the trabectedin arm received subsequent pazopanib, which was approved during study recruitment, compared with 28% in the dacarbazine arm. However, there was no difference in OS benefit of pazopanib compared to placebo in a large RCT.

Monk BJ, Herzog TJ, Kaye SB, et al. Trabectedin plus pegylated liposomal Doxorubicin in recurrent ovarian cancer. *J Clin Oncol* 2010; 28:3107.

Design: Phase III, randomized, open-label, active-controlled, trial evaluating trabectedin & PLDH vs. PLDH in patients with confirmed epithelial ovarian, fallopian tube, or primary peritoneal carcinoma who had received only one prior platinum-based chemotherapy regimen and experienced persistence, recurrence, or progression (n=672).

Results: Median PFS was 7.3 months with trabectedin/PLDH v 5.8 months with PLD (hazard ratio, 0.79; 95% CI, 0.65 to 0.96; P = .0190). For platinum-sensitive patients, median PFS was 9.2 months v 7.5 months, respectively (hazard ratio, 0.73; 95% CI, 0.56 to 0.95; P = .0170). Overall response rate (ORR) was 27.6% for trabectedin/PLDH v 18.8% for PLD (P = .0080); for platinum-sensitive patients, it was 35.3% v 22.6% (P = .0042), respectively. ORR, PFS, and overall survival among platinum-resistant patients were not statistically different. An interim survival analysis showed the difference in OS between treatment arms to be very small and non-significant, with a median OS of 20.5 months in the trabectedin combination group and 19.4 months in the PLDH monotherapy group (HR 0.85, p=0.15).

An exploratory hypothesis generating analysis suggested an increased survival benefit in those who were partially platinum-sensitive with a significant 41% decrease in the risk of death (HR = 0.59; 95% CI, 0.43–0.82; P = 0.0015; median survival 23.0 versus 17.1 months). These results must be interpreted with caution as research questions, not well validated evidence.

Toxicity	PLD (n = 330)				Trabectedin/PLD (n = 333)			
	Grade 3		Grade 4		Grade 3		Grade 4	
	No.	%	No.	%	No.	%	No.	%
Hematologic								
Neutropenia	46	13.9	28	8.5	96	28.8	113	33.9
Leukopenia	24	7.3	8	2.4	82	24.6	28	8.4
Thrombocytopenia	6	1.8	2	0.6	34	10.2	27	8.1
Anemia	15	4.5	1	0.3	31	9.3	10	3.0
Febrile neutropenia	6	1.8	1	0.3	15	4.5	8	2.4
Nonhematologic								
HFS	61	18.5	4	1.2	13	3.9	0	0
Mucosal inflammation	19	5.8	0	0	7	2.1	0	0
Stomatitis	16	4.8	1	0.3	3	0.9	0	0
Fatigue	8	2.4	1	0.3	19	5.7	1	0.3
Nausea	8	2.4	0	0	29	8.7	0	0
Vomiting	7	2.1	0	0	33	9.9	1	0.3
AST increase	1	0.3	1	0.3	21	6.3	3	0.9
ALT increase	1	0.3	0	0	95	28.5	8	2.4

Other Events of Interest	PLD (n = 330)		Trabectedin/PLD (n = 333)	
	No.	%	No.	%
Alopecia	44	13	40	12
Alkaline phosphatase increase	24	7	68	20
Neuropathy	24	7	34	10
Bilirubin conjugated increase/hyperbilirubinemia	18	5	51	15

Recommendation: Exclude due to lack of clinical benefit.

Asfotase alfa (Strensiq)
18mg/0.45mL, 28mg/0.7mL, 40mg/mL, 80mg/0.8mL for SC inj
Jill Johnson, Pharm.D., BCPS
12-10-15

FDA indication: treatment of patients with perinatal/infantile- and juvenile-onset hypophosphatasia (HPP).

HPP: The signs and symptoms of hypophosphatasia vary widely and can appear anytime from before birth to adulthood. These include rickets, softening and weakening of the bones (osteomalacia), bone deformity and a greater incidence of fractures. Hypophosphatasia can also lead to chronic debilitating pain, muscle weakness, generalised seizures because of vitamin B6 deficiency, and renal and respiratory complications. The most severe forms of the condition tend to occur before birth and in early infancy. Infants who present with hypophosphatasia in the first 6 months of life have a high mortality rate. Approximately 50–100% of infants die within the first year of life, primarily because of respiratory failure. The forms of hypophosphatasia that appear later in childhood or in adults are associated with substantially lower mortality rates than those that appear in infancy, but are often debilitating and lead to bone deformities that may result in delayed walking, limb weaknesses, skeletal pain and nontraumatic fractures. 2.3 The prevalence of severe forms of hypophosphatasia is unknown in England. However, in Europe, the rate is estimated as 1 per 300,000 live births. Milder forms, in which signs and symptoms have a later onset, are more common and are estimated to be present in 1 per 6370 of the population. A clinical expert approximated that 7 people are diagnosed with perinatal- and infantile-onset hypophosphatasia each year in England. In 2011, there were 187 hospital admissions for hypophosphatasia in England.

Pediatric Dose:

Perinatal/infantile-onset HPP: 2mg/kg TIW or 1mg/kg 6x/w; may increase dose to 3mg/kg TIW.
Max is 9mg/kg/w.

Juvenile-onset HPP: 2mg/kg TIW or 1mg/kg 6x/w

Note: do not use the 80mg vial for pts weighing <40kg (exposure is less than what is achieved w/ lower concentration vials.)

Evidence:

- The evidence uses historical controls for comparison which is not as robust as RCTs to make inferences. Additionally, the “N” in the trials is extremely low.

From the FDA’s database:

http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/125513Orig1s000StatR.pdf :

5.3 Conclusions and Recommendations There appears to be sufficient evidence in supporting the proposed efficacy claims for asfotase alfa in the treatment of perinatal/infantile-onset HPP. The claims reflected within the applicant’s submitted product labeling are supported by the results presented in this review. It should be Reference ID: 3821607 25 emphasized that all hypothesis testing was considered exploratory given that the agreed upon endpoints (i.e., overall survival and ventilator-free survival), planned data integrations, and subsequent historical control comparisons were all determined well into the execution of the relevant perinatal/infantile-onset HPP studies. Consequently, all previously presented inferential statistics (e.g., p-values) within this review document are considered supportive and not confirmatory, and no inferential statistics should be presented within the final product labeling. Conversely, the evidence in supporting the proposed efficacy claims for asfotase alfa in the treatment of juvenile-onset HPP is weak from a statistical perspective; hence the clinical review team will determine the sufficiency of this evidence from a clinical perspective.

NICE’s preliminary recommendations: <https://www.nice.org.uk/guidance/GID-HYPOPHOSPHATASIAASFOTASEALFAID758/documents/evaluation-consultation-document>

1.1 Asfotase alfa is not recommended, within its marketing authorisation, for long-term enzyme replacement therapy in paediatric-onset hypophosphatasia to treat the bone manifestations of the disease. Jan 7, 2016 is the deadline for public comment. April 2016 will be their final ruling.

Clinical evidence

4.3 The company did a systematic literature review to identify studies evaluating the clinical effectiveness of asfotase alfa for treating paediatric-onset hypophosphatasia. It found 4 open-label phase II studies of asfotase alfa (2 of which had associated extension studies):

- ENB-002-08, a non-randomised 24-week single-arm study in 11 people of 36 months or younger with infantile-onset hypophosphatasia
- ENB-003-08, an extension study of ENB-002-08 that is evaluating 10 people for up to 5 years
- ENB-010-10, a non-randomised, dose-comparison study of asfotase alfa treatment for up to 48 months in 59 people of 5 years or younger with infantile-onset hypophosphatasia
- ENB-006-09, a randomised 24-wk dose-comparison study in 13 people of 5–12 y with infantile- or juvenile-onset hypophosphatasia
- ENB-008-10, an extension study of ENB-006-09 that is evaluating 12 people for up to 5 y
- ENB-009-10, a randomised, 24-wk concurrent control study in 19 people of 13–66 years with paediatric-onset hypophosphatasia.

Only ENB-002-08 and ENB-006-09 have finished. The company stated that patients included in the studies of asfotase alfa presented with clinical symptoms that were characteristic of their age at onset of hypophosphatasia and enrolment, and that a broad range of outcomes measures were collected across studies to reflect the symptoms of the disease in each age group.

4.4 The company also identified 3 retrospective non-interventional studies:

- ENB-011-10, a retrospective natural history study of infants w/ severe perinatal- and infantile-onset hypophosphatasia. Data on survival and the need for invasive ventilation were taken from medical records of children up to 5 y.
- ALX-HPP-502, a retrospective natural history study of children w/ juvenile-onset hypophosphatasia (5–15 y). The study focused on functional assessments of physical abilities, changes in growth (height and weight) and skeletal improvement (severity of rickets).
- ALX-HPP-502s, a single-centre substudy of ALX-HPP-502. Data for additional functional measures were taken from medical records and videos were obtained from a longitudinal natural history database to characterise gait.

4.5 The primary outcome of ENB-002-08 and ENB-010-10 was change in severity of rickets on skeletal radiographs from baseline to week 24, measured by the Radiographic Global Impression of Change (RGI-C) scale. The RGI-C is a 7-point rating scale that ranges from –3 (indicates severe worsening of hypophosphatasia-associated rickets) to +3 (indicates complete or near complete healing of hypophosphatasia-associated rickets). An RGI-C score of +2 or more is considered to be a response to treatment in people with hypophosphatasia. Secondary outcomes included height and weight Z-scores and the number of people needing respiratory support. The Z-score indicates how many standard deviations an infant's height or weight is from the mean of the general population.

4.6 In ENB-002-08, treatment with asfotase alfa resulted in a mean and median change in RGI-C scores from baseline to week 24 of 1.67 and 2 respectively ($p=0.0039$). Most people had RGI-C score between 2 and 3 (7 out of 11; 63.6%). No patients had a RGI-C score of 3 by week 24 ('complete or near complete healing'). However, by week 24 of ENB-003-08, 9 out of 9 people followed-up had a RGI-C score of 2 or more.

4.7 The company provided the results of an interim analysis of 28 people included in ENB-010-10. The company's interim analysis suggested treatment with asfotase alfa resulted in a mean change in RGI-C score from baseline to week 24 of +1.7 (p

4.29 For the company's comparative analysis of overall survival in people with infantile-onset hypophosphatasia, the ERG noted that the results were biased in favour of asfotase alfa for 2 reasons:

- Year of diagnosis: Despite no disease-modifying treatment, the company showed that the probability of survival for people with infantile-onset hypophosphatasia had improved over the years. Of the historical control group, 13 people were diagnosed before 1990, 14 between 1990 and 1999, and 21 after 2000, compared with all 11 people receiving asfotase alfa diagnosed after 2005.
- Age at enrolment: The historical control group probably included more people younger than 1 month and younger than 1 week (people with hypophosphatasia younger than 1 month are at higher risk of death than older people).

4.30 The ERG considered that the lower mean age and lower age at onset in the historical control group may bias the results of ENB-006-09 in favour of asfotase alfa. However, it considered that the patient populations were more comparable in this analysis than the populations included in the other 2 comparative analyses provided by the company.

4.31 The ERG agreed that people receiving asfotase alfa in the company's comparative analysis of people with juvenile-onset hypophosphatasia showed clear improvements in skeletal structure, growth and gait compared with the historical control and the pre-treatment group. The ERG commented that, without data on baseline characteristics, it was unclear whether the groups were comparable. Therefore, the precise benefit of asfotase alfa treatment was not clear.

4.32 The ERG stated that, although there is considerable follow-up in some of the asfotase alfa studies, it was only a fraction of the expected lifetime treatment as proposed by the company. The ERG explained that it cannot be assumed that treatment works equally well or even at all in everyone, and that the effectiveness of treatment may diminish over time. The ERG concluded that the long-term efficacy and safety of asfotase alfa was uncertain, and that stopping rules for asfotase alfa should be considered given the many differences between people with paediatric-onset hypophosphatasia.

4.37 The ERG noted that the company's unadjusted approach for estimating survival and need for invasive ventilation in the economic model may have been biased:

- The historical controls included people from the time of diagnosis, whereas clinical studies can only include people who survive to study enrolment.

- There were differences in the year of diagnosis.
- The survival curves were estimated from birth rather than from the start of treatment.

The ERG highlighted that the survival analyses provided by the company in response to a request for clarification showed that the company's method of estimating survival in the economic model was potentially biased. The ERG concluded that the company should have attempted to match the populations between asfotase alfa and best supportive care and taken into account the age at enrolment and year of disease when estimating survival in its economic model.

See section 5.10-5.13 for NICE's take on "Cost to the NHS and personal social services"—insightful.

RECOMMENDATION: Exclude, code 1. Re-evaluate after April 2016.

Talimogene Laherparepvec (Imlygic, aka "T-VEC")

106 (1 million) PFU/mL, 108 (100million) PFU/mL in single-use vials for injection into cutaneous, SC, and/or nodal lesions

Jill Johnson, Pharm.D., BCPS

12/10/15

FDA-approval: for the local treatment of unresectable cutaneous, SC, and nodal lesions in patients with melanoma recurrent after initial surgery.

Limitations: has not been shown to improve OS or have an effect on visceral metastases.

Evidence:

1. FDA Briefing Document. Cellular, Tissue, and Gene Therapies Advisory Committee and Oncologic Drugs Advisory Committee Meeting. April 29, 2015. BLA 125518 talimogene laherparepvec (Amgen). Found in Jill's dropbox under talimogene.
2. Study 005/05 (Andtbacka RHI, Kaufman HL, Collichio F, et al. Talimogene laherparepvec improves durable response rate in patients with advanced melanoma. J Clin Oncol. 2015. Published ahead of print as 10.1200/JCO.2014.58.3377).

This trial randomized 436 melanoma pts to GMCSF or T-Vec. 1` endpt was DRR (obj response lasting >6m per independent assessment) 2` endpts were OS and ORR. T-Vec resulted in a higher DRR (P<0.001) and longer median OS (P=0.051) (NS), however, the FDA pointed out that 14 of the control patients vs 4 T-Vec patients were designated as non-responders and were not assessed for tumor response. (Please see excerpt from the FDA Briefing Document below):

5.4.1 Duration of Response Assessment

The protocol stipulated that "subjects were to receive treatment until Week 24 (even in the presence of disease progression, including the appearance of new lesions), or achievement of a CR." Differential early discontinuation of study treatment and response assessment, in particular by Week 24 (Month 6), may reflect subject or investigator bias, based on knowledge of the treatment assignment. Table 10 lists, in 3- month increments, the number of subjects who discontinued study treatment. There were more control group subjects than talimogene laherparepvec group subjects who discontinued study treatment at or before 3 months, 56.0% versus 29.2%. This imbalance in drop-outs could have created bias, in terms of assessment of responses, that would favor the talimogene laherparepvec arm.

Table 10. Cumulative Number of Subjects who Discontinued Treatment at Different

Study Arm	Number of subjects at randomization	At or before 3 Months	At or before 6 Months	At or before 9 Months	At or before 12 Months	At or before 16 Months	At or before 18 Months
Talimogene laherparepvec	295	86 (29.2%)	172 (58.3%)	226 (76.6%)	266 (90.2%)	277 (93.9%)	291 (98.6%)
Control	141	79 (56.0%)	106 (75.2%)	111 (78.7%)	124 (87.9%)	125 (88.7%)	127 (90.1%)

Evaluation Time Points

Source: Adapted from BLA eCTD ISS (Integrated Summary of Safety): Figure IAS-1.1.

While a subject was receiving study treatment, the response assessment schedule included monthly clinical visits, and imaging scans every 12 weeks. When a subject discontinued treatment, he or she should return in 30 days for the End of Treatment (EOT)/Early Termination visit, when the last response assessment would occur. After the EOT visit, the subject would not receive any additional response assessments, but would be followed for survival at 3-month intervals. However, subjects who temporarily stopped treatment because they did not have any remaining injectable lesions did not have an EOT visit; rather, these subjects continued to be followed for response. Therefore, the comparatively much higher percentage of subjects in the control arm who discontinued study treatment by Week 24, suggests that control subjects may have been assessed for

tumor response for a shorter time than talimogene laherparepvec subjects. For example, eight (5.7%) of the control group subjects, but none of the talimogene laherparepvec group subjects, had their last tumor assessment within the first 28 days. This differential follow-up may have influenced the study results for the primary endpoint, and may have also influenced the study safety results.

6.2 Secondary Endpoint: Overall Survival

An interim analysis (IA) of OS occurred at the time of the primary analysis of DRR, when DRR was statistically significant in the comparison between the two arms. At this time, 250 deaths had been recorded. This IA of OS yielded a p-value of 0.075 (Applicant's analysis). Therefore the primary analysis of OS was to occur at 290 deaths. No other IA of OS occurred. The descriptive analysis of OS at the end of study (EOS) identified one additional death in the talimogene laherparepvec arm during the additional follow-up period between the time of primary analysis of OS and EOS.

The event-driven OS primary analysis, at 290 events, set the analysis cut-off date (ACOD) to March 31, 2014. As of the ACOD, there were 189/295 (64%) confirmed deaths in the talimogene laherparepvec arm and 101/141 (72%) confirmed deaths in the control arm. The primary analysis using the un-adjusted log-rank test yielded a p-value of 0.051. The estimates of median OS (in months) and the 95% confidence intervals (CIs) were 23.3 (19.6, 29.7) for the talimogene laherparepvec arm and 18.9 (16.2, 24.0) for the control arm. The estimate of the hazard ratio was 0.79 (0.62, 1.00).

The proportion of subjects who were randomized but not treated was 4/295 (1.4%) in the talimogene laherparepvec arm and 14/141 (9.9%) in the control arm. Due to this substantial difference between the two arms, the FDA performed a detailed analysis of time of event/censoring and reason for censoring, to examine the potential for bias due to censoring that may be related to risk of death ("informative censoring") or to arm assignment.

Censoring due to the ACOD is considered non-informative. The FDA identified a total of 10 subjects who were censored for reasons other than the ACOD and therefore may represent informative censoring. Seven of these 10 observations were censored soon after randomization, with six censored within 16 days and one censored on Day 86. The potentially informative censoring distributed disproportionately in the control arm (7/141, 5%), compared to the talimogene laherparepvec arm (3/295, 1%). For the seven subjects in the control arm, the "reason for ending study" was "consent withdrawn" in six subjects and "lost to follow-up" in one subject. For the three subjects in the talimogene laherparepvec arm, the "reason for ending study" was "consent withdrawn" in two subjects and "subject randomized in error; subject was ineligible [for enrollment] due to brain mets" in one subject. Thus, the "reason for ending study" was "consent withdrawn" in eight of the 10 subjects with potentially informative censoring. As of the analysis cut-off date, the survival status of these 10 subjects is unknown. The FDA performed several post hoc sensitivity analyses on OS by varying the survival status and censoring times of these 10 subjects. One such FDA sensitivity analysis imputed the censoring times of these 10 subjects using the ACOD as the last known alive date. This sensitivity analysis yielded a p-value of 0.155 and a hazard ratio of 0.84 (0.66, 1.07). Please refer to Figure 5 for a comparison of the results between the primary analysis and this sensitivity analysis. While the survival curves between the two arms, in the sensitivity analysis, continue to visually suggest some difference in time to death, the presence of potentially informative censoring increases the uncertainty about the presence and magnitude of comparative effect on OS in the T-Vec arm.

Recommendation: Exclude. Await confirmatory trial which may establish OS. Also need further safety data because even with the disproportionate advantage in this trial given to T-Vec, the AEs were substantial.

Mepolizumab 100mg/vial (Nucala) SC preservative-free solution for inj.
Micah Sukany, Jill Johnson, Pharm.D.
12/1/15

FDA indication: as add-on maintenance treatment of severe asthma in adults and children ≥ 12 y with eosinophilic phenotype.

MOA: IL-5 antagonist (IgG1 kappa). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activation, and survival of eosinophils. Mepolizumab reduces IL-5 signaling and reduces the production and survival of eosinophils. MOA in asthma has not been established.

Dose: 100mg Q4w

Study Design:

In this R, DB, **double-dummy study**, **576 patients** ages 12-82y w/ recurrent asthma exacerbations and evidence of eosinophilic inflammation despite high doses of ICS were randomized to either a **75-mg IV dose or a 100-mg SC dose of mepolizumab, or placebo Q4w X 32w**. The 1st outcome was the **annualized frequency of clinically significant exacerbations**, which were defined as **worsening of asthma such that the treating physician elected to administer systemic glucocorticoids for at least 3d** or the patient visited an ED or was hospitalized.

Patients had a clinical diagnosis of asthma and a **FEV1 of <80% of the predicted value** (in the case of adults) or an FEV1 of <90% of the predicted value or a ratio of the FEV1 to the forced vital capacity (FVC) of less than 0.8 (in the case of adolescents <18y). In addition, pts were required to have ≥ 1 of the following three test results: **FEV1 reversibility of more than 12%**, positive results on methacholine or mannitol challenge at visit 1 or 2 or during the previous year, and FEV1 variability ($\geq 20\%$) between 2 clinic visits in the past 12m. **All patients had to have had ≥ 2 asthma exacerbations in the previous 1y that were treated with systemic glucocorticoids while they were receiving treatment with at least 880 μ g of fluticasone propionate or the equivalent by inh/d and ≥ 3 m of treatment with an additional controller.** In addition, all patients had to have an eosinophil count of at least 150 cells/uL in the peripheral blood at screening or ≥ 300 cells/uL in the previous year.

Results:

The estimated rates of clinically significant exacerbations per patient per year were 0.93 in the IV-mepolizumab group, 0.83 in the SC-mepolizumab group, and 1.74 in the placebo group.

The exacerbation rate was reduced by 47% (95%CI, 29 to 61) with IV mepolizumab and by 53% (95%CI, 37 to 65) w/ SC mepolizumab, compared w/ placebo (P<0.001 for both comparisons).

The proportion of pts w/ an exacerbation that resulted in an ED visit or hospitalization was 9% in the IV-mepolizumab group, 6% in the SC-mepolizumab group, and 13% in the placebo group. Exacerbations necessitating an ED visit or hospitalization were reduced by 32% w/ IV mepolizumab and by 61% w/ SC mepolizumab.

At w 32, the mean increase from baseline in FEV1 was 100 ml greater w/ IV mepolizumab than w/ placebo (P=0.02) and 98 ml greater w/ SC mepolizumab than w/ placebo (P=0.03). Improvement from baseline in the SGRQ score was 6.4 and 7.0 pts greater in the IV and SC mepolizumab groups, respectively, than in the placebo group (minimal clinically important change, 4 pts), and the improvement in the ACQ-5 score was 0.42 points and 0.44 points greater in the two mepolizumab groups, respectively, than in the placebo group (minimal clinically important change, 0.5 points) (P<0.001 for all comparisons). **The safety profile of mepolizumab was similar to that of placebo.**

Ortega, HG, et al. "Mepolizumab treatment in patients with severe eosinophilic asthma" New England Journal of Medicine 2014 September 25:371(13):1198-207.

Study Design:

In this phase III, DB, PC trial, n=525 w/ severe allergic asthma requiring QD ICS were randomized to **receive placebo or SC omalizumab q2 or 4 weeks**, depending on baseline IgE level and body weight. **ICS doses were kept stable over the initial 16 w of treatment and tapered during a further 12-w treatment period.** The 1st endpt was the **# of exacerbation episodes** experienced by a patient during the steroid reduction period and during the stable steroid phase. **An asthma exacerbation was defined as a worsening of asthma symptoms, as determined by 1 or more of the criteria listed above, that was severe enough to require treatment with oral or intravenous corticosteroids or a doubling of the subject's baseline inhaled beclomethasone dipropionate (BDP) dose.**

Patients: **Male or female allergic asthmatics aged 12-75 years** who were symptomatic despite treatment with ICSs were eligible if they met the following criteria: duration of asthma, ≥ 1 year; positive immediate responses on skin prick testing to at least 1 common allergen, including *Dermatophagoides farinae*, *Dermatophagoides pteronyssinus*, cockroach (whole body), dog, or cat; total serum IgE ≥ 30 IU/mL to ≤ 700 IU/mL; **FEV1 reversibility of $\geq 12\%$ within 30 minutes after administration of albuterol (90-180 μ g); baseline FEV1 $\geq 40\%$ and $\leq 80\%$ of predicted; and treatment with 420 to 840 μ g/day of BDP or its equivalent ICS for ≥ 3 months prior to randomization.**

Results: Omalizumab treatment resulted in **significantly fewer asthma exacs/subject and in lower %s of subjects experiencing an exacerbation than Plac treatment during the stable steroid phase (0.28 vs 0.54 [P = .006] and 14.6% vs 23.3% [P = .009], respectively)** and during the steroid reduction phase (0.39 vs 0.66 [P = .003] and 21.3% vs 32.3% [P = .004], respectively).

Busse, Williams, MD, et al. "Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma." Journal of Allergy and Clinical Immunology. 2001 August 108(2):155-314.

Table 2. Summary of Efficacy Outcomes.*

Outcome	Placebo (N=191)	Intravenous Mepolizumab (N=191)	Difference from Placebo (95% CI)	P Value	Subcutaneous Mepolizumab (N=194)	Difference from Placebo (95% CI)	P Value
Mean rate of clinically significant exacerbations	1.74	0.93	47 (28 to 60)†	<0.001	0.83	53 (36 to 65)†	<0.001
Mean rate of exacerbations requiring hospitalization or emergency department visit	0.20	0.14	32 (-41 to 67)†	0.30	0.08	61 (17 to 82)†	0.02
Mean rate of exacerbations requiring hospitalization	0.10	0.06	39 (-66 to 77)†	0.33	0.03	69 (9 to 89)†	0.03
Change from baseline in FEV ₁ — ml							
Before bronchodilation	86±31	186±32	100 (13 to 187)	0.02	183±31	98 (11 to 184)	0.03
After bronchodilation	30±34	176±34	146 (50 to 242)	0.003	167±33	138 (43 to 232)	0.004
Change from baseline in score on Asthma Control Questionnaire	-0.50±0.07	-0.92±0.07	-0.42 (-0.61 to -0.23)	<0.001	-0.94±0.07	-0.44 (-0.63 to -0.25)	<0.001
Change from baseline in score on St. George's Respiratory Questionnaire	-9.0±1.2	-15.4±1.2	-6.4 (-9.7 to -3.2)	<0.001	-16.0±1.1	-7.0 (-10.2 to -3.8)	<0.001

* Plus-minus values are means ±SE.

† The between-group difference in this category is the percent reduction as compared with the placebo group.

Independent group says new Glaxo asthma drug far too expensive (Reuters 12/21/15)

The Boston-based Institute for Clinical and Economic Review (ICER) reports that the price of mepolizumab (Nucala—GlaxoSmithKline) should be up to 76% lower to justify its value. The nonprofit analyzed the once-monthly injectable drug for severe asthma, finding that it should be priced at \$7,800 to \$12,000 a year, compared with the current list price of \$32,500 a year. While the drug significantly reduces asthma attacks and symptoms and lessens a patient's need for oral steroids, ICER said that the price was not cost-effective, especially because there is uncertainty about the long-term benefits. ICER said that its latest draft report will be available for public comment until January 12.

Cost:

	Pt wt (kg)	IgE pretreatment serum IgE units/mL	Dose	Freq	AWP/30d (12/28/15)
Omalizumab SC	30-90	>30-100	150mg	Q4w	\$1090.79
	>90-150	>30-100	300mg	Q4w	\$2181.58
	30-90	>100-200	300mg	Q4w	\$2181.58
	>90-150	>100-200	225mg	Q2w	
	30-60	>200-300	300mg	Q4w	\$2181.58
	>60-90	>200-300	225mg	Q2w	
	>90-150	>200-300	300mg	Q2w	\$4363.16
	30-70	>300-400	225mg	Q2w	
	>70-90	>300-400	300mg	Q2w	\$4363.16
	>90	>300-400	Do not administer		
	30-70	>400-500	300mg	Q2w	\$4363.16
	>70-90	>400-500	375mg	Q2w	
	>90	>400-500	Do not administer		
	30-60	>500-600	300mg	Q2w	\$4363.16
	>60-70	>500-600	375mg	Q2w	
	>70	>500-600	Do not administer		
	30-60	>600-700	375mg	Q2w	
	>60	>600-700	Do not administer		
Mepolizumab SC			100mg	Q4w	\$3000.00

Campbell 2010. USA **Moderate to severe persistent asthma uncontrolled with ICS \$287,200/QALY (£176,369/QALY)** Adding omalizumab to usual care improves QALYs at an increase in direct medical costs. The value increases when omalizumab response is used to guide long-term treatment. Ref: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4314644/pdf/srep08191.pdf>

Current omalizumab PA criteria:

ASTHMA

1. Is the patient 12 years of age or older ¹ ?	<input type="checkbox"/> Yes <input type="checkbox"/> No If yes, go on to next question. If no, stop and deny coverage.
2. Does the patient have a diagnosis of moderate or severe persistent asthma with either a positive skin test or with in vitro reactivity to a perennial aeroallergen?	<input type="checkbox"/> Yes <input type="checkbox"/> No If yes, go on to next question. If no, stop and deny coverage.
3. Does the patient have a total serum IgE level ≥ 30 IU/mL?	<input type="checkbox"/> Yes <input type="checkbox"/> No If yes, go on to next question. If no, stop and deny coverage.
4. Has the patient been prescribed and had filled inhaled corticosteroids/LABA combination for a minimum of the past 3 of 4 months prior to this request?	<input type="checkbox"/> Yes <input type="checkbox"/> No If yes, go on to next question. If no, stop and deny coverage.
5. Has the patient been determined to be dependent on systemic steroids to prevent serious asthma exacerbations ² ?	<input type="checkbox"/> Yes <input type="checkbox"/> No If no, go on to next question. If yes, stop and deny coverage.
6. Does the patient have FEV1 >80% at the time he/she is requesting the first prior authorization ³ ?	<input type="checkbox"/> Yes <input type="checkbox"/> No If yes, deny.
Patients must be 12 or older with the diagnosis of asthma not controlled by continued inhaled corticosteroids and with either a positive skin test or with in vitro reactivity to a perennial aeroallergen. They (arbitrarily) should have 75% ICS adherence rate. Xolair failed to show a benefit in patients with FEV1 >80% at initiation. Xolair also failed to reduce exacerbations in pts requiring maintenance systemic steroids.	
Note: Xolair® (omalizumab) is FDA approved as add-on therapy to optimal asthma therapy. Currently there is not peer-reviewed published literature to support its use as monotherapy in asthma and therefore will not be covered in this manner.	
DOSE is 150-375mg SC q2 or 4w as determined by serum total IgE level measured before the start of therapy. (See chart in the package insert.)	
If approved for coverage, PA is good for 3 months. Re-authorization for a PA will require the patient to be compliant with optimal asthma drug therapy as per the current NHLBI Asthma guidelines ⁴ .	

Proposal for mepolizumab:

Option 1: Cover same tier as omalizumab (patent expiration Jan 2020). Require PA regarding asthma. No coverage for urticaria. EBD utilization 2015Q2 was 18 users/45 Rxs, \$112046 (~\$450K/y).

Option 2: Exclude, code 13.

Daratumumab (Darzalex®)

Antineoplastic agent: Anti-CD38 monoclonal antibody

Daratumumab is a human IgG1_k monoclonal antibody directed against CD-38. By binding to CD38, daratumumab inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity, antibody dependent cell mediated cytotoxicity, and antibody dependent cellular phagocytosis.¹

FDA Approved Indication: Multiple myeloma (MM), relapsed/refractory: Daratumumab is currently indicated for treatment of multiple myeloma in patients who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.

Vial Size and Cost:

5mL single-dose vial (100mg/5mL)	\$540/vial [†]
20mL single-dose vial (400mg/20mL)	\$2160/vial [†]

[†]AWP \$108/mL

Dosing & Administration:²

- The recommended dose of daratumumab is **16 mg/kg body weight** administered as an intravenous infusion according to the following dosing schedule:

Weeks of Treatment	Schedule	Cost/treatment for 70kg patient ³	Cost/phase for 70kg patient
Weeks 1 – 8	Weekly	\$6048	\$48,384 (total of 8 - 16mg/kg doses)
Weeks 9 – 24	Every 2 weeks		\$48,384 (total of 8 - 16mg/kg doses)
Weeks 25 and beyond ^a	Every 4 weeks		\$6048 q 4 weeks indefinitely

^aContinued until disease progression

Clinical Studies:

Phase 1-2 trial (dose-escalation and dose-expansion study)¹

	8 mg/kg Cohort ^b (N=30)	16 mg/kg Cohort ^c (N=42)
Discontinuation of therapy ^c , N (%) (Reason (N))	30 (100) (Disease progression (30))	28 (66.7) (Disease progression (23), physician decision (4), adverse event ^d (1))
Overall Response Rates (ORR), %	10%	36%
CR, N (%)	0	2 (4.8)
VGPR, N (%)	0	2 (4.8)
PR, N (%)	3 (10)	11 (26)
Reduction of at least 50% in level of M protein or free light chains, N (%)	4/27 (15%)	19/41 (46%)
Estimated median progression free survival, months (95% CI)	2.4 (1.4-2.5)	5.6 (4.2-8.1)
Overall survival rate at 12 months, % (95% CI)	77 (52-90)	77 (58-88)

^bBoth cohorts' (8 mg/kg and 16 mg/kg) median number of prior lines of therapy was 4; range 3-10 and 2-12, respectively

^cAt clinical cutoff date Jan 9th, 2015

^dGrade 5 pneumonia deemed unrelated to study drug

There was an open-label trial¹ evaluating daratumumab monotherapy in patients with relapsed or refractory multiple myeloma who had received at least 3 prior lines of therapy including a proteasome inhibitor and an immunomodulatory agent or who were double-refractory to a proteasome inhibitor and an immunomodulatory agent.

Efficacy results from Study 1¹

	16 mg/kg (N=106)
Overall response rate (ORR), %(95% CI)	29.2 (20.8 – 38.9)
Stringent complete response (sCR), N (%)	3 (2.8)
Complete response (CR), N (%)	0
Very good partial response (VGPR), N (%)	10 (9.4)
Partial response (PR), N (%)	18 (17)
Median time to response, month (range)	1 (0.9 – 5.6)
Median duration of response, month (range)	7.4 (1.2 – 13.1+)
Estimated median progression free survival, months (95% CI)	3.7 (2.8 – 4.6)
Overall survival rate at 12 months, % (95% CI)	65 (51.2 – 75.5)
Serious treatment-emergent adverse events, N (%) ^e	32 (30)
Grade 3/4, N (%)	24 (23)

Abbreviations: ORR, sCR+CR+VGPR+PR; CI, confidence interval

^eNo patient discontinued treatment due to adverse events

Adverse Reactions:¹

		Daratumumab 16 mg/kg (N=156)
		Incidence
Infusion reaction, N (%)		75 (48)
	Second infusion, %	5
	Subsequent infusions, %	4
Serious adverse event, N (%)		51 (33)
	Pneumonia, %	6
	General physical health deterioration, %	3
	Pyrexia, %	3
Treatment delay due to adverse event [†] , N (%)		24 (15)
Treatment discontinuation due to adverse event, N (%)		6 (4)

[†]Most commonly due to infection

Recommendation: Exclude from coverage until more data on overall survival is available.

References:

1. Lokhorst HM, Plesner T, Laubach JP, et al. Targeting CD38 with Daratumumab Monotherapy in Multiple Myeloma. *N Engl J Med.* 2015;373(13):1207-1219.
2. Darzalex (daratumumab) [prescribing information]. Horsham, PA: Janssen Biotech, Inc.; November 2015.
3. Moreau P, Pylypenko H, Grosicki S, et al, "Subcutaneous Versus Intravenous Administration of Bortezomib in Patients With Relapsed Multiple Myeloma: A Randomised, Phase 3, Non-Inferiority Study," *Lancet Oncol*, 2011, 12(5):431-40.

Metastatic Melanoma, rev JJ12-11-15

Oral Therapy

1st line therapy if BRAF+:

	Vemurafenib ¹ (960 mg po bid)	Dabrafenib ² (150 mg po bid)	Trametinib ⁴ (2 mg po daily)	Trametinib + dabrafenib ⁵ Phase II	Trametinib+ Dabrafenib ^{6, 17} Phase III trial n=823	Trametinib+ Dabrafenib ⁷ Phase III trial (open label) n=704	Vemurafenib + Cobimetinib ¹⁸ Phase III trial N=495
BRAF status of patients enrolled	All BRAF mut pos	All BRAF mut pos	All BRAF mut pos	All BRAF mut pos	All BRAF mut pos	All BRAF mut pos	Mostly BRAF Mut pos; up to 21% could not be evaluated.
Comparison	Dacarbazine	Dacarbazine	Dacarbazine or paclitaxel	Dabrafenib	Dabrafenib	Vemurafenib	Vemurafenib
Previous lines of tx allowed	None	None (except IL-2)	0 or 1 (but no BRAF inh or ipi)	No restriction stated	None	None	None
Response rate (%)	48%	50%	22%	76% vs 54%	67%	64%	CR or PR: 68% vs 45% CR alone 10% vs 4% ORR 69.6% vs 50%; CRR 15.8% v 10.5%
PFS (mo)	5.3 ^a	5.1	4.8	9.4 vs 5.8	9.3 vs. 8.8 mo Final update: 11 vs 8.8	11.4 vs. 7.3 mo	9.9m vs 6.2m (HR 0.51; 95%CI 0.39-0.68; p<0.001); Update per 2015 abstract ²⁰ at 14.2mf/u; cobl- veml 12.25m vs 7.2m (HR: 0.58; 95%CI 0.46-0.719)
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)	At 6 months: 93% alive vs. 85% (p=0.02) Final results: 25.1m vs 18.7m (HR 0.71; 95%CI 0.55-0.92); p=0.0107; 1yOS 74% vs 68% 2yOS 51% vs 42%	HR 0.69, (p=0.0049) At 12 months: 72% alive vs. 65% (p=0.005)	Median OS Not reached in either group; 9m OS rates 81.1% vs 72.5%; Death HR 0.65 (95%CI:0.42-1) Updated from abstract ¹⁹ . After 18.5m f/u, OS was 23.3m v 17.4m; HR=0.7, 95%CI 0.55-0.9; p=0.005
Current coverage	PA	PA	PA requires dabrafenib	PA	PA	PA	TBD
NCCN 2.2016	Category 1	Category 1	Category 1	Category 1	Category 1	Category 1	Category 1

^a Median PFS of chemotherapy groups were 1.5 - 2.7 mo. Response rates <15%

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

Osimertinib (Tagrisso)
Andrew Mullings, Pharm.D.
12/25/2015

Product Summary: is a third generation TKI now indicated for the treatment of EGFR T790M-mutant non-small cell lung cancer (NSCLC) following resistance to frontline EGFR TKI (erlotinib, gefitinib, and afatinib) therapy.

Current Guidance: NCCN guidelines currently recommend initiating osimertinib or continuing an EGFR if progression occurs unless patient is symptomatic with systemic progression and multiple lesions. Options at that point include first-line systemic therapy or osimertinib. ASCO, based on a low quality of evidence and low strength of recommendation, chemotherapy or recommend another EGFR TKI as second line therapy.

Evidence: The efficacy of TAGRISSO was demonstrated in two multicenter, single-arm, open-label clinical trials, Study 1 and Study 2, in patients with metastatic EGFR T790M mutation-positive NSCLC who had progressed on prior systemic therapy, including an EGFR TKI. All patients were required to have EGFR T790M mutation-positive NSCLC and received osimertinib daily. According to FDA data, Baseline patient and disease characteristics were: median age 63 years, 13% of patients were ≥75 years old, female (68%), White (36%), Asian (60%), metastatic (96%), sites of brain metastases (39%), World Health Organization (WHO) performance status of 0 (37%) or 1 (63%), 1 prior line of therapy [EGFR-TKI treatment only, second line, chemotherapy-naïve (31%)], 2 or more prior lines of therapy (69%).

Efficacy Table

Efficacy Parameter	Study 1 (N=201)	Study 2 (N=210)	Overall (N=411)
Objective Response Rate	57% (50 - 64)	61% (54 - 68)	59% (54 - 64)
Complete Response	0	1%	0.5%
Partial Response	57%	60%	59%

Safety

Adverse Reaction	Osimertinib	
	All Grades	Grade 3-4
	%	%
Diarrhea	42	1.0
Nausea	17	0.5
Decreased Appetite	16	0.7
Constipation	15	0.2
Stomatitis	12	0
Rash	41	0.5
Dry Skin	31	0
Nail Toxicity	25	0
Pruritus	14	0
Eye disorders	18	0.2
Cough	14	0.2
Fatigue	14	0.5
Back Pain	13	0.7
Headache	10	0.2
Pneumonia	4	2.2
Venous thromboembolism	7	2.4

Cost Analysis			
Agent	Dose	Cost Per Unit	Total Cost
Osimertinib	80mg daily	\$15300 #30	\$15300.00
Afatinib	40mg daily	\$7768.22 #30	\$7768.22
Erlotinib	150mg daily	\$8050.79 #30	\$8050.79
Gefitinib	250mg daily	\$8040.00 #30	\$8040.00
Docetaxel	75mg/m2 Q3weeks	\$309.22 (20mg vial)*	\$1560.00
		\$1560.00 (140mg vial)	

Package Insert. Tagrisso. 2015.

Mitsudomi T, Tsai C, Shepherd F, et al. AZD9291 in pre-treated T790M positive advanced NSCLC: AURA2 Phase II study. Presented at: 16th World Conference on Lung CA; September 6-9; Denver, CO. Abst 1406.

Yang JC, Ahn M, Ramalingam SS, et al. AZD9291 in pre-treated T790M positive advanced NSCLC: AURA study Phase II extension cohort. Presented at: 16th World Conference on Lung Cancer; 9/6-9/9/15. Denver, CO. Abst 943

Recommendation: *Due to the lack of comparative efficacy and safety data, recommend exclusion.*

Elotuzumab (EMPLICITI®)
Janna Hawthorne, Pharm.D.

FDA-approved indications: Treatment of multiple myeloma (MM) in combination with lenalidomide (Revlimid®) and dexamethasone in patients who have received 1 to 3 prior therapies. (Orphan drug)

Comparators:

Drug Name	Dosing	Dosage Form	Price (28 days)
Empliciti® (elotuzumab)	Based on weight and cycle (based on 28 day cycles)	300 mg & 400 mg IV solution	\$2,131.20 per 300 mg vial & \$2,841.60 per 400 mg vial
	Pt weighing 45 kg: Cycle 1 & 2 – 10 mg/kg on days 1, 8, 15, & 22: 1,800 mg = 4.5 bottles = \$14,208.00 Cycle 3+ – 10 mg/kg on days 1 & 15: 900 mg = 3 bottles = \$6,393.60		
Pomalyst® (pomalidomide)	4 mg daily (day 1-21 of 28 day cycle)	1 mg, 2 mg, 3 mg, & 4 mg capsule	\$698.67/capsule X 21 = \$14,671.98
Kyprolis® (carfilzomib)	Based on BSA and cycle	60 mg IV solution	\$2,234.34 per 60 mg vial
	Pt with a BSA of 1.73m ² : Cycle 1: 20 mg/m ² on days 1 & 2, 27 mg/m ² on day 8, 9, 15 & 16: 256 mg = \$11,171.70 Cycle 2-12: 27 mg/m ² on days 1, 2, 8, 9, 15, & 16: 280 mg = \$11,171.70 Cycle 13+27 mg/m ² on days 1, 2, 15, & 16: 180 mg = \$6,703.02		
Farydak® (panobinostat)	20 mg every other day (3 times per week) during weeks 1 and 2 of a 28 day cycle	10 mg, 15 mg, & 20 mg capsule	\$1,372/capsule X 6 = \$8,232.00
Ninlaro® (ixazomib)	4 mg daily (day 1, 8, & 15 of a 28 day cycle)	2.3 mg, 3 mg, & 4 mg capsule	\$3,468.00/capsule X 3 = \$10,404.00

MOA: Signaling lymphocytic activation molecule family member 7 (SLAMF7) is expressed on most myeloma and natural killer cells but not on normal tissue. Elotuzumab is a humanized IgG1 MAB that exhibits immunostimulatory activity on NK cells by activating the SLAMF7 pathway. Elotuzumab also mediates antibody-dependent cellular cytotoxicity on myeloma cells through the CD16 pathway.

Adverse Drug Events: Infusion reactions, opportunistic infections (mainly herpes zoster and fungal), second 1' malignancies, hepatotoxicity, fatigue, peripheral neuropathy, hyperglycemia, and fever

Evidence of efficacy in multiple myeloma:

1. In a randomized, phase III, open-label, controlled trial. Pts w/ MM who progressed after 1-3 previous therapies were randomized to receive either **elotuzumab plus lenalidomide and dexamethasone** versus **lenalidomide plus dexamethasone alone**.

Elotuzumab Group	Cycle 1 & 2: 10 mg/kg IV elotuzumab on days 1, 8, 15, & 22 Cycles 3+: 10 mg/kg IV elotuzumab on days 1 & 15	All cycles: • 25 mg daily IV lenalidomide on days 1 – 21 • 40 mg PO dexamethasone on the days without elotuzumab OR 8 mg IV dexamethasone plus 28 mg PO dexamethasone on days with elotuzumab dosing
Control Group		All cycles: • 25 mg daily IV lenalidomide on days 1 -21 • 40 mg PO dexamethasone on days 1, 8, 15, & 22

Co-primary endpoints were PFS and overall response rate (ORR) while 2' endpoints were OS and the severity of pain or interference with daily life. The study was continued until the final OS end point of 427 deaths was met. Patients were followed for a medium follow-up time of 24.5 m.

Results:

- 1' outcome at 1 y for the elotuzumab group versus control group was 68% (95%CI 63-73%) and 57% (95%CI 51-62%) and the rate of 1' outcomes at 2 y for these groups was 41% (95%CI 35-47%) versus 27% (95%CI 22-33%), respectively.
- Median PFS in the elotuzumab group vs control group was 19.4 months and 14.9 months (p <0.001).
- ORR were 79% in the elotuzumab group vs 66% in the control group (p<0.001) with a median survival of 26 m compared to 17.3 m (NO STATS GIVEN).
- Partial response: 33% of the elotuzumab group vs 28% in the control group
- Duration of response was 21m in the elotuzumab group vs 17 m in the control group. As for the 2' endpts, no statistical difference was found in change from baseline pain severity or pain interference and no detriment in the health-related QOL was reported. SAEs were reported in 65% of the elotuzumab group vs 57% of the control group. Considering the 65% with SAEs, 34% of elotuzumab pts developed grade 3 or 4 neutropenia and 77% developed grade 3 or 4 lymphocytopenia. Considering the 57% w/ SAEs in the control group, 49% developed grade 3 or 4 neutropenia and 49% developed grade 3 or 4 lymphocytopenia. The rate of herpes zoster infection was also greater in the elotuzumab group than in the control group.

Summary: PFS was stat signif at 19.4m (E) vs 14.9m (control) in pts with progressing multiple myeloma after multiple therapies have been exhausted. ORR was also significantly better with the addition of this elotuzumab and no adverse reactions on QOL or pain severity were noted to be different between groups. No stats were provided for OS but was numerically longer for elotuzumab by 8.7m.

Recommendations: Efficacy has been demonstrated in patients who have met FDA labeled indication criteria. Although this medication is more expensive than others, I would recommend to add it to formulary and require a PA.

OUTCOME of EBRx: Cover with a PA.

References:

1. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma, *The New England Journal of Medicine*. 2015; 373(3):621-31.
2. Empliciti [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2015.
3. Liu YC, Szmania S, Rhee F. Profile of elotuzumab and its potential in the treatment of multiple myeloma. *Blood Lymphat Cancer*. 2014(4):15-27.
4. Empliciti. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH. Available at: <http://online.lexi.com>. Accessed January 18, 2016.

EBRx PA Criteria
Elotuzumab (Empliciti)

is FDA-approved for: treatment of multiple myeloma in combination with lenalidomide and dexamethasone in patients who have received 1-3 prior therapies.

Criteria for new users

- | |
|--|
| 1. Dx of multiple myeloma |
| 2. Must have been treated with at least 1 prior therapy. (prior lenalidomide therapy may count as a prior therapy) |
| 3. Must have documented progression after most recent therapy. |

Revision History:

Date	What changed	Pharmacist's initials
1/29/2016	I wrote the criteria.	JJ

References:

1. Lonial S, Dimopoulos M, Palumbo A, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. *The New England Journal of Medicine*. 2015; 373(3):621-31.
2. Empliciti [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2015.
3. Liu YC, Szmania S, Rhee F. Profile of elotuzumab and its potential in the treatment of multiple myeloma. *Blood Lymphat Cancer*. 2014(4);15-27.
4. Empliciti. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH. Available at: <http://online.lexi.com>. Accessed January 18, 2016.

**Ixazomib – Ninlaro
Tanner Simon P4
January 2016**

FDA Indication:

Ixazomib is a proteasome inhibitor used in combination w/ lenalidomide & dexamethasone for the treatment of pts w/ MM who have received at least one prior therapy.

Comparators:

Proteasome Inhibitors			
	How Supplied	Route of Administration	AWP
Ninlaro (ixazomib)	2.3, 3, & 4 mg	Capsule, Oral	\$3468 per capsule \$10404 per 28 day cycle
Velcade (bortezomib)	3.5 mg	IV Sub-Q	\$1932 Price of treatment cycle varies based on pt BSA
Kyprolis (carfilzomib)	60 mg	IV Sub-Q	\$2077.20 Price of treatment cycle varies based on pt BSA

Dosing of ixazomib taken in combination with lenalidomide and dexamethasone:

	28-Day Cycle							
	Week 1		Week 2		Week 3		Week 4	
	Day 1	Days 2-7	Day 8	Days 9-14	Day 15	Days 16-21	Day 22	Days 23-28
Ixazomib	4 mg		4 mg		4 mg			
Lenalidomide	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg	2.5 mg		
Dexamethasone	40 mg		40 mg		40 mg		40 mg	

Mechanism of Action:

Ixazomib is a reversible proteasome inhibitor of the 20S proteasome that preferentially binds the β_5 subunit of the 20S proteasome. The combination of ixazomib, lenalidomide & dexamethasone demonstrated synergistic cytotoxic effects in MM cells that are resistant to bortezomib.

Adverse Drug Events: Thrombocytopenia, diarrhea, constipation, nausea, vomiting, peripheral neuropathy, peripheral edema, cutaneous reactions (rash), hepatotoxicity, and embryo-fetal toxicity.

Drug Interactions: Strong CYP3A4 INDUCERS such as rifampin, phenytoin, carbamazepine, and St. John's Wort.

Evidence:

1. Ixazomib, an Investigational Oral Proteasome Inhibitor (PI), in Combination with Lenalidomide and Dexamethasone (IRd), Significantly Extends Progression-Free Survival (PFS) for Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (RRMM): The Phase 3 Tourmaline-MM1 Study

In this phase 3 trial ixazomib in combination with lenalidomide & dexamethasone was evaluated in a R, DB, PC, MC in pts w/ relapsed and/or refractory MM who had received at least one prior therapy. There was a total of 722 patients in this trial. Pts were randomized 1:1 (360 ixazomib regimen vs 362 placebo regimen). R was stratified by the number of prior lines of therapy, myeloma international staging system & whether or not the pt had previous PI therapy. Trx was continued until disease progression or unacceptable toxicities occurred.

Inclusions: M/F pts ≥ 18 y/o, MM (symptomatic on initial diagnosis), measurable disease (Serum M-protein ≥ 1 g/dL (≥ 10 g/L), Urine M-protein ≥ 200 mg/24 hours, Serum free light chain assay: involved free light chain level ≥ 10 mg/dL (≥ 100 mg/L), provided that the serum free light chain ratio is abnormal), pts w/ relapsed or refractory MM w/ 1-3 prior trx, ANC $\geq 1,000$, Plt $> 75,000$, Tbili $\leq 1.5 \times$ ULN, ALT & AST $< 3 \times$ ULN, CrCl > 30 , ECOG 0-2, pts who have received prior allogeneic transplant must have no GVHD, (-) pregnancy test, abstinence.

Exclusions: pt is refractory to lenalidomide or PI therapy, female pregnant/breast feeding, failure to recover from prior chemo (grade 1 tox), major surgery w/n 14d b4 R, radiotherapy w/n 14d R, CNS involvement, infection requiring antibiotic w/n 14d R, diagnosis of Waldenstrom's macroglobulinemia, POEMS, plasma cell leukemia, β_2 -microglobulin amyloidosis, myelodysplastic syndrome, or myeloproliferative syndrome, uncontrolled (HTN, CA, HF, unstable angina, or MI w/n 6m), treatment w/ strong CYP1A2 inhibitors, strong CYP3A4 inducers, or use of ginkgo bilboa or st. john's wort w/n 14d R, active Hep B, C, or HIV, comorbid illness (PN that could lead to false +), psychiatric illness, known allergy to study med, inability to swallow, or diagnosed/trx of another malignancy.

Results: The 1st outcome measured was PFS, 2nd was OS. Statistical issues were noted. The 1st interim analysis of PFS stated statistical significance, the final analysis determined PFS was not statistically significant. Final analysis results are below

- PFS: HR 0.86 (95% CI, 0.70-1.06); events 48.1% (N) vs. 51.9% (placebo). The median PFS in months for N was 19.7m (95% CI, 17.7-26.9) vs 17.7m (95% CI, 15.4-21.2). 2m (~60d) improvement in PFS that was NOT statistically significant.
- OS: HR 0.87 (95% CI, 0.64-1.18); deaths 22.5% (N) vs 24.9% (placebo). OS is NOT statistically significant.

Conclusion: Due to the statistical discrepancies, a reliable estimate of PFS or OS could not be determined.

Recommendation:

Exclude until further studies/maturing of data give a better idea of drug efficacy. Per clinicaltrials.gov this trial NCT01564537 has a completion date of May 2019.

References:

1. Moreau, Philippe, et al. "Ixazomib, an Investigational Oral Proteasome Inhibitor (PI), in Combination with Lenalidomide and Dexamethasone (IRd), Significantly Extends Progression-Free Survival (PFS) for Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (RRMM): The Phase 3 Tourmaline-MM1 Study (NCT01564537)." *Blood* 126.23 (2015): 727-727.
2. Ixazomib Package Insert. Cambridge, MA: Takeda Pharmaceutical Company Limited; November 2015.
3. Lexi-comp, accessed 1/13/2016.
4. FDA; US Dept of HHS Statistical Review and Evaluation, NDA 208462, Ninlaro, Multiple Myeloma. Statistical Reviewer Yun Want, PhD, et al. Reference ID 3841087. Accessed 1/25/2016. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2015/208462Orig1s000StatR.pdf (see page 4)

Antihemophilic Factor Recombinant Pegylated (Adynovate)

Andrew Mullings, PharmD

1/27/2016

	Adynovate	Eloctate
Indications	Adolescents and Adults (12 years and older) with Hemophilia A: - On-demand treatment and control of bleeding episodes - Routine prophylaxis to reduce the frequency of bleeding episodes	Adults and Children with Hemophilia A: - Control and prevention of bleeding episodes - Perioperative management (surgical prophylaxis) - Routine prophylaxis to prevent or reduce the frequency of bleeding episodes
On-Demand Dosing	Minor bleeds – 10-20 IU/kg every 12-24hrs Moderate bleeds – 15-30 IU/kg every 12-24hrs Major bleeds – 30-50 IU/kg every 8-24hrs	Minor/moderate bleeds – 20-30 IU/kg every 24-48hrs Major bleeds – 40-50 IU/kg every 12-24hrs
Prophylaxis Dosing	40-50 IU/kg, two times per week. Adjust the dose based on the patient's clinical response	50 IU/kg every 4 days; it may be adjusted based on patient response with dosing in the range of 25-65 IU/kg at 3-5 day intervals
ABR on Prophylaxis (Annualized bleeding rate)	All Bleeds: Median 1.9 twice weekly All Bleeds: Median 41.5 on-demand	All Bleeds: Median 1.60 on twice weekly individualized prophylaxis All Bleeds: Median 3.59 on weekly prophylaxis All Bleeds: Median 33.6 on-demand
% of Bleeds Treated with 1 or 2 infusions	85.4% of bleeds were treated with 1 infusion 96.2% of bleeds were treated with 1 or 2 infusions	87.3% of bleeds were treated with 1 infusion 97.7% of bleeds were treated with 1 or 2 infusions
Vial sizes (IU per vial)	250, 500, 1000, 2000	250, 500, 750, 1000, 1500, 2000, 3000
Shelf life	1 month	6 months
Per per unit	\$2.38	\$2.38
*Indirect comparison		

Recommendation: Consider placing on same tier at same coverage as Eloctate

EBRx: Tier 4 PA

ADYNOVATE® (antihemophilic factor [recombinant], PEGylated) Prescribing Information. Baxalta US, Inc: Westlake Village, CA. November 2015.

Mahlangu, Johnny, et al. "Phase 3 study of recombinant factor VIII Fc fusion protein in severe hemophilia A

ADYNOVATE® (antihemophilic factor [recombinant], PEGylated) AMCP Dossier. December 2015.

Coagulation Factor X (Human) (Coagadex)
Brett Bailey, Pharm.D. Candidate

FDA-approved indication: The treatment of adults and adolescents aged ≥ 12 years w/ hereditary Factor X deficiency for (1) on- demand treatment and control of bleeding episodes and (2) perioperative management of bleeding in pts w/ mild hereditary Factor X deficiency.

Background: Hereditary Factor X deficiency is a rare bleeding disorder (prevalence ~ 1:1,000,000) for which no specific coagulation factor replacement therapy is currently available in the US. Factor-X deficient pt are generally treated with FFP or PCC products. These medications contain numerous other plasma proteins and are not labeled with the specific Factor X content. PCCs are associated with a risk of thrombotic AEs. FFP requires large volumes because of the low Factor X content, which increases the risk of adverse transfusion reactions including circulatory overload and transfusion related acute lung injury (TRALI). The availability of a purified Factor X concentrate would increase treatment options by providing a more accurate dosing regimen and lesser exposure to other plasma proteins. FDA granted this product Orphan Drug Status (No. 07-2469) on November 8, 2007, Fast Track Designation on April 12, 2012, and Priority Review on September 6, 2013.

MOA: COAGADEX temporarily replaces the missing Factor X needed for effective hemostasis in the coagulation cascade.

Dosage Form: COAGADEX is a plasma-derived, sterile, purified concentrate of human coagulation Factor X that contains sucrose as a stabilizer available as lyophilized pwr for reconstitution in single-use vials containing ~250 IU or 500 IU of Factor X activity. The exact potency/content is listed on the vial label. When reconstituted using the Sterile Water for Injection supplied w/ the kit, the final concentration is ~100 IU/mL.

Dosing:

Bleeding episodes: IV: 25 units/kg/dose. Administer at a rate of 10 to 20 mL/minute w/in 1 h of reconstitution. Repeat q24h until bleeding stops.

Perioperative management of bleeding: IV:

Pre-surgery: the calculated dose should raise plasma factor X levels to 70 to 90 units/dL (or % of normal) using the following equation:

Number of factor X units required = Body weight (kg) x desired factor X increase (%) x 0.5 (Maximum daily dose: 60 units/kg/day)

Post-surgery: The calculated dose should maintain plasma factor X levels at ≥ 50 units/dL (or % of normal) until patient is no longer at risk of bleeding; Maximum daily dose: 60 units/kg/day

Dosing for Special Populations: No dosing adjustments for renal or hepatic impairment. Pregnant and Breastfeeding patients should take into account the risk of exposure to the infant, as these effects have not been studied.

Drug Interactions: Use with caution in pts receiving other plasma products that may contain Factor X, (e.g. FFP, PCC) based on MOA. Factor Xa inhibitors reduce the effect of Coagadex.

AEs: infusion site erythema, infusion site pain, fatigue, and back pain.

Pricing: \$9.29/unit

Expected Coagulation Factor X Price for Perioperative Treatment (Using 40 Units/kg Average Dose in Ten03)		
Weight	45 kg Child	100 kg Adult
Pre-Surgery	\$16,257.50/dose	\$37,160.00/dose
Post- Surgery	Must maintain levels ≥ 50 units/dl	
Prices rounded to the nearest 250 Units per packaging		

Clinical Trials:

From PI and abstract (no peer reviewed, published manuscript to date):

1. Ten01: COAGADEX was studied in a prospective, open-label, MC, non-randomized phase III study in 16 pts w/ severe/moderate factor X deficiency. COAGADEX was administered on demand or for short-term prophylaxis for 6 m to 2 y until ≥ 12 bleeding episodes had been treated with the product. In this study, 16 patients experienced a total of 187 bleeds. 98% of bleeds were controlled with 1 or 2 infusions of COAGADEX. 98.4% of bleeds were treated successfully (defined as "excellent" or "good" by patients and an independent review board).

2. Ten03: Two pts were enrolled in a non-randomized, prospective study in pts w/ mild to severe factor X deficiency (plasma concentration of factor X < 20 IU/dL) undergoing planned surgery. Both pts in Study Ten 03 had 2 separate surgical procedures. Pts were given a loading dose before the procedure to raise factor X level to 70-90 IU/dL. Doses after surgery were given to maintain factor X level above 50 IU/dL. No thrombotic events or other evidence of thrombogenicity were reported.

Conclusion: Coagadex provides an effective safe treatment for patients with Factor X deficiency, a condition previously not well treated.

Recommendation: Approve w/ PA. Allow for patients with Factor X deficiency undergoing elective surgery.

EBRx Vote Result: T4PA. **Criteria:** 1. Factor X deficiency, defined as Factor X activity $< 70\%$, 2. Undergoing elective surgery

References:

Austin S, Norton M, et al. Safety and efficacy of FACTOR X, a new high-purity factor X concentrate: a phase 3 study in patients with hereditary factor X deficiency. Poster presented at the 9th Annual Scientific Symposium of the Hemostasis and Thrombosis Research Society (HTRS), New Orleans, April 16-18 2015.

Escobar M, Auerswald G, Austin S, et al. Efficacy and safety of FACTOR X, a new high-purity factor X concentrate, in subjects with factor X deficiency undergoing surgery. Poster presented at the 9th Annual Scientific Symposium of the Hemostasis and Thrombosis Research Society (HTRS), New Orleans, April 16-18 2015.

Federal Food and Drug Administration. "Coagadex: Package Insert." October 2015. Accessed online at: <http://www.fda.gov/downloads/BiologicsBloodVaccines/BloodBloodProducts/ApprovedProducts/LicensedProductsBLAs/FractionatedPlasmaProducts/UCM468127.pdf>

Alectinib HCl (ALECENSA®)
Janna Hawthorne, Pharm.D.

FDA-approved indications: Treatment of metastatic anaplastic lymphoma kinase (ALK)+ metastatic non-small cell lung cancer (NSCLC) in patients who have progressed on or are intolerant to crizotinib (Xalkori®).

Comparators:

Drug Name	Dosing	Dosage Form	Price (AWP) for 28d or 30d
Alecensa® (alectinib HCl), supplied in bottle of 240	600 mg BID	150 mg capsule	\$61.64/capsule X 240 = \$14,793.60
Zykadia® (ceritinib), supplied in bottles of 70	750 mg daily	150 mg capsule	\$107.98/capsule X 140 = \$15,117.60

Mechanism of Action: ALK gene mutations occur within cancer cells and result in expression of ALK fusion protein. This protein alters the signaling and expression of ALK and results in increased proliferation and tumor survival. Alecensa® works as a TKI and inhibits ALK. This inhibition results in a downstream effect of decreased cell viability. Alecensa® works against most of the clinically observed acquired ALK resistant mutations to crizotinib (Xalkori®).

Adverse Drug Events: hepatotoxicity, inflammation of the lungs, bradycardia, myalgia, fatigue, constipation, edema

Evidence of efficacy in ALK-positive NSCLC:

1. Shaw, et al. conducted a phase II single-group, open-label, multicenter study in patients with ALK+, crizotinib-resistant, NSCLC. Pts were given 600 mg alectinib BID. ECOG 0-2, age ≥18, no previous ceritinib. Must have had previous crizotinib.

- 1 endpoint was the proportion of pts who achieved an OR as gauged by the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1.
- 2 endpoints were also assessed by RECIST version 1.1 and looked at OR and disease control in the CNS, and CNS progression. Other 2 endpoints: OS, safety, duration of response, and PFS.
- ¼ of pts had received previous CTX

87 pts were enrolled in the study and notably, 69 had measurable disease at baseline. Of these 69 patients after 4.8 m of therapy, 48% had a confirmed partial response, 32% has stable disease, and 16% had progressive disease as their best response. An updated analysis occurred after 9.9 m of therapy and analysis showed that 52% had OR. The estimated median PFS among all 87 patients was 8.1 months and the estimated overall survival as 12 months was 71%. At baseline 16 pts had measurable CNS disease and at the time of updated analysis, 4 pts (25%) had achieved a partial response and 12 pts (75%) received an OR with a median duration of CNS response of 11.1 months. AEs: 36% constipation, 33% fatigue, 24% myalgia, and 23% peripheral edema. Grade 3 or 4 AEs occurred with 8% of pts experiencing elevated CPK and 5% experiencing elevated AST/ALT. Global health status was assessed by means of the EORTC QLQ-C30 and QLQ-LC13 questionnaires and improvement was noted at 6 w and was sustained for ≥ 2 consecutive visits and was generally sustained until the EOT. A decrease in fatigue was noted from baseline demographics of study participants.

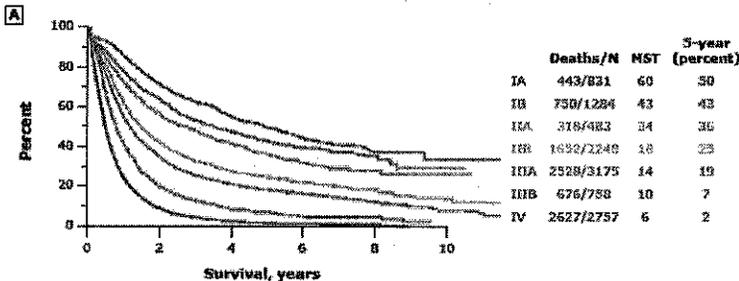
2. Ignatius Ou, et al. conducted a phase II, open-label, MC study in pts with crizotinib-refractory, ALK-rearranged NSCLC. Participants were given 600 mg alectinib BID. The 1' objectives were to determine ORR in pts who had and had not undergone previous CTX. 2' objectives: safety and tolerability profile, PFS, OS, and evaluate the efficacy of alectinib in the CNS. In this study, 138 pts began treatment but only 122 were considered response evaluable based on presence of measurable target lesions. Baseline demographics showed that 61% of the 122 patients had CNS metastases and of these pts, 42% had measurable CNS metastases and 73% had received prior brain radiation. Also at baseline, 80% of the patients had undergone some form of CTX. Analysis showed that there was a 49% ORR at 30 w and a 50% ORR at 47 w.

- Of the 96 pts w/ previous CTX, 44% had ORR at 30 w and a 45% ORR at 47 w.
 - For pts w/ previous CTX, PFS was 8.9 months.
- For the remaining 26 pts who had never had chemotherapy, 69% had ORR
 - PFS was 13 m in pts w/o previous CTX

Of the 35 patients with measurable CNS lesions @ baseline, 57% had ORR; 20% had a CR.

Of the 84 patients with baseline CNS metastases, 27% achieved a CNS complete response and the overall CNS disease control rate was 83%. The average CNS duration of response for these patients was 10.3 months. AEs: 33% constipation, 26% fatigue, 25% peripheral edema, 17% myalgia, and 11% asthenia.

UpToDate NSCLC OS data:



Summary: Alectinib has no comparative efficacy evidence in pts w/ ALK-positive NSCLC resistant to, or progressed after crizotinib therapy. It appears to produce an ORR in pts w/ CNS mets. Although the 2 above trials lack comparative arms, the OS chart from UpToDate shows 1 y OS for IIB and IV are 20% and 40%, respectively.

Recommendations: Options: 1. Exclude due to lack of comparative trials (even to placebo). 2. Cover w/ PA considering OS data from UTD. Re-evaluate crizotinib coverage for ALK+ NSCLC.

Results: Exclude due to no shown benefit and no coverage of Xalkori

References:

1. Shaw AT, Gandhi L, Gadgeel S, et al. Alectinib in ALK-Positive, Crizotinib-Resistant, Non-Small-Cell Lung Cancer: A Single-Group, Multicentre, Phase II Trial. *The Lancet Oncology*. 2015; [http://dx.doi.org/10.1016/S1470-2045\(15\)00488-X](http://dx.doi.org/10.1016/S1470-2045(15)00488-X)
2. Ignatius Ou SH, Ahn, JS, Petris LD, et al. Alectinib in Crizotinib-Refractory ALK-Rearranged Non-Small-Cell Lung Cancer: A Phase II Global Study. *Journal of Clinical Oncology*. 2015; <http://jco.ascpubs.org/cgi/doi/10.1200/JCO.2015.63.9443> [epub ahead of print]
3. Alecensa. Lexi-Drugs. Lexicomp. Wolters Kluwer Health, Inc. Hudson, OH. Available at: <http://online.lexi.com>. Accessed January 18, 2016.
4. McKeage, K. Alectinib: A Review of Its Use in Advanced ALK-Rearranged Non-Small Cell Lung Cancer. *Drugs*. 2015; 75:75-82.
5. UpToDate, NSCLC Prognosis. Accessed 1/21/16. <http://www.uptodate.com/contents/overview-of-the-initial-evaluation-treatment-and-prognosis-of-lung-cancer?source=machineLearning&search=nscl+prognosis&selectedTitle=1~150§ionRank=1&anchor=H3#H5>

Sebelipase Alfa (Kanuma)
20mg/10mL (10mL) IV preservative-free solution single use vials
Jill Johnson, Pharm.D.
1/5/16

Manufacturer: Alexion Pharmaceuticals; this is an orphan drug. It is a recombinant human enzyme replacement therapy. FDA Approved for: treatment of patients w/ lysosomal acid lipase (LAL) deficiency (Wolman's disease in infants).

Dose: IV Inf QE in pts w/ rapidly progressive LAL def in the 1st 6 months of life, and QOW in all other patients

Cost:

	AWP (\$)	Dose	AWP/4weeks (child 40kg)	AWP/4weeks (Adult 70kg)
Sebelipase alfa 20mg/10mL vial	1200/ml, \$12,000/10mL vial	Initial: IV 1mg/kg QW Max: IV 3mg/kg QOW	\$48K (2 vials/w X4w) \$36K (6vials/w X 4w)	\$96,000 (4 vials/w X 4w) \$264,000 (11 vials/w X 4w)

Evidence:

¹N=66 MC, R, DB, placebo-controlled of 1mg/kg QOW. The PC phase was 20w long and was followed by open label treatment for all patients. ⁵
^{1`} endpoint was normalization of ALT. ^{2`} endpoints . At 20 w, 31% of S pts had normal ALT, 7% of placebo did, P=0.03. AEs were similar in each group. Steatosis was less in the S group but did not reach significance. 2 of the 3 SAES were in the S group, one was study drug-related. 5 of the 35 in the S group had one or more positive antidrug-antibody tests during the 20 w study period.

²Lysosomal acid lipase deficiency should be suspected in patients with substantial hypercholesterolemia without a clear family history, especially if it is accompanied by a low HDL cholesterol level, elevated aminotransferase level, or fatty liver, and it should also be suspected in any patient with a diagnosis of micronodular cirrhosis on liver biopsy. A simple blood-based enzymatic assay is clinically available for patients in whom the diagnosis is suspected. LAL deficiency is "underrecognized and can be misdiagnosed as familial hypercholesterolemia or nonalcoholic fatty liver disease".

Refs:

1. Burton BK, Balwani M, et al. A phase 3 trial of sebelipase alfa in lysosomal acid lipase deficiency. N Engl J Med. 2015;373:1010-20.
2. Rader DJ. Lysosomal acid lipase deficiency-A new therapy for a genetic lipid disease. N Engl J Med. 2015;373:1071-73. (editorial) {note author received a grant from Synageva and spoke at the National Lipid Association on LAL deficiency sponsored by Synageva but did not accept compensation. He DOES accept fees from advisory boards from Pfizer, Novartis, Eli Lilly, Alnylam, Aegerion, and CSL Behring}.

Proposal: Exclude the drug. The evidence includes only surrogate endpoints at this time and does not yet show a correlation that the drug reduces progression to end stage fibrotic liver disease.

EBRx: Exclude, code 1.

Necitumumab – Portrazza
800mg/50mL solution IV infusion, single dose vial
Tanner Simon P4
January 2016

FDA Indication:

Necitumumab in combination with gemcitabine and cisplatin is first line treatment of metastatic squamous NSCLC.

Comparators:

Targeted Therapies for Non-Small Cell Lung Cancer				
	Target	Route of Administration	How Supplied	AWP
Necitumumab	EGFR Inhibitor	IV	800 mg/50 mL	\$4,800 (/50mL) \$14,400 per cycle
Bevacizumab	Angiogenesis Inhibitor	IV	100 mg/4 mL 400 mg/16 mL	\$832.74 (/4mL) \$3,330.96 (/16mL)
Ramucirumab	Angiogenesis Inhibitor	IV	100 mg/10 mL 500 mg/50 mL	\$1,224.00 (/10mL) \$6,120.00 (/50mL)
Erlotinib	EGFR Inhibitor with mutations	Oral	25 mg 100 mg 150 mg	\$2,591.45 (/30) \$7,117.85 (/30) \$8,050.79 (/30)
Afatinib	EGFR Inhibitor with mutations	Oral	20 mg 30 mg 40 mg	\$7,768.22 (/30) \$7,768.22 (/30) \$7,768.22 (/30)
Gefitinib	EGFR Inhibitor with mutations	Oral	250 mg	\$8,040.00 (/30)
Osimertinib	EGFR Inhibitor with T790M Mutation	Oral	40 mg 80 mg	\$13,596.60 (/31)
Crizotinib	ALK Gene	Oral	200 mg 250 mg	\$16,158.77 (/60) \$16,157.77 (/60)
Ceritinib	ALK Gene	Oral	150 mg	\$7,558.80 (/70) \$15,117.60 per cycle
Alectinib	ALK Gene	Oral	150 mg	\$14,793.60 (/240)

Dosing of Necitumumab: 800 mg as an IV infusion over 60 minutes on days 1 and 8 of each 3 weeks cycle prior to gemcitabine and cisplatin infusion.

Mechanism of Action: Necitumumab is a second generation, recombinant, human immunoglobulin G1 epidermal growth factor receptor (EGFR) monoclonal antibody that binds to EGFR with high affinity, competing with natural ligands and thereby preventing receptor activation and downstream signaling.

US Boxed Warning: Cardiopulmonary arrest and hypomagnesemia

Adverse Drug Events: Cardiopulmonary arrest, hypomagnesemia, venous & arterial thromboembolic events, dermatologic toxicities (rash, acne, pruritus, etc.), infusion related reactions (fever, chills, or breathing problems), and embryo fetal toxicity

Drug Interactions: No significant interactions.

Evidence:

1. Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous NSCLC

(SQUIRE): an open-label, randomized, controlled phase 3 trial:

R, MC, open-label, controlled trial conducted in 1093 pts receiving gemcitabine and cisplatin first-line chemotherapy for metastatic squamous NSCLC. Inclusions: pts ≥ 18 y/o w/ confirmed stage IV squamous NSCLC; ECOG 0-2; adequate organ fxn. WBC $\geq 3,000$; Plt $\geq 100,000$; HGB ≥ 9.5 ; Tbili $\leq 1.5 \times$ UNL; AST & ALT $\leq 5 \times$ UNL in presence of liver mets; AST & ALT $\leq 2.5 \times$ ULN with no mets; SCr $< 1.2 \times$ ULN; eGFR > 50 ; and availability of archived tumor tissue for analysis of biomarkers. Exclusions: previous chemo for advanced NSCLC; major surgery in 4w b4 randomization; chest irradiation w/in 12w b4 randomization; presence of brain mets that were symptomatic or needed ongoing tx w/ steroids or anticonvulsants; CAD; uncontrolled HF; NCI-CTCAE version 3.0 grade 2 or worse PN. The pts were randomized 1:1 to receive necitumumab plus gemcitabine and cisplatin or gemcitabine and cisplatin alone. The main outcome measured was OS. PFS and ORR were also assessed.

Results:

- OS: HR 0.84 (95%CI 0.74-0.96); Death 77% (N) vs 81% (placebo). **NNT for overall survival is 25 pts.** The median OS was 11.5m (95%CI 10.4-12.6) N vs 9.9m (95%CI, 8.9-11.1) placebo; **1.6m (48 days) improvement in OS**
- PFS: HR 0.85 (95% CI 0.74-0.98); Deaths 79% (N) vs 76% (placebo). The median PFS was 5.7m (95% CI 5.6-6.0) N vs 5.5m (CI 95% 4.8-5.6) placebo; **0.2m (16 days) improvement in PFS**
- Harm: Grade 3 & 4 rxns were assessed. The greatest difference of grade 3 rxns in the tx arm vs placebo was skin rxn. 44 (8%) N vs 3 (<1%) placebo. **NNH was calculated at 14 pts.**

NCCN 4.2016:

For the 2016 update (Version 3), the NCCN Panel added the necitumumab/cisplatin/gemcitabine regimen (category 3) for patients with metastatic squamous cell NSCLC. This category 3 rec reflects the fact that the NCCN Panel does not prefer the addition of necitumumab to the regimen based on toxicity, cost, and limited improvement in efficacy when compared with cisplatin/gemcitabine. A recent phase 3 randomized trial only showed a slight improvement in OS (11.5m vs 9.9m. The stratified HR was only 0.84. In addition, there were more grade 3 or higher AEs in pts receiving the N regimen (72%) than in those receiving Gem/cisp (62%). Although a recent paper suggests that adding N to Cisp/gem adds value and is cost effective, the NCCN Panel does not agree.

Recommendation from student:

Exclude. Re-evaluate when new data emerges or in 1 year (January 2017).

EBRx P&T outcome: Exclude, code 1; reevaluate in 1 year (Jan 2017)

References:

1. Thatcher, Nick, et al. "Necitumumab plus gemcitabine and cisplatin versus gemcitabine and cisplatin alone as first-line therapy in patients with stage IV squamous non-small-cell lung cancer (SQUIRE): an open-label, randomised, controlled phase 3 trial." *The Lancet Oncology* 16.7 (2015): 763-774.
2. Necitumumab Package Insert. Indianapolis, IN: Eli Lilly and Company; November 2015.
3. Lexi-comp, accessed 1/13/2016.
4. NCCN.org. NSCLC. http://www.nccn.org/professionals/physician_gls/pdf/nscl.pdf. Accessed 1/25/2016.

EBD Report
Gerri Bemberg, Pharm.D.

Top 10 Drug Categories by Plan Cost		
Category	Number of Rxs	Plan Cost
Antidiabetics	122,062	\$18,067,719
Analgesics – Anti-Inflammatory	71,758	\$12,146,203
Psychotherapeutic & Neurological Agent	8,717	\$9,003,677
Antineoplastics & Adjunctive Therapies	13,302	\$7,606,463
Antiasthmatic & Bronchodilator Agents	48,190	\$5,716,615
Antivirals	21,300	\$5,038,843
Dermatologicals	36,733	\$4,421,171
ADHD/Anti-Narcolepsy	30,860	\$3,877,962
Analgesics – Opioid	113,301	\$2,982,252
Contraceptives	82,279	\$2,974,117

Top Drugs By Plan Spend	
Product Name	Therapeutic Category
Humira	Analgesics – Anti-Inflammatory
Lantus	Antidiabetics
Copaxone	Psychotherapeutic & Neurological Agents
Enbrel	Analgesics – Anti-Inflammatory
Gleevec	Antineoplastics & Adjunctive Therapies
Novolog	Antidiabetics
Advair	Antiasthmatic & Bronchodilator Agents

Top 10 Drugs by Avg Ingredient Cost		
Product	Therapeutic Category	Avg Ingredient Cost
Cinryze	Hematological Agents – Misc	\$40,098.05
Lumizyme	Endocrine & Metabolic Agents – Misc	\$39,228.30
Alphanate/Von Willebrand	Hematological Agents – Misc	\$36,723.92
Cuprimine	Assorted Classes	\$35,282.32
Harvoni	Antivirals	\$32,956.00
Sovaldi	Antivirals	\$30,240.00
Viekira Pak	Antivirals	\$28,522.88
Cerezyme	Hematopoietic Agents	\$25,693.20
Kalydeco	Respiratory Agents – Misc	\$24,807.60
Targretin	Antineoplastics & Adjunctive Therapies	\$17,426.03