



AGENDA

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

February 24, 2015

1:00 p.m.

EBD Board Room – 501 Building, Suite 500

- I. *Call to Order..... Dr. Kat Neill, Chairman*
- II. *Approval of November 3, 2014 Minutes Dr. Kat Neill, Chairman*
- III. *Introduction of New Committee Member Dr. Kat Neill, Chairman*
- IV. *Delivery Coordination Workgroup.....Dr. David Keisner, UAMS*
- V. *Hepatitis C ReviewDr. Jill Johnson, UAMS*
- VI. *Zetia Review.....Dr. Jill Johnson, UAMS*
- VII. *Singulair Review.....Dr. David Keisner, UAMS*
- VIII. *New Drugs.....Dr. Jill Johnson, UAMS*
- XV. *EBD Report.....Dr. David Keisner, UAMS*

Upcoming Meetings

April 6, 2015

August 3, 2015

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

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

State and Public School Life and Health Insurance Board Clinical and Fiscal Drug Utilization and Evaluation Committee Minutes February 24, 2015

The State and Public Life and Health Insurance Board, Drug Utilization and Evaluation Committee (DUEC) met on Monday February 24, 2015 at 1:00 p.m., in the EBD Board Room, 501 Woodlane, Little Rock, AR.

Voting Members present:

Dr. Melodee Harris - Teleconference
Dr. Kat Neill - Chairman
Dr. Appathurai Balamurugan - Tele
Larry Dickerson
Dr. Hank Simmons – Vice Chairman
Dr. John Kirtley
Dr. Scott Pace - Teleconference

Non-Voting Members present:

Dr. Jill Johnson
Connie Bennett - Teleconference
Dr. David Keisner

Members absent:

Dr. William Golden

Lori Eden, Director of Operations, Employee Benefits Division

OTHERS PRESENT

Dwight Davis, Geri Bemberg, UAMS College of Pharmacy; Sherry Bryant, Ethel Whittaker, Janna Keathley, Gretchen Baggett, Tracy Tidwell, EBD; Gini Ingram, ACHI; Marc Watts, ASEA; Steve Johnston, N. Nordisk; Charlene Kaiser, Amgen; Takisha Sanders, Health Advantage; Wayne Whitley, Ronda Walthall, AHTD; Sharon Jackson, GSK; Bridgett Johnson, Pfizer; Andy Davis, Arkansas Democrat Gazette; Martha Hill, Jim Chapman, Brian Strickland, Gilead; Sam Smothers, Astra Zeneca

CALL TO ORDER

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

APPROVAL OF MINUTES

The request was made by Dr. Neill to approve the November 3, 2014 minutes. Dr. Simmons made the motion to approve. Dickerson seconded. All were in favor.

Minutes Approved.

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

Dr. Neill, introduced the new committee member. Dr. Melodee Harris was absent at the November meeting. Ms. Harris is an Advanced Nurse Practitioner, who is replacing Dr. Matthew Hadley.

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

Delivery Coordination Workgroup Report: *by Dr. David Keisner, UAMS*

Drugs used in the treatment of Cancers and non-cancer drugs were reviewed by the DCWG and a report made to the DUEC on February 24th. Recommendations from this report are outlined below.

	Current Coverage	Proposed Coverage for 2015
<u>Relapsed CLL:</u> Zydelig (Idelalisib)	New Drug-Excluded	T4 PA
<u>Metastatic Melanoma</u> Tafinlar +Mekinist (dabrafenib+trametinib)	Individual drugs T4 PA, combo	T4 PA for combo
Opdivo (nivolumab)	New Drug - Exclude	Exclude
<u>Denosumab</u> Xgeva-bone metastases – J0897 Prolia-osteoporosis – J0897	Medical, no PA required T4 PA	T4 PA T4 PA

Dr. Simmons motioned to recommend to the board to exclude drugs covered under medical until further review. Dr. Kirtley seconded. All were in favor.

Motion Approved

Dickerson motioned to approve the Delivery Coordination recommendations. Dr. Simmons seconded. All were in favor.

Motion Approved

HEPATITIS C REVIEW: *by, Dr. Jill Johnson, UAMS*

Dr. Johnson reported previously the plan has covered five categories of patients who are affected with Hepatitis C. Harvoni and Viekira were not previously covered.

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 HCV infection documented by at least 1 measurement of serum HCV RNA >10,000 IU/mL AND a positive anti-HCV antibody, HCVRNA, or HCV genotype test > 6 months prior to access to drug therapy.	
2. The patient must be free of using illicit drugs for the past 6 months.	Any positive drug screen 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.	
4. If the patient has cirrhosis, there must be NO signs of decompensation (ascites, episodes of spontaneous bacterial peritonitis, hepatic encephalopathy, esophageal or gastric varices or a history of variceal bleeding.	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 must not have liver disease due to any cause other than HCV infection (chronic hepatitis B infection, autoimmune hepatitis, alcoholic hepatitis, nonalcoholic steatohepatitis, hemochromatosis, Wilson's disease, alpha1 Antitrypsin deficiency, cholangitis) ruled out prior to HCV treatment.	These patients were excluded from the clinical trials.
6. Cirrhosis must be shown by liver biopsy and be metavir score F3 or F4.	The noninvasive tests FIB-4 and APRI and cannot differentiate F3 from F4, which in some cases require a longer duration of therapy. Therefore, it is necessary to ascertain with a liver biopsy whether the patient is F3 or F4.
A. 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?	
2. Has the patient previously received any treatment for HCV infection? If so, what regimen and duration?	
3. Has the patient tested positive for HIV?	There are no data in HCV treatment-experienced HIV patients.

Recommendation to cover the least expensive of Sofosbuvir, Harvoni, and Viekira due to no head to head data. The meds are very expensive. Dr. Keisner reported case management is required with Sovaldi. Bennett reported there are no patients covered since January 2015. However, there were six prescriptions filled in 2014 for Sofosbuvir.

Dr. Johnson recommended the patient must have a liver biopsy. Patient must not have liver disease due to other causes. Recommendation to add either Harvoni or Viekira by diagnosis based on the cost of the agents. In addition, evaluate them periodically.

Dr. Simmons motioned to accept the recommendations that the patient must have a liver biopsy, must not have liver disease due to other causes, add either Harvoni or Viekira by diagnosis based on the cost of the agents. In addition, updates to evidence will be evaluated periodically. Ensure communication to providers are in place through a case management strategy defined prior coverage before the medicine is covered. Dr. Kirtley seconded. All were in favor.

Motion Approved

ZETIA REVIEW: : by, *Dr. Jill Johnson, UAMS*

Dr. Johnson briefly reported that Zetia was reviewed for seven (7) years in post ACS (highest risk population). The evaluation looked at the causes of death. However, the research has not been published in a peer-reviewed process. After seven (7) years in post ACS patients, 34.7% of patients had an end point vs. 32.7%, only a 2% difference in causes of death. In one (1) year, 350 patients would need to be treated with the combo to prevent one end point. Patients should continue with statin use. No change to coverage was recommended at this time.

SINGULAIR REVIEW: *by, Dr. Jill Johnson, UAMS*

Dr. Keisner reported the average cost of the pill was .40 per pill in 2014. The overall findings do not suggest that one medication within any of the classes evaluated is significantly more effective or harmful than the other medications with the same class, with the exception of zileuton being more harmful than the other LMs. Dr. Keisner recommended remove the PA from montelukast and exclude Zyflo CR.

Recommendation:

	Current Coverage	Proposed Coverage for 2015
Singulair (montelukast) Zyflo (zileuton)	T1 PA T2 PA	T1 (remove PA) Exclude (90 day communication to members)

Dr. Simmons motioned to remove the PA from montelukast and exclude Zyflo CR. Dr. Kirtley seconded. All were in favor.

Motion Approved

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

Discussion: Recommendation that new drugs covered under the medical benefits are excluded from coverage until reviewed to be consistent with the Prescription benefits process.

Johnson reported on new drugs. The review covered products released October 16th – December 15th 2014.

Recommended Additions:

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	DUEC VOTE
Spiriva Spr Respimat	tiotropium bromide inhal aerosol 2.5mcg/act	\$357/60 doses (2 inhalations once daily)	New formulation. For long-term, once daily, maintenance treatment of bronchospasm associated w/COPD and for reducing COPD exacerbations	Spiriva Handihaler = \$357/30caps.(two inhalations from one capsule once daily) Tier 2	Tier 2
Zenep	pancrelipase (lip-prot-amyl) DR cap 40000-136000-218000units	\$131/100	New formulation. For cystic fibrosis, pancreatotomy, and pancreatic insufficiency	pancrelipase (tier 1). Creon, Pertzye, Ultrase, Viokace, Zenpep are tier 2.	T3*and exclude Ultresa & Pertzye. Connie said there was no utilization on either of those. Therefore, no member communication necessary.

Recommended Additions (continued):

BRAND	GENERIC	PRICING	INDICATION	SIMILAR	DUEC
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NAME	NAME	(AWP)		THERAPIES ON FORMULARY/AWP	VOTE
Uceris Aer mg/act	Uceris Aer mg/act	\$312/bottle /28 doses	For mild to moderate ulcerative colitis. Dose = 1 metered dose twice daily for 2 weeks, then once daily for 4 weeks.	mesalamine 4gm/60ml enema (tier 1). Dose= daily for 3-6 weeks or until remission. \$24.60/enema	T4
Asmanex HFA Aer	mometasone furoate inha aerosol suspension	120 metered doses(200mcg)=\$220	Treatment of asthma	Asmanex Twisthaler 120metered doses (220mcg) = \$315.	T3
Trumenba inj	meningococcal grp B vaccine IM susp prefilled syringe	\$277/1	Meningococcal infection prophylaxis		Cover, \$0 copay.
Gardasil 9 inj	human papilloma virus 9-valent recomb vac IM susp	\$195/dose	For HPV infection prophylaxis. Gardasil 9 covers 9 types of HPV- 5 more than original Gardasil	Gardasil \$176/dose	Cover, \$0 copay
Gardasil 9 inj	human papilloma virus 9-valent recomb vac IM susp prefilled syringe	\$197/dose	For HPV infection prophylaxis. Gardasil 9 covers 9 types of HPV- 5 more than original Gardasil	Gardasil \$176/dose	Cover/ \$0 co-pay
SPECIALTY DRUGS					
Tybost	cobicistat 150mg tabs	\$216/30 tabs	Indicated specifically for use as a booster drug - FDA restricts the indication for the drug's use to enhance the potency of two once daily protease inhibitors - Reyataz and Prezista. It is not intended for use with twice daily dosing of these drugs.		T3PA with criteria to ascertain dx of HIV, proper concurrent therapy (once daily darunavir or atazanavir) , and QL 30/30.
Harvoni tabs 90-400	Ledipasvir sofosbuvir	\$113,400/12 weeks of therapy	Once daily for treatment of Hepatitis C. Duration+=8-24 weeks		T4PA

Recommended Additions (continued):

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	DUEC VOTE
Esbriet caps 267mg	pirfenidone cap 267mg	\$9,630/month	Treatment of idiopathic pulmonary fibrosis. Dose = 3 caps (801mg) three times a day.	Ofev	T4PA
Humira inj 10mg/0.2ml prefilled Syringe	adalimumab prefilled syringe kit	\$3,496/2 pens	New dose.	Other Humira pens - Specialty tier	T4PA
Obizur inj	antihemophilic factor (RECOMB Porc) RPFVIII For inj 500 units	\$3,095/500 units	Administered IV for hemophilia		T4PA

Recommended Exclusions:

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	DUEC VOTE
NON SPECIALTY DRUGS					
Trulicity	dulaglutide	\$586/carton of 4 pens	Treatment of type 2 diabetes in combination with diet and exercise. Dose=0.75-1.5mg SQ once weekly.	Byetta (daily injection) - \$511/month. Victoza (daily injection) - \$705/month. Bydureon (once weekly) - \$528/month. Byetta and Victoza are tier 3 with a PA. Bydureon is excluded by the plan.	13
Sumavel	sumatriptan solu jet-injector 4mg/0.5ml	\$1,032/6 syringes	New dosage. For treatment of migraine	Sumavel excluded by plan. Sumatriptan covered tier 1 with quantity limit. Sumatriptan 6mg = \$107/5 vials	13
Mitigare	colchicine caps 0.6mg	\$6.86/0.6mg capsule	Treatment/prevention of gout flares. Dose= 0.6mg once or twice daily.	Colcrys 0.6mg tab = \$6.54/tab. Tier 3. Generic colchicine tablets off the market	13
Xarelto Starter Therapy Pak	rivaroxaban starter therapy pak - 15mg(#42) & 20mg(#9)	\$12.58/tab	New packaging. Oral anticoagulant	Xarelto - tier 2. \$12.58/tab	13

Recommended Exclusions (continued):

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	DUEC VOTE
Bionect Aer 0.2%	hyaluronate sodium foam 0.2%	\$219/114gm	Management/symptom relief of skin irritation/dermatitis	Bionect Cream 0.2% 25gm/\$164 Bionect Gel 0.2% = \$163. Not excluded by plan. Tier 3but no utilization.	13
Akynzeo caps	Netupitant Palonosetron caps 300-0.5mg	\$571/cap	Treatment of chemotherapy induced nausea/vomiting prophylaxis. Dose= 1 capsule by mouth as a single dose	first in class	13
Relyyxs Pad	lidocaine-menthol-patch 4-5%	\$625/15 patches	Topical pain patch		13
Zenpep evaluation	*Exclude Ultresa & Pertzye. No utilization - no member communication necessary.				
Belsomra tabs	suvorexant	\$315/30 tabs	Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. Dose=10-20mg once daily.	First in class. Schedule IV	RP in the Classic plan. Exclude (code 13) in the high deductible plan.
Trezix caps	acetaminophen-caffeine-dihydrocodeine caps	\$2.63/capsule	For moderate to severe pain. Schedule III		13
Hysingla ER tab	hydrocodone bitartrate ER 24 hr abuse deterrent	\$8-\$41/tab	Extended release (abuse deterrent) for severe pain.	Zohydro ER excluded by plan. Immediate release hydrocodone combination products, apap-codeine, fentanyl patch, oxycodone combinations, oxycodone controlled release covered as tier 1.	13

Recommended Exclusions (continued):

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/A WP	Code
SPECIALTY DRUGS					
Plegridy	peginterferon beta-1A solution pen-injector, pen-injector starter kit, prefilled syringe, prefilled syringe starter kit	\$5,726/2 pens	SQ inj therapy for relapsing forms of multiple sclerosis, in which interferon-beta-1a is pegylated to extend its half-life to permit a less frequent dosing schedule (q2w)		13
Ofev	nintedanib esylate	\$9,600/month	Treatment of idiopathic pulmonary fibrosis. Dose = 150mg(one capsule) twice daily.	Esbriet	1
Lidopin cre 3.25%	lidocaine HCl Cream 3.25%	\$837/28gm			13
Sunapryn Suspension	tramadol for oral sus compounding kit	\$499/kit			4
A.A.G.C Kit cre Teroderm	amatadine-amitript-gabapentin-cycloben cream compounding kit	\$249/kit			4
Active-prep Cre Kit I	flurbiprofen-cyclobenzaprine cream compounding kit	\$3,220/kit			4
Active-Prep cre kit IV	tramadol-gabapentin-menthol-camphor cream compounding kit	\$3,129/kit			4

Recommended Exclusions (continued):

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/A WP	Code
Rexaphenac cream 1%	diclofenac sodium cream 1%	\$1,716/kit			4
Active-prep cre kit II	ketoprofen-baclofen-gabapentin cream compounding kit	\$2,412/kit			4
Active-prep cre kit III	ketoprofen-lidocaine-gabapentin cream compounding kit	\$2,839/kit			4
Active-prep cre kit V	itraconazole-phenytoin compounding kit	\$4,375/kit			4
Ketoprofen cream 10%	ketoprofen bulk cream 10%	\$4,638/kit			4
Ciferex caps	folic acid-cholecalciferol caps 1mg-3775 units	\$650/30	Hematopoietic mixture. Not found in Clinical Pharmacology		3
Ocuvel caps	multiple vitamins w/minerals & FA cap 1mg		Multivitamin w/minerals and FA	multiple generics	7
Feriva tab 21/7	FE asparto gly-B-12-FA-C-DSS succinic acid-ZN	\$226/28	Hematopoietic mixture.		7
Floriva CHW tabs	PED multiple vitamin & minerals w/Fl chew tabs	\$352/90 tabs	pediatric multiple vitamin + minerals+ FL	Sodium fluoride chew tabs (generic) = \$0.10/tab.	7

Recommended Exclusions (continued):

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	Code
Floriva Drops 0.25mg	sodium fluoride-Vit D liquid drops 0.25ng.nk-400units/ml	\$113/50ml bottle		Sodium fluoride chew tabs (generic) = \$0.10/tab.	7
TL Folate tabs	prenatal vit w/FE fum-methylfolate-FA tab	\$0.26/tab	Prenatal vitamin	multiple generics	7
Solaice Pad	capsaicin-menthol topical patch	\$573/15 patches	Not found in Clinical Pharmacology.		3
Xigduo XR	dapagliflozin[Farxiga] - metformin	\$374/30 tabs	For treatment of type 2 diabetes	Farxiga - excluded by plan	13
Escavite LQ Drop	pediatric multiple vitamin w/Fl-Fe drops	\$98.85/50ml bottle	pediatric multiple vitamin + Fl + FE		7
Prenate Mini cap	prenatal vit w/FECB-FEASP-METH-FA-DHA cap 18-0.6-0.4-350mg	\$142.50/30	Prenatal vitamin	multiple generics	7
Nicomide	niacinamide w/Zn-CU-methylfol-SE-CR	\$214/60	Nutritional supplement-multivitamin		7
Velma Pad	methyl salicylate-lidocaine-menthol patch	\$600/15 pads	Not found in Clinical Pharmacology		3
Eligen	cyanocobalamin-salcaprozate sodium	\$55.20/30 tabs	Oral B-12		7
Silvera Pain Pad Relief	capsaicin-lidocaine-menthol patch	\$600/30	Not found in Clinical Pharmacology		3
Adazin Cream	benzo-capsaicin-lido-methyl salicylate cream	\$1,475/50gm tube	Not found in Clinical Pharmacology		3

Not Reviewed/DCWG

Gamunex-C inj 40gm/400 ml	immune globulin (human) IV or subcutaneous soln 40gm/400ml	\$4,864/40 0ml vial	To treat immune deficiency.	Bivigam, Flebogamma, Gamastan S/D, Octagam - specialty tier	Table for DCWG.
Lemtrada inj	alemtuzumab IV inj 12mg/1.2ml	\$23,700/1 2mg	For treatment of relapsing forms of multiple sclerosis. Because of its safety profile, the prescribing info indicates that the use should be limited for people who have had an inadequate response to 2 or more MS therapies. Limited Distribution. Dose = 12mg IV x 5days, then for 3 consecutive days one year later.		Table for DCWG.
Vazculep inj	phenylephrine iv solution		Administered IV for treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia.		Not included in the pharmacy benefit. Not to be PA'd by EBRx.
Perikabiven Emu	amino ac/dext/lipid/electrolyte IV emul		Parenteral nutrition.		Not included in the pharmacy benefit. Not to be PA'd by EBRx.
Epinephrine inj 1mg/ml	epinephrine HCl PF IV solution		IV epinephrine		Not included in the pharmacy benefit. Not to be PA'd by EBRx.
Vasopressin inj 20 unit/ml	vasopressin IV solution		For IV infusion		Not included in the pharmacy benefit. Not to be PA'd by EBRx.
Spherusol inj	coccidioides immitis skin test antigen	\$708/vial	For the detection of delayed-type hypersensitivity to coccidioides immitis in individuals with a history of pulmonary coccidioidomycosis		Not to be PA'd by EBRx.

Not Reviewed/DCWG (continued)

Iluvien	fluocinolone acetonide intravitreal implant	\$10,560/i mplant	Treatment of diabetic macular edema in patients previously treated with a course of corticosteroids and did not have a significant rise in intraocular pressure. The implant is designed to release flucinolone for 36 months.	Retisert - excluded by plan	Medical procedure. Not to be PA'd by EBRx.
Treanda inj	bendamustine IV solution	\$4,828/1 80mg vial	For chronic lymphocytic leukemia and non-Hodgkin's lymphoma. Administered IV		covered. Hospital drug.

Dr. Simmons motioned to approve the new and excluded drugs. Dr. Kirtley seconded. All were in favor.

Motion Approved

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

Dr. Keisner reported in 2014 the pharmacy spent almost \$28 million less than 2013. The PMPM decreased for Non Medicare Members from \$70.00 to \$53.00. The PMPM decreased for Medicare Members who have the prescription drug plan from \$221.00 to \$200.00. The savings was a result of changes from the DUEC, raising pharmacy co-pays, and migration to the high deductible plan.

The PSE plan saved 15.2 million and ASE saved \$12 million. The difference in the plans are PSE does not offer coverage to medicare eligible retirees.

Meeting Adjourned

	A	B	C	D
1	<u>Delivery Coordination Workgroup Report</u>			
2				
3	<u>Members:</u>			
4	David Keisner PharmD- EBRx			
5	Jill Johnson, PharmD - EBRx			
6	Geri Beth Bemberg PharmD-EBRx managed care resident			
7	Henry Simmons, MD PhD- Medical Director Arkansas Poison Control			
8	Sidney Keisner PharmD- Board Certified Oncology Pharmacist at VA Little Rock			
9	Kati Beth Lewis, PharmD- Clinical Pharmacist at Blue Cross			
10	Stephen Sorsby, MD- Medical Director at Qualchoice / Barry Fielder, PharmD			
11				
12		<u>Current Coverage</u>	<u>Proposed Coverage</u>	
13	<u>Relapsed CLL</u>			
14	Zydelig (Idelalisib)	New Drug-Excluded	T4PA	
15				
16	<u>Metastatic Melanoma</u>			
17	Tafinlar+Mekinist (dabrafenib+trametinib)	Individual drugs T4 PA, combo excluded	T4PA for combo	
18	Opdivo (nivolumab)	New Drug-Exclude	Exclude	
19				
20				
21	<u>denosumab</u>			
22	Xgeva-bone metastases - J0897	medical, no PA required	T4PA	
23	Prolia-osteoporosis - J0897	T4PA	T4PA	

IDELALISIB (ZYDELIG)

MOA:

- inhibits of phosphatidylinositol 3-kinase (PI3K δ) kinase which is expressed in normal and malignant B-cells
- Induces apoptosis and inhibits proliferation in cell lines derived from malignant B-cells and in primary tumor cells.
- Inhibits several cell signaling pathways, including B-cell receptor signaling and the CXCR4 and CXCR5 signaling, which are involved in trafficking and homing of B-cells to the lymph nodes and bone marrow.
- Treatment of lymphoma cells resulted in inhibition of chemotaxis and adhesion, and reduced cell viability.

Follicular B cell non-Hodgkin Lymphoma (FL)

FDA approved indication: Relapsed FL in patients who have received at least two prior systemic therapies.

Relapsed FL		
	Single arm ¹ n = 72	Other treatment options for relapsed follicular lymphoma
Patients	-relapsed within 6 months of rituximab/alkylating agent -had received ≥ 2 prior regimens *median # of prior therapies: 4	Chemotherapy Radioimmunotherapy (ibritumomab, tositumomab) Hematopoietic cell transplant
Dosing	150 mg PO bid until disease progression or unacceptable toxicity	
Response rate (%)	[primary endpoint] 54% (CR 8%; PR 46%)	
<p>Indolent lymphoma study (60% follicular lymphoma)²:</p> <p style="padding-left: 20px;">Median duration of therapy: 7 mo</p> <p style="padding-left: 20px;">Median overall survival: 20 mo</p> <p style="padding-left: 20px;">Median progression free survival: 11 mo</p>		

References:

1. Zydelig package insert
2. Gopal AK et al. PI3K δ inhibition by idelalisib in patients with relapsed indolent lymphoma. N Engl J Med. 2014 Mar 13;370(11):1008-18.

Chronic Lymphocytic Leukemia (CLL)

FDA approved indication: Relapsed CLL, in combination with rituximab, in patients for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.

Relapsed CLL		
	Idelalisib + rituximab vs. placebo + rituximab n = 220	Other regimens for relapsed/refractory CLL/SLL patients who are not candidates for chemo
Patients	-Previously treated with progression of disease -Unable to receive cytotoxic agent (due to myelosuppression or comorbidities)	<u>Ibrutinib</u> Phase III: vs. ofatumumab: OS: at 12 mo: 90% vs. 81% PR: 43% vs. 4.1%
Dosing	Rituximab: q2w x 5, then q3w x 3 (first does 375 mg/m ² ; subsequent doses 500 mg/m ²) Idelalisib: 150 mg PO bid -pt in placebo group with progression were allowed to enroll in separate idelalisib study -pt in idelalisib group with progression could increase dose to 300 mg bid	<u>Bendamustine/Rituximab:</u> Phase II: OR/CR: 59%/9% Phase III: vs. Rituximab/chlorambucil: OR/CR: 89%/11% vs. 83%/4%
Median duration of treatment	Idelalisib group: 3.8 mo Placebo group: 2.9 mo **study terminated early due to improved outcomes**	<u>High dose methylprednisolone/Rituximab:</u> OR/CR: 78-93%/14-36% Median PFS 7-15 mo Median OS 20 mo [infectious complications: 30%]
PFS (mo)	[Primary endpoint] At 24 weeks: 93% vs. 46% Median: not reached vs. 5.5 mo (HR 0.15; 95% CI 0.08 to 0.28; P<0.001)	<u>Alemtuzumab:</u> OR/CR: 33-49%/2% Median OS: 16-19 mo [very immunosuppressive]
Response rate (%)	81% vs. 13% (P<0.001; all partial responses) Lymph node response rate: 93% vs. 4% (P<0.001)	<u>Alemtuzumab/Rituximab:</u> OR/CR: 53%/18%
Overall survival	At 12 mo: 92% vs. 80% (p=0.02)	<u>Lenalidomide:</u> OR/CR: 32-47%/7-9% [OR 13% for pt with del(17p)]
Toxicity	BBW: diarrhea/colitis; hepatotoxicity; GI perforation, pneumonitis Other: pyrexia, fatigue, nausea, chills	<u>Lenalidomide+R:</u> OR/CR: 66%/12%

Relapsed Small Lymphocytic Leukemia (SLL)

FDA approved indication: Relapsed SLL in patients who have received at least two prior systemic therapies.

Relapsed SLL		
	Single arm n = 26	Other treatment options for relapsed SLL
Patients	-relapsed within 6 months of rituximab/alkylating agent -had received ≥ 2 prior regimens *median # of prior therapies: 4	Same as CLL
Dosing	150 mg PO bid until disease progression or unacceptable toxicity	
Response rate (%)	[primary endpoint] 58% (CR 0%; PR 58%) Median duration of response: 11.9 mo	

Reference: Zydelig package insert

Metastatic Melanoma

Oral Therapy

	Vemurafenib ¹ (960 mg po bid)	Dabrafenib ³ (150 mg po bid)	Trametinib ⁴ (2 mg po daily)	Trametinib + dabrafenib ⁵ Phase II	→ New Data →	Trametinib+ Dabrafenib ⁶ Phase III trial n=423	Trametinib+ Dabrafenib ⁷ Phase III trial n=704 [open label]
BRAF status of patients enrolled	All BRAF mut pos	All BRAF mut pos	All BRAF mut pos	All BRAF mut pos		All BRAF mut pos	All BRAF mut pos
Comparison	Dacarbazine	Dacarbazine	Dacarbazine or paclitaxel	Dabrafenib		Dabrafenib	Vemurafenib
Previous lines of tx allowed	None	None (except IL-2)	0 or 1 (but no BRAF inh or ipi)	No restriction stated		None	None
Response rate (%)	48%	50%	22%	76%		67%	64%
PFS (mo)	5.3 ^a	5.1	4.8	9.4		9.3 vs. 8.8 mo	11.4 vs. 7.3 mo
Median overall survival (if available)	13.2 mo vs. 5.6 mo [HR 0.62 (95% CI, 0.49-0.77)] ²	HR 0.61 (95% CI, 0.25-1.48)	*HR 0.54 (95% CI, 0.32 to 0.92)	At 12 months: 79% alive (vs. 70%; p not reported)		At 6 months: 93% alive vs. 85% (p=0.02)	At 12 months: 72% alive vs. 65% (p=0.005)
Current coverage	PA	PA	PA	Excluded		TBD	TBD

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

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

Immune Therapy

	Ipilimumab⁸ (3 mg/kg IV every 3 weeks x 4 doses)	Pembrolizumab⁹ (2 mg/kg IV every 3 weeks)		Nivolumab¹⁰ (3 mg/kg IV every 2 weeks) (n=120)
BRAF status of patients enrolled	Either	Either	→ New Data →	Either
Comparison	gp100 vaccine (considered placebo)	Pembrolizumab 10 mg/kg every 3 wk		none
Previous lines of tx allowed	≥1	≥1 (ipilimumab and, if BRAF mutation +, a BRAF inhibitor)		≥1 (ipilimumab and, if BRAF mutation +, a BRAF inhibitor)
Response rate (%)	37.5%	26% (similar between groups)		32% (CR 3.3%)
PFS (mo)	2.86 ^b	5.5 (22 weeks)		Not reported
Median overall survival (if available)	*10.1 mo vs. 6.4 mo [HR 0.66 (95% CI, 0.51-0.87) 1 yr survival: 45.6% vs. 25.3%	No difference between two doses 1 yr survival for 2 mg/kg group: 58%		Not reported
Current coverage	PA	exclude		TBD

References:

1. Chapman PB et al. N Engl J Med 2011;364:2507-16.
2. Chapman PB et al. J Clin Oncol (Meeting Abstracts) May 2012 vol. 30 no. 15_suppl 8502
3. Hauschild A et al. Lancet 2012; 380: 358–65.
4. Flaherty KT et al. N Engl J Med 2012;367:107-14.
5. Flaherty KT et al. N Engl J Med 2012;367:1694-703.
6. Long GV et al. N Engl J Med 2014; 372(1):30-9.
7. Robert C et al. N Engl J Med 2015; 372(1):30-9.
8. Hodi FS et al. N Engl J Med 2010;363:711-23.
9. Robert et al. Lancet 2014;384:1109-17
10. Nivolumab Prescribing Information

Leukotriene Modulator Review

2014

Drug Label Name	Utilizing Members	Number of Rxs	Plan Cost Paid Amount	Average Amount Due/Unit	Cost/Day
Drug Class: 4450 - LEUKOTRIENE MODULATORS**					
MONTELUKAST TAB 10MG	1039	5,746	\$84,974.91	\$0.44	\$0.45
MONTELUKAST CHW 5MG	146	637	\$7,926.07	\$0.40	\$0.40
MONTELUKAST CHW 4MG	69	286	\$3,548.31	\$0.40	\$0.40
MONTELUKAST GRA 4MG	8	10	\$971.08	\$3.24	\$3.24
MONTELUKAST SODIUM	1,262	6,679	\$97,420.37	\$0.44	\$0.44
ZYFLO CR TAB 600MG	5	36	\$85,587.04	\$19.81	\$79.25
ZYFLO CR	5	36	\$85,587.04	\$19.81	\$79.25
ZAFIRLUKAST TAB 20MG	11	62	\$6,843.02	\$1.63	\$3.26
ZAFIRLUKAST TAB 10MG	1	1	\$106.25	\$1.77	\$3.54
ZAFIRLUKAST	12	63	\$6,949.27	\$1.63	\$3.26
SINGULAIR TAB 10MG	3	18	\$1,230.96	\$2.44	\$2.44
SINGULAIR GRA 4MG	1	1	\$0.00	\$0.00	\$0.00
SINGULAIR	4	19	\$1,230.96	\$2.30	\$2.30
Total for Drug Class: 4450 -	1,283	6,797	\$191,187.64	\$0.83	\$0.85

DERP summary on Controller Medications for Asthma:

"Overall findings do not suggest that one medication within any of the classes evaluated is significantly more effective or harmful than the other medications within the same class, with the exception of zileuton being more harmful than the other LMs."

Recommendations

Remove PA from montelukast

Exclude Zyflo CR

Pharmacy Spend Report

Parameter	2014	2013	Difference
Eligibility	152,631	150,359	2272
Total Plan Paid	\$117,242,990	\$145,172,348	(\$27,929,358)
Total Rxs	2601270	2702335	-101,065
Rxs PMPM	1.42	1.5	-0.08
Plan Paid PMPM (all members)	\$64.01	\$80.46	(\$16.45)
Non-Medicare PMPM	\$53.41	\$69.99	(\$16.58)
Medicare PMPM	\$200.79	\$221.02	(\$20.23)
Avg. Rx Cost (before copay)	\$62.52	\$68.23	(\$5.71)
Avg. Copay	\$17.44	\$14.51	(\$2.93)
Generic Rate (%)	88%	84%	4%

Savings Breakdown

	<u>2014</u>	<u>2013</u>	<u>Difference</u>
Compounds*	\$211,592	\$1,248,210	-\$1,036,618
Diabetic test strips	\$749,255	\$2,987,448	-\$2,238,194
Testosterone (coverage change in May 2013)	\$119,985	\$571,290	-\$451,306
Lovaza (coverage change May 2013)	\$0	\$227,291	-\$227,291
SNRI's (antidepressants)	\$795,319	\$5,129,576	-\$4,334,257
SSRI's (antidepressants)	\$537,397	\$1,460,301	-\$922,905
Lyrica (fibromyalgia)	\$171,083	\$1,440,635	-\$1,269,551
ARB's (antihypertensives)	\$656,651	\$1,974,041	-\$1,317,390
ARB Combos (antihypertensives)	\$1,182,656	\$3,342,154	-\$2,159,497
statins (lipid lowering)	\$994,224	\$2,042,311	-\$1,048,087
PPI's (reflux)	\$1,095,553	\$2,023,379	-\$927,826
valacyclovir (antiviral)	\$432,297	\$1,212,003	-\$779,706
Fibric acid (triglyceride lowering)	\$339,579	\$1,105,291	-\$765,712
Nicotinic Acid (lipid lowering)	\$156,556	\$602,898	-\$446,342
clopidogrel (antiplatelet)	\$186,328	\$1,096,511	-\$910,183
OAB's (overactive bladder)	\$346,842	\$693,901	-\$347,058
Nasal steroids (allergic rhinitis)	\$361,075	\$858,736	-\$497,661
OC's (oral contraceptives)	\$2,365,085	\$3,085,010	-\$719,925
bisphosphonates (osteoporosis)	\$346,842	\$713,477	-\$366,635
YTD pharmacy Savings			-\$20,766,143

*compound spend Jan-Sep

ASE PLAN YEAR 2013

	Week 1	Week 2	Week 3	Week 4	Week 5	Total			
Catamaran	\$ -	\$ 4,630,813.91	\$ 1,682,591.80	\$ 1,608,900.94		\$7,922,306.65	January	Actives/COBRA	\$46,326,685.60
Catamaran	\$ 1,480,087.53	\$ 1,600,740.85	\$ 1,462,933.62	\$ 1,690,710.83		\$6,234,472.83	February	Non-Medicare	\$7,825,061.16
Catamaran	\$ 1,514,459.62	\$ 1,677,771.57	\$ 1,679,223.25	\$ 1,589,793.92	\$ 1,482,412.01	\$7,943,660.37	March	Medicare	\$28,020,759.57
Catamaran	\$ 1,653,678.54	\$ 1,564,978.52	\$ 1,647,439.37	\$ 1,569,564.56		\$6,435,660.99	April		<u>\$82,172,506.33</u>
Catamaran	\$ 1,514,612.72	\$ 1,612,011.91	\$ 1,565,104.90	\$ 1,522,485.85	\$ 1,629,773.50	\$7,843,988.88	May		
Catamaran	\$ 1,372,736.76	\$ 1,638,046.21	\$ 1,490,946.95	\$ 1,483,201.01	\$ 1,510,057.09	\$7,494,988.02	June		
Catamaran	\$ -	\$ 1,423,112.69	\$ 1,505,945.87	\$ 1,441,552.50		\$4,370,611.06	July		
Catamaran	\$ 1,484,477.81	\$ 1,490,356.50	\$ 1,518,521.51	\$ 1,465,447.48	\$ 1,598,978.71	\$7,557,782.01	August		
Catamaran	\$ 1,623,838.90	\$ 1,521,539.73	\$ 1,583,931.87	\$ 1,535,834.54		\$6,265,145.04	September		
Catamaran	\$ 1,566,727.05	\$ 1,635,971.37	\$ 1,590,821.12	\$ 1,481,142.17		\$6,274,661.71	October		
Catamaran	\$ 1,416,959.11	\$ 1,534,643.06	\$ 1,686,793.66	\$ 1,435,955.16	\$ 1,584,099.87	\$7,658,450.86	November		
Catamaran	\$ 1,225,843.88	\$ 1,751,657.21	\$ 1,553,564.97	\$ 1,639,711.85		\$6,170,777.91	December		
						<u>\$82,172,506.33</u>			

ASE PLAN YEAR 2014

	Week 1	Week 2	Week 3	Week 4	Week 5				
Catamaran	\$ 1,324,794.69	\$ 1,530,212.52	\$ 1,237,951.52	\$ 1,270,067.55	\$ 1,349,832.55	\$ 6,712,858.83	January	Actives/COBRA	\$ 37,835,766.00
Catamaran	\$ 1,276,084.25	\$ 1,360,367.56	\$ 1,196,296.31	\$ 1,329,637.76		\$ 5,162,385.88	February	Non-Medicare	\$ 5,673,162.58
Catamaran	\$ 1,375,805.42	\$ 1,293,281.38	\$ 1,287,486.80	\$ 1,305,150.94		\$ 5,261,724.54	March	Medicare	\$ 26,751,589.35
Catamaran	\$ 1,036,858.48	\$ 1,545,241.70	\$ 1,199,452.97	\$ 1,351,200.23		\$ 5,132,753.38	April		<u>\$ 70,260,517.93</u>
Catamaran	\$ -	\$ 2,614,037.72	\$ 1,254,584.14	\$ 1,347,224.32	\$ 1,290,176.66	\$ 6,506,022.84	May		
Catamaran	\$ 1,169,864.72	\$ 1,402,364.49	\$ 1,310,187.89	\$ 1,219,512.07	\$ 1,386,824.04	\$ 6,488,753.21	June		
Catamaran	See June above	\$ -	\$ 2,423,458.47	\$ 1,410,770.81		\$ 3,834,229.28	July		
Catamaran	\$ 1,260,069.67	\$ -	\$ 2,672,458.30	\$ 1,375,709.87	\$ 1,218,279.91	\$ 6,526,517.75	August		
Catamaran	\$ 1,367,379.26	\$ 1,255,416.81	\$ 1,505,140.72	\$ 1,252,788.15		\$ 5,380,724.94	September		
Catamaran	\$ 1,302,547.93	\$ 1,389,947.87	\$ -	\$ 2,801,510.05	\$ 1,324,990.74	\$ 6,818,996.59	October		
Catamaran	\$ -	\$ 2,827,535.45	\$ 1,441,950.95	\$ 1,446,007.00		\$ 5,715,493.40	November		
Catamaran	\$ 1,101,601.44	\$ 1,549,938.68	\$ 1,418,606.12	\$ 1,478,905.13	\$ 1,171,005.92	\$ 6,720,057.29	December		
						<u>\$ 70,260,517.93</u>			

Difference \$ (11,911,988.40) decrease

PSE PLAN YEAR 2013

	Week 1	Week 2	Week 3	Week 4	Week 5				
Catamaran	\$ -	\$ 3,967,767.14	\$ 1,139,474.96	\$ 1,285,523.04		\$ 6,392,765.14	January	Actives/COBRA	\$ 56,390,745.26
Catamaran	\$ 1,130,812.70	\$ 1,193,071.62	\$ 1,218,438.03	\$ 1,228,002.90		\$ 4,770,325.25	February	Non-Medicare	\$ 7,923,498.42
Catamaran	\$ 1,209,303.48	\$ 1,322,827.27	\$ 1,266,707.12	\$ 1,247,058.09	\$ 1,256,794.70	\$ 6,302,690.66	March	Medicare	\$ 633,989.41
Catamaran	\$ 1,190,202.23	\$ 1,309,822.68	\$ 1,108,023.95	\$ 1,228,831.24		\$ 4,836,880.10	April		<u>\$ 64,948,233.09</u>
Catamaran	\$ 1,198,524.77	\$ 1,197,261.99	\$ 1,184,126.20	\$ 1,201,619.44	\$ 1,166,645.62	\$ 5,948,178.02	May		
Catamaran	\$ 1,194,567.81	\$ 1,227,052.90	\$ 1,131,722.97	\$ 1,285,618.74	\$ 1,243,761.89	\$ 6,082,724.31	June		
Catamaran	\$ -	\$ 1,115,522.99	\$ 1,143,069.60	\$ 1,162,862.64		\$ 3,421,455.23	July		
Catamaran	\$ 1,104,318.33	\$ 1,310,095.46	\$ 1,189,213.61	\$ 1,138,276.78	\$ 1,148,603.28	\$ 5,890,507.46	August		
Catamaran	\$ 1,276,093.85	\$ 1,143,586.13	\$ 1,226,799.25	\$ 1,302,422.93		\$ 4,948,902.16	September		
Catamaran	\$ 1,205,133.17	\$ 1,281,863.87	\$ 1,280,591.89	\$ 1,207,310.01		\$ 4,974,898.94	October		
Catamaran	\$ 1,178,618.73	\$ 1,234,504.56	\$ 1,171,897.18	\$ 1,257,732.77	\$ 1,410,814.87	\$ 6,253,568.11	November		
Catamaran	\$ 1,164,385.27	\$ 1,280,213.42	\$ 1,295,232.48	\$ 1,385,506.54		\$ 5,125,337.71	December		
						<u>\$ 64,948,233.09</u>			

PSE PLAN YEAR 2014

	Week 1	Week 2	Week 3	Week 4	Week 5				
Catamaran	\$ 1,322,014.40	\$ 1,314,615.96	\$ 728,519.79	\$ 814,176.60	\$ 814,802.26	\$ 4,994,129.01	January	Actives/COBRA	\$ 42,375,826.17
Catamaran	\$ 758,432.26	\$ 816,684.71	\$ 868,770.23	\$ 901,292.73		\$ 3,345,179.93	February	Non-Medicare	\$ 6,835,361.60
Catamaran	\$ 908,919.67	\$ 839,609.97	\$ 857,261.80	\$ 919,260.14		\$ 3,525,051.58	March	Medicare	\$ 474,596.09
Catamaran	\$ 733,109.52	\$ 1,028,720.60	\$ 755,527.55	\$ 891,464.25		\$ 3,408,821.92	April		<u>\$ 49,685,783.86</u>
Catamaran	\$ -	\$ 1,758,616.70	\$ 827,662.02	\$ 829,941.53	\$ 901,504.62	\$ 4,317,724.87	May		
Catamaran	\$ 920,991.17	\$ 881,806.09	\$ 932,364.53	\$ 909,898.34	\$ 1,058,960.94	\$ 4,704,021.07	June		
Catamaran	See June Above	\$ -	\$ 1,811,720.33	\$ 948,499.05		\$ 2,760,219.38	July		
Catamaran	\$ 938,413.93	\$ -	\$ 1,971,019.71	\$ 827,694.06	\$ 865,990.93	\$ 4,603,118.63	August		
Catamaran	\$ 1,078,103.63	\$ 816,471.45	\$ 855,351.86	\$ 946,575.05		\$ 3,696,501.99	September		
Catamaran	\$ 968,022.50	\$ 974,622.52	\$ -	\$ 2,036,015.85	\$ 959,809.00	\$ 4,938,469.87	October		
Catamaran	\$ -	\$ 2,061,613.17	\$ 1,098,188.05	\$ 985,017.52		\$ 4,144,818.74	November		
Catamaran	\$ 836,467.60	\$ 1,105,942.65	\$ 1,168,654.98	\$ 1,178,788.74	\$ 957,872.90	\$ 5,247,726.87	December		
						<u>\$ 49,685,783.86</u>			

Difference \$ (15,262,449.23) decrease



AGENDA

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

February 24, 2015

1:00 p.m.

EBD Board Room – 501 Building, Suite 500

- I. *Call to Order* *Dr. Kat Neill, Chairman*
- II. *Approval of November 3, 2014 Minutes* *Dr. Kat Neill, Chairman*
- III. *Introduction of New Committee Member* *Dr. Kat Neill, Chairman*
- IV. *Delivery Coordination Workgroup* *Dr. David Keisner, UAMS*
- V. *Hepatitis C Review* *Dr. Jill Johnson, UAMS*
- VI. *Zetia Review* *Dr. Jill Johnson, UAMS*
- VII. *Singulair Review* *Dr. David Keisner, UAMS*
- VIII. *New Drugs* *Dr. Jill Johnson, UAMS*
- XV. *EBD Report* *Dr. David Keisner, UAMS*

Upcoming Meetings

April 6, 2015

August 3, 2015

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

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

Hepatitis C
EBRx Prior Authorization Criteria
02/13/2015
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 HCV infection documented by at least 1 measurement of serum HCV RNA >10,000 IU/mL AND a positive anti-HCV antibody, HCV RNA, or HCV genotype test > 6 months prior to access to drug therapy.	
2. The patient must be free of using illicit drugs for the past 6 months.	Any positive drug screen 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)	
4. If the patient has cirrhosis, there must be NO signs of decompensation (ascites, episodes of spontaneous bacterial peritonitis, hepatic encephalopathy, esophageal or gastric varices or a history of variceal bleeding).	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 must have liver disease due to any cause other than HCV infection (chronic hepatitis B infection, autoimmune hepatitis, alcoholic hepatitis, nonalcoholic steatohepatitis, hemochromatosis, Wilson's disease, alpha1 antitrypsin deficiency, cholangitis) ruled out prior to HCV treatment.	These patients were excluded from the clinical trials.
6. Cirrhosis must be shown by liver biopsy and be metavir score F3 or F4.	The noninvasive tests FIB-4 and APRI cannot differentiate F3 from F4, which in some cases require a longer duration of therapy. Therefore, it is necessary to ascertain with a liver biopsy whether the patient is F3 or F4.

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?	
2. Has the patient previously received any treatment for HCV infection? If so, what regimen and duration?	
3. Has the patient tested positive for HIV?	There are no data in HCV treatment-experienced HIV patients.

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 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

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. No interferon and relapse reported to be 13%.	Not covered.	Not covered, even at F3 because no interferon.	Not covered, even at F3 because no interferon.
		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. 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. Ledipasvir+sofos. Afdhal, et al. Ledipasvir+sofos has efficacy. No SOC control arm.		Boceprevir & telaprevir triple therapy is effective. Unknown which of the 3 is more effective. Must have Q80K negativity for simeprevir. QUEST-1 & -2.		
2	GT1 treatment naïve, noncirrhosis, interferon-INeligible	Contains interferon.	Not covered. Relapse rate 13%.	Not covered. Contains interferon.	Covered if metavir score F3. Harvoni 8w (LONESTAR, ION-3)	Covered if metavir score F3. GT1a or b: with Ribavirin for 12 w. (PEARLIII/IV).

		Sofosbuvir: PHOTON-1 (via PI) showed sofos +R to be effective. No control arms. Ledipasvir+sofos. Afdhal, et al. Ledipasvir+sofos has efficacy. No SOC control arm.				
3	GT1 treatment naïve, decompensated cirrhosis <u>AND listed for liver transplant,</u>	Not covered.	Not covered.	Not covered.	Harvoni 12w (ION-1, but only 16% had cirrhosis; results not broken down by cirrhosis)	Viekira 12w (TURQUOISEII)
4	GT1 treatment naïve, compensated cirrhosis, interferon-eligible	Covered for 12 w combined w/ PR.	Not covered.	Not covered	Not covered. No interferon.	Not covered. No interferon.
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 Ledipasvir+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.		
5	GT1 treatment naïve, compensated cirrhosis, interferon-INeligible	Not covered. These patients cannot take interferon.	93% (all F3 or F4), Sofos/Sime12w	Not covered. Contains interferon.	99% w Harvoni 12w (only 16% had comp cirrhosis)	94% w/ Viekira+Riba 12 (100% w/cirrhosis) 99% Viekira 12w (13% were F3)
		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.		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.		
	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. Noncirrhosis must be F3.	GT1 SVR 93% (Kowdley, et al.) GT1a SVR=95.2% w/12w ViekR GT1b SVR=100% w/12w (PEARL-II) Noncirrhosis must be F3.
		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 SVR was 93% with R1ba, 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.	GT1a SVR80% w/12w GT1a SVR 92.9% w/24w GT1b100% w/12w (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)		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.)
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.
				No data.		
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: Viekira+R 12w, SVR 96% (SAPPHIRE-II-excluded F3 & F4) NO DATA in F3s

						GT1b: Viekira+R 12w, SVR 100% (PEARL-II) NO DATA in F3s
			COSMOS was prior null responders, not prior relapsers	PROMISE. ASPIRE.		
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: Viekira 12w, SVR 93.3% GT1b: Viekira 24w, 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. 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. 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 telaprevir is effective. Had 23-27% cirrhotics. Sofosbuvir: COSMOS. Cohort 2 (prior nonresponders, metavir 4) shows sofos is effective.		Bacon BR, et al. Boceprevir evidence. PROMISE provides evidence that simeprevir12PR12, PR12 is effective. McHutchison provides evidence that T12PR24 is effective.		
11	GT1, treatment experienced, coinfectd 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.
12	GT2 trtmt naïve, w/or w/o compensated	Not covered. Peginterferon + ribavirin is covered and should be dosed according to patient weight.	Not covered	Not covered.	Not covered	Not covered.

	cirrhosis					
		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.				
	GT	Sofosbuvir PR	Sofosbuvir/Simep	Simeprevir PR	Harvoni	Viekira Pak
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 take interferon, compensated cirrhotic	Sofosbuvir + R 12w without Peg. SVR 88% (VALENCE)	Not covered.	Not covered.	Not covered.	Not covered.
		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	Sofosbuvir PR	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.	No data.	No data.	No data.	No data.
		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 in GT3 w/ SR24, however, no control arm. PHOTON showed efficacy in GT3 with SR24.				
17	GT3 treatment naïve, NONcirrhotic, unable to take interferon	F3s: Sofosbuvir + Ribavirin 24w (SVR was 92%) (VALENCE)	No data.	No data.	No data.	No data.
		Noncirrhotics have time to wait for emerging non-interferon-containing regimens. The data are not sufficient at this time to support treating this population to date.				
18	GT3 treatment-experienced, compensated cirrhosis, interferon INeligible	Covered with ribavirin X24 weeks (SVR 60%)VALENCE	No data.	No data.	No data.	No data.
		FUSION & POSITRON; the alternative is PR and these patients are either interferon-experienced or ineligible for it.				
GT4						
19	GT4, interferon eligible, treatment naïve, NONcirrhotics	SPR 12w (SVR96%)NEUTRINO	No data.	No data.	No data.	No data.
		NEUTRINO showed 96% for GT4, however, noncirrhotics have time to await emerging drugs.				
20	GT4, interferon eligible, treatment naïve, compensated cirrhosis	Cover with PR X12w.	No data.	No data.	No data.	No data.
		NEUTRINO. Not as much time to wait.				
21	GT4, interferon ineligible	Not covered.	No data.	No data.	No data.	No data.
		Evidence is in abstract form only from April 2014 EASL meeting. Ruane PJ, et al.		Awaiting trial results per AASLD guidelines.		

GT5						
22	GT5	Not covered.	No data.	No data.	No data.	No data.
		NEUTRINO included an N=1 GT5 patient.				
GT6						
23	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/ μ L),
- Neutropenia (ANC < 500/ μ L),
- Development of colitis, non-alcoholic pancreatitis or ophthalmologic disorders,
- Seizure disorder,
- Poorly controlled thyroid dysfunction;
- hyperthyroidism (TSH \geq 2 x the upper limit of normal (ULN) and \leq 10 x ULN) or hypothyroidism (TSH < the lower limit of normal (LLN) and > 0.1 μ IU/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 2-13-2015
 Jill Johnson, Pharm.D., BCPS

Note: All noncirrhosis must be Metavir F3 to treat.

GT1			
1	GT1 treatment naïve, noncirrhosis, interferon eligible	Sofosbuvir PR X12w 89%	\$115,642
2	GT1 treatment naïve, noncirrhosis, interferon-INeligible	Harvoni 8w Viekira + R 12w	\$75,600 \$102,347
3	GT1 treatment naïve, decompensated F4 cirrhosis <u>AND listed for liver transplant,</u>	Harvoni 12w Viekira 12w	\$113,400 \$99,983
4	GT1 treatment naïve, compensated cirrhosis (F4),interferon-eligible	Sofosbuvir PR X 12w Harvoni 12w Viekira 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) Viekira + R 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). Viekira 12w: GT1a SVR 80% (TURQUOISE-II) Viekira 24w: GT1a SVR 92.9% (TURQUOISE-II) Viekira 12w: GT1b 100% (TURQUOISE-II)	Not a good response \$113,400 \$99,983 \$199,966 \$99,983
8	GT1 Prior nonresponder to BPR or TPR, noncirrhosis	F3s are covered: Harvoni 12w 94% (39% had received prev tx with PR;61% had received prev tx w/ PI)(45% were prev nonresponders; 55% were prev relapsers).	\$113,400
9	GT1 Prior relapsers after PR, noncirrhosis	Sime12PR48 SVR79-83% (PROMISE,ASPIRE)	\$138,992

		Harvoni 12w SVR=93.6% (ION-2) ViekiraR12: GT1 SVR=95.3% (SAPPHIRE-II) ViekiraR12: GT1b SVR=100% (PEARL-II)	\$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) Viekira 12w (GT1a) (SVR 93.3%)(Turquoise-II) Viekira 24w (GT1b) (SVR 100%) (Turquoise-II)	\$360,864 \$138,992 \$113,400 \$99,983 \$199,966
11	GT1, treatment experienced, coinfectd 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	Sofosbuvir + Ribavirin 12 w	\$103,163
	GT3		
16	GT3 treatment naïve, with or without compensated cirrhosis if able to take interferon	PR24w	\$29,680
17	GT3 treatment naïve, NONcirrhotic, unable to take interferon	SR 24	\$206,326
18	GT3 treatment-experienced, compensated cirrhosis, interferon INeligible	SR 24	\$206,326
	GT4		
19	GT4, interferon eligible, treatment naïve, NONcirrhotics	F3s: SPR12w	\$115,642
20	GT4, interferon eligible, treatment naïve, compensated cirrhosis	SPR12w	\$115,642
21	GT4, interferon ineligible	Not covered.	
	GT5		

22	GT5	Not covered.	
	GT6		
23	GT6	Not covered.	

DUEC New Drugs Oct 16-Dec 15, 2014

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	Consultant NOTES	DUEC VOTE	DUEC DATE	IB VOTE	IB DATE	Connie Notes
NON-SPECIALTY DRUGS										
Trulicity	dulaglutide	\$586/carton of 4 pens	Treatment of type 2 diabetes in combination with diet and exercise. Dose=0.75-1.5mg SQ once weekly.	Byetta (daily injection) - \$511/month. Victoza (daily injection) - \$705/month. Bydureon (once weekly) - \$528/month. Byetta and Victoza are tier 3 with a PA. Bydureon is excluded by the plan.	Exclude due to extended duration. QW dulaglutide was noninferior to QD liraglutide for HbA1c. But the risk of pancreatitis/panc cancer/thyroid cancer led to us avoiding the extended dosing of this class of drugs.		2015 02 24			
Sumavel	sumatriptan solu jet-injector 4mg/0.5ml	\$1,032/6 syringes	New dosage. For treatment of migraine	Sumavel excluded by plan. Sumatriptan covered tier 1 with quantity limit. Sumatriptan 6mg = \$107/5 vials	Exclude. Code 13.		2015 02 24			
Miltigare	colchicine caps 0.6mg	\$6.86/0.6mg capsule	Treatment/prevention of gout flares. Dose= 0.6mg once or twice daily.	Colcrys 0.6mg tab = \$6.54/tab. Tier 3. Generic colchicine tablets off the market.	Exclude. Code 13. Colcrys costs less.		2015 02 24			
Xarelto Starter Therapy Pak	rivaroxaban starter therapy pak - 15mg(#42) & 20mg(#8)	\$12.58/tab	New packaging. Oral anticoagulant	Xarelto - tier 2. \$12.58/tab	Exclude. Code 13. The starter pack is confusing and per students who work in pharmacies, patients fail to come get the correct size and MDs write for refills on these starter packs. The extra plan cost (\$38) is a one-time cost.		2015 02 24			
Bionect Aer 0.2%	hya luronate sodium foam 0.2%	\$219/114gm	Management/symptom relief of skin irritation/dermatitis	Bionect Cream 0.2% 25gm/\$164 Bionect Gel 0.2% = \$163. Not excluded by plan. Tier 3 but no utilization.	This is the only foam spray. Soln/Cm/Gel/Lotion also available.		2015 02 24			
Akynzeo caps	netupitant-palonosetron caps 300-0.5mg	\$571/cap	Treatment of chemotherapy induced nausea/vomiting prophylaxis. Dose=1 capsule by mouth as a single dose	first in class	There are available MACd ondansetron + brand Emend (aprepitant) that hasn't been compared HTH against Akynzeo. EBRx P&T recommended exclusion due to no HTH data. It is difficult to say if this drug would be used for CTX-induced vomiting or for post-op or nonspecified vomiting. If covered, it will need a QL.		2015 02 24			Catamaran coverage recommendation: AKYNZEO approved for prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of cancer chemotherapy, including, but not limited to, highly emetogenic chemotherapy. Standard QL is 2 caps/month, and the post limit approval amount is 4 caps/month in the Antiemetic coverage policy.
Rellyks Pad	lidocaine-menthol-patch 4-5%	\$625/15 patches	Topical pain patch		Exclude.		2015 02 24			
Spiriva Spr Respimat	tiotropium bromide inhal aerosol 2.5mg/act	\$357/60 doses (2 inhalations once daily)	New formulation. For long-term, once daily, maintenance treatment of bronchospasm associated w/COPD and for reducing COPD exacerbations	Spiriva Handihaler = \$357/30caps.(two inhalations from one capsule once daily) Tier 2	Cover T2, same as other tiotropium.		2015 02 24			
Zenpep	pancrellipase(lip-prot-amy) DR cap 40000-136000-218000units	\$131/100	New formulation. For cystic fibrosis, pancreatedomy, and pancreatic insufficiency	pancrellipase (tier 1). Creon, Pertyze, Ultrase, Viokace, Zenpep are tier 2.	Cover. Consider excluding Ultrase & Pertyze due to cost and lack of dosing options.		2015 02 24			
Uceris Aer mg/act	budesonide rectal foam	\$312/bottle/28 doses	For mild to moderate ulcerative colitis. Dose = 1 metered dose twice daily for 2 weeks, then once daily for 4 weeks.	mesalamine 4gm/60ml enema (tier 1). Dose= daily for 3-6 weeks or until remission. \$24.60/enema	T3PA. Criteria: Dx of UC with involvement of further than 10cm into the colon. And only if the patient has tried adequately dosed 5-ASA oral products.		2015 02 24			
Belsomra tabs	suvorexant	\$315/30 tabs	Treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance. Dose=10-20mg once daily.	First in class. Schedule IV	Exclude. Code 13		2015 02 24			
Trezix caps	acetaminophen-caffeine-dihydrocodeine caps	\$2.63/capsule	For moderate to severe pain. Schedule III		Exclude. Code 13.		2015 02 24			

Asmanex HFA Aer	mometasone furoate inha aerosol suspension	120 metered doses(200mcg)=\$220	Treatment of asthma	Asmanex Twisthaler 120metered doses (220mcg) = \$315. Tier 3	T3	2015 02 24				
Hysingla ER tab	hydrocodone bitartrate ER 24 hr abuse deterrent	\$8-\$41/tab	Extended release (abuse deterrent) for severe pain.	Zohydro ER excluded by plan. Immediate release hydrocodone combination products, apap-codeine, fentanyl patch, oxycodone combinations, oxycodone controlled release covered as tier 1.	Exclude. Code 13	2015 02 24				
SPECIALTY DRUGS										
Tybost	cobicistat 150mg tabs	\$216/30 tabs	Indicated specifically for use as a booster drug - FDA restricts the indication for the drug's use to enhance the potency of two once daily protease inhibitors - Reyataz and Prezista. It is not intended for use with twice daily dosing of these drugs.		To be prescribed with darunavir or atazanavir as the cytochrome P450 inhibitor. It is not interchangeable with ritonavir. Options: 1. T3 with no restrictions. Or 2. T3PA with criteria to ascertain dx of HIV, proper concurrent therapy (once daily darunavir or atazanavir), and QL.	2015 02 24				
Plegridy	peginterferon beta-1A solution pen-injector, pen-injector starter kit, prefilled syringe, prefilled syringe starter kit	\$5,726/2 pens	SQ inj therapy for relapsing forms of multiple sclerosis, in which interferon-beta-1a is pegylated to extend its half-life to permit a less frequent dosing schedule (q2w)		Exclude, Code 13. There are no HTH trials with peginterferon and Rebif or Betaseron. CochSysRev shows that dosing/frequency affects efficacy. Rebif or Betaseron are superior to Avonex in reducing MS exacerbations. We need comparative data to know that Plegridy is at least not inferior to either Rebif or Betaseron.	2015 02 24				
Harvoni tabs 90-400	ledipasvir-sofosbuvir	\$113,400/12 weeks of therapy	Once daily for treatment of Hepatitis C. Duration=8-24 weeks		Cover, PA.	2015 02 24				Catamaran coverage: New combination product HARVONI (ledipasvir/sofosbuvir). Ensures appropriate use for the treatment of chronic hepatitis C (CHC) genotype 1 infection in adults. Requires patients not use other medications to treat HCV infection, patients have not previously received a regimen containing sofosbuvir, patients do not have severe renal impairment or end-stage renal disease, and that the medication is prescribed by or in consultation with a specialist.
Esbriet caps 267mg	pirfenidone cap 267mg	\$9,630/month	Treatment of idiopathic pulmonary fibrosis. Dose = 3 caps (801mg) three times a day.	Ofev	Cover, PA.	2015 02 24				
Ofev	nintedanib esylate	\$9,600/month	Treatment of idiopathic pulmonary fibrosis. Dose = 150mg(one capsule) twice daily.	Esbriet	Exclude. Code 1.	2015 02 24				
Humira inj 10mg/0.2ml prefilled syringe	adalimumab prefilled syringe kit	\$3,496/2 pens	New dose.	Other Humira pens - specialty tier	Cover where other Humira is.	2015 02 24				
Gamunex-C inj 40gm/400ml	immune globulin (human) IV or subcutaneous soln 40gm/400ml	\$4,864/400ml vial	To treat immune deficiency.	Bivigam, Flebogamma, Gamastan S/D, Octagam - specialty tier	T4. Place on DCWG future agenda.	2015 02 24				
Obizur inj	antihemophilic factor (RECOMB Porc) RPFVIII for inj 500 units	\$3,095/500 units	Administered IV for hemophilla		T4 PA. Criteria: Dx of hemophilla	2015 02 24				

Lemtrada inj	alemtuzumab IV inj 12mg/1.2ml	\$23,700/12mg	For treatment of relapsing forms of multiple sclerosis. Because of its safety profile, the prescribing info indicates that the use should be limited for people who have had an inadequate response to 2 or more MS therapies. Limited Distribution. Dose = 12mg IV x 5days, then for 3 consecutive days one year later.		Exclude in pharmacy program. Medical PA: Dx of RRMS, EDSS of <5, and disease duration of <10y. Deny access if history of thyroid disease.		2015 02 24			
Lidopin cre 3.25%	lidocaine HCl Cream 3.25%	\$837/28gm			Exclude. There are 4 OTC lidocaine 4% creams (AneCream, LC-4 Lidocain, L-M-X4, Predator). There is also a Rx 3.75% topical cream (Lidovex).		2015 02 24			
Sunapryn Suspension	tramadol for oral sus compounding kit	\$499/kit			kit		2015 02 24			
A.A.G.C Kit cre Teroderm	amataidine-amitript-gabapentin-cycloben cream compounding kit	\$249/kit			kit		2015 02 24			
Active-prep Cre Kit I	flurbiprofen-cyclobenzaprine cream compounding kit	\$3,220/kit			kit		2015 02 24			
Active-Prep cre kit IV	tramadol-gabapentin-menthol-camphor cream compounding kit	\$3,129/kit			kit		2015 02 24			
Rexaphenac cream 1%	diclofenac sodium cream 1%	\$1,716/kit			kit		2015 02 24			
Active-prep cre kit II	ketoprofen-baclofen-gabapentin cream compounding kit	\$2,412/kit					2015 02 24			
Active-prep cre kit III	ketoprofen-lidocaine-gabapentin cream compounding kit	\$2,839/kit			kit		2015 02 24			
Active-prep cre kit V	itraconazole-phenytoin compounding kit	\$4,375/kit			kit		2015 02 24			
Ketoprofen cream 10%	ketoprofen bulk cream 10%	\$4,638/kit			kit		2015 02 24			
							2015 02 24			
Vazculep inj	phenylephrine iv solution		Administered IV for treatment of clinically important hypotension resulting primarily from vasodilation in the setting of anesthesia.		Not in the scope of pharmacy benefits/DCW		2015 02 24			
Perikabiven Emu	amino ac/dext/lipid/electrolyte IV emul		Parenteral nutrition.		Not in the scope of pharmacy benefits/DCW		2015 02 24			
Epinephrine inj 1mg/ml	epinephrine HCl PF IV solution		IV epinephrine		Not in the scope of pharmacy benefits/DCW		2015 02 24			
Vasostriect inj 20 unit/ml	vasopressin IV solution		For IV infusion		Not in the scope of pharmacy benefits/DCW		2015 02 24			
Ciferex caps	folic acid-cholecalciferol caps 1mg-3775 units	\$650/30	Hematopoietic mixture. Not found in Clinical Pharmacology		no info		2015 02 24			
Ocuvel caps	multiple vitamins w/minerals & FA cap 1mg		Multivitamin w/minerals and FA	multiple generics	vitamin		2015 02 24			
Feriva tab 21/7	FE asparto gly-B-12-FA-C-DSS succinic acid-ZN	\$226/28	Hematopoietic mixture.		vitamin		2015 02 24			
Floriva CHW tabs	PED multiple vitamin & minerals w/Fl chew tabs	\$352/90 tabs	pediatric multiple vitamin + minerals+ FL	Sodium fluoride chew tabs (generic) = \$0.10/tab.	vitamin		2015 02 24			
Floriva Drops 0.25mg	sodium fluoride-Vit D liquid drops 0.25ng.nk-400units/ml	\$113/50ml bottle		Sodium fluoride chew tabs (generic) = \$0.10/tab.	vitamin		2015 02 24			
TL Folate tabs	prenatal vit w/FE furr-methylfolate-FA tab	\$0.26/tab	Prenatal vitamin	multiple generics	vitamin		2015 02 24			
Solaice Pad	capsaicin-menthol topical patch	\$573/15 patches	Not found in Clinical Pharmacology.		no info		2015 02 24			

Consideration of New Drugs from Oct 16 to Dec 15, 2014

Xigduo XR	dapagliflozin [Farxiga] - metformin	\$374/30 tabs	For treatment of type 2 diabetes	Farxiga - excluded by plan	already excluded		2015 02 24				
Escavite LQ Drop	pediatric multiple vitamin w/FI-FE drops	\$98.85/50ml bottle	pediatric multiple vitamin + FI + FE		vitamin		2015 02 24				
Prenate Mini cap	prenatal vit w/FECA- FEASP-METH-FA-DHA cap 18-0.6-0.4-350mg	\$142.50/30	Prenatal vitamin	multiple generics	vitamin		2015 02 24				
Nicomide	niacinamide w/Zn-CU-methylfol-SE-CR	\$214/60	Nutritional supplement-multivitamin		vitamin		2015 02 24				
Trumenba inj	meningococcal grp B vaccine IM susp prefilled syringe	\$277/1	Meningococcal nfection prophylaxis		ACIP recommended vaccine. Already covered		2015 02 24				
Gardasil 9 inj	human papilloma virus 9-valent recomb vac IM susp	\$195/dose	For HPV infection prophylaxis. Gardasil 9 covers 9 types of HPV- 5 more than original Gardasil	Gardasil \$176/dose	ACIP recommended vaccine. Already covered		2015 02 24				
Gardasil 9 inj	human papilloma virus 9-valent recomb vac IM susp prefilled syringe	\$197/dose	For HPV infection prophylaxis. Gardasil 9 covers 9 types of HPV- 5 more than original Gardasil	Gardasil \$176/dose	ACIP recommended vaccine. Already covered		2015 02 24				
Velma Pad	methyl salicylate-lidocaine-menthol patch	\$600/15 pads	Not found in Clinical Pharmacology		no info		2015 02 24				
Eligen	cyanocobalamin-salcaprozate sodium	\$55.20/30 tabs	Oral B-12		vitamin		2015 02 24				
Silvera Pain Pad Relief	capsaicin-lidocaine-menthol patch	\$600/30	Not found in Clinical Pharmacology		no info		2015 02 24				
Adazin Cream	benzo-capsaicin-lido-methyl salicylate cream	\$1,475/50g tube	Not found in Clinical Pharmacology		no info		2015 02 24				
Treanda inj	bendamustine IV solution	\$4,828/180mg vial	For chronic lymphocytic leukemia and non-Hodgkins's lymphoma. Administered IV		DCW/already covered		2015 02 24				
Spherusol inj	coccidioides immitis skin test antigen	\$708/vial	For the detection of delayed-type hypersensitivity to coccidioides immitis in individuals with a history of pulmonary coccidioidomycosis		Medical/DCW		2015 02 24				
Iluvien	fluocinolone acetonide intravitreal implant	\$10,560/implant	Treatment of diabetic macular edema in patients previously treated with a course of corticosteroids and didn't have a significant rise in intraocular pressure. The implant is designed to release fluocinolone for 36 months.	Retisert - excluded by plan	Medical/DCW		2015 02 24				

Dulaglutide (Trulicity)

Celeste Davis

November 24, 2014

Labeled uses: Adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

Comparators:

Medication	Dose	AWP Cost per Unit	AWP Cost per Month
Dulaglutide	1.5 or 0.75 mg/0.5 mL	\$292.99	\$1,172.00 (4 weekly inj)
Albiglutide (Tanzeum)	30mg or 60 mg	97.79	\$391.16 (4 weekly inj)
Liraglutide (Victoza)	1.8 mg/day	\$235.44 (18 mg/3mL)	\$470.88 (2 pens/mth)
Exenatide (Byetta)	20 mcg/day	\$512.51 (250 mcg/ml/2.4 ml and 250 mcg/ml/1.2 mL)	\$1,024.00 mth
Metformin	500-2000 mg	\$144.95 (100; 1000 mg)	\$4/mth
Sitagliptin	100 mg/day	\$361.04 (30; 100 mg)	\$361.04 mth

Script Wise Database; accessed via RESTAT Web Interface

(URL: <https://scriptwise.restat.com/Citrix/AccessPlatform/site/default.aspx>) on 11/12/14.

Contraindications: History of hypersensitivity, patient or family history of medullary thyroid carcinoma or Multiple Endocrine Neoplasia syndrome type 2.

Toxicities: Boxed warning for Thyroid C-cell tumors; pancreatitis reported. REMS requirement for evaluation of risk/benefit in medullary thyroid tumor and pancreatitis. Pregnancy Category C.

Drug interactions: androgens (C); Corticosteroids (C); Insulin (D); Sulfonylureas (D); Thiazide Diuretics (C); somatRIPTAN (D); Pegvisomant (C); LHRH Analogs (C); Danazol (C)

Evidence:

Monotherapy with the once-weekly GLP-1 analogue dulaglutide for 12 weeks in patients with Type 2 diabetes: dose-dependent effects on glycemic control in a randomized, double-blind, placebo-controlled study

Design: 12 week, double-blind, placebo-controlled, dose-response trial randomized N=167 patients who were antihyperglycemic medication-naïve or had discontinued metformin monotherapy. Mean baseline HbA1c was 7 to 7.8% with treatment of once-weekly injections of placebo or dulaglutide (0.1, 0.5, 1.0 or 1.5 mg). A two week screening and 4-8 week washout period was completed prior to baseline HbA1C followed by a 12 week treatment and 4 week safety follow up.

Findings: A significant dose-dependent reduction in HbA1c was observed across doses (P < 0.001). HbA1c reductions in the 0.5, 1.0 and 1.5 mg dulaglutide groups were greater than in the placebo group. Dose-dependent reductions in fasting plasma glucose were also observed ranging from -0.9, -1, -1, 0% for doses and placebo. Dose-dependent weight loss was seen with all doses (P = 0.009), but none of the groups were different from placebo. The most common adverse events were nausea and diarrhea.

Grunberger G, Chang A, et al. Monotherapy with the once-weekly GLP-1 analogue dulaglutide for 12 weeks in patients with Type 2 diabetes: dose-dependent effects on glycemic control in a randomized, double-blind, placebo-controlled study. *Diabetic Medicine*. 2012 June; 29: 1260-67.

Efficacy and Safety of Dulaglutide Added Onto Pioglitazone and Metformin versus Exenatide in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-1)

Design: 52 week, randomized, parallel, double blinded placebo controlled trial. Study randomized patients to dulaglutide 1.5 mg, dulaglutide 0.75 mg, exenatide 10 mcg BID, or placebo. Patients were treated with metformin (1,500-3,000 mg) and pioglitazone (30-45 mg). Mean baseline HbA1c was 8.1%. All patients underwent a metformin (1,500-3,000 mg/day) and pioglitazone (30-45 mg/day) lead-in period that lasted up to 12 weeks and was continued for the duration of the study; other oral antihyperglycemic medications were discontinued. Two doses of dulaglutide (1.5 mg and 0.75 mg) were evaluated along with exenatide and placebo. Placebo patients continued until week 26 and were then randomized to dulaglutide 1.5 mg or dulaglutide 0.75 mg.

Findings: HbA1c change from baseline to primary end point was -1.36% for dulaglutide 1.5 mg, -1.07 % for dulaglutide 0.75 mg, -0.80 % for exenatide, -0.46% for placebo. Both dulaglutide doses were superior to placebo at 26 weeks and exenatide at 26 and 52 weeks. Greater percentages of patients reached HbA1c targets with dulaglutide 1.5 mg and 0.75 mg than with placebo and exenatide. At 26 and 52 weeks, total hypoglycemia incidence was lower in patients receiving dulaglutide 1.5 mg than in those receiving exenatide. No dulaglutide-treated patients reported severe hypoglycemia and most common gastrointestinal adverse events for dulaglutide were nausea, vomiting, and diarrhea. Events were mostly mild to moderate and transient. Number of patients rescued at week 26: dulaglutide 1.5 mg, 4 (1.4%); dulaglutide 0.75 mg, 12 (4.3%); exenatide, 11 (4.0%); placebo, 22 (15.6%). Number of patients rescued at week 52: dulaglutide 1.5 mg, 9 (3.2%); dulaglutide 0.75 mg, 25 (8.9%); exenatide, 24 (8.7%); placebo to dulaglutide 1.5 mg, 1 (1.6%); placebo to dulaglutide 0.75 mg, 3 (4.8%).

Wysham C, Blevins T, et al. Efficacy and Safety of Dulaglutide Added Onto Pioglitazone and Metformin versus Exenatide in Type 2 Diabetes in a Randomized Controlled Trial (AWARD-1). *Diabetes Care* 2014;37:2159-2167.

Efficacy and Safety of Dulaglutide versus Sitagliptin after 52 weeks in Type 2 Diabetes in a Randomized Controlled Trial (Award-5)

Design: 104 week, randomized, parallel, multicenter, double blind control trial. Study randomized patients (N=1,098) to dulaglutide 1.5 mg, dulaglutide 0.75mg, sitagliptin 100mg or placebo by adaptive and fixed means. Mean baseline of population characteristics were 54 years, HbA1C% 8.1%, and diabetes duration of 7 years and weight of 86.4 kg. Patients were given a lead in period that lasted up to 11 weeks. Metformin therapy was initiated above 1,500 mg daily for six or more weeks prior to randomization and all other OAM's were discontinued. Primary outcome was a mean change in A1C from baseline over 52 weeks via intent to treat analysis.

Findings: Mean change to A1C% at week 52 was -1.10 and -0.87 for dulaglutide 1.5 and 0.75mg and -0.39 for sitagliptin. P< 0.001. No events of hypoglycemia noted. GI events for dulaglutide included nausea, vomiting, and diarrhea. Mean weight changes at 52 weeks were -3.03 and -2.60 kg for dulaglutide 1.5 mg and 0.75 mg, sitagliptin -1.53 kg with P<0.001.

Nauck M, Weinstock R, et al. Efficacy and Safety of Dulaglutide versus Sitagliptin after 52 weeks in Type 2 Diabetes in a Randomized Controlled Trial (Award-5). Diabetes Care 2014;37:2149–2158.

Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomized, open-label, phase 3, non-inferiority trial

Design: AWARD-6 was a randomized, open-label, parallel-group, multicenter, phase 3, non-inferiority study, comparing the safety and efficacy of once-weekly dulaglutide with once-daily liraglutide in metformin-treated patients with uncontrolled type 2 diabetes. The study had three periods: screening (2 weeks), randomization (at week 0) immediately followed by treatment (26 weeks), and safety follow-up (4 weeks).

Findings: 269 participants in each group completed treatment at week 26. Reduction in HbA1c was -1.42% in the dulaglutide group and -1.36% in the liraglutide group. Mean treatment difference in HbA1c was -0.06% (95% CI -0.19 to 0.07, P <0.0001) between the two groups. The most common gastrointestinal adverse events were nausea, 20% in dulaglutide group vs 18% in liraglutide group), diarrhea 12% vs 12%; dyspepsia 8% vs 6%; and vomiting 7% vs 8% with similar rates of study drug discontinuation because of adverse events between the two groups; 6% in each group. The hypoglycemia rate was 0.34 and 0.52 events per patient per year, respectively, and no severe hypoglycemia was seen.

Dungan K, Povedano S, et al. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomized, open-label, phase 3, non-inferiority trial. Lancet 2014; 384: 1349–57.

FDA Requirements for required/post-marketing studies:

- 26 week, randomized, double blind control trial for pediatric patient's age 10-17 years evaluating dosing, efficacy, and safety.
- Evaluation study for toxicity in immature rats
- 15 year Medullary thyroid carcinoma case registry to identify increase in incidence related to use of Trulicity
- *Clinical trial to assess renal function decline, major adverse cardiovascular events, pancreatic cancer, pancreatitis, immune-mediated reactions, hypoglycemia, hepatic, GI, supraventricular arrhythmias, and conduction disorders.*
- 26 week RCT comparing 0.75 mg and 1.5 mg dosing to insulin glargine in Type 2 DM and moderate or severe renal impairment population.
- RCT, double blinded to evaluate incidence of major adverse cardiovascular outcomes.

Summary: Dulaglutide has been shown to lower HbA1C% as monotherapy and add on therapy in patients with type 2 diabetes. It is weight loss promoting and has concerning side effects requiring a REMS for pancreatitis and thyroid tumor. Although non-inferior in head to head trials, no vast superiority was noted in HbA1C% reduction, weight loss, or side effect profile.

Recommendation: Exclude from coverage.

Pancrelipase (Zenpep) 40000-136000-218000 units

Creon Oral		
Strength (lip-pro-amy)	Price	Price/capsule
3000-9500-15000	\$82.66 (70)	\$1.180
6000-19000-30000	\$143.58 (100)	\$1.436
12000-38000-60000	\$280.74 (100)	\$2.807
24000-76000-120000	\$551.36 (100)	\$5.514
36000-114000-180000	\$868.40 (100)	\$8.684
Pancreaze Oral		
Strength (lip-pro-amy)	Price	Price/capsule
4200-10000-17500	\$100.63 (100)	\$1.006
10500-25000-43750	\$251.64 (100)	\$2.516
16800-40000-70000	\$403.96 (100)	\$4.04
21000-37000-61000	\$503.12 (100)	\$5.031
Pertzye Oral		
Strength (lip-pro-amy)	Price	Price/capsule
8000-28750-30250	\$198.75 (100)	\$1.988
16000-57500-60500	\$398.75 (100)	\$3.988
Ultresa Oral		
Strength (lip-pro-amy)	Price	Price/capsule
13800-27600-27600	\$326.70 (100)	\$3.267
20700-41400-41400	\$483.41 (100)	\$4.834
23000-46000-46000	\$593.63 (100)	\$5.936
Zenpep Oral		
Strength (lip-pro-amy)	Price	Price/capsule
3000-10000-16000	\$138.04 (100)	\$1.38
6000-17000-27000	\$181.70 (100)	\$1.817
10000-34000-55000	\$260.34 (100)	\$2.603
15000-51000-82000	\$376.01 (100)	\$3.76
20000-68000-109000	\$510.76 (100)	\$5.108
40000-136000-218000	\$1008 (100)	\$10.08

Recommendation: Exclude Ultresa, Pertzye due to lack of dosing options, cost relative to others in the same dose range. Note: Generally, dose escalation occurs within one brand for a given patient.

1. Cover all strengths of Creon, Zenpep and Pancreaze.

Budesonide (Uceris) rectal foam 2mg/metered dose
Cody Rogoff, P4
1/19/15

Labeled uses: glucocorticosteroid indicated for the induction of remission in patients with active mild to moderate distal ulcerative colitis extending up to 40 cm from the anal verge.

Comparator Drugs:

	Price (AWP)	Dose		Price per 6 week course
budesonide (Uceris) foam	\$307.20/33.4g [one canister with 14 doses]	1 BID x 2 weeks, then 1 q day x 4 weeks	28 doses then 28 doses, 4 canisters over 6 w.	56 doses/6 weeks initially= \$1228.80
hydrocortisone(Cortifoam) foam	\$340.40/15g [one canister with 14 doses]	1 applicatorful once or twice daily x2-3 weeks, then every other day thereafter	(assume max) 42 doses, then 11 more doses, 53 doses total, 4 cannisters.	53 doses/6 weeks if taking max dose= \$1361.60 32 doses/6 weeks if min dose= \$1021.20
budesonide (Uceris) 9mg 24 hour tablet	\$1,600.56/30 tablets	Once daily for up to 8 weeks		42 tablets= \$2,240.78
Budesonide (Entocort EC) 3mg capsule	\$1,884.53/ 100 tablets of 3mg	3 tabs q am for up to 8 weeks for episode of Crohn's		126 tablets= \$2,374.50

* Note: Entocort EC is not indicated for UC. Only for Crohn's Disease

MOA: glucocorticosteroid activity; controls the rate of protein synthesis; depresses the migration of polymorphonuclear leukocytes, fibroblasts; reverses capillary permeability and lysosomal stabilization at the cellular level to prevent or control inflammation.

Dosing: 1 metered dose twice daily for 2 weeks followed by 1 metered dose administered once daily for 4 weeks.

Contraindications: Known hypersensitivity to budesonide or any of the ingredients in UCERIS rectal foam.

Adverse Reactions decreased blood cortisol (17%), adrenal insufficiency(4%), and nausea(2%). Also note increased susceptibility to infection and symptoms of steroid withdrawal in those transferring from systemic glucocorticosteroid therapy.

Drug Interactions: Has not been studied in the rectal foam. They have inferred from the oral formulations the following interactions: CYP3A4 Inhibitors (e.g., ketoconazole, grapefruit juice): May cause increased systemic corticosteroid effects; avoid concomitant use.

Clinical Trials:

1. Trial from Package insert

Design: Safety and efficacy of UCERIS rectal foam were evaluated in 2 replicate, R, DB, PC, MC trials (Study 1 and 2). Participants in the trials were adult patients w/ active mild-to-moderate distal ulcerative colitis w/ disease extending at least 5 cm but no further than 40 cm from the anal verge (confirmed by endoscopy). Patients had to have a Modified Mayo Disease Activity Index(MMDAI) score between 5 and 10, inclusive, a rectal bleeding subscore of 2 or 3, and an endoscopy subscore of 2 or 3. [Oral and rectal corticosteroids, and rectal 5-aminosalicylic acid (5-ASA) products were prohibited during the course of the trials, but were allowed as rescue

therapy. Oral 5-ASA products were allowed at doses ≤ 4.8 grams/day. In each of these trials, 90% were Caucasian, 7-8% were African American, and 3% were Asian or Other.

- The primary endpoint was the proportion of subjects who were in remission after 6 w of treatment. Remission was defined as a decrease or no change in the stool frequency subscore from baseline, a rectal bleeding subscore of 0, and an endoscopy score of 0 or 1.

Results: Studies 1 and 2 showed achievement of remission in more Uceris pts vs placebo. Both studies revealed a statistically significant decrease in rectal bleeding subscore at week 6.

Table 4: Efficacy Results: Studies 1 and 2

Efficacy Endpoint	Study 1			
	UCERIS Rectal Foam N=155	Placebo N=152	p-value ^b	Treatment Difference (95% CI)
Remission at Week 6 ^a	38.3%	25.8%	0.032	12.6% (1.5%, 23.7%)
Rectal Bleeding subscore = 0 at Week 6	46.6%	28.0%	0.002	18.6% (7.2%, 30%)
Efficacy Endpoint	Study 2			
	UCERIS Rectal Foam N=134	Placebo N=147	p-value ^b	Treatment Difference (95% CI)
Remission at Week 6 ^a	44.0%	22.4%	< 0.001	21.6% (10.8%, 32.4%)
Rectal Bleeding subscore = 0 at Week 6	50.0%	28.6%	<0.001	21.4% (10.3%, 32.6%)

^aRemission was defined as an endoscopy subscore of 0 or 1, a rectal bleeding subscore of 0, and a decrease or no change in stool frequency subscore from baseline.

^bp-values obtained from the Cochran-Mantel-Haenszel (CMH) test.

CI: Confidence Interval

2. Budesonide foam vs. hydrocortisone acetate foam in the treatment of active ulcerative proctosigmoiditis

Design: N=251 proctosigmoiditis pts, R to either budesonide foam or hydrocortisone foam for 8w

Results: Remission rates were comparable in the budesonide and hydrocortisone groups, 53 and 52 percent, respectively. The mean disease activity index for the two groups decreased to a similar extent, from 7.2 +/- 1.9 and 7 +/- 2 to 3.6 +/- 3.1 and 3.9 +/- 3.4 in the budesonide and hydrocortisone groups, respectively. In a subgroup of patients who had not responded to rectal administration of mesalamine, 52% of pts who received budesonide responded favorably to the foam, as compared with 37% patients who received hydrocortisone (P = NS). Low plasma cortisol occurred in 3 percent of the budesonide group and in none of the hydrocortisone patients. **Similar efficacy and safety of the two foams.**

Bar-Meir S1, Fidler HH, Faszczyk M, Bianchi Porro G, Sturniolo GC, Mickisch O, Müller R, Greinwald R, Chowers Y, Grobeta V. *Dis Colon Rectum*. 2003 Jul;46(7):929-36.

3. Cortifoam (hydrocortisone foam) PI. Accessed 1/20/15.

This ref notes the distance of the colon for which the drug is effective. (10cm)

Note: Hydrocortisone foam reaches 10cm into the colon while Uceris foam reaches 40cm. Both are indicated for UC. Hydrocortisone is indicated as adjunctive treatment.

Recommendation: Cover with a PA for UC patients who have failed adequately dosed 5-ASA products and who have UC involvement beyond 10cm into the colon.

Outcome: Cover with a PA for UC patients who have failed adequately dosed 5-ASA products and who have UC involvement beyond 10cm into the colon.

suvorexant (Belsomra) 5mg, 20mg, 15mg, 20mg
Abbey Merry, P4
1/26/15

Labeled Uses: Treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance.

Comparator Drugs:

	AWP (\$)
Suvoxrexant	10.52
Zolpidem	4.63
Eszopiclone	11.67
Ramelteon	10.13
Temazepam	0.88

MOA: Suvorexant blocks the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R, which is thought to suppress wake drive. Antagonism of orexin receptors may also underlie potential adverse effects such as signs of narcolepsy/cataplexy.

Contraindications: Narcolepsy

Adverse Effects: drowsiness, headache, dizziness, abnormal dreams, abnormality in thinking, amnesia, anxiety, behavioral changes, CNS depression, drug abuse, drug dependence, exacerbation of depression, hallucination, hypnagogic hallucinations, sleep driving, suicidal ideation, increased serum cholesterol, diarrhea, xerostomia, lower extremity weakness, sleep paralysis, cough, upper respiratory tract infection

Drug Interactions: Substrate of CYP2C19 (minor) and CYP3A4 (major), avoid use with alcohol, azelastine, conivaptan, strong CYP3A4 inducers and inhibitors, furoic acid, idelalisib, orphenadrine, paraldehyde, sodium oxybate, thalidomide

Suvorexant in Patients with Insomnia: Results from Two 3-Month Randomized Controlled Clinical Trials.

Design: n=2040 nonelderly (18-64 years) and elderly (>65 years) patients with insomnia participated in two randomized, DB, placebo-controlled, parallel-group, 3-month trials with an optional 3-month double-blind extension. Efficacy was assessed at week 1, month 1, and month 3 by patient-reported sleep time and time to sleep onset and polysomnography (PSG) endpoints of wakefulness after persistent sleep onset and latency to onset of persistent sleep.

Results: Suvorexant 40/30 was superior to placebo on all endpoints except LPS at month 3 in trial 2 and suvorexant 20/15 was superior to placebo in subjective endpoints and most individual time points, time to sleep onset and LPS, in both trials. PSG showed approximate decreases in LPS of 10 min and wakefulness after sleep onset of 20 minutes. Suvorexant was well tolerated and did not show significant rebound or withdrawal symptoms when discontinued.

Herring WJ, Conner KM, et al. Suvorexant in patients with insomnia: results from two 3-month randomized controlled clinical trials. *Biological Psychiatry*. 2014; 10:003

Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant.

Design: n=492 patients participated in a randomized, double-blind, placebo-controlled, 2-period (4 weeks per period) crossover polysomnography study. Patients were randomized to receive 10 mg, 20 mg, 40 mg, or 80 mg in one period and placebo in the other. Polysomnography was performed on night 1 and week 4 of each period with primary endpoint of sleep efficiency on night 1 and week 4 with secondary endpoints of wake after sleep onset and latency to persistent sleep.

Results: Suvorexant significantly (p value <0.01) demonstrated dose-related improvements over placebo for primary endpoint of sleep efficiency at night 1 and week 4 and for secondary endpoints of sleep induction and maintenance. Total sleep time increases ranged from 22-62 minutes with 2%-4.1% more time spent in REM sleep. Suvorexant was well tolerated.

Herring WJ, Snyder E, et al. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. *Neurology*. 2012; 79(23):2265-74

Recommendation: Due to the high cost of suvorexant compared to other available medications for insomnia, I recommend that it is excluded from coverage.

Outcome: Excluded from coverage.

Acetaminophen 320.5mg-Caffeine 30mg-Dihydrocodeine 16mg(TREZIX)

Catherine Lee
January 29, 2015

Labeled Uses: treatment of moderate to moderately severe pain.

MOA: Dihydrocodeine attaches to opiate receptors in the brain leading to inhibition of pain pathways
Acetaminophen blocks PG synthesis in CNS and stops pain impulse in periphery
Caffeine is a CNS stimulant which in combination with the other drugs increases analgesic relief

Dose: 320.5mg/30/16mg Acetaminophen-Caffeine-Dihydrocodeine bitartrate oral capsule
• 2 capsules q 4 hours prn (max 10 capsules/day)

Comparators:

Available Forms	Standard Dosing	AWP (\$) / #100	30 day supply (USD)
APAP/Caffeine/Dihydrocodeine (Trezix) capsules	2 caps q 4 hours PRN (MDD=10 caps)	262.50	787.50
Hydro/APAP 10-325 mg tablet	1 QID	81.55	195.72
Hydro/APAP 5-325 mg tablet	1-2 QID	54.22	433.76
Codeine/APAP 30-300mg tablets	1-2 q 4h (MDD=12/d)	61.40	221.04
Codeine/APAP 60-300mg tablet	1-2 q 4h (MDD=12/d)	93.67	337.21



trezixrx.com/Conversion_Chart.html access 1/15/15

Black Box Warning: Death due to ultra-rapid metabolism of Codeine to Morphine/ Hepatotoxicity

Contraindications: Increased sensitivity to related drug products, management of post-op pain in pediatric populations who received tonsillectomy/adenoidectomy; respiratory depression, asthma, hypercapnia, paralytic ileus

Toxicities: CNS depression, skin reactions, hepatotoxicity

Drug Interactions: Azelastine (nasal spray), Orphenadrine, Paraldehyde, Pimozide, Stiripentol, Thalidomide, lobenguane I-123

Evidence: In a randomized, double-blind, 8w comparison of long-acting dihydrocodeine (60mg) versus short-acting dihydrocodeine (30mg), 60 patients, aged 18-75 diagnosed with chronic non-malignant pain and reported using 150-300mg codeine daily, were referred to a clinic to assess outcome of pain. They were randomized to two groups: those who received LA dihydrocodeine every 8 to 12 hours and a placebo 4 QID and the other group who received SA dihydrocodeine 4 to 6 times daily and LA dihydrocodeine placebo q 12h. The primary outcome was stability in pain intensity. In conclusion, max pain (p=0.73) and minimum pain (p=0.85) indicated no statistical significance between giving LA v SA dihydrocodeine for pain management.

Note: No head-to-head trials are currently available for this product and its comparators.

Recommendation: Exclude from coverage; not enough information exists. Many alternative analgesics exist. Also, less cost alternatives.

References:

1. "Lexicomp." *Trezix*. Web. 16 Jan. 2015. <http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/6266>.
2. "Trezix." *MedLibrary.org*. WraSer Pharmaceuticals, LLC. Web. 16 Jan. 2015.
3. **FDA.gov** <http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.DrugDetails> accessed 1/15/15
4. <http://medlibrary.org/lib/rx/meds/trezix-1/> Accessed 1/18/15
5. Pedersen, Line, et al. "A Randomized, Double-blind, Double-dummy Comparison of Short- and Long-acting Dihydrocodeine in Chronic Non-malignant Pain." *PAIN*® 155: 881-88. *www.journals.elsevier.com*. Web. 21 Jan. 2015. <http://ac.els->

Hydrocodone bitartrate ER 24 hour (Hysingla ER) Abuse Deterrent
Cody Rogoff, P4
1/19/15

Labeled uses: indicated for the management of pain severe enough to require daily, around-the-clock, long-term opioid treatment and for which alternative treatment options are inadequate.

Comparator Drugs:

	Dosage forms	Dosing	Price (AWP)	Price per Equivalent Daily Dose	Price per 30ds
hydrocodone bitartrate (Hysingla ER) extended-release tablets with abuse deterrent	20mg, 30mg, 40mg, 60mg, 80mg, 100mg, 120mg	Once daily If Opioid naïve start 20mg q day	60 tablets (20mg): \$473.04	\$7.88 per tablet \$7.88 per day	\$236.40
Hydrocodone bitartrate (Zohydro ER) capsule	10mg, 15mg, 20mg, 30mg, 40mg, 50mg	BID	100 tablets (10mg): \$702.00	\$7.02 per tablet \$14.04 per day	\$421.20
Oxycodone (Oxycontin) ER 12 hour abuse deterrent	10mg, 15mg, 20mg, 30mg, 40mg, 60mg, 80mg [generic in 10, 20, 40, 80mg]	BID	20 tablets (10mg): \$66.32	\$3.32 per tablet \$6.64 per day	\$199.20
Hydrocodone/APAP	Hydrocodone: 2.5mg, 5mg, 7.5mg, and 10mg APAP: 300mg or 325mg	Every 4-6 hours	100 tablets (5/325mg): \$62.50	\$0.62 per tablet \$2.48 per day (if q6h)	\$74.40

Note: HysinglaER PI shows a 1:1 mg conversion for po oxycodone to hydrocodone.

MOA: binds to opioids receptors in the CNS, causing inhibition of ascending pain pathways, altering the perception of and response to pain; produces generalized CNS depression.

Contraindications: Significant respiratory depression, acute or severe bronchial asthma, and known or suspected paralytic ileus and GI obstruction.

Adverse Reactions: QTc prolongation at doses higher than 160mg daily. Other adverse reactions include: constipation, nausea, vomiting, fatigue, upper respiratory tract infection, dizziness, headache, and somnolence.

Drug Interactions: Drugs that inhibit CYP3A4 activity may cause decreased clearance of hydrocodone which could lead to an increase in hydrocodone plasma concentrations. CNS depressants: Increased risk of respiratory depression, hypotension, profound sedation, coma or death. The use of MAO inhibitors or tricyclic antidepressants with HYSINGLA ER may increase the effect of either the antidepressant or HYSINGLA ER.

Abuse-Deterrent: HYSINGLA ER is formulated with physicochemical properties intended to make the tablet more difficult to manipulate for misuse and abuse, and maintains some extended release characteristics even if the tablet is physically compromised. To evaluate the ability of these physicochemical properties to reduce the potential for abuse of HYSINGLA ER, a series of in vitro laboratory studies, pharmacokinetic studies and clinical abuse potential studies was conducted. When subjected to an aqueous environment, HYSINGLA ER gradually forms a viscous hydrogel (i.e., a gelatinous mass) that resists passage through a hypodermic needle. Intranasal use is difficult due to granules falling to the floor. However, abuse of HYSINGLA ER by the intravenous, intranasal, and oral routes is still possible.

Conversion:

- A. From IR Hydrocodone: administer total daily dose of hydrocodone as single once daily dose
- B. From other opioids: use table to calculate equivalent daily dose of hydrocodone and reduce by 25% to reduce chance of overdose.

Clinical Trials:

1. Efficacy and safety of once-daily, XR hydrocodone in individuals previously receiving hydrocodone/acetaminophen combination therapy for chronic pain.

Design: Data were analyzed from 2 Phase III trials, a 12w R, PC and an open-label, 52-week trial. In both trials, a dose-titration period with Hysingla ER was followed by respective periods of fixed-dose DB, RCT or open-label, flexible-dose maintenance treatment. Pain intensity was assessed using a numerical rating scale (0-10, 0 = no pain). For the RCT, primary and sensitivity analyses of pain scores used different approaches to handle missing data. Safety data for both studies were summarized.

Results: In the RCT, the mean baseline pain score was 7.3. Pain relief was greater with Hysingla ER than placebo during double-blind treatment. In the open-label, flexible-dose trial, the majority of patients were maintained on their titrated dose. Mean baseline pain score was 6.3, about 57% of patients completed the 1-year maintenance period, and mean pain scores were between 3.6 and 4.1 during the maintenance period. Use of supplemental pain medication decreased or was maintained during the maintenance treatment with Hysingla ER. In patients whose primary pretrial analgesic was hydrocodone/acetaminophen combination tablets, **single-entity Hysingla ER was effective in reducing pain intensity and in maintaining analgesia over time without need for continued dose increase.** HYD's safety and tolerability profiles were similar to other opioid analgesics.

Bartoli A, Michna E, He E, Wen W. Postgrad Med. 2015 Jan;127(1):5-12. Epub 2014 Dec 16.

Author Information: San Francisco Pain Management Center , San Francisco, CA , USA.

Article was not full text and critiquable.

2. Trial from Package Insert

Design: The efficacy and safety of HYSINGLA ER was evaluated in a R, DB, PC, MC, 12-week clinical trial in both opioid-experienced and opioid-naïve patients with moderate to severe chronic low back pain.

Results: HYSINGLA ER provided greater analgesia compared with placebo. There was a statistically significant difference in the weekly average pain scores at Week 12 between the two groups. This trial evaluated responders, not EVERYONE who received the drugs.

*There were no head-to-head trials of Hysingla ER with any opioid or products containing abuse deterrents.

Requirements by the FDA: The FDA is requiring post-marketing studies of Hysingla ER to assess the effects of the abuse-deterrent features on the risk for abuse of Hysingla ER and the consequences of that abuse in the community.

<<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm423977.htm>>

Recommendation: Not enough evidence. Do not cover.

Outcome: Exclude. Not proven that abuse deterrent dosage forms actually deter abuse. Many alternative hydrocodone products and other opiates on the market for less cost.

Nintedanib (Ofev)
 Jill Johnson, Pharm.D., BCPS
 11/24/14, revised 2/17/15

Labeled uses: Idiopathic pulmonary fibrosis

Comparators:

Drug	AWP per unit	Units per month	AWP per month
Nintedanib	\$160.00	60	\$9600
Pirfenidone	\$34.67	270	\$9360.90

Drug Interactions: Inducers and inhibitors of CYP 3A4, P-glycoprotein, and ABCB1

Evidence:

Phase II trial on the efficacy and safety of nintedanib in IPF

- o **Design:** N=432, R to placebo or 1 of 4 doses of nintedanib (50 mg QD, 50 mg BID, 100 mg BID, or 150 mg BID) for 52w.
 - o 1' endpt: annual rate of decline in FVC b/w groups
 - o 2' endpts:
 - o changes from baseline in FVC,
 - o the total score on the St. George's Respiratory Questionnaire (SGRQ),
 - o incidence of acute exacerbations, and
 - o survival rates at the end of the trial;
 - o safety
- o **Results:** Nintedanib 150 mg BID showed a lower rate of decline in FVC compared to placebo (0.1L vs. 0.22L, P = 0.02).
 - o This group also had significant differences in secondary end-points such as having a slightly improved quality of life based on SGRQ score (4 point difference, p = 0.007), a lower incidence of acute exacerbations (2.4 vs 15.7 per 100,000 patient-years, p = 0.02), and a trend toward fewer deaths (2 vs. 8, p = 0.06). Nintedanib 100 mg twice daily also had a trend toward fewer deaths (2 vs. 8, p = 0.06). Nintedanib was also determined to be safe. However, diarrhea (55.3% vs. 15.3%), nausea (23.5% vs. 9.4%), vomiting (12.9% vs. 4.7%), and an increase in LFTs (7.1% vs. 0%) which were reversible upon dose reduction or withdrawal of medication, were higher w/ nintedanib.

Richeldi L, Costabel U. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med.* 2011; 365(12):1079-87. UI: 21992121

Phase III trials on efficacy and safety of nintedanib in IPF

- o **Design:** 2 R, DB, MC, parallel-group, 52w phase 3 studies named IMPULSIS-1 (n=515) and IMPULSIS-2 (N=551). 1' endpt was rate of FVC decline for nintedanib 150 mg BID vs placebo. 2' end-points: time to 1st acute exacerbation, change from baseline in the SGRQ, absolute change from baseline in FVC, risk of an acute exacerbation, and death that occurred between randomization and 4 weeks after the last dose of nintedanib or placebo was given. Safety was also compared.
- o **Results:** In both trials, the group taking nintedanib had a rate of decline in FVC that was < half of that of the placebo group (-114.7 mL vs. -239.9 mL in IMPULSIS-1 and -113.6 mL vs. -207.3 mL in IMPULSIS-2, p < 0.001 ((Note: no MCID has been established))). There were also statistical differences in 2' endpts in IMPULSIS-2 that were not significant in IMPULSIS-1 which are as follows: the time to acute exacerbations in the nintedanib group was greater than in the placebo group (HR=0.38, CI=0.9-0.77, P = 0.005), and there was a smaller increase in SGRQ score from baseline in the nintedanib group compared to placebo indicating a slower decline in quality of life (2.8 pts. vs. 5.48 pts., P = 0.02). There was no difference in a pooled analysis of both trials between groups in death that occurred between randomization and four weeks after the last dose of nintedanib or placebo. However, there was a slight trend in favor of nintedanib for a decrease in mortality from any cause compared to placebo (5.5% vs. 7.8%, P = 0.14). Nintedanib was also determined to be safe, although diarrhea (61.5% vs. 18.6%, 63.2% vs. 18.3%), nausea (22.7% vs. 5.9%, 26.1% vs. 7.3%), vomiting (12.9% vs. 2%, 10.3% vs. 3.2%), and an increase in LFTs (4.9% vs. 0.5%, 5.2% vs. 0.9%) which were reversible upon dose reduction or withdrawal of medication, were more common in the nintedanib group.
- o **SGRQ is St. George's Respiratory Questionnaire.** 4pt difference was MCID but drug achieved only 2.5 points change.

Pooled Results from IMPULSIS-1 and -2

	Nintedanib 150mg bid (n=634)	Placebo (n=421)	Difference vs placebo (95%CI)
Adjusted absolute mean change from baseline in FVC (mL)	-94.5	-205.0	110.6 (83.2, 137.9)
Adjusted absolute mean change from baseline in FVC (% predicted)	-2.9	-6.1	3.2 (2.4, 4)
	N=638	N=423	
Number (%) of patients w/ at least 1 acute exacerbation (investigator-reported)	31 (4.9)	31 (7.6)	ns
Number (%) of adjudicated acute exacerbation events, confirmed	4 (0.6)	4 (0.9)	
	N=623	N=416	
SGRQ symptoms domain, Adj mean change from baseline	1.82	3.67	-1.85 (p=0.12)
	N=617	N=414	
SGRQ activity domain, adj mean change form baseline	4.24	6.54	-2.3 (p=0.02)
	N=611	N=417	
SGRQ impact domain, adj mean change from baseline	3.83	4.98	-1.15 (p=0.24)

Note: Text states there was no significant between-group difference in the adj mean change in total SGRQ score at 52w.

Richeldi L, Bois RM. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Eng J Med*. 2014; 370(22):2071-82. UI: 24836310

~~It is argued in the literature (2014 Chest) that surrogate endpoints in IPF have no established validity. All cause mortality is promoted as the endpoint that should be used in phase 3 trials. Critics say that for an orphan disease like IPF, that manufacturers will not strive to meet that goal in attempting to produce novel agents for this disease state (RCTs would be too expensive and too long). Others point out that simply showing rate of decline in FVC for a given year does not predict rate of decline during the second year. So, at this point, there is no established surrogate for IPF.~~

Recommendation: Exclude from coverage. (revised by JJ)

Outcome: Exclude due to no improvement in longer life or QOL.

Alemtuzumab (Lemtrada)

Ashley Wilson
December 2014

Labeled Indications: relapsing forms of multiple sclerosis (MS)

Comparators:

Lemtrada (alemtuzumab)	Year 1 (IV 5 doses): \$118,500	Subsequent years (IV 3 doses): \$71,100
Rebif (interferon beta-1a)	Yearly cost (SQ 3X/w): \$80,730	
Betaseron (interferon beta-1a)	Yearly cost (SQ qd): \$78,777.95	
Copaxone (glatiramer acetate)	Yearly cost (SQ 20mg daily): \$81,176	Yearly cost (SQ 40 mg TIW): \$72402.72
Tysabri (natalizumab)	Yearly cost (IV 300mg q4w): \$72,992.40	
Gilenya (fingolimod)	Yearly cost (PO once daily): \$79,939.69	

Contraindications: Patients infected with HIV

Toxicities/Adverse Reactions: Autoimmune conditions (immune thrombocytopenia and antglomerular basement membrane disease), Serious and life threatening infusion reactions, Increased risk of malignancies (thyroid cancer, melanoma, and lymphoproliferative disorders), Thyroid disorders, Infections, Rash, Headache, Pyrexia, Fatigue, Insomnia, Urticaria, Arthralgia, Diarrhea, Dizziness, Flushing, Vomiting

Drug Interactions: Belimumab (X), Clozapine (X), Dipyron (X), Echinacea (D), Leflunomide (D), Natalizumab (X), Pimecrolimus (X), Roflumimast (D), Tacrolimus (X), Tofacitinib (X), Live Vaccines (X)

Evidence:

Alemtuzumab for patients with relapsing MS after disease-modifying therapy: a RCT phase 3 trial

- Design:** MC, R, rater-masked, controlled phase 3 clinical trial. N=798 randomized in a 1:2:2 ratio to IFN beta-1a (44µg/day 3 times weekly- 202 patients) or alemtuzumab 12 (426 patients) or 24 mg/day (IV cycles 5 days at month 0, then 3 days at month 12). The alemtuzumab 24 mg/day group (170 patients) was discontinued to recruit more patients into the alemtuzumab 12 mg group, but was included in the safety analysis. **Inclusion criteria:** pt age 18-55, RRMS, disease duration ≤10 years, >2 attacks in the previous 2 years w/ at least one relapse while on interferon beta or glatiramer after at least 6m of treatment, expanded disability status scale (EDSS) of ≤ 5, and cranial and spinal MRI lesions fulfilling protocol-defined criteria. **Exclusion criteria:** progressive forms of MS, previous cytotoxic drug use or investigational therapy, treatment w/in the previous 6m w/ natalizumab, MTX, azathioprine, or ciclosporin, and history of clinically significant autoimmunity other than MS.
- Results:** Both rate of relapse and sustained accumulation of disability (SAD, defined as an increase from baseline of at least one EDSS point) over 6m were significantly in favor of alemtuzumab. The mean disability improved from baseline in the alemtuzumab group, while it declined in the IFN beta-1a group. Both outcomes were still significant after sensitivity analyses to account for dropouts before and after treatment initiation and unmasked EDSS assessments. EDSS assessment and assessment of whether or not a patient had met the definition of relapse was decided by 6 independent masked neurologists. Alemtuzumab was also superior in all subgroup analyses. Alemtuzumab patients experienced more infusion-associated reactions, infections, and thyroid disorders than the IFN beta-1a patients.

Outcome	IFN beta-1a	Alemtuzumab	p-value
Annual relapse rate (ARR)	0.52	0.26	<0.0001
SAD	21.13%	12.71%	0.0084
Sustained reduction of disability	12.93%	28.82%	0.0002

Coles, A.J. et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. 2012. Lancet. Vol 380; 1829-1839.

Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 Clinical Trial

- Design:** MC, R, rater-masked, controlled clinical trial. 198 (151 alemtuzumab and 47 IFN beta-1a) of 334 patients participated in the extension phase of the original CAMMS223 original 36-month study. **Original inclusion criteria:** treatment-naïve RRMS, EDSS scores ≤ 3, disease duration ≤ 3 years, ≥ 2 relapses in the previous 2 years, and the presence of at least one gadolinium-enhancing lesion on a screening MRI scan. Patients were assigned in 1:1:1 ratio into IFN beta-1a (44µg/day 3 times weekly) or alemtuzumab 12 or 24 mg/day (3 annual IV cycles of 3 to 5 days each). All CAMMS223 patients were encouraged to participate in extension period. The use of disease-modifying therapies, including IFN beta-1a and alemtuzumab (after dose suspension lifted – suspended due to immune thrombocytopenia developed in 3 patients with one fatality in original study) were allowed. **Post hoc intention-to-treat analyses were performed through 60m after randomization.** Patients that participated in the extension study had lower rate of SAD in original study than those who did not participate. IFN beta-1a patients that participated in the extension study also had a lower annual relapse rate (ARR) than IFN beta-1a patients that did not participate in the extension study. Between 36-60m, only 9 alemtuzumab patients were retreated.

- Results:** Mean SAD improved for alemtuzumab patients at 60m compared with baseline, whereas a worsening in SAD was seen in IFN beta-1a patients. This disability improvement was also seen at 36m in the original study, however between 36-60m EDSS worsened in both groups. EDSS score worsened in both groups from 36-60m. Alemtuzumab relapse rate was lower than IFN beta-1a from baseline to 60 months and was also lower between 36-60 months, however not significant between 36-60 months (p value 0.072). ARR reduction in original study was similar in both groups. The estimated percentage of relapse-free patients at month 60 in the extension study was significantly higher after alemtuzumab than IFN beta-1a, **however after sensitivity analyses censoring for additional treatments during 36-60 months, the ARRs of both groups were lower and there was not a significant difference between treatment groups.** This sensitivity analysis could not be obtained from 0 to 60 months. **Notable AEs with alemtuzumab were similar to original study including, infusion-associated reactions, infections, and secondary autoimmunity.** All AEs were reported less frequently in patients who received additional alemtuzumab in the 36-60 month period than in the initial study. Infections were mild-mod usually w/in 1m of infusion w/ no life-threatening infections reported. **Thyroid disease was seen in 30% of alemtuzumab patients vs 4% of IFN beta-1a patients** and appeared from 6-61 months after first alemtuzumab infusion. Incidence of thyroid disease peaked at year 3 and declined thereafter. No additional cases of ITP occurred during the extension period. One case of anti-glomerular basement membrane disease occurred in a 12-mg alemtuzumab patient at 39 months after the second annual cycle of alemtuzumab.

Outcome	IFN beta-1a	Alemtuzumab	p-value
EDSS change from baseline to 60 months	0.46	-0.30	0.0002
EDSS change from 36-60 months	0.26	0.20	0.71
Relapse rate from baseline to 60 months	0.35	0.11	<0.0001

Coles, A.J. et al. Alemtuzumab more effective than interferon beta-1a at 5-year follow-up of CAMMS223 Clinical Trial. 2012. Neurology. Vol 78;1069-1078.

Conclusion: Alemtuzumab shows clinical benefit against other first line therapy (IFN beta-1a) for MS in ARR and SAD, however it does have more adverse effects associated with it.

Recommendation: Approve for coverage with PA. Patients must have RRMS, EDSS of ≤ 5 , and disease duration of < 10 years.

Outcome: Exclude in pharmacy program. Medical PA: Dx of RRMS, EDSS of <5, and disease duration of <10y. Deny access if history of thyroid disease.