AGENDA

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

October 26, 2015

1:00 p.m.

EBD Board Room – 501 Building, Suite 500

I.	*Call to Order*	*Dr. Hank Simmons, Chairman*
II.	*Approval of August 3, 2015 Minutes*	*Dr. Hank Simmons, Chairman*
III.	*Delivery Coordination Workgroup*	*Dr. Geri Bemberg, UAMS*
IV.	*Second Review of Drugs*	*Dr. Jill Johnson, UAMS*
V.	*New Drugs*	*Dr. Jill Johnson, UAMS*
VI.	*Evidence-Directed Rebate Discussion*	*Dr. David Keisner, UAMS*
VII.	*EBD Report*	*Dr. Geri Bemberg, UAMS*

Upcoming Meetings

February 1, 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
October 26, 2015

The State and Public Life and Health Insurance Board, Drug Utilization and Evaluation Committee (DUEC) met on Monday October 26, 2015 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. Melodee Harris - Telephone
Larry Dickerson
Dr. Hank Simmons Chairman

Non-Voting Members present:
Dr. Jill Johnson
Connie Bennett
Dr. Geri Bemberg

Members absent:
Dr. Appathurai Balamurugan
Dr. William Golden
Dr. John Kirtley

Lori Eden, Deputy Executive Director, Employee Benefits Division

OTHERS PRESENT
Dwight Davis, David Keisner, Grant F., UAMS College of Pharmacy; Sherry Bryant, Ethel Whittaker, Janna Keathley, Cindy Hastngs, Shay Burleson, EBD; Marc Watts, ASEA; Charlene Kaiser, Amgen; Takisha Sanders, Health Advantage; Ronda Walthall, Wayne Whitley, AHTD; Arlene Chan-Mouton, ACHI; Jon McGuire, GSK; Bridgett Johnson, Pfizer; Takisha Sanders, Jessica Akins, Health Advantage; Jim Chapman, Brian Strickland, Gilead; Sam Smothers, Astra Zeneca; Frances Bauman, Nova Nordisk; Sean Teague, Merck

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 August 3, 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 October 26th. Recommendations from this report are outlined below.

	Current Coverage	**Proposed Coverage for 2015**
Non-small cell lung cancer (NSCLC) Crizotinib (Xalkori)	Exclude	Exclude
Metastatic Melanoma Pembrolizumab (Keytruda)	Exclude	Medical PA

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

Daliresp (roflumilast) – From the PI:

8 RCTs on nonreversible obstructive lung disease (FEV1/FVC<70% and <12% improvement in FEV1 in response to 4 puffs of albuterol):

Psychiatric events including suicidality occurred in 5.9% of Daliresp 500mg pts and 3.3% of placebo pts. NNH is 39 for these events.

Zetia (Ezetimibe) – A Cholesterol absorption inhibitor ezetimibe (Zetia).

Cuprimine (penicillamine) – FDA approved for treatment of Wilson's disease, cystinuria, or as adjunctive treatment of severe, active rheumatoid arthritis.

Uceris (budesonide) – For treatment of Crohn's disease.

Evekeo (amphetamine) – For the treatment of exogenous obesity and narcolepsy

	Max dose	Total Cost/Rx	AWP Cost/Unit	AWP/Day	Copay	Plan Cost/30 Day	Plan Cost/Unit
(Evekeo) Amphetamine 5 mg	40 mg		5.95	**47.60**	60	1368	
(Evekeo) Amphetamine 10 mg	60 mg		5.95	**35.70**	60	1011	
Modafinil 100 mg	100mg	505.13	22.93	**22.93**	15	490.13	16.34
Modafinil 200 mg	200mg	745.79	35.17	**35.17**	15	730.79	24.36
Dextroamphetamine IR 5 mg			2.72	**5.44**	15		1.00
Dextroamphetamine IR 10 mg			2.67	**5.34**	15		
Methamphetamine 5 mg IR tab			4.58	**11.46**	15		
Mixed amphetamine salts (gen. Adderall IR) 5 mg			1.24	**2.48**	15		
Mixed amphetamine salts (gen. Adderall IR) 7.5 mg		37.32	1.25	**2.50**	15		
Mixed amphetamine salts (gen. Adderall IR) 12.5 mg			1.54	**3.08**	15		
Mixed amphetamine salts (gen. Adderall IR) 15 mg			1.71	**3.42**	15		
Mixed amphetamine salts (gen. Adderall IR) 30 mg			1.84	**3.68**	15		

Proposal:

1. Exclude Daliresp.
2. Require prior authorization for Zetia; approve coverage on Tier-3 with a PA.
3. Exclude Evekeo 5 & 10 mg tabs. There are several alternative for use for each indication. Letters should be sent to prescribers and the 5 utilizers stating Evekeo will be excluded from coverage effective 1/1/16.
4. Exclude methamphetamine tablets. The indication is ADHD and obesity. There are several ADHD alternatives that are less costly.
5. Exclude Cuprimine 250 mg caps; cover Depen titratabs 250 mg tabs and Trientine Syprine 250 mg caps on Tier-4 with a PA.
6. Budesonide (Uceris) – Cover on Tier-3 with a PA.

Dickerson motioned to approved Dr. Johnson's recommendations for 2nd review of drugs. Dr. Neil seconded. All were in favor.

Motion Approved.

Palbociclib (Ibrance): *by, Dr. Geri Bemberg, UAMS*

Antineoplastic Agent, Cyclin-Dependent Kinase Inhibitor

Used in combination with letrozole for initial endocrine-based therapy for metastatic disease in postmenopausal women with ER-positive, HER2-negative advanced disease as initial treatment for metastatic disease.

125 mg. once daily x 21 days, followed by a 7-day rest period to complete a 28-day treatment cycle (in combination with continuous letrozole); continue until disease progression or unacceptable toxicity. The medicine has been excluded since June 23, 2015 Board meeting.

Dr. Bemberg's recommendation is to approve coverage on Tier-4 with a PA.

Dr. Pace motioned to approve Dr. Bemberg's recommendations, including the Delivery of Coordination Group recommendtions. Dickerson seconded. All were in favor.

Motion Approved.

NEW DRUGS: *by Dr. Jill Johnson, UAMS*

Johnson reported on new drugs. The review covered products released June 15 – September 28, 2015.

Recommended Additions

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	DUEC VOTE
Breo Ellipta 200-25mcg/inh	Fluticasone Furoate-vilanterol aero powder	$337/60	Asthma	T1-albuterol/ipratropium. T2 - Advair(ST), Combivent, Spiriva, Tudorza	Tier 3
Humalog Kwik-pen 200 unit/ml	Insulin Lispro (human) pen injector	$68.82/ml	Insulin	Line extension. Humalog 100 unit/ml T2-34.41/ml	Tier 2
Entresto	Sacubitril-valsartan tab	$450/30 days	Heart Failure	ARBs referenced price	Tier 3PA
Finacea Aer 15%	Azelaic acid foam 15%	$477/45gm	Acne	Finacea Gel 15% T3 $279/50gm	Tier 3 QL of 50g/30d
Lidocaine Pad 5%	Lidocaine patch 5%	$10.27 patch	Local anesthetic – topical	Numerous generic lidocaine patches. Plan currently requires a PA for lidocaine patches	Tier 1PA
Morphine Sul conc 100mg/5ml	Morphine sulfate oral conc 100mg/5ml	$0.84	Pain	Line extension. Other strengths covered.	Tier 1
Brilinta 60mg	Ticagrelor	$5.71/tab	Inhibits platelet aggression	Line extension other strengths available	Tier 3
Zubsolv 11.4.2.9mg and 2.9.071mg	Buprenorphine-naloxone SL tabs	$8.44 and $16.89/tab	Opiate Agonist Dependence	Line extension	Cover All Strengths, T3PA
SPECIALTY DRUGS					
BRAND NAME	**GENERIC NAME**	**PRICING (AWP)**	**INDICATION**	**SIMILAR THERAPIES ON FORMULARY/AWP**	**DUEC VOTE**
Invega Trinz Inj	Paliperidone palmitate IM extended release (3 month depot)	$7,231/819mg	Atypical antipsychotic	Invega Sustenna (monthly) covered T3. 234 mg/$2,410	T4PA, Move Sustenna to T4 as well.
Glatopa inj 20mg/ml	Glatiramer prefilled syringe kit 20mg syringe	$216/20mg syringe	Multiple Sclerosis	Line extension	T4PA Exclude Copaxone w/90 days notice
Orkambi Tabs	Lumacaftor-ivacaftor	$23,907/28 days	Cystic Fibrosis	Other products cov.	T4PA
Daklinza Tabs	Daclatasvir	$25,200/ month	Use with sofosbuvir		T4 PA
Technivie tabs	Ombitasvir-paritaprevir-ritonavir tabs	$30,632/ month	Use with ribavirin		T4 PA
Zarxion inj	Filgrastim-SNDZ	300mcg=$330 480mcg=$526	Biosimilar colony stimulating factor	AWP/dose: Neupogen 300mcg=$389; 480mcg=$619 Granix 300mcg=$345.70; 480mcg=$550.45	T4PA

Recommended Exclusions

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	EXCLUSION CODE
Avar Aer 9.5-5%	Sulacetamide Sodium w/sulfur foam	$5.82/gm	Acne	Other sulfacetamide sodium w/sulfur foam excluded. Sulfacetamide sodium 10% topical solution T1	13
Ovace Plus Foam	Sulfacetamide sodium 9.8% foam	$5.82/gm	Acne	Other sulfacetamide sodium w/sulfur foam excluded. Sulfacetamide sodium 10% topical solution T1	13
GNP Burn Spray	Lidocaine aerosol 0.5%	$4.78/can	Topical local anesthetic	Some topical lidocaine covered T1	13
Amicar Sol 0.25GM/ML	Aminocaproic acid oral soln	$12.22/ml	Hemorrhage	50mg Tabs cov. $3.85/tab	13
Rexulti	Brexpiprazole tabs	$1038/30 tabs	Depression/ schizophrenia	T1-clozapine, olanzapine, risperidone, quetiapine, ziprasidone. T2-Abilify(PA) Seroquel XR(QL)	13
Prestalia Tabs	Perindopril-amlodipine	$176.10/30	Hypertension (ACE/oral calcium channel blocker)	T1-Perindopril (8mg tab = $1.15) amlodipine ($0.08/10mg)	13
Oralair Child Pak Sample	Grass mixed pollen tab sl therpak	Sample kit	Allergenic extracts	Line extension	13
Epiduo Forte Gel	Adapalene-benzoyl peroxide gel 0.3-2.5%	$477/45gm	Acne	Line extension.	13
Otrexup inj 7.5/0.4ml	Methotrexate soln PF auto-injector 7.5ml/0.4ml	$172/pen	Line extension	Other methotrexate soln PF auto-injectors excld	13
Zecuity Pad 6.5 mg/4 hours	Sumatriptan succinate TD iontophoretic patch	$346/patch	Migraine headaches	Generics (T1) naratriptan, rizatriptan, sumatriptan.	13
Viibryd Kit Starter	Vilazodone starter kit 7-10mg & 23-20mg	$227/kit	Depression	Line extension. Viibryd excluded on plan	4, 13
Addyi	Flibanserin 100mg	$960/30 days	For hypoactive sexual desire disorder in premenopausal women		13 further discussion 02/01/16

SPECIALTY DRUGS					
BRAND NAME	**GENERIC NAME**	**PRICING (AWP)**	**INDICATION**	**SIMILAR THERAPIES ON FORMULARY/AWP**	**EXCLUSION CODE**
Praluent inj	Alirocumab subcutaneous soln pen-injector	$1,344/month	Use in addition to diet & maximally tolerated statin therapy in adult patients w/ heterozygous familial hypercholesterolemia or patients w/clinical atherosclerotic CV disease such as MI or stroke, who require additional lowering of LDL cholesterol		1
Kuvan powder 500mg	Sapropterin powder packet 500mg	$196/packet	PKU	Other dosage covered. Specialty Tier. 100mg powder packet=$40 100mg tab=$40	1
Repatha	Evolocumab subcutaneous prefilled syringe or auto-injector	140mg q2w= $1300/month 420mg once monthly= $1950/month	Atherosclerosis, heterozygous & homozygous familial hypercholesterolemia		1

Tabled for December DUEC

Synjardy tabs	Empagliflozin (Jardiance) & metformin	$411/month	SGLT2-inhibitor + metformin for type 2 diabetes	Priced same as plain Jardiance. Other SGLT2-1 excluded on plan.	
Envarsus XR tabs 0.75mg, 1mg, 4mg	Tacrolimus SR 24hr tabs	$560/30 (4mg)	Once daily dosing for prophylaxis of organ rejection	Tacrolimus 5mg IR AWP= $22/cap	

Dr. Neil motioned to approve Breo Ellipta and remain at Tier 3. Dr. Pace seconded. All were in favor.

Motion Approved.

Dickerson motioned to modify the report to cover Humalog at Tier 4. Pace seconded. All were in favor.

Motion Approved.

Dickerson motioned to approve the recommendations for the Non-Specialty Drugs. The drug Addyi has been excluded for further discussion in the 02/01/2016 meeting. Dr. Neil seconded. All were in favor.

Motion Approved.

Dr. Pace motioned to approve the recommendations for the Specialty Drugs. Dr. 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

EVIDENCE BASED REBATES: *by Dr. David Keisner, UAMS*

Dr. Keisner reported EBD is working with EBRX to develop the non-clinical process of rebate contracting. Dr. Keisner reported on the clinical process of rebate contracting. The process is similar to reference pricing in terms of how drugs are reviewed. If all the drugs are the same and one is cheaper; the cheaper is the preferred. Under these circumstances the committee may instruct Dr. Keisner to obtain a rebate contract for drugs that are in the perspective category. There are upcoming opportunities with a possible eleven (11) preferred drugs in one category. Dr. Keisner is requesting an additional meeting for instructions on how to move forward with the rebate opportunities.

Pace reported it's essential to maintain drug specific for each rebate contract to keep the integrity of the evidence base rebating process. In addition, Pace recommended contracts be at least three (3) years to provide stability to the manufactory and the member. Dr. Neil is in-agreement with Pace, and also recommended the committee develop the process as they move forward. Pace is also concerned with the security of data that will be shared in the contracts for potential manufactory's who are bidding.

Dr. Bemberg recommended have a special meeting prior to the February, 2016 meeting for discussion and review of ideas for recommendations. Pace requested a listing of the top thirty (30) categories by cost. Dr. Keisner will provide the information.

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

There was no additional information

Meeting Adjourned

August 11, 2015

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

	Current Coverage	**Proposed Coverage**
Non-small cell lung cancer (NSCLC)		
Crizotinib (Xalkori)	Excluded	Exclude
Metastatic Melanoma		
Pembrolizumab (Keytruda)	Excluded	Medical PA

FYI: Extending the PA for nivolumab (Opdivo) to also include coverage for Squamous-Cell Non-Small Cell Lung Cancer.

Palbociclib (Ibrance)
Antineoplastic Agent, Cyclin-Dependent Kinase Inhibitor

Labeled indications: Used in combination with letrozole for initial endocrine-based therapy for metastatic disease in postmenopausal women with ER-positive, HER2-negative advanced disease as initial treatment for metastatic disease

Dosing: 125 mg once daily x 21 days, followed by a 7-day rest period to complete a 28-day treatment cycle (in combination with continuous letrozole); continue until disease progression or unacceptable toxicity

Current EBD Coverage: Excluded as of 6/1/15 Board meeting

	1st line Treatment[1]	**Prior Endocrine Therapy[2]**
Study design	Open label Phase 2 trial; 165 postmenopausal women w/ adv ER+, HER- breast cancer who had not received any systemic tx Treatment Palbociclib 125mg qd x 3 weeks followed by 1 week off for 28-day cycles + continuous 2.5mg letrozole daily **OR** Continuous 2.5mg letrozole daily	Double-blind Phase 3 trial; 521 pts w/ adv HR+, HER2- breast cancer who had relapsed or progressed during prior endocrine therapy Treatment Palbociclib 125mg qd x 3 weeks, followed by 1 week off + fulvestrant 500mg IM q14d x 1st 3 injections, and then q 28 days **OR** Placebo + fulvestrant Premenopausal/perimenopausal pts received goserelin for the duration of study tx
PFS (median)	20.2 mo vs 10.2 mo for letrozole alone CI: 0.319-0.748, p=0.0004	9.2 mo vs 3.8 mo for fulvestrant alone CI: 0.32-0.56, p<0.001
Overall Survival	37.5 mo vs 33.3 mo for letrozole alone HR: 0.813; CI: 0.492-1.345 (wasn't powered to assess)	Not yet reached

References
1. Finn RS, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclin in combination with letrozole versus letrozole alone as first-line treatment of estrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomized phase 2 study. Lancet Oncol 2015;16:25-35.
2. Turner NC, et al. Palbociclib in Hormone-Receptor-Positive Advanced Breast Cancer. N Engl J Med 2015;373:209-19.

Evidence Directed Rebate Management David Keisner, PharmD

Proposal: Adopt Policy similar to reference pricing

Reference Pricing:

For many drug classes, a review of the medical literature reveals no evidence of clinical superiority between the many drug products available in that class and large differences in price. In other words, each of the products is thought to be as effective as any of the other products in that given category, and no single product stands out as being therapeutically superior. When this unique set of circumstances exists, reference pricing is put into place. In reference pricing a gold standard product is selected for the drug class. The gold standard product is as effective as all of the other drugs in the category, but it costs significantly less.

The cost per unit of the gold standard drug product would serve as the reference price for all of the other products in the class. This reference price is the maximum the plan will pay per unit (or pill) with the member responsible for the remaining cost.

Evidence Directed Rebate Management:

For many drug classes, a review of the medical literature reveals no evidence of clinical superiority between the many drug products available in that class ***and negligible difference in price.***. In other words, each of the products is thought to be as effective as any of the other products in that given category, and no single product stands out as being therapeutically superior. When this unique set of circumstances exists, ***Rebate Contracting may be explored***. ***In evidence based rebate contracting a*** gold standard product **(or products)** are ***Negotiated*** for the drug class. The gold standard product is as effective as all of the other drugs in the category, but it costs significantly less.

The gold standard products(s) will serve as the preferred medication. The non-preferred products will be excluded or be designated as "step therapy" (ST) with failure of the preferred products required to obtain coverage. Nothing in the agreements will take precedence over the clinical appropriateness or prior authorization criteria set forth by the DUEC/Board.

Example: Targeted Immune Modulators

Preferred	*Non-Preferred*
Adalimumab (Humira)	
Etanercept (Enbrel)	
Abatacept (Orencia)	
Anakinra (Kineret)	
Apremilast (Otezla)	
Cetrolizumab (Cimzia)	
Golimumab (Simponi)	
Infliximab (Remicade)	
Ustekinumab (Stelara)	
Tocilizumab (Actemra)	
Tofacitinib (Xeljanz)	

AGENDA

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

October 26, 2015

1:00 p.m.

EBD Board Room – 501 Building, Suite 500

I. Call to Order..... Dr. Hank Simmons, Chairman

II. Approval of August 3, 2015 Minutes ..... Dr. Hank Simmons, Chairman

III. Delivery Coordination Workgroup.....Dr. Geri Bemberg, UAMS

IV. Second Review of Drugs ..... Dr. Jill Johnson, UAMS

V. New Drugs..... Dr. Jill Johnson, UAMS

VI. EBD Report .....Dr. Geri Bemberg, UAMS

Upcoming Meetings

February 1, 2016

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

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Amphetamine (Evekeo®)
5mg & 10mg tablets
J. Johnson, Pharm.D., BCPS
10/26/15

Amphetamine tablets are FDA approved for exogenous obesity, ADHD, or narcolepsy. Currently the plans do not cover drugs for obesity. To date there are no comparative trials with amphetamine and modafinil, a stimulant commonly used for narcolepsy.

This emerged through an abbreviated new drug application (ANDA) approval in 2012. Benzedrine was the previous brand amphetamine sulfate product but is no longer on the market. Evekeo is listed as a brand drug without a generic available and did not appear on the "new drug list" because it sought ANDA instead of NDA and was not assigned a new GPI number. The plan has 5 utilizers of Evekeo during 2015 Q2.

	Max dose	Total cost/Rx	AWP cost/unit	AWP/day	Copay	Plan cost/30d	Plan cost/unit
(Evekeo) Amphetamine 5mg	40mg		5.95	47.60	60	1368	
(Evekeo) Amphetamine 10mg	60mg		5.95	35.70	60	1011	
Modafinil 100mg	100mg	505.13	22.93	22.93	15	490.13	16.34
Modafinil 200mg	200mg	745.79	35.17	35.17	15	730.79	24.36
Dextroamphetamine IR 5mg			2.72	5.44	15		1.00
Dextroamphetamine IR 10mg			2.67	5.34	15		2.91
Methamphetamine 5mg IR tab			4.58	11.46	15		9.58
Mixed amphetamine salts (generic Adderall IR) 5mg			1.24	2.48	15		
Mixed amphetamine salts (generic Adderall IR) 7.5mg		37.32	1.25	2.50	15		
Mixed amphetamine salts (generic Adderall IR) 12.5mg			1.54	3.08	15		
Mixed amphetamine salts (generic Adderall IR) 15mg			1.71	3.42	15		
Mixed amphetamine salts (generic Adderall IR) 30mg			1.84	3.68	15		

Costs are based on actual plan costs from 2015 Q2. Amphetamine 10mg is priced the same/unit as the 20mg, so it should be dose-optimized if used.

Proposal:

1. **Exclude Evekeo 5 & 10mg tabs. There are several alternatives for use for each indication. Letters should be sent to prescribers and the 5 utilizers stating Evekeo will be excluded from coverage effective 1/1/16.**
2. **Exclude methamphetamine tablets. The indication is ADHD and obesity. There are several ADHD alternatives that are less costly.**

Ezetimibe in Acute Coronary Syndromes

Jordan Brazeal, PharmD June 25, 2015

Overview

The cholesterol absorption inhibitor ezetimibe (Zetia®) has been available in the U.S. since 2002. Its role in reducing cardiovascular risk has been controversial because of the results of the SEAS and ENHANCE trials, both of which showed that ezetimibe provided additional LDL-lowering effects when added to statin therapy but demonstrated no clinical outcomes (reduction in mortality or morbidity). It was not until last week, when the New England Journal of Medicine published the IMPROVE-IT trial, that ezetimibe was shown to improve clinical outcomes. This write-up serves to highlight the study.

The IMPROVE-IT Study Results

The IMPROVE-IT study was a randomized, double-blind, placebo-controlled trial involving 18,144 subjects hospitalized with acute coronary syndrome (ACS) in the preceding 10 days. ACS was defined as an acute myocardial infarction (STEMI or NSTEMI) or high-risk unstable angina. A notable exclusion criterion was use of statin therapy with LDL-lowering capability greater than 40 mg of simvastatin. Subjects were randomized to receive either simvastatin and placebo or simvastatin and ezetimibe. The primary endpoint was a composite of death from cardiovascular disease, major coronary event, or nonfatal stroke.

The primary endpoint occurred in 32.7% of the ezetimibe group and 34.7% in the control group ($p = 0.016$; CI, 0.89-0.99). The end point was carried heavily by MI and ischemic stroke. Nonfatal MI occurred in 12.8% and 14.4% of the intervention and control groups ($p = 0.002$; CI, 0.80-0.95). Ischemic stroke occurred in 3.4% and 4.1% of the intervention and control groups ($p=0.008$; CI, 0.67-0.94). Death from any cause, death from cardiovascular causes, and death from coronary heart disease did not differ significantly between groups. Safety profiles and discontinuation rates were also similar between groups.

Discussion

According to current best evidence, patients younger than 75 with atherosclerotic cardiovascular disease (ASCVD), such as ACS, merit treatment with a high-intensity statin (atorvastatin 40 or 80 mg and rosuvastatin 20 or 40 mg). The desired outcome in treating with high-intensity statin therapy is not to lower LDL but to reduce coronary event rates. The IMPROVE-IT study limited itself in two ways: 1) it excluded patients who were on appropriate risk reduction therapy for ACS, and 2) it largely precluded patients from being placed on appropriate statin therapy. It is true that ezetimibe demonstrated improved outcomes when compared with a medium-intensity statin in a patient population requiring a high-intensity statin. But without comparing ezetimibe to the intervention that is considered the gold standard for the patient population in question, it remains unknown whether ezetimibe is truly worthy of use in reducing cardiovascular risk.

In spite of the limitations, there may be a use for ezetimibe in conjunction with a medium-intensity statin for patients with ASCVD who are older than 75. This recommendation comes from data in the Supplementary Appendix, which showed a 20.3% relative risk reduction ($p = 0.005$; CI, 0.704-0.092) in this age group. The guidelines recommend a medium-intensity statin in this population.

Recommendations

Require prior authorization with the following approval criteria:

1. Age ≥75
2. Claim for low- to medium-intensity statin in the past 90 days
3. History of MI or diagnosis of unstable angina

Denial criteria:

1. Most recent claim for high-intensity statin, lookback of 90 days

References

Cannon CP, Blazing MA, Giugliano RP, et al. Ezetimibe added to statin therapy after acute coronary syndromes. N Engl J Med 2015;372(25):2387-97

Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA Guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation, published online November 12, 2013.
http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a.citation

Penicillamine & Trientine--Chelators
Jill Johnson, Pharm.D., BCPS
10/1/15

Penicillamine is an old drug used as a chelating agent. FDA-approved for treatment of Wilson's disease, cystinuria, or as adjunctive treatment of severe, active rheumatoid arthritis.

Mechanism: chelates with lead, copper, mercury and other heavy metals for form stable, soluble complexes that are excreted in the urine. It also depresses circulating IgM rheumatoid factor, depresses T-cell but not B-cell activity; combines with cysteine to form a compound which is more soluble, thus cystine calculi are removed.

Available as Cuprimine 250mg capsules or as Depen Titratab 250mg tablets.

Utilization for 2015 Q2 :

	Rxs	AWP cost	Ing cost	Disp fee	Plan pd	Plan Cost/cap	Copay per Rx
Cuprimine 250mg capsules (#360)	2	26310.46	23679.42	7	23606.42	65.57	40 (T2)

Comparative Costs:

Generic Name	Brand	AWP cost/unit	AWP cost/maximally dose/day per Wilson's dz patient	Current coverage	Proposed coverage
Penicillamine	Cuprimine 250mg caps Valeant Pharmaceuticals	$315.26/cap	2000mg/day=8 caps/day= $2522.08/day $75662.40/month	T2	Exclude; send letters to the 2 utilizers as notice they will need to call their doctor for a Rx for tablets
Penicillamine	Depen titratabs 250mg tabs MEDA Pharmaceuticals	64.91/tab	2000mg/day=8 tabs/day= $519.28/day $15,578.40/month	T2	T4PA
Trientine	Syprine 250mg caps Valeant Pharmaceuticals	255.20/cap	2000mg/day=8 caps/day= $2041.60/day $61,248.00/month	T2	T4PA

Trientine (Syprine) is a chelating agent as well. The max dose is 1500-2000 mg/day and has the FDA approval for treatment of Wilson's disease in patients who are intolerant of penicillamine.

Evidence:

WILSON'S DISEASE

Wilson's disease is an autosomal recessively inherited copper overload disorder affecting about 1/30,000 that leads to hepatic &/or neurologic symptoms. Efficacy is satisfactory for available medical treatment for hepatic disease but disappointing in the neurologic patients, including the risk of neurologic deterioration after the initiation of chelation therapy. Current guidelines demand lifelong medical treatment because the copper uptake cannot be controlled by a low-copper diet. Less toxic therapy should be tried first, such as zinc therapy. Zinc therapy can be insufficient in patients with hepatic disease with or w/o acute hemolytic anemia. Penicillamine or trientine improved more than 90% of symptomatic hepatic cases.[1] Investigational treatment with tetrathiomolybdate combined with zinc preserved neurologic function better than trientine plus zinc in patients with neurologic disease.

1. Weiss KH, Stremmel W. Clinical considerations for an effective medical therapy in Wilson's disease. Annals of the New York Academy of Sciences. 2014;1315:81-85. (Review Article)

2. Brewer GJ, Askari F, et al. Treatment of Wilson disease with ammonium tetrathiomolybdate: IV. Comparison of tetrathiomolybdate and trientine in a double-blind study of treatment of the neurologic presentation of Wilson disease. Arch Neurol. 2006. 63(4):521-7.

3. Penicillamine for Wilson's disease. Coch Sys Rev protocol only. No results. 2012.

4. From UpToDate (accessed 10/1/15):

SUMMARY AND RECOMMENDATIONS — Patients with Wilson disease require lifelong therapy. Discontinuation of therapy can lead to the development of acute liver failure. Treatment should be given in two phases: stabilizing the patient by removing tissue copper that has accumulated and then preventing reaccumulation. The following includes recommendations consistent with those proposed by the American Association for the Study of Liver Diseases (table 1).

Asymptomatic patients — In asymptomatic patients identified through screening, we recommend treatment with a chelating agent (such as D-penicillamine (Cuprimine 250mg capsules, manufactured by Valeant Pharmaceuticals International, Inc. or Depen titratabs 250mg tabs manufactured by Meda Pharmaceuticals) or trientine (Syprine 250mg capsules, manufactured by Valeant Pharmaceuticals International, Inc.) (**Grade 1B**). Zinc may be used in patients who are reluctant to use a chelating agent or who are intolerant of them, but liver biochemical test should be monitored at least every four months and a chelating agent added if these tests worsen (**Grade 1B**). Evolving consensus has been to use trientine because of its relatively favorable side-effect profile. Copper balance should be monitored regularly in such patients by obtaining a 24-hour urine collection and by estimating nonceruloplasmin bound copper.

Symptomatic patients — Symptomatic patients should be treated with a chelating agent (D-penicillamine or trientine) until stable. As noted above, trientine may be preferred because it has fewer side effects than D-penicillamine and appears to be less likely to exacerbate neurologic symptoms. (See 'Adverse effects' above.)

Patients typically require six months to five years of higher-dose treatment, after which they can be transitioned to maintenance therapy. Prior to the transition, patients should be clinically well, have normal serum aminotransferases, and hepatic synthetic function, non-ceruloplasmin-bound copper in the normal range (<15 mcg/dL or 150 mcg/L), and 24-hour urinary copper repeatedly in the range of 200 to 500 mcg (3 to 8 micromoles) per day. Maintenance therapy can be achieved with zinc or with lower doses of a chelator, and patients should be monitored regularly as described above.

Pregnancy — Pregnancy appears to be safe in patients on D-penicillamine and trientine, but we suggest the dose be reduced to approximately 30 to 50 percent of the pre-pregnancy dose during the first trimester since both drugs are known to be teratogenic in animal models and may impair wound healing should a cesarean section or episiotomy be required (**Grade 2C**). Case reports have suggested that zinc may be a safer and effective alternative, but experience is limited. (See 'D-penicillamine and pregnancy' above and'Trientine and pregnancy' above and 'Zinc and pregnancy' above.)

Acute liver failure — Patients presenting with acute liver failure due to Wilson disease require liver transplantation. Plasmapheresis, exchange transfusion, hemofiltration, molecular absorbant recirculating system (MARS), or dialysis may be performed while transplant is being awaited. Albumin dialysis may also be beneficial but experience is limited. As noted above, recovery with supportive therapy has been described. (See 'Acute liver failure' above.)

RHEUMATOID ARTHRITIS

5. Suarez-Almazor ME, Belseck E, Spooner C. Penicillamine for treating rheumatoid arthritis (RA). Cochrane Database of Systematic Reviews 2000, Issue 4. Art. No.: CD001460. DOI: 10.1002/14651858.CD001460.

D-penicillamine appears to have a clinically and statistically significant benefit on the disease activity of patients with RA. Its efficacy appears to be similar to that of other disease modifying anti-rheumatic drugs (DMARDs), but with a significantly higher toxicity. Odds ratio was 4.95 (95%CI 2.38-10.30) for withdrawals and dropouts due to AEs. Its effects on long-term functional status and radiological progression are not clear from this review. Penicillamine is a penicillin derived compound. Studies showed that this could be used to treat RA originally in 1950. It was frequently used in the past, but its use has declined with the increasing use of other disease modifying anti-rheumatic drugs (DMARDs), such as methotrexate. The purpose of this summary was to find out if penicillamine is helpful in the treatment of RA. Penicillamine was seen to be beneficial for all ranges of dosages for disease activity on tender joint pain, physician global assessment and sed rate. No major differences were observed between placebo and low dose penicillamine (<500 mg/day). For higher dosages, patients on penicillamine were twice as likely to withdraw, overall, than those receiving placebo 500 to <1000 mg/day. D-penicillamine appears be have a clinical and statistical benefit on the disease activity of patients with RA. Its benefit is similar to that of other such drugs, such as DMARDs. More adverse reactions are seen in patients being treated with D-penicillamine.

RETINOPATHY OF PREMATURITY IN PRETERM INFANTS

6. Qureshi MJ, Kumar M. D-Penicillamine for preventing retinopathy of prematurity in preterm infants. Cochrane Database of Systematic Reviews 2013, Issue 9. Art. No.: CD001073. DOI: 10.1002/14651858.CD001073.pub2.

Administration of prophylactic D-penicillamine in preterm infants does not prevent acute or severe ROP, death or neurodevelopmental delay. D-penicillamine cannot be recommended for the prevention of ROP based on the available evidence. Retinopathy of prematurity (ROP) is an eye disease of premature infants that continues to be a serious problem. The drug D-penicillamine, given by mouth, is commonly used to treat poisoning by iron or copper or other heavy metals. In research studies of D-penicillamine used for another problem that premature infants have (high bilirubin), it was observed that the treated infants had less ROP. However, **this systematic review did not show any significant benefits of this drug for the outcomes of ROP, death or development of nerves. Thus, the use of this drug cannot be recommended for the prevention of ROP based on available evidence.**

PRIMARY SCLEROSING CHOLANGITIS

7. Klingenberg SL, ChenW. D-penicillamine for primary sclerosing cholangitis (PSC). Cochrane Database of Systematic Reviews 2006, Issue 1. Art. No.: CD004182. DOI: 10.1002/14651858. CD004182.pub3.

One randomized trial was identified and included in the review. It was of low methodological quality. The trial compared D-penicillamine versus placebo in 70 patients with PSC. Compared with placebo, D-penicillamine therapy had no significant effect on mortality (RR 1.14, 95%CI 0.49 to 2.64), liver transplantation (RR 1.11, 95%CI 0.39 to 3.17), hepatic histologic progression (RR 1.17, 95%CI 0.79 to 1.74), or

cholangiographic deterioration (RR 0.87, 95%CI 0.43 to 1.79).D-penicillamine led to a significant D-penicillamine for PSC improvement in the serum aspartate aminotransferase (WMD -23.00 U/L; 95% CI -30.66 to -15.34), but not in serum bilirubin level (WMD 0.40 mg/L; 95% CI -0.19 to 0.99) and serum alkaline phosphatases activity (WMD 44.00 U/L; 95% CI -37.89 to 125.89). There were significantly more AEs in patients receiving D-penicillamine (P = 0.013). **There is not sufficient evidence to support or refute the use of D-penicillamine** for patients with PSC. We do not recommend the use of D-penicillamine for patients with PSC outside randomized trials.

PRIMARY BILIARY CIRRHOSIS

8. Gong Y, Klingenberg SL, Gluud C. D-penicillamine for primary biliary cirrhosis (PBC). Cochrane Database of Systematic Reviews 2004, Issue 4. Art. No.: CD004789. DOI: 10.1002/14651858. CD004789.pub2.

D-penicillamine did not appear to reduce the risk of mortality, but significantly increased the occurrences of adverse events in patients with PBC. We do not support the use of D-penicillamine for patients with PBC. PBC is an uncommon, chronic liver disease of unknown etiology. D-penicillamine, a cupruretic drug, has been tested in randomised clinical trials and is used to treat patients with PBC. **After combining results from seven trials, D-penicillamine did not appear to improve survival of patients and was associated with a four-time increase of AEs. There were no significant differences between D-penicillamine and placebo/no intervention with respect to clinical changes, liver histology, and liver biochemistry.**

CYSTIC FIBROSIS-RELATED ARTHRITIS

9. Thornton J, Rangaraj S. Disease modifying anti-rheumatic drugs in people with cystic fibrosis(CF)-related arthritis. Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD007336. DOI: 10.1002/14651858.CD007336.pub3.

Although it is generally recognised that cystic fibrosis-related arthritis can be episodic and resolve spontaneously, treatment with analgesics and anti-inflammatory agents may be needed. But when episodic symptoms progress to persistent disease, DMARDs may be needed to limit the course of the disease. It is disappointing that no RCTs to rigorously evaluate these drugs could be found. This systematic review has identified the **need for a well-designed adequately powered RCT to assess the efficacy and safety of DMARDs for the management of CF-related arthropathy** and hypertrophic osteoarthropathy in adults and children with CF. However, given the infrequency of CF-related arthritis and the range of symptoms and severity, RCTs may not be feasible and well-designed non-randomised observational studies may be more appropriate. Studies should also better define the two conditions.

Budesonide (Uceris)
Re-review 10/26/2015
Jill Johnson, Pharm.D., BCPS

EBD

		Notes	FDA-approval	Current (10/26/15)	Proposed
Uceris	Budesonide tab SR 24h 9mg	In April 2013, I recommended T3PA, 1. Dx of UC, 2. failure of or intolerant to sulfasalazine, 3. failure of or intolerance of mesalamine oral or rectal. Instead, the DUEC and IB voted to exclude the drug for new users now and give current users 90d to change to something else.	• active Crohn's Disease, mild-moderate involving the ileum and/or ascending colon; 9mg QD X8w, may repeat an 8w course for recurring episodes. • Maintenance of remission of Crohn's disease, mild-moderate involving the ileum and/or ascending colon; 6mg QD X3m, then taper. Continued dosing beyond 3m has not been demonstrated to result in substantial benefit. • Ulcerative colitis, active, mild-moderate, to induce remission; 9mg qd X 8w	Excluded	T3PA, 1. Dx of UC or Crohn's, 2. failure of or intolerant to sulfasalazine, 3. failure of or intolerance of mesalamine oral or rectal.
Uceris	Budesonide Foam	3/17/15 the foam was placed at T4.	FDA-approved for remission induction in patients with active mild-moderate distal UC extending up to 40cm from the anal verge: • Initial, 2mg (one metered dose of rectal foam) BID X2w • Maintenance, 2mg (one metered dose) QD X 4w	T4	T4

From the Pharmacists' Letter 3/13: Uceris is budesonide like Entocort EC...but not interchangeable. Both work locally in the GI tract to reduce systemic steroid effects...but they target different areas. Entocort EC targets the ileum and right colon for Crohn's disease...Uceris targets the entire colon for ulcerative colitis. UC tx is based on disease location and severity...patient preferences...and cost. Pts w/ distal disease may achieve remission w/ rectal mesalamine (Rowasa, etc) or hydrocortisone (Cortenema, etc)...but pts w/ more extensive disease usu need oral therapy. 5-ASA products (mesalamine, etc) are still first-line for inducing and maintaining remission in mild-mod dz.

Uceris would be an alternative to oral prednisone if 5-ASA products aren't effective. Uceris will cost about $1200/m; vs as little as $4 per month for prednisone. But adrenal suppression is unlikely when Uceris is used short-term.

Efficacy in Crohn's:

14 studies (1805 patients) were included:
--Nine (779 patients) compared budesonide to conventional corticosteroids, 3 (535 patients) were placebo-controlled, and 2 (491 patients) compared budesonide to mesalamine.
Findings:

Oral 9 mg budesonide X 8w was significantly **more effective** than placebo for induction of clinical remission.

- 47% (115/246) of budesonide pts achieved remission at 8 w compared to 22% (29/133) of placebo pts (RR 1.93, 95% CI 1.37 to 2.73; 3 studies, 379 patients).

Budesonide X8w was significantly **less effective** than conventional steroids for induction of remission.

- 52% budesonide pts achieved remission at week 8 compared to 61% of pts who received conventional steroids (RR 0.85, 95% CI 0.75 to 0.97; 8 studies, 750 patients).

Budesonide was significantly **less effective** than conventional steroids among patients with severe disease (CDAI > 300)

- (RR 0.52, 95% CI 0.28 to 0.95). Studies comparing budesonide to mesalamine were not pooled due to heterogeneity (I2 = 81%).

One study (n = 182) found budesonide X8w to be **superior to mesalamine** for induction of remission.

- 68% (63/93) of budesonide pts were in remission at 8w compared to 42% (37/89) of mesalamine pts (RR 1.63, 95%CI1.23-2.16).
- The other study found **no statistically significant difference** in remission rates at 8w.
- 69% (107/154) of budesonide pts were in remission at 8 w compared to 62% (132/242) of mesalamine patients (RR 1.12, 95% CI 0.95 to 1.32).
- **Fewer AEs** occurred in those treated with budesonide compared to conventional steroids (RR 0.64, 95% CI 0.54 to 0.76) and budesonide was better than conventional steroids in preserving adrenal function (RR for abnormal ACTH test **0.65**, 95% CI 0.55 to 0.78).
- Authors' conclusions: Budesonide is more effective than placebo for induction of remission in Crohn's disease. Although short-term efficacy with budesonide is < with conventional steroids, particularly in those with severe disease or more extensive colonic involvement, the likelihood of AEs and adrenal suppression with budesonide is lower. The current evidence does not allow for a firm conclusion on the relative efficacy of budesonide compared to 5-ASA products.

Efficacy of oral budesonide in UC:

- Oral budesonide was significantly less likely to induce clinical remission than oral mesalamine after 8 weeks of therapy (RR 0.72, 95% CI 0.57 to 0.91).
- There was no significant benefit of oral budesonide in comparison to placebo for inducing clinical remission after 4 weeks of treatment (RR 1.41, 95% CI 0.59 to 3.39).
- A small pilot study reported no statistically significant difference in endoscopic remission between budesonide and prednisolone (RR 0.75, 95% CI 0.23 to 2.42). The study was small and not powered to evaluate the impact of budesonide on clinical remission.
- Suppression of plasma cortisol was significantly more common in prednisolone treated patients (RR 0.02, 95% CI 0.0 to 0.33). Two multicenter studies are ongoing.
- Authors' conclusions: At present, there is no evidence to recommend the clinical use of oral budesonide for the induction of remission in active UC. Mesalamine is superior to budesonide for the treatment of active UC.

Efficacy of rectal foam budesonide in UC:

2 identically designed, R, DB, PC trials evaluated the efficacy of budesonide foam for induction of remission in 546 pts w/ mild-mod UC proctitis or ulcerative proctosigmoiditis who received budesonide foam 2 mg/25 mL BID X2w, then QD X4w, or placebo.
RESULTS: Remission at w6 occurred significantly more frequently among pts receiving budesonide foam than placebo (Study 1: 38.3% vs 25.8%; P ¼ .0324; Study 2: 44.0% vs 22.4%; P < .0001). A significantly greater % of pts receiving budesonide foam vs placebo achieved rectal bleeding resolution (Study 1: 46.6% vs 28.0%; P ¼ .0022; Study 2: 50.0% vs 28.6%; P ¼ .0002) and endoscopic improvement (Study 1: 55.6% vs 43.2%; P ¼ .0486; Study 2: 56.0% vs 36.7%; P ¼ .0013) at week 6. Most AEs occurred at similar frequencies between groups, although events related to changes in cortisol values were reported more frequently with budesonide foam. There were no cases of clinically symptomatic adrenal insufficiency. CONCLUSIONS: Budesonide rectal foam was well tolerated and more efficacious than placebo in inducing remission in pts w/ mild-mod ulcerative proctitis and ulcerative proctosigmoiditis.

References:
1. UpToDate, "Budesonide in the treatment of inflammatory bowel disesase", accessed 10/13/15.
2. Resaie A, et al. Budesonide for induction of remission in Crohn's disease. Cochrane Database of Systematic Reviews 2015, Issue 6. Art. No.: CD000296. DOI: 10.1002/14651858.CD000296.pub4.
3. Sherlock ME, Seow CH, Steinhart AH, Griffiths AM. Oral budesonide for induction of remission in ulcerative colitis. Cochrane Database of Systematic Reviews 2010, Issue 10. Art. No.: CD007698. DOI: 10.1002/14651858.CD007698.pub2.

DUEC									
June 15, 2015-Sept 28, 2015									
BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	Consultant NOTES-Jill Johnson, Pharm.D., BCPS	DUEC Date	DUEC Vote	IB Date	IB Vote
NON-SPECIALTY DRUGS									
Breo Ellipta	fluticasone furoate-vilanterol aero powder BA 200-25mcg/inh	$337/60	asthma	T1-albuterol/ipratropium. T2-Advair(ST), Combivent, Spiriva, Tudorza T-3 Atrovent inhaler, DuoNeb, Symbicort(ST). Breo Ellipta 100-25mcg excluded.	T2 (handout)	2015 10 26			
Humalog Kwik-pen 200unit/ml	insulin lispro (human) pen injector	$68.82/ml	insulin	Line extension. Humalog 100unit/ml - T2 - $34.41/ml	EXCLUDE, Code 4 (convenience kit policy)	2015 10 26			
Avar Aer 9.5-5%	sulfacetamide sodium w/sulfur foam	$5.82/gm	acne	Other sulfacetamide sodium w/sulfur foam excluded. Sulfacetamide sodium 10% topical solution T1	Exclude, code 13.(See Sulfacetamide-Sulfer Products Handout) Exclude. There is a 60g generic foam 10%/5% for $2.72/g instead of $5.82/g cost..	2015 10 26			
Ovace Plus Foam	sulfacetamide sodium 9.8% foam	$5.82/gm	acne	Other sulfacetamide sodium w/sulfur foam excluded. Sulfacetamide sodium 10% topical solution T1	Exclude-Code 13	2015 10 26			
Entresto	sacubitril-valsartan tab	$450/30 days	heart failure	ARBs referenced price	T3PA	2015 10 26			
GNP Burn Spray	lidocaine aerosol 0.5%	$4.78/can	topical local anesthetic	some topical lidocaine covered T1	Exclude Code 13. T1 alternatives.	2015 10 26			
Amicar Sol 0.25GM/ML	aminocaproic acid oral soln	$12.22/ml	hemorrhage	50omg tabs covered. $3.85/tab	Exclude, code 13 (handout)	2015 10 26			
Rexulti	brexpiprazole tabs	$1,038/30 tabs	depression/schizophrenia	T1-clozapine,olanzapine,risperidone,quetiapine,ziprasidone. T2-Abilify(PA) Seroquel XR(QL)	Exclude Code 13. (handout)	2015 10 26			
Prestalia TABS	perindopril-artinne-amlodipine	$176.10/30	hypertension (ACE/oral calcium channel blocker	T1-perindopril (8mg tab = $1.15) amlodipine ($0.08/10mg)	Exclude, code 13	2015 10 26			
Oralair Child Pak Sample	grass mixed pollen tab sl therpak	sample kit	Allergenic extracts	line extension	Exclude. Curr Opin Otolaryngol Head Neck Surg 2014, 22:211–215 is a systematic review (June 2014) that shows SCIT is better than SLIT for symptom control, rescue med use and AEs in indirect comparisons. SL. After 1st dose adm in MD office, can be taken at home. Adult dose is 300mg IR daily. Kids ≥10 take 100mgIR on day1, 200mg IR on day 2, then 300mg IR daily thereafter. This dosage form is 300 only so there may be smaller strengths coming. Pt must have access to epinephrine autoinjector. One trial: Depigmented polymerized extract stimulated dose-dependent T-cell proliferation and cytokine production. Patients treated with preseasonal SCIT showed improved combined scores during peak season at year 2 (median 3.93, interquartile range 0.77-6.27 vs median 5.86 for placebo, 3.11-8.36, P < 0.01). Most secondary outcomes were significantly better for active treatment. Side-effects were minimal, with no grade 3 or 4 reactions.Pfaar O.	2015 10 26			
Epiduo Forte Gel	adapalene-benzoyl peroxide gel 0.3-2.5%	$477/45gm	acne	Line extension. Other adapalene combo products excluded. Epiduo excluded	Exclude, Code 13	2015 10 26			
Finacea Aer 15%	azelaic acid foam 15%	$306/50gm	Acne	Finacea Gel 15% - T3-$279/50gm	T3 QL of 50g/30d	2015 10 26			
Lidocaine Pad 5%	lidocaine patch 5%	$10.27/patch	local anesthetic - topical	numerous generic lidocaine patches. Plan currently requires a PA for lidocaine patches.	T1PA	2015 10 26			
Otrexup inj 7.5/0.4ml	methotrexate soln PF auto-injector 7.5ml/0.4ml	$172/pen	line-extension	other methotrexate soln PF auto-injectors excluded	EXCLUDE. Vials available and MUCH less cost. Trial comparing oral and inj MTX in RA showed inj better at achieving ACR20 & ACR70, but not ACR50. Inconsistent results.	2015 10 26			

Morphine sul conc 100mg/5ml	morphine sulfate oral conc 100mg/5ml	$0.84/ml	Pain	Line extension. Other strengths covered	T1 or Exclude code 13; available: Generic: 10 mg/5 mL (5 mL, 15 mL, 100 mL, 500 mL); 20 mg/5 mL (5 mL, 100 mL, 500 mL); 100 mg/5 mL (15 mL, 30 mL, 120 mL, 240 mL) AWP: Solution (Morphine Sulfate (Concentrate) Oral) 20 mg/mL (100 mL): $84; 100mg/5mL (100mL), $84 Solution (Morphine Sulfate Oral) 10 mg/5 mL (100 mL): $14.40, 20 mg/5 mL (100 mL): $19.20	2015 10 26			
Zecuity Pad 6.5mg/4 hours	sumatriptan succinate TD iontophoretic patch	$346/patch	Migraine headaches	Generics (T1) - naratriptan, rizatriptan, sumatriptan. T2-Relpax. T3-Amerge, Axert, Frova, Imitrex, Maxalt, Zolmitriptan, Zomig, Zomig Spray	Exclude code 13	2015 10 26			
Synjardy tabs	empagliflozin[Jardiance] & metformin	$411/month	SGLT2-inhibitor + metformin for type 2 diabetes	Priced same as plain Jardiance. Other SGLT2-I excluded on plan	T2; cover empagliflozin too.	2015 10 26			
Viibryd Kit Starter	vilazodone starter kit 7-10mg & 23-20mg	$227/kit	depression	Line extension. Viibryd excluded on plan	Exclude code 13 and code 4.	2015 10 26			
Brilinta 60mg	ticagrelor	$5.71/tab	inhibits platelet aggregation	Line extension - other strength covered T3	T3. We currently cover Brilinta other strengths at T3.	2015 10 26			
Zubsolv 11.4-2.9mg and 2.9-0.71mg	buprenorphine-naloxone SL tabs	$8.44 and $16.89/tab	opiate agonist dependence	Line extension - other strengths excluded by plan	Voted at April DUEC to cover Zubsolv 8.6-2.1 w/PA & QL of 62/31, with plans to revisit at Sept DUEC. Should probably be consistent and cover all strengths or none of the strengths. (Or decide we only want to cover certain strengths?) **Zero current utilizers**	2015 10 26			
Addyi	flibnserin 100mg	$960/30 days	for hypoactive sexual desire disorder in postmenopausal women		GB: Opportunity to discuss continued coverage of ED meds?	2015 10 26			
SPECIALTY DRUGS									
Invega Trinz inj	paliperidone palmitate IM extended release (3 month depot)	$7,231/819mg	Atypical antipsychotic	Invega Sustenna (monthly) covered T3. 234mg/$2,410	For EBD, Invega Sustenna is T3. Trinza is for pts who have been adequately treated w/ 4m of Invega sustenna. Trinza is administered IM q3m.	2015 10 26			
Glatopa inj 20mg/ml	glatiramer prefilled syringe kit 20mg/ml	$216/20mg syringe	Multiple sclerosis	line extension. Generic for Copaxone. Copaxone 20mg = $244(dosed daily) Copaxone 40mg = $500.80(dosed 3x/week)	T4PA; exclude all brand Copaxone with 90 days current user notice	2015 10 26			
Orkambi Tabs	lumacaftor-ivacaftor	$23,907/28 days	Cystic fibrosis	Other cystic fibrosis products covered by plan include Cayston, Kalydeco, and Pulmozyme	T4PA	2015 10 26			
Daklinza tabs	daclatasvir	$25,200/month	Use with sofosbuvir for the treatment of patients with chronic heaptitis C genotype 3		T4PA	2015 10 26			
Technivie tabs	ombitasvir-paritaprevir-ritonavir tabs	$30,632/month	Use in combination with ribavirin for the treatment of hepatitis C genotype 4 infections in patients without scarring and poor liver function(cirrhosis)		T4PA	2015 10 26			

Praluent Injection	alirocumab subcutaneous soln pen-injector	$1,344/month	Use in addition to diet and maximally tolerated statin therapy in adult patients with heterozygous familial hypercholesterolemia or patients with clinical artherosclerotic cardiovascular disease such as heart attacks or storkes, who require additional lowering of LDL cholesterol		Exclude. Code 1. (Handout)	2015 10 26			
Kuvan Powder 500mg	sapropterin powder packet 500mg	$196/packet	PKU	other dosage covered. Specialty tier. 100mg powder packet=$40 100mg tab = $40	Exclude, Code 1.	2015 10 26			
Repatha	evolocumab subcutaneous prefilled syringe or auto-injector	140mg q 2 weeks = $1300/month. 420mg once monthly = $1950/month	atherosclerosis, heterozygous & homozygous familial hypercholesterolemia		Exclude. Code 1.	2015 10 26			
Zarxion Inj	filgrastim-SNDZ	300mcg=$330; 480mcg=$526	biosimilar colony stimulating factor	AWP Per dose: Neupogen 300mcg=$389; 480mcg=$619 Granix 300mcg=$345.70; 480mcg=$550.45 Zarxion 300mcg=$330; 480mcg=$526	Generic for Neupogen. Granix is other generic. Consider lower copay for generics. Net cost to plan is less for brand Neupogen unless the generics are also placed in T4 for now.	2015 10 26			
Envarsus XR tabs 0.75mg, 1mg, 4mg	tacrolimus SR 24hr tabs	$560/30-4mg	once daily dosing for prophylaxis of organ rejection	Tacrolimus 5mg immediate release AWP = $22/cap	With Envarsus, administer 80% of the total IR daily dose. With AstagrafXL, administer in a 1:1 ratio (mg:mg) using previously established total daily dose of IR. Administer once daily. Generic IR tacrolimus is BID dosing. 5mg #60 is $1338. Brand Astagraf XL is QD dosing. 5mg #60 is $1427.04. Brand Envarsus XR 4mg #60 is $1120.32. IR tacrolimus 5mg BID=8mgQD of EnvarsusXR	2015 10 26			
COMPOUND KITS/BULK CHEMICALS/NO INDICATION									
Allo-Pax	levocetirizine-loratadine cream 5-5% compound kit				Exclude code 4.	2015 10 26			
K10-Lido Kit	triamcinolone inj 1mg/ml and lidocaine inj 2% kit				Exclude code 4.	2015 10 26			
Triamsil Pak Combipak	triamcinolone/silicone gel therapy kit				Exclude code 4.	2015 10 26			
Fanatrex Susp 25mg/ml	gabapentin oral susp 25mg/ml compound kit				Exclude code 4.	2015 10 26			
Tabradol Susp 1mg/ml	cyclobenzaprine w MSM oral suspension compound kit				Exclude code 4.	2015 10 26			
ADV Allergy Collecti	hydrocortisone cream kit 2.5%				Exclude code 4.	2015 10 26			
Dermacinrx Kit Pharmapa	chlorhexidine sol-mupirocin cr-dimeth cr - silicone tape kit				Exclude code 4.	2015 10 26			
Hyalucil Cream	sodium hyaluronate-fluorouracil cream compounding kit				Exclude code 4.	2015 10 26			
Dermacinrx Duo Patch	lidocaine patch 5% and menthol-methyl sal patch therapy pak				Exclude code 4.	2015 10 26			
Derma SilkRX Pak Diclopak	declofenac sod DR tab 75mg and capsaicin cre ther pak				Exclude code 4.	2015 10 26			
Flexizol Pak Combipak	diclofen DR tab 75mg-ranitidine tabl 150mg-lido cream 3.75% THPK				Exclude code 4.	2015 10 26			
Clin Single Kit Use	clindamycin phosphate inj 300mg/2ml kit				Exclude code 4.	2015 10 26			

Vancomycin sus +syrspen	vancomycin oral susp compound kit				Exclude code 4.	2015 10 26			
Equapax Pak	atorvastatin & coenzyme Q10 ther pak				Exclude code 4.	2015 10 26			
Dermacinrx Pak	lidocaine patch & capsaicin cream therapy pak				Exclude code 4.	2015 10 26			
Dermacinrx PAK	diclofenac soln-capsaicin cream ther pak				Exclude code 4.	2015 10 26			
Colliginix Mis	Dimethicone-allantoin bandage				Exclude code 4.	2015 10 26			
Pro-C-Dure Kit	triamcinolone acetonide injection kit				Exclude code 4.	2015 10 26			
Beta 1 Kit	betamethasone sod phos & acet inj kit 30mg/5ml				Exclude code 4.	2015 10 26			
BL Injection Kit	Bupiv PF inj & lido PF inj &povi-iod swab kit				Exclude code 4.	2015 10 26			
Triamsil Pak Multipak	triamcinolone/silicon gel//silicon tape pack				Exclude code 4.	2015 10 26			
EPIsnap Kit	epinephrine convenience kit 1mg/ml (epi, needles, alcohol swabs, syringes				Exclude code 4.	2015 10 26			
Omega-3/D-3 Kit Wellness	omega-3-acid eithy esters cap 1Gm & Vit D cap 1000u/kit				Exclude code 4.	2015 10 26			
Triamsil Kit combipak	triamcinolone&dimeth gel&silicone tape				Exclude code 4.	2015 10 26			
Flexepax Mis	cycloben&capsaicin/menthol patch				Exclude code 4.	2015 10 26			
Napropax Mis	naproxen/capsaicin/menthol patch				Exclude code 4.	2015 10 26			
IBU/Minrex pak	ibuprofen 800mg & multiple minerals cap therapy pack				Exclude code 4.	2015 10 26			
Dermapak Pak Plus	tretinoin cre & men-zinc oxide oint & silicone tape pak				Exclude code 4.	2015 10 26			
Clin-Lido	clindamycin 300mg/lido-epi injection				NA. Medical Drug.	2015 10 26			
Moxifloxacin IV	moxifloxacin 400mg/250ml IV solution				NA. Medical drug.	2015 10 26			
Phenylephrin Inj	phenylephrine-NACL PF Pref sy 1mg/1ml				NA. Medical drug.	2015 10 26			
Fentanyl Cit inj	Fentanyl citrate-NACL soln PREF syringe 500mcg/50ml				NA. Medical drug.	2015 10 26			
Hydromorph inj	hydromorphone - NaCl Sol pref syringe				NA. Medical drug.	2015 10 26			
Morphine sul inj	morphine sulfate-NACL sol pref syringe				NA. Medical drug.	2015 10 26			
Fentanyl/Bup inj	fentanyl - bupivacaine-NaCl inj				NA. Medical drug.	2015 10 26			
Ephedrine inj	ephedrine-NACL pf Pref syr 50mg/10ml				NA. Medical drug.	2015 10 26			
Methohexital Inj	methohexital sodium soln pref syringe				NA. Medical drug.	2015 10 26			
Ketamine HCL inj	Ketamine-NaCl soln pref syringe				NA. Medical drug.	2015 10 26			
Neostigmine inj	neostigmine methylsulfate soln pref syr				NA. Medical drug.	2015 10 26			
Hurriseal	dental desensitizine product				Exclude code 13; OTC alternatives.	2015 10 26			
Mencaps Pad	capsaicin-menthol topical patch				Patch (Alivio External)0.03-5% (15): $897.50 Patch (Capsiderm External) 0.0375-5% (15): $695.00 Patch (Neuvaxin External)0.0375-5% (15): $872.00 Patch (RelyyT External)0.025-5% (15): $626.40 Patch (Sinelee External)0.0375-5% (15): $688.32; 0.05-5% (15): $688.32 Patch (Solaice External)0.05-5% (15): $756.32	2015 10 26			
Silmanix Cream	capsaicin-menthol-histamine cream				No info in Drugs Facts & Comparisons.	2015 10 26			
Rematex Cream	capsaicin-menthol-methyl salicylate cream				No Info in Drugs Facts & Comparisons besides monotherapy w/ capsaicin cream for PHN.	2015 10 26			
Triferric Soln	ferric pyrophosphate citrate soln 27.2mg/5ml				NA Medical. Pts would get this intradialytically via admixture with bicarbonate concentrate dialysate.	2015 10 26			
Co-Veratrol Caps	ubiquinol-Vit B12-resveratrol-FA caps				No trials in PubMed.	2015 10 26			
Lidothol Pad	lidocaine-menthol patch				Exclude, code 13. Alternative is lidocaine patch T1PA.	2015 10 26			

Fluticasone furoate/Vilanterol (Breo Ellipta)
Andrew Mullings, Pharm.D.
7/21/2015

Drug name	COPD Dosing	Asthma Dosing	Dosage Form	AWP
Fluticasone/vilanterol 200mcg/25mcg (Breo Ellipta)	1 INH Qdaily	1 INH Qdaily	DPI	$337.26
Fluticasone/vilanterol 100mcg/25mcg (Breo Ellipta)	1 INH Qdaily	1 INH Qdaily	DPI	$337.26
Budesonide/Formoterol 80/4.5, 160/4.50 (Symbicort)	2 INH BID	2 INH BID	MDI	$300.42(80) $343.40 (160)
Fluticasone/Salmeterol 250mcg/50mcg, 500/50 (Advair Diskus)	1 INH BID	1 INH BID	DPI	$387.50
Formoterol/mometasone 100mcg/5mcg, 200mcg/5mcg (Dulera)	1-2 INH BID*	2 INH BID	MDI	$307.78

*No FDA indication, dosing provided by 2015 GOLD guidelines

Efficacy Evidence: In COPD, ICS/LABA combination therapy demonstrates improved in lung function and health status while providing a reduction in exacerbations in patients with moderate to very severe disease level compared to the individual components[1,4]. Currently, the GOLD 2015 guidelines recommend ICS/LABA combinations to those in GOLD classifications "C" and "D" (which includes those with FEV_1 predicted >50%). The mortality benefit in combination therapy is questionable. The TORCH trial evaluated the effect of combination FLU/SAL vs FLU monotherapy vs SAL monotherapy vs placebo in patients with prebronchodilator FEV_1 <60% predicted (average baseline FEV_1 of 44% predicted)[7]. FLU/SAL demonstrated trend toward decreased mortality rate after 3 years compared to placebo (12.6% vs 15.2% P=0.052) but failed to show any difference compared to the LABA alone[7]. Of note, the SUMMIT trial evaluating mortality of Breo Ellipta comparing to its individual components recently concluded with results expected early 2016. Comparative effectiveness evidence between particular products is lacking. In patients with mod-sev persistent asthma, combination ICS/LABA therapy is the preferred step (Step 3) in the NAEPP guidelines[2]. Use of combination ICS/LABA therapy in inadequately controlled asthma demonstrates improved lung function, symptom free days, and use of rescue inhaler compared to monotherapy[3].

Safety Evidence:

- In COPD, ICS/LABA therapy is associated with an increased risk of pneumonia (NNT = 17/ three years)[4]. Other common adverse effects are similar to individual components including oral candidiasis, hoarse voice, and skin bruising with inhaled ICS.
- In asthma, LABAs should only be used in combination with an ICS due to the increased risk of severe exacerbations, hospitalizations, and death associated with LABA monotherapy[5]. In asthma, the data available concerning the risk of catastrophic asthma events or death on ICS/LABA combination therapy is conflicting and unclear[6].

Recommendation: Given the price similarity between the products, cover Breo Ellipta at same tier as other ICS/LABA combos.

1. Global Initiative for Chronic Obstructive Lung Disease: Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (Updated 2015). www.goldcopd.org
2. National Asthma Education and Prevention Program: Expert panel report III: Guidelines for the diagnosis and management of asthma. Bethesda, MD: National Heart, Lung, and Blood Institute, 2007. (NIH publication no. 08-4051) www.nhlbi.nih.gov/guidelines/asthma/asthgdln.htm
3. Greenstone IR, Ni Chroinin MN, Masse V, et al. Combination of inhaled long-acting beta2-agonists and inhaled steroids versus higher dose of inhaled steroids in children and adults with persistent asthma. Cochrane Database Syst Rev 2005; :CD005533.
4. Nannini L, Poole P, Milan SJ, Holmes R, Normansell R. Combined corticosteroid and long-acting beta-agonist in one inhaler versus placebo for chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2013, Issue 11. Art. No.: CD003794. DOI: 10.1002/14651858.CD003794.pub4
5. http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm200776.htm
6. http://www.uptodate.com/contents/treatment-of-moderate-persistent-asthma-in-adolescents-and-adults?source=search_result&search=ics+laba&selectedTitle=1%7E119
7. Calverley PM, et al. "Salmeterol and Fluticasone Propionate and Survival in Chronic Obstructive Pulmonary Disease". *The New England Journal of Medicine*. 2007. 356(8):775-789.

Humalog (insulin lispro) Kwik Pen Injection (200u/ml) 3mL
Andrew Mullings, Pharm.D.
7/9/2015

Labeled Uses: Humalog is a short acting injectable insulin indicated for glycemic control in adult patients with either diabetes mellitus type 1 or 2.

Comparator Drugs:

Brand	Dose*	AWP	30 Day Supply Needed	30 Day Supply Cost
Humalog Pen 200u/ml 3mL pen	**150 units daily**	**$206.50**	**8 pens**	**$1652.00**
Humalog Pen 100u/ml 3mL pen	**150 units daily**	**$103.25**	**15 pens**	**$1548.75**
Humalog Vial 100u/ml 3mL pen	**150 units daily**	**$80.17**	**15 vials**	**$1202.55**

*Dosing Assumes 250kg patient receiving 1.2u/kg/day with 50% deliver as short acting insulin

Recommendation: Humalog 200u/ml Kwik pen offers a new formulation offering twice the concentration and in turn, twice the amount of deliverable insulin per pen. However, the new formulation can result in higher costs secondary to lessen flexibility with number of pens dispensed. Recommended to exclude from coverage.

Outcome: Exclude, code 13

Sulfacetamide-Sulfur Products
6/1/2015

		Sulfacetamide	Sulfur	Package size	Cost ($AWP)		
Sulfacetamide Sodium-Sulfur	Cream	9.80%	4.80%	57g	$530.56	$9.31	
Plexion	Cream	9.80%	4.80%	57g	$589.50	$10.34	
Avar-e Emollient	Cream	10.0%	5%	57g	$567.40	$9.95	Cream Cost/g
Avar-e Green	Cream	10.0%	5%	57g	$582.20	$10.21	
Prascion RA	Cream	10.0%	5%	45g	$87.84	$1.95	
SSS 10-5	Cream	10.0%	5%	?	?		
Avar-e LS	Cream	10.0%	2%	57g	$542.65	$9.52	
BP 10-1	Emulsion	10.0%	1%				Emulsion Cost/g
Cerisa Wash	Emulsion	10.0%	1%	170.1g	$44.40	$0.26	
Avar Cleanser	Emulsion	10.0%	5%	227g	$519.92	$2.29	
Prascion	Emulsion	10.0%	5%	170.3g	$109.76	$0.64	
Rosanil Cleanser	Emulsion	10.0%	5%	170g	$382.02	$2.25	
Sulfacetamide Sodium-Sulfur	Emulsion	10.0%	5%	170g	$94.00	$0.55	
Clarifoam EF	Foam	10.0%	5%	60g	$384.24	$6.40	Foam Cost/g
SSS 10-5	Foam	10.0%	5%	?	?		
Sulfacetamide Sodium-Sulfur	Foam	10.0%	5%	60g	$163.46	$2.72	
Avar Aerosol	Foam	9.5%	5%	100g	$582.00	$5.82	
Avar LS Aer	Foam	10%	2%	100g	$582.00	$5.82	
Rosanil	Kit	10.0%	5%	1	$220.08	$220.08	
Sumaxin CP	Kit	10.0%	4%	1	$615.48	$615.48	
Sulfacetamide Sod-Sulfur Wash	Kit	9.0%	4.50%	539g	$362.05	$362.05	
Sumadan	Kit	9.0%	4.50%	1	$469.39	$469.39	
Rosula Wash	Liquid	10.0%	4.50%	340.2g	$438.67	$1.29	Liquid Cost/g
Avar LS Cleanser	Liquid	10.0%	2%	227g	$528.40	$2.33	
Plexion Cleanser	Liquid	9.80%	4.80%	285g	$545.10	$1.91	
Sumadan Wash	Liquid	9.0%	4.50%	454g	$426.19	$0.94	
	Liquid	9.0%	4%	473mL	$159.85	$0.34	Liquid Cost/mL
Sumaxin Wash	Liquid	9.0%	4%	473mL	$442.10	$0.93	
Zencia	Liquid	9.0%	4%	473mL	$95.25	$0.20	
Plexion	Lotion	9.80%	4.80%	57g	$589.50	$10.34	Cost/g
Sulfacetamide Sodium-Sulfur	Lotion	9.80%	4.80%	57g	$530.56	$9.31	

Sulfacetamide-Sulfur Products
6/1/2015

Prascion FC	Pad	10.0%	5%	30	$199.24	$6.64	Cost/pad
Rosula	Pad	10.0%	5%	30	$262.67	$8.76	
Sulfacetamide Sodium-Sulfur	Pad	10.0%	4%	60	$511.39	$17.05	
Sumaxin	Pad	10.0%	4%	60	$572.28	$19.08	
Avar LS	Pad	10.0%	2%	30	$303.60	$10.12	
Avar	Pad	9.50%	5%	30	$303.60	$10.12	
Plexion Cleansing Cloth	Pad	9.80%	4.80%				
SS 10-2	Solution	10%	2%	?	?		
Sulfacetamide Sodium-Sulfur	Suspension	8.0%	4%	473mL	$140.24	$0.30	Suspension Cost/mL
SulfaCleanse 8/4	Suspension	8.0%	4%	473mL	$341.58	$0.72	
Sumaxin TS	Suspension	8.0%	4%	473mL	$447.91	$0.95	

Sulfacetamide Topicals

2015

Labeled Uses for sulfacetamide:

- Topical antibiotic indicated for seborrheic dermatitis and seborrhea sicca (dandruff). Also for secondary bacterial infections of the skin due to organisms susceptible to sulfonamides.
- *Seborrheic dermatitis* - Apply to affected areas twice daily. As the condition improves, the interval between applications may be lengthened to once or twice weekly to prevent recurrence.

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

Labeled uses for combination sulfacetamide/sulfur:

- To aid in the treatment of: Acne rosacea/acne vulgaris/seborrheic dermatitis; use 1-3x/d

Comparators:

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

Sulfacetamide/Sulfur combos

		Sulfacetamide Sodium	Sulfur	Quantity (Package size)	Cost ($AWP) (date 6/1/15)	
☐ Avar	Pad	9.5%	5%	30	$303.60	
☐ Avar Cleanser	Emulsion	10%	5%	227g	$519.92	
☐ Avar LS	Pad	10%	2%	30	$303.60	
☐ Avar LS Cleanser	Liquid	10%	2%	227g	$528.40	
☐ Avar-e Emollient	Cream	10%	5%	57g	$567.40	
☐ Avar-e Green	Cream	10%	5%	57g	$582.20	

		Sulfacetamide Sodium	Sulfur	Quantity (Package size)	Cost ($AWP) (date 6/1/15)	
Avar-e LS	Cream	10%	2%	57g	$542.65	
BP 10-1	Emulsion	10%	1%			
Cerisa Wash	Emulsion	10%	1%	170.1g	$44.40	
Clarifoam EF	Foam	10%	5%	60g	$384.24	
Plexion	Cream	9.8%	4.8%	57g	$589.50	
Plexion	Lotion	9.8%	4.8%	57g	$589.50	
Plexion Cleanser	Liquid	9.8%	4.8%	285g	$545.10	
Plexion Cleansing Cloth	Pad	9.8%	4.8%			
Prascion	Emulsion	10%	5%	170.3g	$109.76	
Prascion FC	Pad	10%	5%	30	$199.24	
Prascion RA	Cream	10%	5%	45g	$87.84	
Rosanil	Kit	10%	5%	1	$220.08	
Rosanil Cleanser	Emulsion	10%	5%	170g	$382.02	
Rosula	Pad	10%	5%	30	$262.67	
Rosula Wash	Liquid	10%	4.5%	340.2g	$438.67	
SS 10-2	Solution	10%	2%	?	?	
SSS 10-5	Cream	10%	5%	?	?	
SSS 10-5	Foam	10%	5%	?	?	
Sulfacetamide Sodium-Sulfur	Suspension	8%	4%	473mL	$140.24	
		10%	5%	30g	$208.01	
$208.01	Liquid	9%	4%	473mL	$159.85	
		9%	4.5%	454g	$153.43	
		9.8%	4.8%	285g	$490.60	
		10%	2%	227g	$432.32	
Sulfacetamide Sodium-Sulfur	Cream	9.8%	4.8%	57g	$530.56	
		10%	2%	57g	$444.01	
		10%	5%	57g	$444.02	
Sulfacetamide Sodium-Sulfur	Lotion	9.8%	4.8%	57g	$530.56	
		10%	5%	30g	$145.92	

		Sulfacetamide Sodium	Sulfur	Quantity (Package size)	Cost ($AWP) (date 6/1/15)	
☐ Sulfacetamide Sodium-Sulfur	Emulsion	10%	5%	170g	$94.00	
☐ Sulfacetamide Sodium-Sulfur	Foam	10%	5%	60g	$163.46	
☐ Sulfacetamide Sodium-Sulfur	Pad	10%	4%	60	$511.39	
		10%	5%	30	$199.10	
☐ Sulfacetamide Sod-Sulfur Wash	Kit	9%	4.5%	539g	$362.05	
☐ SulfaCleanse 8/4	Suspension	8%	4%	473mgL	$341.58	
☐ Sumadan	Kit	9%	4.5%	1	$469.39	
☐ Sumadan Wash	Liquid	9%	4.5%	454g 473mL	$426.19 $442.10	
☐ Sumaxin	Pad	10%	4%	60	$572.28	
☐ Sumaxin CP	Kit	10%	4%	1	$615.48	
☐ Sumaxin TS	Suspension	8%	4%	473mL	$447.91	
☐ Sumaxin Wash	Liquid	9%	4%	473mL	$442.10	
☐ Zencia	Liquid	9%	4%	473mL	$95.25	

Sulfacetamide-Sulfur in Urea (Emulsion) 10%/5% (355mL) is $249.40. Same gel 45g ($220.46).
Sumadan XLT External Kit, 9-4.5% (539g) is $469.39.

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

- Sulfonamides have been known to cause Stevens-Johnson syndrome in hypersensitive patients.
- Non-susceptible organisms may proliferate with the use of this product.
- Local irritation or sensitization during long-term therapy may occur

Drug Interactions: This product is incompatible with silver preparations.

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

Outcome: Exclude Rosula, code 13

Sacubitril-Valsartan (Entresto or LCZ696)
Sara Schneider, P4
August 2015

Labeled Uses: Chronic heart failure (HF) patients (NYHA Class II-IV) with reduced ejection fraction.

Comparator Drugs:

	Dose for Heart Failure (mg)	AWP (Cost per month for 60 tablets)
Entresto (sacubitril*/valsartan)	24/26 49/51 97/103 [target dose] given BID	$450
Enalapril	10-20 BID	$116-$166 (actually cheaper b/c it is MAC'd)
Valsartan	160 BID	$300 (this is actually cheaper b/c it is MAC'd)

*Sacubitril is not available as a lone product in the U.S.
Notes: In SOLVD and CONSENSUS (enalapril HF trials, the mean achieved dose was 17-18mg/d. Valsartan 160mg BID is target dose in monotherpay for HF. Enalapril 20mg BID is max HF dose.

MOA: Contains a neprilysin inhibitor, sacubitril, and an ARB, valsartan. Neprilysin is a neutral endopeptidase that contributes to the breakdown of endogenous vasoactive peptides, such as natriuretic peptides and bradykinin. Inhibition of neprilysin hinders aldosterone secretion and increases natriuresis. Valsartan blocks renin-angiotensin-aldosterone system (RAAS), which leads to vasodilation and increased excretion of sodium and water.

Contraindications: Pregnancy, patients with a history of angioedema related to previous ACE inhibitor or ARB therapy, concomitant use or use within 36 hours of ACE inhibitors, or concomitant use of aliskiren in patients with diabetes.

Adverse Reactions: Symptomatic hypotension, impaired renal function, hyperkalemia, angioedema, cough, dizziness, decreased hemoglobin/hematocrit.

Drug Interactions:
Entresto may increase the levels/effects of: antihypertensives, lithium, NSAIDs, potassium-sparing diuretics, HCTZ
Levels/effects of Entresto may be increased by: ACE inhibitors, barbiturates, heparin, MAOIs, PDE-5 inhibitors
Levels/effects of Entresto may be decreased by: methylphenidate, NSAIDs

Evidence:
Angiotensin-Neprilysin Inhibition versus Enalapril in Heart Failure (PARADIGM-HF)
Design: The multi-center, R, DB, double-dummy, parallel group, active-controlled study to evaluate the long-term effects of LCZ696 200 mg (target dose 97+103) BID. 1` endpoint was CV death and 1st hospitalization for HF as compared to enalapril 10 mg BID in patients with class II-IV heart failure and reduced EF of <40% (later changed to EF <35% in 12/2010). 2` outcomes include: time to death from any cause, change from baseline to 8 m in the clinical summary score on the Kansas City Cardiomyopathy Questionnaire (KCCQ), time to a new outset of atrial fibrillation, and time to the first occurrence of a decline in renal function.

Trial consists of 2 main periods: (1) a single-blind run-in period of enalapril 10 mg BID for all patients for 2 w, followed by a single-blind run-in period of LCZ696 100 mg BID for 1-2 w then LCZ696 200 mg BID for 2-4 weeks to ensure adequate side-effect profile of the study drugs at target doses, and (2) a double-blind randomized 1:1 treatment period of either enalapril 10 mg BID or LCZ696 200 mg BID in the 8399 patients. Study visits occur every 2-8 w for the first 4 m of the DB period and q4m thereafter. The median duration of F/U was 27 m.

PARADIGM HF is an event-driven trial. All randomized patients will remain in the trial until 2410 patients have experienced a CV death or HF hospitalization (would provide a power of 97% to detect a 15% risk reduction in the primary end point) or until the 1`endpoints are overwhelming statistically significant for the patients.

Results:

Outcome	LCZ696 (N=4187) no. (%)	Enalapril (N=4212) no. (%)	Hazard Ratio (95% CI)	P Value
Primary composite outcome				
CV Death or 1st hosp for worsening HF	914 (21.8)	1117 (26.5)	0.80 (0.73-0.87)	<0.001
Death from CV causes	558 (13.3)	693 (16.5)	0.80 (0.71-0.89)	<0.001
1st hosp for worsening HF	537 (12.8)	658 (15.6)	0.79 (0.71-0.89)	<0.001
Secondary outcomes				
Death from any cause	711 (17.0)	835 (19.8)	0.84 (0.76-0.93)	<0.001
Change in KCCQ clinical summary score** at 8 m§	-2.99±0.36	-4.63±0.36	1.64 (0.63-2.65)	0.001
New-onset atrial fibrillation	84 (3.1)	83 (3.1)	0.97 (0.72-1.31)	0.83
Decline in renal function	94 (2.2)	108 (2.6)	0.86 (0.65-1.13)	0.28

**KCCQ clinical summary score is a 0-100 pt scale with higher scores indicating fewer symptoms.

§A 5pt change on the KCCQ score is a minimal clinically important difference.

The trial was terminated early when the margin for overwhelming benefit for both CV mortality and the primary outcome had been crossed. After excluding the patients who died during the trial, the KCCQ score improved by 0.95 points on a 0-100 point scale in the LCZ696 group. New-onset AF and decline in renal function are not statistically significant. NNT to prevent one 1` event and 1 CV death is 22 and 32, respectively. After randomization, 14% of the LCZ696 patients experienced symptomatic hypotension versus 9.2% of the enalapril patients. For every 21 patients, 1 will experience symptomatic hypotension. Elevated SrCr ≥2.5 mg/dL, elevated serum K+ >6.0 mmol/L, and cough occurred more often in the enalapril group.
McMurray JJV, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med. 2014; 371(11): 993-1004. (Funded by Novartis)
Additional concerns: In the letters to the editor for the PARADIGM-HF trial, it was stated that neprilysin degrades amyloid-β (Aβ) peptides which are commonly associated with Alzheimer's disease. Inhibition of neprilysin can lead to increased levels of Aβ and subsequent cognitive impairment; however, neprilysin is 1 of more than 20 enzymes that assist in removing Aβ peptides. Cognition, memory, and dementia-related adverse effects were not increased in the LCZ696 group in the trial. Neprilysin has been shown to inhibit prostate-cancer cell invasion in vitro and to improve disease-free survival in breast cancer. There was no increase in risk of cancer associated with the trial and a 2 year carcinogenicity study with rodents that received the neprilysin inhibitor component of LCZ696 did not show an increase risk of tumors.

The dose of the 2 comparator drugs in the trial was not equivalent. The maximum dose of the ARB (valsartan 320 mg daily) in addition to the neprilysin inhibitor (sacbutril) was compared to a moderate dose of enalapril (20 mg daily vs the maximum dose of 40 mg daily). In the CONSENSUS, SOLVD-treatment, SOLVD-prevention trials, the target dose for enalapril was set at 40mg/day versus placebo; however, the mean dose of enalapril was 17-18 mg/day because many patients could not tolerate the higher dose.
Delahaye F, de Gevigney G. Is the optimal dose of angiotensin-converting enzyme inhibitors in patients with congestive heart failure definitely established?. J Am Coll Cardiol. 2000; 36(7):2096-2097.

PARADIGM-HF did not provide the information in the trial regarding smoking status and pts w/ a history of severe pulmonary disease. Smaller population of African Americans, females and pts ≥75 years in age included in the study.

Student Recommendation: PARADIGM-HF shows statistically and clinically significant results in the rate of reduction in CV death or hosp for HF with the use of LCZ696 vs enalapril. Include in formulary with PA restrictions. Patient must be at least 18 years old with chronic HF (NYHA Class II-IV) in addition to a reduced EF of ≤35%, and take a stable dose of a beta blocker without symptomatic hypotension or a history of angioedema. Deny if patient is taking concurrent ACEI (due to a previous trial w/ a different neprilysin inhibitor which increased angioedema).

EBRx Outcome and RECOMMENDATION: T3PA with a 90 d look back. **Criteria: Age ≥18, Dx of** chronic HF (NYHA Class II-IV) in addition to a reduced EF of ≤35%, and take a stable dose of a HF-specific beta blocker without symptomatic hypotension or a history of angioedema. Deny if patient is taking concurrent ACEI (due to a previous trial w/ a different neprilysin inhibitor which increased angioedema).

Aminocaproic Acid Oral Solution 0.25g/ml (Amicar)

Andrew Mullings

8/27/15

Labeled Indications: To enhance hemostasis when fibrinolysis contributes to bleeding (causes may include cardiac surgery, hematologic disorders, neoplastic disorders, abruptio placentae, hepatic cirrhosis, and urinary fibrinolysis)

Current relevant utilizations: Used off-label for bleeding control associated with dental procedures on oral anticoagulant therapy (rinsed), oral bleeding in congenital and acquired coagulation disorders, and bleeding control in severe thrombocytopenia.

Product	Cost (AWP)	Dosing
Aminocaproic Acid Oral Solution 0.25g/ml (Amicar) (236.5ml)	$2890.00/236.5mL	Prevention of dental procedure bleeding in patients on oral anticoagulant therapy Oral rinse: Hold 4 g/10 mL in mouth for 2 minutes then spit out. Repeat every 6 hours for 2 days after procedure Control of bleeding with severe thrombocytopenia 1-4 g every 4-8 hours or 1 g/hour

Evidence:

Used off-label for bleeding control associated with dental procedures on oral anticoagulant therapy (rinsed)

Data concerning usage of aminocaproic acid is driven by a prospective randomized trial comparing bleeding complications in patients who had a warfarin dose reduction compared to antifibrinolytic therapy + stable warfarin dose. Antifibrinolyric therapy included both tranexamic acid and aminocaproic acid. Patients who received antifibrolyric therapy post operatively did not experience significant higher bleeding risk. However, current guidelines recommend patients reducing warfarin 2-3 days prior to the procedure or use a prohemostatic agent with the same strength and evidence.

Oral bleeding in congenital and acquired coagulation disorders

Data concerning use in patients in this indication is limited to clinical trials (no data available). Much of the use is said to be driven by clinical experience. Of note, a recent Cochrane review states there is insufficient evidence from RCTs to assess the most effective and safe hemostatic treatment to prevent bleeding in people with haemophilia or other congenital bleeding disorders undergoing surgical procedures.

Bleeding control in severe thrombocytopenia

A Cochrane review on the indications concludes “the evidence available for the use of antifibrinolytics in haematology patients is very limited“. The review goes on to discuss that aminocaproic acid may be a useful adjuncts to platelet transfusions and their complications, but did have enough data to assess for a possible increase in thromboembolic events.

Recommendation to EBRx Committee: Due lack of evidence supporting the particular usage of the oral solution of the product. Recommend excluding from coverage.

Outcome of the Committee: Exclude from coverage. Evidence for use Is not strong. If needed IV solution could be used to compound a pint. IV is available in 250mg/mL (20mL vial) for $6.12/vial (AWP).

1. Lucas ON and Albert TW, “Epsilon Aminocaproic Acid in Hemophiliacs Undergoing Dental Extractions: A Concise Review,” *Oral Surg Oral Med Oral Pathol*, 1981, 51(2):115-20.[PubMed 6782532]
2. Mannucci P, “Hemostatic Drugs,” *N Engl J Med*, 1998, 339(4):245-53. [PubMed 9673304]
3. Souto JC, Olover A, Zuazu-Jausoro I, et al, “Oral Surgery in Anticoagulated Patients Without Reducing the Dose of Oral Anticoagulant: A Prospective Randomized Study,” *J Oral Maxillofac Surg*, 1996, 54(1):27-32.[PubMed 8530996]
4. Coppola A, Windyga J, Tufano A, Yeung C, Di Minno MN. Treatment for preventing bleeding in people with haemophilia or other congenital bleeding disorders undergoing surgery. Cochrane Database Syst Rev. 2015 Feb 9;2:CD009961. doi: 10.1002/14651858.CD009961.pub2. Review. PubMed PMID: 25922858.
5. Wardrop D, Estcourt LJ, Brunskill SJ, Doree C, Trivella M, Stanworth S, Murphy MF. Antifibrinolytics (lysine analogues) for the prevention of bleeding in patients with haematological disorders. Cochrane Database Syst Rev. 2013 Jul 29;7:CD009733. doi: 10.1002/14651858.CD009733.pub2. Review. PubMed PMID: 23897323.

Brexpiprazole (REXULTI®)
Jordan Brazeal, Pharm.D.

FDA-approved indications: Treatment of schizophrenia (SCZ) and as an adjunctive therapy to antidepressants in the treatment of major depressive disorder (MDD).

Comparators (in ascending order of cost):

Drug name	SCZ dosing	MDD dosing	Price (AWP) 30 days
Rexulti® (brexpiprazole)	*2 to 4 mg/day*	*2 mg/day*	*$34.62/tablet X 30 tablets = $1,038.60*
Geodon® (ziprasidone)	20 to 40 mg/day	Not indicated	$8.86/tablet X 60 tablets = $531.83
Zyprexa® (olanzapine)	10 to 20 mg/day	5 to 12.5 mg/day (with fluoxetine, Symbyax®)	SCZ: $596.79 to $1,193.58 MDD: $317.84 to $654.76
Seroquel® (quetiapine)	300 to 400 mg/day	150 to 300 mg/day	$6.85/tablet X 90 tablets = $617.18
Risperdal® (risperidone)	4 to 8 mg/day	Not indicated	$12.00/tablet X 30 tablets = $720.01
Latuda® (lurasidone)	40 mg/day	Not indicated	$30.78/tablet X 30 tablets = $923.40
Abilify® (aripiprazole)	10 to 15 mg/day	2 to 15 mg/day	$32.11/tablet X 30 tablets = $963.27
Saphris® (asenapine)	10 to 20 mg/day	Not indicated	$16.66/tablet X 60 tablets = $999.58
Fanapt® (iloperidone)	12 to 24 mg/day	Not indicated	$1,242.76 to $1,990.21
Invega® (paliperidone)	3 to 12 mg/day	Not indicated	$34.00/tablet X 30 to 90 tablets = $1,019.87 to $3,059.61

Black Box Warnings: Increased mortality in elderly patients with dementia-related psychosis; increased risk of suicidal thoughts and behaviors

Evidence of efficacy in SCZ:
Correll, et al. (abstract only available), conducted a randomized, double-blind, placebo-controlled study in patients experiencing acute exacerbations of SCZ. Participants were given brexpiprazole 0.25, 2, or 4 mg/day or placebo for 6 weeks. Outcomes included change from baseline to week 6 in total score of Positive and Negative Symptom Scale (PANSS, primary outcome) and Clinical Global Impressions Scale (CGI) severity score (secondary outcome). After 6 weeks, brexpiprazole 2 and 4 mg demonstrated statistically significant differences compared to placebo in PANSS (-8.72 and -7.64) and CGI (-0.33 and -0.38). Subjects on brexpiprazole experienced more akathisia compared to placebo (2 mg: 4.4%; 4 mg: 7.2%; placebo: 2.2%; NNH_{2mg} = 46; NNH_{4mg} = 20), and also experienced more weight gain (2 mg: 1.45 kg; 4 mg: 1.28 kg; placebo: 0.42 kg).

Kane, et al. (abstract only available), conducted a randomized, double-blind, placebo-controlled trial in patients with acute SCZ. Study subjects were given brexpiprazole 1, 2, or 4 mg/day or placebo for 6 weeks. Primary endpoint was change from baseline at week 6 in PANSS total score, and secondary endpoint was change at week 6 from baseline CGI severity score. Versus placebo, brexpiprazole 4 mg demonstrated a significant reduction in PANSS at week 6 (-6.72, p = 0.0022) and in CGI (-0.38, p = 0.0015). Brexpiprazole 1 and 2 mg did not differ significantly from placebo. Akathisia was more common in the placebo group than in the treatment groups (7.1% versus 4.2% to 6.5%). There was more weight gain in the brexpiprazole-treated groups (1.23—1.89 kg versus 0.35 kg).

Summary for SCZ:
The minimally important clinical difference (MCID) for the PANSS is estimated to be around a 15.3-point reduction, or 11.2-point reduction if the CGI is also used (Hermes ED, et al.). According to this information, brexpiprazole did not meet the MCID for the PANSS in either trial. Furthermore, brexpiprazole causes akathisia and weight gain at rather high rates.

Evidence of efficacy in MDD:

In a randomized, double-blind, placebo-controlled study by Thase, et al. (abstract only available), subjects with MDD who had had inadequate response to 1-3 antidepressant treatments (ADTs) were given brexpiprazole 1 or 3 mg/day or placebo for 6 weeks. Primary endpoint was change from baseline at week 6 in Montgomery-Asberg Depression Rating Scale (MADRS), and secondary endpoint was change in Sheehan Disability Score (SDS). Brexpiprazole 3 mg compared to placebo produced significant reduction in MADRS (-8.29 vs -6.33; $p = 0.0079$); brexpiprazole 1 mg did not differ significantly from placebo in MADRS. Neither dose of brexpiprazole differed in SDS compared to placebo. Akathisia was noted significantly more in the brexpiprazole-treated groups than with placebo (1 mg: 4.4%; 3 mg: 13.5%; placebo: 2.3%; $NNH_{1mg} = 48$; $NNH_{3mg} = 9$). Brexpiprazole also caused more weight gain (1 mg: 6.6%; 3 mg: 5.7%; placebo: 0.9%; $NNH_{1mg} = 18$; $NNH_{3mg} = 21$).

Another study by Thase, et al. (abstract only available), evaluated an identical patient population as the previous trial. Patients were randomized to brexpiprazole 2 mg/day or placebo for 6 weeks. Primary efficacy endpoint was change from baseline at week 6 in MADRS; secondary endpoint was change in SDS. Brexpiprazole 2 mg significantly reduced MADRS compared to placebo (-8.36 vs -5.15, $p = 0.0002$), and also improved SDS (-1.35 vs -0.89, $p = 0.0349$). Brexpiprazole was also associated with more akathisia (7.4% vs 1.0%, NNH = 16) and weight gain (8.0% vs 3.1%, NNH = 21).

Summary for MDD:
The MCID for the MADRS is estimated to be around 1.6 to 1.9 (Duru G and Fantino B); changes at or above these values result in better remission rates. In both MDD trials, brexpiprazole in adjunct with ADTs produced a reduction in MADRS beyond the MCID. As in the SCZ trials, brexpiprazole in MDD also causes high rates of akathisia and weight gain.

Conclusion:
Despite demonstration of efficacy against placebo in SCZ and MDD, brexpiprazole does not demonstrate any benefit over previously available antipsychotics for identical indications. There are cheaper options available, all of which cause, at minimum, comparable adverse effects.

Recommendation: Exclude, code 13.

EBRx Vote Result: Exclude.

References:
Correll CU, Skuban A, Ouyang J, et al. Efficacy and Safety of Brexpiprazole for the Treatment of Acute Schizophrenia: A 6-Week Randomized, Double-Blind, Placebo-Controlled Trial. Am J Psychiatry. 2015;appiajp201514101275 [epub ahead of print]

Duru G and B Fantino. The clinical relevance of changes in the Montgomery-Asberg Depression Rating Scale using the minimum clinically important difference approach. Curr Med Res Opin. 2008;24(5):1329-35

Hermes ED, Sokoloff D, Stroup TS, Rosenheck RA. Minimum clinically important difference in the Positive and Negative Symptom Scale with data from the Clinical Antipsychotics Trial of Intervention Effectiveness (CATIE). J Clin Psychiatry. 2012;73(4):526-32

Kane JM, Skuban A, Ouyang J, et al. A multicenter, randomized, double-blind, controlled phase 3 trial of fixed-dose brexpiprazole for the treatment of adults with schizophrenia. Schizophr Res. 2015;164(1-3):127-35

Thase ME, Youakim JM, Skuban A, et al. Adjunctive brexpiprazole 1 and 3 mg for patients with major depressive disorder following inadequate response to antidepressants: a phase 3, randomized, double-blind study. J Clin Psychiatry. 2015 Aug 4 [epub ahead of print]. PMID: 26301771

Thase ME, Youakim JM, Skuban A, et al. Efficacy and safety of adjunctive brexpiprazole 2 mg in major depressive disorder: a phase 3, randomized, placebo-controlled study in patients with inadequate response to antidepressants. J Clin Psychiatry. 2015 Aug 4 [epub ahead of print]. PMID: 26301701

Azelaic Acid 15% Foam (Finacea)
Cassandra Baggett, P4
September 2015

Labeled Uses: topical treatment of the inflammatory papules and pustules of mild to moderate rosacea

MOA: Exact mechanism unknown. In vitro, azelaic acid possessed antimicrobial activity against *Propionibacterium acnes* and *Staphylococcus epidermidis*. May decrease microcomedo formation.

Contraindications: none

Adverse Reactions: hypopigmentation, eye and mucous membranes irritation, application site burning, stinging, paraesthesia, tenderness, pruritus, dryness, erythema

Drug Interactions: no known significant interactions

Evidence:
A phase 3 randomized, double blind, vehicle-controlled trial of azelaic acid foam 15% in the treatment of papulopustular rosacea

- Design:
  - A phase 3 randomized, double blind, vehicle-controlled, parallel-group, multicenter study
  - 484 patients were randomized to azelaic acid foam and 477 patients were randomized to vehicle; all patients applied foam to entire face each morning and evening
  - Participants were male and female, age range was 18 years and older with moderate to severe papulopustular rosacea (PPR)
  - Treatment period lasted 12 weeks; evaluation at baseline, evaluation for safety and efficacy at weeks 4, 8, 12 and at the end of follow-up period that lasted 4 weeks following end of treatment (EoT); evaluation concluded with one final end-of-study visit
- Endpoints/Results:
  - First coprimary efficacy outcome: therapeutic success rate defined by an investigator global assessment (IGA) score of clear or minimal (with at least 2 step improvement) at EoT; results favored AzA foam group (32%) vs. vehicle group (23.5%), P< 0.001 at EoT
  - Second coprimary efficacy outcome: nominal change in mean inflammatory lesion count (ILC) from baseline to EoT as determined by the total number of facial papules and pustules; results favored AzA foam group (-13.2) vs vehicle (-10.2), P<0.001 at EoT
  - Secondary endpoints: changes in other manifestations of PPR, and participant assessment of treatment response, tolerability, cosmetic preferences, and quality of life; assessment not included in journal article
  - Adverse event rates were low in both groups, mainly occurred at the application sites (pain, pruritus, dryness), no drug-related severe or serious AE; cutaneous AEs improved at the study progressed
  - Drug interactions were not mentioned in this study (exclusion criteria included any medication to treat rosacea within 6 weeks before randomization and systemic use of any medications to treat rosacea)

Draelos Z, Elewski B, et al. A phase 3 randomized, double blind, vehicle-controlled trial of azelaic acid foam 15% in the treatment of papulopustular rosacea. *Cutis*. 2015; 96:54-61, A1-2

Comparator Drugs:

Drug	Formulation	Dosing Interval	Price/package	Current coverage (before 9/24/15)	Proposed coverage (after 9/24/15)
Soolantra (ivermectin) 1%	Cream	Once daily	$330.00/30g	Tier 3 QL of 1/30 days	Same
MetroCream (metronidazole) 0.75%	Cream	Twice daily	$682.92/45g	Brand penalty copay	Same
Rosadan (metronidazole) 0.75%	Cream	Twice daily	$290.46/45g	Brand penalty copay	Same
Metronidazole 0.75%	Cream	Twice daily	$118.35/45g MAC at $2.63/g	Tier 1	Same
Noritate (metronidazole) 1%	Cream	Once daily	$822.96/60g	Tier 2	Same
Metrogel (metronidazole) 1%	Gel (pump)	Once daily	$411.06/55g	Brand penalty copay	Same
Rosadan (metronidazole) 0.75%	Gel	Twice daily	$290.46/45g	Brand penalty copay	Same
Metronidazole 0.75%	Gel	Twice daily	$121.50/45g MAC at $2.70/g	Tier 1	Same
Metronidazole 1%	Gel	Once daily	$277.26/55g	Tier 1	Same
Finacea (azelaic acid) 15%	Gel	Twice daily	$306.01/50g	Tier 3	Same
Finacea (azelaic acid) 15%	**Foam**	**Twice daily**	**$306.01/50g**	**n/a**	**Tier 3** **QL 50g/30 days**
MetroLotion (metronidazole) 0.75%	Lotion	Twice daily	$784.98/59mL	Brand penalty copay	Same
Metronidazole 0.75%	Lotion	Twice daily	$172.87/59mL MAC at $2.93/mL	Tier 1	Same

Student Recommendation & Summary: Provide the same coverage as Finacea 15% gel for the Finacea 15% foam formulation – Tier 3 with a QL of 50 g per 30 days. Azelaic acid 15% foam shows statistically and clinically significant results in the treatment of papulopustular rosacea. Patients, with sensitive skin, often prefer foam to traditional vehicles (gel, cream, ointment) due to improved appearance and ease of application with reduced need to manipulate inflamed skin. In the study, the vehicle was thought to contribute to improved skin condition due to its lipid component in the foam formulation. The azelaic foam has no price difference when compared to the azelaic acid gel. The deciding factor between formulations for a patient receiving azelaic acid would be personal preference.

EBRx Outcome: Cover Tier 3 with a QL of 50 g per 30 days

Sumatriptan iontophoretic transdermal system 6.5mg/4hr (Zecuity)

Kaitlin Bates, P4

September 2015

Labeled use: Acute treatment of migraine with or without aura in adults

Mechanism of Action: Sumatriptan is a selective agonist for serotonin receptors (5-HT_{1B} and 5-HT_{1D}) on intracranial blood vessels and sensory nerves of the trigeminal system. It causes cranial vessel constriction and inhibition of the release of pro-inflammatory neuropeptides (such as substance P, calcitonin gene-related peptide). The iontophoretic system (single-use patch) is applied to the upper arm or thigh. It uses low-level electrical energy to transport the drug across the skin. When activated, the electrical current is started and the positively charged drug moves away from the anode. A controlled amount of sumatriptan is delivered into the bloodstream over 4 hours.

Contraindications: Hypersensitivity to sumatriptan or any component of the formulation, including allergic contact dermatitis to the TD patch; ischemic heart disease (including Prinzmetal angina, angina pectoris, MI, or silent myocardial ischemia); cerebrovascular syndromes (including strokes and transient ischemic attacks); history of hemiplegic or basilar migraine; peripheral vascular disease (including ischemic bowel disease); uncontrolled hypertension; use within 24 hours of ergotamine derivatives; use within 24 hours of another 5-HT_1 agonist; concurrent administration or within 2 weeks of discontinuing an MAO type A inhibitor; Wolff-Parkinson-White syndrome or arrhythmias associated with other cardiac accessory conduction pathway disorders; severe hepatic impairment

Adverse reactions: Allergic contact dermatitis; myocardial ischemia, MI, and Prinzmetal's angina; arrhythmias; chest, throat, neck, and/or jaw pain/tightness/pressure; cerebrovascular events; other vasospasm reactions; medication overuse headache; serotonin syndrome; increase in blood pressure; anaphylactic reactions

Drug interactions: Ergot-containing drugs, MAO inhibitors, other 5-HT_1 agonists, SSRIs, SNRIs, TCAs

Evidence:

PREDICT study: Phase III Research into the Efficacy of Transdermal Sumatriptan in Acute Migraine

- **Design:**
  - R, DB, PC trial conducted at 38 sites in the US, ITT analysis
  - n=530 randomized to identical patches: sumatriptan iontophoretic TS (6.5mg over 4 hrs) or placebo (NaCl)
    - Safety analysis applied a patch: sumatriptan TD system (n=234) vs. placebo (n=235); n=469
    - ITT analysis activated a patch: sumatriptan TD system (n=226) vs. placebo (n=228); n=454
  - Patients remained on the study until one moderate-to-severe migraine occurred or for 2 months.
  - Patients rated their baseline headache pain on a 4-point scale (0=none, 1=mild, 2=moderate, 3=severe) and only applied the study patch if the score was 2 or 3. At 0.5, 1, 2, 3, 4, 6, 12, and 24 hours after patch activation, patients recorded headache pain severity and the presence/absence of nausea, phonophobia, photophobia, and the use of rescue medications.
  - Adverse effects were recorded through 30 days after patch removal; skin irritation was recorded at 4 (within 10 min from patch removal), 6, 12, and 24 hours after patch activation (0=no redness, 4=intense skin redness, blisters or broken skin)
- **Endpoints/Results:**
  - **<u>Primary end point: proportion of patients who were headache pain-free 2 hours after patch activation</u>**
    - 18% sumatriptan TD system vs. 9% placebo (p=0.0092). This significant difference continued for all subsequent time points through 12 hrs (p≤0.0357).
  - Secondary end points:
    - Headache pain relief:
      - 1 hr postdose: 29% sumatriptan TD system vs. 19% placebo (p=0.0135).
      - 2 hrs postdose: 52.9% sumatriptan TD system vs. 28.6% placebo (p<0.0001).
      - Significant difference continued for all subsequent time points through 12 hrs (p≤0.01).
    - Freedom from nausea, photophobia, or phonophobia:
      - Nausea-free 1 hr postdose: 71% sumatriptan TD system vs. 58% placebo (p=0.0251).
      - Photophobia-free 2 hrs postdose: 51% sumatriptan TD system vs. 36% placebo (p=0.0028).
      - Phonophobia-free 2 hrs postdose: 55% sumatriptan TD system vs. 39% placebo (p=0.0002).
      - Significant differences continued for all subsequent time points through 12 hours after patch activation.

- Migraine-free (headache pain-free and nausea-, photophobia-, and phonophobia-free) 2 hrs postdose: 16% sumatriptan TD system vs. 8% placebo (p=0.0135).
- Rescue medication use after 24 hrs: 60% sumatriptan TD system vs. 40% placebo did not use rescue medication (p<0.0001).
- Tolerability: Proportion of patients who had 1 or more treatment-emergent AEs, 50% sumatriptan TD system vs 44% placebo; mostly application-site reactions (pain, paresthesia, pruritus, reaction).
    - Discontinued medication because of application-site rxns: 5 patients (2.1%) in sumatriptan group vs 3 patients (1.3%) in placebo group.
    - Triptan sensations: 3.4% sumatriptan vs. 0.4% placebo

- Limitations:
    - No data comparing TDS vs other sumatriptan formulations or other migraine drugs
    - Patients were excluded who have a hx of failed response to sumatriptan tx, which may have favored sumatriptan TDS.

Goldstein J, Smith TR, Pugach N, et al. A sumatriptan iontophoretic transdermal system for the acute treatment of migraine. Headache. 2012;52(9):1402-10.

12 Month Open Label Follow-up Study

- Open-label, non-comparative, long-term study with consistent tolerability/efficacy data
- n=183 continued to treat moderate or severe headache pain for up to 12 months. Max of 6 patches were used within 30 days and not >2 patches in 24 hrs. Patients applied 2089 patches all-together.
- Efficacy similar to Phase III Trial: 2 hrs post dose, 23.8% headache pain free, 58.2% headache pain relief, 78.9% nausea free, 60.1% phonophobia free, 53.4% photophobia free, and 20.7% migraine free.
- Tolerability: 45% application site AE, 3.3% nausea, 3.3% upper RTI, 2.2% nasopharyngitis, 1.6% triptan AE
- Limitation: Possible attrition bias

Smith TR, Goldstein J, Singer R, et al. Twelve-month tolerability and efficacy study of NP101, the sumatriptan iontophoretic transdermal system. Headache. 2012;52(4):612-24.

Comparator Drugs	Dose	AWP (1 dose)	AWP (per HA)
Zecuity (sumatriptan succinate iontophoretic transdermal system) Apply 1 patch (6.5mg/4hr), may apply a second patch in 2 hrs after activation, MDD=13mg or 2 patches	**6.5mg/4hr (1)**	**$346.80**	**$693.60 (#2)**
sumatriptan tablet 25mg, 50mg, or 100mg at onset, may repeat in 2 hrs, MDD=200mg	25mg (1) 50mg (1) **100mg (1)**	$1.36 (MAC) $1.26 (MAC) **$1.26** (MAC)	$10.88 (#8) $5.04 (#4) **$2.52 (#2)**
sumatriptan nasal solution 5mg, 10mg, or 20mg in one nostril, may repeat in 2 hrs, MDD=40mg	5mg/ACT (1) **20mg/ACT (1)**	$38.43 (MAC) **$34.99** (MAC)	$307.44 (#8) **$69.98 (#2)**
sumatriptan succinate SC injection kit Inject 6mg (4mg if AE) SQ, may repeat in 1 hr, MDD=12mg	**4mg/0.5mL (0.5 mL)** 6mg/0.5mL (0.5 mL)	**$180** (MAC) $150.20 (MAC)	**$540 (#3)** $300.40
rizatriptan ODT 5 or 10mg at onset, may repeat in 2 hrs, MDD=30mg	5mg (1) **10mg (1)**	$9.98 (MAC) **$9.98** (MAC)	$59.88 (#6) **$29.94 (#3)**
zolmitriptan ODT 2.5mg or 5mg at onset, may repeat in 2 hrs, MDD=10mg	2.5mg (1) **5mg (1)**	$12.79 (MAC) **$14.13** (MAC)	$51.15 (#4) **$28.26 (#2)**
Zomig brand (zolmitriptan nasal solution) 2.5mg or 5mg at onset, may repeat in 2 hrs, MDD=10mg	2.5mg (1) **5mg (1)**	$62.67 **$62.67**	$250.68 (#4) **$125.34 (#2)**

Bold print indicates approximate equipotent dosing according to dailymed.nlm.nih.gov

Summary:

The sumatriptan iontophoretic TDS is effective and well-tolerated. It may be useful in pts w/ GI sxs and migraines (N/V, gastroparesis) who do not tolerate oral medications. The sumatriptan patch is similar in efficacy to the bolded drug strengths above with an approximate 60% HA response at 2 hrs for each formulation and slightly lower response than the sumatriptan injection (70% positive response). However, for those with N/V or gastroparesis, there are other cheaper options including the sumatriptan and zolmitriptan nasal sprays, sumatriptan injection, as well as rizatriptan and zolmitriptan ODT tablets.

Student Recommendation to EBRx Committee: Do not cover. Zecuity is not known to be superior to other cheaper dosage forms; it has only been compared to placebo. There are other options for N/V and gastroparesis patients with migraines.

EBRx Outcome: Exclude coverage.

Glatiramer acetate (Glatopa)

20mg/ml (1ml)

Brand name (generic name)	Dose	Unit Price (AWP)	Total Monthly Cost (AWP)
Glatopa (glatiramer acetate)	20mg/ml (1ml) SC daily	$216.41 per 1ml syringe	$6492.41
Copaxone (glatiramer acetate)	20mg/ml (1ml) SC daily	$244.42 per 1ml syringe	$7332.60
Copaxone (glatiramer acetate)	40mg/ml (1ml) SC 3x/w	$500.80 per 1ml syringe	$6009.60

Future Availability:

Teva's Copaxone final patent was originally set expire on September 1, 2015. However, a court invalidated the September expiration, which would allow for additional generic availability before September. Mylan had filed for an ANDA for the three times weekly generic glatiramer acetate in August 2014, which was accepted by the FDA. Additionally, Mylan had filed for an ANDA for the once daily 20mg/ml formulation back in September of 2009. which was also accepted.

Contracting and Rebate Implications:

Teva's upcoming patent expiration on Copaxone has led it to increase its price of the 20mg/ml daily use product, price the thrice weekly product so that is displays a lower annual cost, and utilize its Shared Solutions patient support and campaigning to convert patients to the thrice weekly formulation.

Although the currently available Copaxone 40mg/ml formulation appears to offer the most cost effective solution based on AWP, further price reductions with generic competition is likely. Price elevation of the daily formulation will likely be offset in the long term with reductions in prices with upcoming generic availability. Contracting and rebating will be crucial to containing costs.

Given the patient population of 51 current users of Copaxone 20mg daily, a calculated total plan cost savings of $24,623.31 per month and $295,479.72 annually would occur with coverage of Glatopa only.

Recommendations: Exclude brand Copaxone, in both formulations upon commercial availability of Glatopa. Cover Glatopa (glatiramer acetate) at the specialty tier.

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Lumacaftor/ivacaftor (Orkambi)

200/125mg tablet

Labeled Uses: Cystic Fibrosis (CF) in patients ≥12y who are homozygous for the F508del mutation in the CFTR gene.
Dose: 200/125mg, take 2 BID (Adults),
Supplied: 112-count tablet box containing a 4w supply (4 weekly cartons of 7 daily blister strips w/ 4 tablets per strip.

Comparator Drugs: treat F508del mutation (defective gating protein) in CF

	Cost (AWP) / 28 days
Lumacaftor + ivacaftor (Orkambi)	$23,907.52 (#112, take 2 BID)
Ivacaftor (Kalydeco)	$28,675.36

Note: Ivacaftor (Kalydeco) is indicated for CF with gene positive testing for the G551D-CFTR mutation OR one of these mutations: G1244E, G1349D, G178R, G551S, S1251N, S1255P, S549N, S549R, R117H.

MOA: Lumacaftor improves the conformational stability of F508del-CFTR. Ivacaftor is a CFTR potentiator.
Contraindication: Caution in advanced liver and kidney (CrCl < 30mL/min) disease
Adverse Reactions: Cataracts, Increased LFTs, chest discomfort, dyspnea
Drug Interactions: CYP3A4 substrates, inhibitors, inducers (Careful with midazolam, triazolam, cyclosporine, everolimus, sirolimus, and tacrolimus)

Evidence:
Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR[2]
Design: N=1,108 pts underwent the TRAFFIC and TRANSPORT trials. Both trials are phase 3, R, DB, PC studies. Arms: Lumacaftor (600mg daily or 400mg BID) + ivacaftor (250mg BID) or placebo. 1`endpt was absolute change from baseline of predicted FEV1 at week 24.

Results:	Change from placebo FEV_1	# of pulmonary exacerbations @ 24w	Decrease of pulmonary exacerbations	Increased BMI	Change from baseline in CQF-R ++QOL score
Lumacaftor 600mg+ ivacaftor 250mg	3.3% (pooled) (95%CI 2.3 to 4.3)	173/368=47%	30% (P=0.001)	0.28 (P<0.001)	3.1 (95%CI 0.8-5.3)
Lumacaftor 400mg + ivacaftor 250mg	2.8% (pooled) (95%CI 1.8 to 3.8)	152/369=41.2%	39% (P<0.001)	0.24 (P<0.001)	2.2 (95%CI 0-4.5)
Placebo		251/371=67.7%			

Pulmonary exacerbation is defined as a new or change in antibiotic therapy (IV, inhaled, or oral) for any 4 or more of the above signs/symptoms. Change in sputum, New or increased hemoptysis, Increased cough · Increased dyspnea, Malaise, fatigue, or lethargy, Temperature above 38°C (equivalent to approximately 100.4°F), Anorexia or weight loss, Sinus pain or tenderness, Change in sinus discharge, Change in physical examination (PE) of the chest, Decrease in pulmonary function by 10%, Radiographic changes indicative of pulmonary infection

++MCID in CQF-R was 4-8.5 points in stable or pulm exacerbation population, respectively. (CHEST 2009; 135:1610 –1618)

A CFTR Potentiator in Patients with Cystic Fibrosis and the G551D Mutation[3]
Design: A total of 167 patients participated in this randomized, double blind, placebo-controlled trial. Patients were randomly assigned to receive 150mg of ivacaftor BID (N=84) or placebo (N=83) for 48 weeks.

Results @ 48w:	FEV_1, Change from baseline	# pts w/ exac (#exac)	Decrease of pulm exac	Increased Weight (kg)
Ivacaftor (Kalydeco)[3]	10.4% (P<0.001)	28/83=33.7% (47 exac)	55% (P<0.001)	2.7 (P<0.001)
Placebo	-0.2%	44/78=56.4% (99 exac)		

Student Recommendation: Cover at highest tier with a PA. Criteria for coverage: Diagnosis of CF, and age ≥12, homozygous for Phe 508 del CFTR mutation, patient must be currently demonstrating compliance w/ the evidence-based standard of care for inhaled therapies for CF (or experience intolerance to one or more of them), and be tobacco-abstinent.

EBRx Committee Outcome: Cover at highest tier with a PA. Criteria for coverage: Diagnosis of CF, and age ≥12, homozygous for Phe 508 del CFTR mutation, patient must be currently demonstrating compliance w/ the evidence-based standard of care for inhaled therapies for CF (or experience intolerance to one or more of them), and be tobacco-abstinent. Deny for therapeutic duplication with Kalydeco (and vice versa). QL of 4/1.

Sources:

1. Orkambi (lumacaftor/ivacaftor) [prescribing information]. Boston, MA: Vertex Pharmaceuticals Incorporated; July 2015.
2. Wainwright CE, Elborn JS, Ramsey BW, et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. N Engl J Med 2015; 373:220.

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3. Ramsey BW, Davies J, McElvaney NG, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med 2011; 365:1663.

*****please see the Lumacaftor-ivacafter FDA Backgrounder_508 in 1Jill, Contracts, EBRx, Lumacaftor-ivacaftor. See starting on page 21 or 24 regarding lack of benefit of Orkambi over Kalydeco in 508del.**

Hepatitis C
EBRx Prior Authorization Criteria

09/10/2015

Jill Johnson, Pharm.D., BCPS

A. For any treatment to eradicate chronic hepatitis C virus (HCV)infection, the following criteria must be met regardless of which regimen is requested:

1. The patient must test positive for chronic HCV infection. Two options: • HCV antibody ≥6m before a positive HCV RNA (viral load) , OR • 2 HCV RNA levels 6 months apart ☐The viral load must be documented._____ ☐The genotype and subtype must be documented._____	The diagnosis of CHRONIC HCV must be made. 15-25% seroconvert on their own and the patient clears the infection. We only treat chronic HCV infection.
2. The patient must be free of using illicit drugs for the past 6 months. ☐A patient-signed statement attesting to this is acceptable.	Any positive drug screen for injectable drug use during treatment stops access to the HCV drugs. Reinfection is a risk for IV drug users.
3. The patient must be free of abusing ethanol for the past 6 months. (defined as >3 glasses/d (1 glass is equivalent to beer 284 mL, wine 125 mL, or distilled spirits 25 mL for females and >4 glasses/d for males). ☐A patient-signed statement attesting to this is acceptable.	
4. If the patient has cirrhosis, there must be NO signs of decompensation (ascites, episodes of spontaneous bacterial peritonitis, hepatic encephalopathy,), unless the patient is currently listed for liver transplant. ☐The drug profile for the past 1 year must be submitted.	Unless currently LISTED on the liver transplant list. Patients with decompensation will not be treated unless currently listed on a verifiable list from a liver transplant center.
5. The patient with liver disease due to any cause other than HCV infection (chronic hepatitis B infection, autoimmune hepatitis, alcoholic hepatitis, , hemochromatosis, Wilson's disease, alpha1 antitrypsin deficiency,) should be referred to a gastroenterologist.	
6. The extent of fibrosis may be shown by liver biopsy, FIB-4, APRI, Fibroscan (transient elastography), or Fibrotest to demonstrate the patient has a Metavir score of F3 or F4.	
7. Patients with extrahepatic manifestations of chronic HCV infection are candidates for therapy regardless of corresponding Metavir score as long as they meet the other requirements above.	
8. If the patient was provided HCV eradication therapy and abandoned therapy, they are not eligible for a second course of treatment. If the patient completed but relapsed or had intolerance to the first course of therapy, then they would be eligible for subsequent treatment depending on what is requested and the clinical evidence. ☐A review of the drug profile for fills provided in the past for HCV eradication drug therapy. Further explanation by the patient/physician may be required.	

B. Other questions which must be collected on EVERY patient seeking drug therapy for HCV infection:

1. Is the patient currently on the liver transplant list? (Decompensated, metavir F4 patients are eligible for treatment, absent contraindications listed in #5 above.)	
2. Has the patient previously received any treatment for HCV infection? If so, what regimen and duration? ☐This info must be captured even if drug was supplied by the manufacturer.	This answer is needed to determine treatment eligibility.
3. HIV positive patients must have absolute CD4 counts above 500 and not require HAART therapy or currently receive HAART therapy if the absolute CD4 count is below 200, to be eligible for HCV eradication treatment. ☐If HIV positive, the absolute CD4 count must be submitted from the past 6 months.	

C. Coverage Policies

The premise for the policies below is multifactorial.

First, chronic HCV is a progressive disease that takes decades to develop cirrhosis or hepatocellular carcinoma and only 20% develop cirrhosis over 20-30 years and 5% die from cirrhosis or liver cancer. Second, achieving a sustained viral response 12 or 24 weeks after the end of drug therapy (SVR12 or SVR24) is not a cure. SVR is a surrogate marker for the actual outcome of liver morbidity or mortality (including decompensated liver cirrhosis, hepatocellular carcinoma, liver transplantation, or death from liver related causes). Thus the objective is not how many patients develop SVRs but how many are spared from ESLD. None of the drug trials evaluated these outcomes. All the studies linking SVR to clinical outcomes are observational studies and are subject to confounding. Additionally, patients who achieve SVR remain at risk for developing HCC, although the risk is lower than if SVR had not been achieved. To date (2/10/15), all data showing a decrease in liver morbidity or mortality included interferon + ribavirin in the HCV eradication therapy. There are no data to show a non-interferon containing regimen for HCV eradication reduces liver-related morbidity or mortality. However, the available observational studies with interferon show achieving an SVR24 correlates to improved quality of life and reduction in fatigue, and approximately an 80% decrease in decompensated liver disease, HCC, liver transplant, and all-cause mortality. It appears that some risk for HCC remains, even in those achieving SVR.

Condition	Number of individuals
Infection with hepatitis C	100
Develop symptoms	20-30
Remain asymptomatic	70-80
Develop chronic infection	75-85
Develop chronic liver disease	60-70
Develop cirrhosis over 20-30 years	5-20
Die from cirrhosis or liver cancer	1-5

Current Data (9/10/15):

	GT1					
		Sofosbuvir PR	Sofosbuvir/Simep	Simeprevir PR	Harvoni	Viekira Pak
1	GT1 treatment naïve, noncirrhosis, interferon eligible	SPR12 covered if Metavir score F3.	Not covered. Relapse reported to be 13%.	Effective.	Effective	Effective.
		Boceprevir: Poordad, et al, showed BPR was effective. Boceprevir: Kwo, et al, showed BPR was effective. Boceprevir: Sulkowski, et al, in HIV+ population, showed B triple tx works. Telaprevir: Sulkowski, et al, in HIV+ population, showed T triple tx works. Sofosbuvir: NEUTRINO showed sofos to be effective. Had 17% cirrhotics.	Cosmos, part of cohort-2. 76% were GT1a. They were F3 or F4. Some in cohort 2 had previous failure of PR.	NEUTRINO Boceprevir & telaprevir triple therapy is effective. Unknown which of the 3 is more effective. Must have Q80K negativity for simeprevir. QUEST-1 & -2.		

		Sofosbuvir: Study 1910. In HIV+ population showed sofosPR is effective. Lawitz, Lalezari, et al. Comparative sofosbuvirPR vs PR trial. 0% cirrhotics. High PR response rate. Lepidasvir+sofos. Afdhal, et al. Ledipasvir+sofos has efficacy. No SOC control arm.				
2	GT1 treatment naïve, noncirrhosis, interferon-INeligible	Contains interferon.	Not covered. Relapse rate 13%.	Not covered. Contains interferon.	Harvoni 8w (LONESTAR, ION-3)	GT1a with ribavirin. GT1b without ribavirin for 12 w. (PEARLIII/IV).
		Sofosbuvir: PHOTON-1 (via PI) showed sofos +R to be effective. No control arms. Lepidasvir+sofos. Afdhal, et al. Ledipasvir+sofos has efficacy. No SOC control arm.	Cosmos, Part of cohort-2.			
3	GT1 treatment naïve, decompensated cirrhosis AND listed for liver transplant,	Not covered.	Not covered.	Not covered.	Harvoni 12w (ION-1, but only 16% had cirrhosis; results not broken down by cirrhosis)	GT1a or 1b: ViekiraR 12w (TURQUOISEII)
					Package insert states, "No dosage adjustment of HARVONI is required for patients with mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, or C). Safety and efficacy of HARVONI have not been established in patients with decompensated cirrhosis".	TURQUOISEII showed GT1a SVR=92% regardless of 12 or 24w. All were cirrhotic. All received R. GT1b,SVR=100%,12w or 24w. Package insert says, "VIEKIRA PAK is not recommended in HCV-infected patients with moderate hepatic impairment (Child-Pugh B). VIEKIRA PAK is contraindicated in patients with severe (Child-Pugh C) hepatic impairment."
4	GT1 treatment naïve, compensated cirrhosis, interferon-eligible	Covered for 12 w combined w/ PR.			Harvoni 12w	ViekiraR 12w (regardless of GT1a/b—add R due to cirrhosis and Turquoise-II data)

	GT1	Sofosbuvir PR	Sofosbuvir/Simep	Simeprevir PR	Harvoni	Viekira Pak
		Boceprevir: Poordad, et al, showed BPR was effective. Had 7-11% cirrhotics. Telaprevir: Jacobson, et al. showed telaprevir is effective. Had 6-7% cirrhotics. NEUTRINO Lepidasvir+sofos. Afdhal, et al. Ledipasvir+sofos has efficacy. No SOC control arm. Had 16% cirrhotics.		QUEST-1 & -2. Had up to 10% cirrhotics. Unknown which of the 3 DAAs is more effective. Must have Q80K negativity for simeprevir. Boceprevir: Poordad, et al, showed BPR was effective. Had 7-11% cirrhotics. Telaprevir: Jacobson, et al. showed telaprevir is effective. Had 6-7% cirrhotics.	SVR was 99% (but only 16% in this population represents compensated cirrhosis.)	Turquoise II-showed a 92%-96% SVR12.
5	GT1 treatment naïve, compensated cirrhosis, interferon-INeligible	Not covered. These patients cannot take interferon.	93% SVR12 (all F3 or F4), Sofos/Sime12w	Not covered.	99% w Harvoni 12w (only 16% had comp cirrhosis)	92.2% w/ ViekiraR 12w
		No peer-reviewed data to support use of non-interferon regimens in this population. COSMOS, Cohort 2, treatment naïve with cirrhosis. Noncomparative trial. Exclusion of "nonvirologic failures", (not ITT). Phase 2. Small N. (We reject COSMOS until it undergoes peer review and is published and available through PubMed.) Osinusi, Meissner, et al. S+R showed 68% SVR24 with weightbased R. Compared only to non-wt-based R.	Relapse high and costliest regimen.	No peer-reviewed data to support use of non-interferon regimens in this population. COSMOS, Cohort 2, treatment naïve with cirrhosis. Noncomparative trial. Exclusion of "nonvirologic failures", (not ITT). Phase 2. Not yet published. Small N. (We reject COSMOS until it undergoes peer review and is published and available through PubMed.) Osinusi, Meissner, et al. S+R showed 68% SVR24 with weightbased R. Compared only to non-wt-based R.		Turquoise-II-100% of this population had cirrhosis, Child-Pugh Class A.
	GT1	Sofosbuvir PR	Sofosbuvir/Simep	Simeprevir PR	Harvoni	Viekira Pak
6	GT1 Prior nonresponders to PR, noncirrhosis	Not covered. Await more advanced disease. SR (without PEG) SVR 10%.		53%SVR w simep12/PR48 (ASPIRE) (not stated number w/ cirrhosis); not covered.	SVR overall for Harvoni12w was 94% (45% were prior non responders; 55% were prior relapsers) but included 20% w/ cirrhosis.	GT1 SVR 93% (Kowdley, et al.) GT1a SVR=95.2% w/ ViekPak 12w GT1b SVR=100% w/ Viek

					Noncirrhosis must be F3.	Pak 12w (PEARL-II)
		Boceprevir: Bacon, et al, showed boceprevir is effective. Telaprevir: McHutchison et al, showed telaprevir is effective. Telaprevir: Zeuzem, et al, showed telaprevir is effective. Sofosbuvir: COSMOS. Cohort 2 (prior nonresponders, metavir 4) shows sofos is effective but had inadequate power and no comparative arms. Optimist-1 and Optimist-2 (sofos+simep), phase 3 began recruiting 4/2014.		From PI: PROMISE showed simeprevir works better than PR. No comparisons to triple tx. COSMOS was noncomparative and no power to determine conclusion. Awaiting Optimist-1 and -2.	ION-2. Harvoni24w SVR=99%.	GT1a overall=SVR96%; GT1b overall=SVR96.7% in SAPPHIRE-II. GT1b SVR93% with RIba, 100% w/o Riba in PEARL-II
7	GT1 Prior nonresponders to PR, compensated cirrhosis	No data. Not covered.	(COSMOS was all F0-2). Not covered.	53%SVR w simep12/PR48 (ASPIRE) (not stated number w/ cirrhosis); not covered.	• SVR overall for Harvoni12w was 93.6% (prior non responders) but included only 20% w/ cirrhosis. • SVR96% for Harvoni+R 12w; SVR 97% for Harvoni 24w in GT1a/comp cirrhotic/previous nonresponder; relapse 3%, 4%, respectively (SIRIUS)	GT1a SVR80% w/ViekiraR 12w GT1a SVR 92.9% w/ViekiraR 24w GT1b100% w/ViekiraR12w (TURQUOISE-II)
		COSMOS was not comparative to other triple therapy or other double therapy.		Other triple therapy is covered and response rates are similar or better with boceprevir regimens. Bacon, et al. McHutchison, et al. Zeuzem, et al. PROMISE (simeprevir PI) ASPIRE (simeprevir PI)	SIRIUS	Turquoise-II—All these pts had cirrhosis (Metavir score >3 by liver biopsy or FibroScan, A Child-Pugh class A of <7; prev telaprevir or bocep users were excluded.) The 80% and 92.9% rates for GT1a confidence intervals overlapped.
8	GT1 Prior nonresponder to BPR or TPR, noncirrhosis	No data.	No data.	No data.	F3s are covered Harvoni12w. (ION-2)	No data. SAPPHIRE-II excluded prev PI pts. Viekira is not recommended if the patient previously failed a PI (Boceprevir, telaprevir, or simeprevir)
				No data.	ION-2 data: 89%	

					had previous bocep or telap exposure. (39% had received prev tx with PR;61% had received prev tx w/ PI)(45% were prev nonresponders; 55% were prev relapsers).	
9	GT1 Prior relapsers after PR, noncirrhosis	Not covered.	No Data.	SVR was 79%(PROMISE), 83%(ASPIRE). Must be Q80K negative. Sample included 20% cirrhotics. Sime12PR48.	Harvoni 12. SVR was 93.6% overall. (55% were relapsers. ION-2).	GT1 a or b: ViekiraR 12w, SVR 96% (SAPPHIRE-II-excluded F3 & F4) **NO DATA in F3s** GT1b: ViekiraR 12w, SVR 100% (PEARL-II) **NO DATA in F3s**
			COSMOS was prior null responders, not prior relapsers	PROMISE. ASPIRE.	ION-2	SAPPHIRE-II.
10	GT1 Prior relapsers after PR, compensated cirrhosis	No data. Not Covered.	(COSMOS)57% were previous nonresponders. Sime/sofos 24w overall SVR was 100% (n=16)	(ASPIRE)77%SVR w/ Sime12PR48 but not reported how many had cirrhosis. NOT Covered.	SVR overall for Harvoni12w was 93.6% (but only 55% were previous relapsers and included only 20% w/ cirrhosis).	GT1a: ViekiraR 24w, SVR 100% GT1b: ViekiraR 12w, SVR 100% (TURQUOISE-II)
	GT1	Sofosbuvir PR	Sofosbuvir/Simep	Simeprevir PR	Harvoni	Viekira Pak
		No peer-reviewed data to support use of non-interferon regimens in this population. COSMOS, Cohort 2, treatment naïve with cirrhosis. Noncomparative trial. Exclusion of "nonvirologic failures", (not ITT). Phase 2. Osinusi, Meissner, et al. S+R showed 68% SVR24 with weightbased R. Compared only to non-wt-based R. Boceprevir: Bacon, et al, showed boceprevir is effective. Had 10-14% cirrhotics Telaprevir: McHutchison et al, showed telaprevir is effective. Had 11-20% cirrhotics. Telaprevir: Zeuzem, et al, showed		Bacon BR, et al. Boceprevir evidence. PROMISE provides evidence that simeprevir12PR12, PR12 is effective. McHutcison provides evidence that T12PR24 is effective.		Turquoise II: in GT1a relapsers, treatment for 24w instead of 12w increased SVR from 93.3 to 100%. GT1b relapsers achieved 100%SVR w/ 12w.

		telaprevir is effective. Had 23-27% cirrhotics. Sofosbuvir: COSMOS. Cohort 2 (prior nonresponders, metavir 4) shows sofos is effective.				
11	GT1, treatment experienced, coinfected w/ HIV	Cover same as without HIV.	Cover same as without HIV.	Cover same as without HIV.	Cover same as without HIV.	Cover same as without HIV.
	GT 2	Sofosbuvir PR	Sofosbuvir/Simep	Simeprevir PR	Harvoni	Viekira Pak
12	GT2 trtmt naïve, w/or w/o compensated cirrhosis	Not covered. Peginterferon + ribavirin is covered and should be dosed according to patient weight.	Not covered	Not covered.	Not covered	Not covered.
		FISSION (GT2, tx-naïve) compared SR12 to PR24 but used higher R dose in the SR12 group, creating a confounder where we can't tell if it was a function of the R dose. Previous data (Osinusi a, et al. Jama 2013;310(8):804-11, showed R dose matters. PHOTON (HIV+ population) provides evidence of efficacy; n=26), however, it did not have a control arm to compare to. Unknown whether PR if more effective.				
13	GT2 treatment(PR)-experienced	Sofosbuvir + R 12w without Peg. SVR 88% (VALENCE)	No data	No data	No data	No data
		FUSION (19% of included pts) showed efficacy in 82% w/ SVR12. No comparative arm. VALENCE (although Valence became a descriptive trial only after a mid-trial protocol amendment.)				
14	GT2 treatment naïve, unable to take interferon, noncirrhotic	Sofosbuvir + R 12w without Peg. SVR 88% (VALENCE)	Not covered.	Not covered.	Not covered.	Not covered.
		FUSION (19% of included pts) showed efficacy. POSITRON (all w/ inability to take interferon) showed SR12 effective. Nothing to compare to.				
15	GT2 treatment naïve, unable to	Sofosbuvir + R 12w without Peg. SVR 88% (VALENCE)	Not covered.	Not covered.	Not covered.	Not covered.

	take interferon, compensated cirrhotic					
		Due to this being the best current alternative in a cirrhotic patient, it is justifiable to treat. FUSION (19% of included pts) showed efficacy. POSITRON (all w/ inability to take interferon) showed SR12 effective.				

	GT3						Daclatasvir/sofosbuvir (Daklinza)
		Sofosbuvir PR or Sofosbuvir-Riba	Sofosbuvir/Simep	Simeprevir PR	Harvoni	Viekira Pak	
16	GT3 treatment naïve, with or without compensated cirrhosis if able to take interferon	Not covered. Sofosbuvir with ribavirin and without peginterferon also not covered. No comparative data to know if it is any better than PR alone. (PR 24 would be preferred.)	No data.	No data.	No data.	No data.	Daclatasvir/sofosbuvir 12 weeks; SVR12=97% w/o cirrhosis SVR12=58% with cirrhosis Relapse 9%
		FISSION showed a worse SVR12 compared to PR24 despite the larger R dose in the SR12 arm. Therefore, may not be as effective as PR24. VALENCE showed efficacy (SVR12up to 99.8%) in GT3 w/ SR24, however, no control arm. PHOTON showed efficacy in GT3 with SR24.					PI and ALLY-3, N=101 tx-naïve w/ GT3 and compensated liver dz
17	GT3 treatment naïve, NONcirrhotic, unable to take interferon	F3s: Sofosbuvir + Ribavirin 24w (SVR was 94.6%) (VALENCE)	No data.	No data.	No data.	No data.	Daclatasvir/sofosbuvir 12 weeks; SVR12=97%
		VALENCE					PI and ALLY-3.
18	GT3 treatment experienced, NONcirrhotic	SR24 SVR12=86.7%					Daclatasvir/sofosbuvir 12 weeks; SVR12=94% Relapse 14%
							PI and ALLY-3, N=51 tx-experienced GT3 and compensated liver dz.
19	GT3 treatment-experienced, compensated cirrhosis, interferon	Covered with ribavirin X24 weeks (SVR 61.7%)VALENCE	No data.	No data.	No data.	No data.	Daclatasvir/sofosbuvir 12 weeks; SVR12=69% Relapse 14%

	INeligible						
		FUSION & POSITRON; the alternative is PR and these patients are either interferon-experienced or ineligible for it.					PI and ALLY-3.

	GT4	Sofosbuvir PR or Sofosbuvir-Riba	Sofosbuvir/Simep	Simeprevir PR	Harvoni	Viekira Pak	Ombitasvir/Paritaprevir/ ritonavir(Technivie)	Daclatasvir PR12w
20	GT4, interferon eligible, treatment naïve, NONcirrhotics	SPR 12w (SVR96%)NEUTRINO	No data.	No data.	No data.	No data.	SVR12=100% with 12w and w/RBV	D12PR36w =SVR100% N=31.
		NEUTRINO showed 96% for GT4, however, the number of patients representing this population is small. N=28					PI and PEARL-1. Without RBV, the SVR12 was 91%; no stats given. Relapse was 5%. With RBV the relapse was 0%; no stats.	Hezode C, Hirschfield GM, et al. Daclatasvir plus PR for tx-naïve cHCV GT1 or 4infeciton: a randomized study. GUT. 2015;64:948-56.
21	GT4, interferon eligible, treatment naïve, compensated cirrhosis	SPR X12w	No data.	No data.	No data.	No data.	No data in cirrhosis; contraindicated with Child-Pugh C	
		NEUTRINO. Not as much time to wait.						
22	GT4, interferon ineligible	Not covered (or desired).	No data.	No data.	No data.	No data.	SVR12=100% with 12w and w/RBV	
		Evidence is in abstract form only from April 2014 EASL meeting. Ruane PJ, et al.					PI and PEARL-1. Without RBV, the SVR12 was 91%; no stats given. Relapse was 5%. With RBV the relapse was 0%; no stats.	
23	GT4, treatment experienced, non cirrhotic						SVR12=100% with 12w and w/ RBV	
							PI and PEARL-1.	
24	GT4, treatment experienced, cirrhosis						No data in cirrhosis; contraindicated with Child-Pugh C.	

	GT5						
25	GT5	Not covered.	No data.	No data.	No data.	No data.	
		NEUTRINO included an N=1 GT5 patient.					
	GT6						
26	GT6	Not covered.	No data.	No data.	No data.	No data.	
		NEUTRINO included an N=6 GT6 patients.					

*In all cases in which ribavirin is covered, the dose must be weight-based.
**Acceptable reasons for interferon ineligibility are listed below and must be documented PREVIOUSLY in the medical record:

- dermatomyositis, immune (idiopathic) thrombocytopenic purpura, inflammatory bowel disease, interstitial lung disease, interstitial nephritis, polymyositis, psoriasis, rheumatoid arthritis, sarcoidosis, systemic lupus erythematosus,
- Significant psychiatric disease necessitating hospitalization or period of disability or a history of psychosis, schizophrenia, bipolar disorder, moderate depression, schizoaffective disorder, suicidal ideation, or suicide attempt documented in the medical record.
- Significant local or systemic adverse reaction to IFN (e.g., hypersensitivity, injection site reactions),
- Significant cognitive impairment,
- Neuropathy,
- Thrombocytopenia (platelets < 25,000/μL),
- Neutropenia (ANC < 500/μL),
- Development of colitis, non-alcoholic pancreatitis or ophthalmologic disorders,
- Seizure disorder,
- Poorly controlled thyroid dysfunction;
- hyperthyroidism (TSH ≥ 2 x the upper limit of normal (ULN) and ≤ 10 x ULN) or hypothyroidism (TSH < the lower limit of normal (LLN) and > 0.1 μIU/mL)
- Retinal disease

***Fibrosis refers to Metavir F3 and cirrhosis refers to F4. A liver biopsy is required to differentiate between the two.

HCV Cliff Notes with all options 9/10/15
Jill Johnson, Pharm.D., BCPS

Note: All noncirrhosis must be Metavir F3 to treat. Underlined/bolded are the preferred treatment regimens for EBD patients.

	GT1		AWP 6/2015
1	GT1 treatment naïve, noncirrhosis, interferon eligible	Sofosbuvir PR X12w 89% Sofosbuvir/simeprevir 12w Simeprevir PR **Harvoni 8w** GT1a Viekira + R 12w GT1b Viekira 12w	$115,642 $180,432 $138,992 $75,600 $102,347 $99,983
2	GT1 treatment naïve, noncirrhosis, interferon-INeligible	**Harvoni 8w** Sofosbuvir/simeprevir 12w GT1a Viekira + R 12w GT1b Viekira 12w	$75,600 $180,432 $102,347 $99,983
3	GT1 treatment naïve, decompensated F4 cirrhosis AND listed for liver transplant,	Harvoni 12w **ViekiraR 12w**	$113,400 $99,983
4	GT1 treatment naïve, compensated cirrhosis (F4),interferon-eligible	Sofosbuvir PR X 12w Harvoni 12w **ViekiraR 12w**	$115,642 $113,400 $99,983
5	GT1 treatment naïve, compensated cirrhosis, interferon-INeligible	Sofos/Sime 12w, 93%SVR12 (All F3/F4) Harvoni 12w, 99%SVR12 (only 16% had comp cirrhosis) **ViekiraR 12w 94%SVR12 (100% w/ cirrhosis)** Viekira 12w 99%SVR12 (13% were F3)	$180,432 $113,400 $102,347 $99,983
6	GT1 Prior nonresponders to PR, noncirrhosis	Simeprevir12PR48, 53%SVR Harvoni 12w 94%, 24w=99% (39% had received prev tx with PR;61% had received prev tx w/ PI)(45% were prev nonresponders; 55% were prev relapsers). **ViekiraR12: GT1 SVR 93% (Kowdley)** ViekiraR12: GT1 SVR=95.2% (SAPPHIRE-II) **Viekira12: GT1b 100% (PEARL-II)**	$138,992 $113,400-$226,800 $102,347 $102,347 $99,983
7	GT1 Prior nonresponders to PR, compensated cirrhosis	Simep12/PR48 53%SVR; (not stated number of cirrhosis) Harvoni 12w 93.6% (but included only 20% w/ cirrhosis). **ViekiraR 12w: GT1a SVR 80% (TURQUOISE-II)** ViekiraR 24w: GT1a SVR 92.9% (TURQUOISE-II) **ViekiraR 12w: GT1b 100% (TURQUOISE-II)** **HarvoniR 12 w: GT1a or 1b 96% (SIRIUS)**	Not a good response $113,400 $102,347 $199,966 $102,347 $115,764

8	GT1 Prior nonresponder to BPR or TPR, noncirrhosis	F3s are covered: **Harvoni 12w 94%**	$113,400
9	GT1 Prior relapsers after PR, noncirrhosis	Sime12PR48 SVR79-83% (PROMISE,ASPIRE) Harvoni 12w SVR=93.6% (ION-2) **ViekiraR12: GT1a SVR=95.3% (SAPPHIRE-II)** **ViekiraR12: GT1b SVR=100% (PEARL-II)**	$138,992 poor response $113,400 $102,347 $102,347
10	GT1 Prior relapsers after PR, compensated cirrhosis	Sime/sofos 24w (SVR100%, n=16) Sime12PR48 (SVR 77%), but not reported #w/prevcirrhosis Harvoni 12w (SVR 93% w/ 55%represent by relapsers; only 20%w/cirrhosis) **ViekiraR 12w (GT1a) (SVR 93.3%)(Turquoise-II)** ViekiraR 24w (GT1b) (SVR 100%) (Turquoise-II)	$360,864 $138,992 $113,400 $102,347 $199,966
11	GT1, treatment experienced, coinfected w/ HIV	**Cover same as without HIV.**	
	GT2		
12	GT2 trtmt naïve, w/or w/o compensated cirrhosis	**PR24w**	$29,680
13	GT2 treatment(PR)-experienced	F3s: **Sofosbuvir+R 12w (SVR88%)**	$103,163
14	GT2 treatment naïve, unable to take interferon, noncirrhotic	F3s: **Sofosbuvir+R 12w (SVR88%)**	$103,163
15	GT2 treatment naïve, unable to take interferon, compensated cirrhotic	**F3s or F4s: Sofosbuvir+R 12w**	$103,163
	GT3		
16	GT3 treatment naïve, with or without compensated cirrhosis if able to take interferon	**PR24w (SVR 99%)** Daclatasvir/sofosbuvir 12w (SVR97% if no cirrhosis/SVR58% w/cirrhosis)	$29,680 $176,400
17	GT3 treatment naïve, NONcirrhotic, unable to take interferon	SR 24_(SVR 94.6% mixed tx-naïve) **Daclatasvir/sofosbuvir 12w** (SVR12=90%)	$206,326 **$176,400**
18	GT3 treatment experienced, NONcirrhotic	SR24 SVR12=86.7% **Daclatasvir/sofosbuvir 12w (SVR12=94%)**	$206,326 **$176,400**
19	GT3 treatment-experienced, compensated cirrhosis, interferon INeligible	SR24 (SVR 61.7%) **Daclatasvir/sofosbuvir 12w (SVR69%)**	$206,326 **$176,400**

	GT4		
20	GT4, interferon eligible, treatment naïve, NONcirrhotics	F3s: **SPR12w** **Ombitasvir/paritaprevir/ritonavir (Technivie) + RBV X12w**	$113,133 (9/10/15) **$91,983 + $393 RBV**
21	GT4, interferon eligible, treatment naïve, compensated cirrhosis	**SPR12w**	$113,133 (9/10/15)
22	GT4, interferon ineligible	Ombitasvir/paritaprevir/ritonavir and w/ RBV X12w	$91,983 + $393 RBV
23	GT4, treatment experienced, non cirrhotic	Ombitasvir/paritaprevir/ritonavir (Technivie) + RBV X12w	$91,983 + $393 RBV
24	GT4, treatment experienced, cirrhosis		
	GT5		
25	GT5	Not covered.	
	GT6		
26	GT6	Not covered.	

Evaluation of PCKS9 Inhibitors

Evolocumab

Data:

TESLA Part B is a randomized trial that evaluated patients ≥ 12 years of age diagnosed with *homozygous familial hypercholesterolemia* (N= 49). A majority of the patient population were also on statins (94% high intensity) and ezetimibe (92%).Baseline LDL was 348 mg/dl. Patients were randomized to evolocumab 420 mg SC q4w or placebo SC Q4 weeks for 12 weeks. LDL was reduced by 23.1% in the evolocumab group compared to an increase of 7.9% in the placebo group.

DESCARTES is the randomized trial that evaluated adults with an LDL ≥75 (N=901) to receive evolocumab 420mg Q2weeks or identical placebo for 52 weeks; ~15% had prior CVD and 12% had diabetes. At 52 weeks, LDL levels decreased 50.6% from 100.4 mg/dl in evolocumab group and increased 8.7% from a baseline of 100.2 mg/dl in the placebo group.

Alirocumab

Data:

ODYSSEY LONG TERM was the largest randomized controlled trial of alirocumab (N=2,341) evaluating alirocumab 150mg Q12 weeks vs placebo in patients on either high intensity statin (47%) or the highest tolerate dose (53%). The population include adults with known *coronary heart disease (69%) or CHD risk equivalent* with two or more additional risk factors (41%,) with an LDL level ≥ 70mg/dl. At 23 weeks, LDL levels were reduced from baseline average of 122.8 to 48.3 mg/dl in the alirocumab group and 122.0 to 118.9 in the placebo group. There was a statically significant number of increased myalgias in the alirocumab group (5.4% vs 2.9% compared to placebo). However, the analysis did show a decreased rate of non-fatal MIs compared to placebo (0.9% vs 2.3%). However, this must be taken into consideration given the fact another large randomized control trial demonstrated higher rates of non-fatal MIs in the alirocumab group (2.5% vs 1.2%) and lower rates of myalgias (4.4% vs 5.0%).

Meta-Analysis for Health Outcomes[3] (these data come from post hoc, exploratory information; statistics analyzed by the manufacturer)

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

Although it is suggested that the PCSK9 inhibitors reduce the odds of all-cause mortality, it is important to consider the magnitude low event rate. Additionally, other outcomes, such a CVD mortality, are not statistically significant. Also, this meta-analysis is composed of data from two separate PCSK9 inhibitors in different populations. Further research is needed into evaluating true benefit of PSCK9s.

Evaluation: Although PCSK9 inhibitors do reduce the certain CVD risk factors, such as LDL-C, meaningful benefit concerning hard endpoints and mortality is lacking. Additionally, the agents are well tolerated with no increase in adverse events. These agents are promising and may offer benefit related to reduced incidence of CVD. However, given the high costs of these agents and lack of hard endpoints, coverage at these times would increase healthcare cost burden with unknown, but promising benefit. Finally, an Institute for Clinical and Economic Review determined the value-based price benchmark for each agent now is $2,177 annually, which is 15% of the current listed price of $14,600. Further research is impending regarding clinical endpoints and should be available in 2017.

1. PCSK9 Inhibitor Therapies for High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks. Institute for Clinical and Economic Review. September 2015.

2. Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis. Ann Intern Med. 2015. PMID: 25915661.

3. Zhang XL, Zhu QQ, Zhu L, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. BMC Med. 2015;13:123. PMID: 26099511