



AGENDA

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

August 4, 2014

1:00 p.m.

EBD Board Room – 501 Building, Suite 500

- I. *Call to Order Dr. Kat Neill, Chairman*
- II. *Approval of April 7, 2014 Minutes, Intro New Member Dr. Kat Neill, Chairman*
- III. *Delivery Coordination Workgroup Report..... Dr. David Keisner, UAMS*
- IV. *2015 Formulary Explanation Dr. David Keisner, UAMS*
- V. *2015 Reference Price Changes..... Dr. David Keisner, UAMS*
- VI. *Hepatitis C discussion..... Dr. Jill Johnson, UAMS*
- VII. *2nd Review of Drugs – Tivicay, Nuvigil..... Dr. Jill Johnson, UAMS*
- VIII. *New Drugs Dr. Jill Johnson, UAMS*
- XI. *EBD Report..... Dr. David Keisner, UAMS*

Upcoming Meetings

November 3rd

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 August 4, 2014

The State and Public Life and Health Insurance Board, Drug Utilization and Evaluation Committee (DUEC) met on Monday August 4, 2014 at 1:00 p.m., in the EBD Board Room, 501 Woodlane, Little Rock, AR.

Voting Members present:

Dr. William Golden
Dr. Kat Neill - Chairman
Dr. Joe Stallings (teleconference)
Larry Dickerson
Dr. Hank Simmons – Vice Chairman
Dr. Matthey Hadley
Dr. John Kirtley Proxy for Dr. Mark McGrew
Dr. Scott Pace

Non-Voting Members present:

Dr. Jill Johnson
Connie Bennett
Dr. David Keisner

Members absent:

Dr. Appathurai Balamurugan

Lori Eden, Director of Operations, Employee Benefits Division

OTHERS PRESENT

Dwight Davis, Geri Bemberg, Shelby McCoy, Justin Speon, UAMS College of Pharmacy; Stella Greene, Sherry Bryant, Ethel Whittaker, EBD; Pam Lawrence, AHH; Marc Watts, ASEA; Warren Tyes, Merck; Steve Johnston, N. Nordisk; Charlene Kaiser, Amgen; Kanita Collins, Health Advantage; Sharon Jackson, Jon Maguire, GSK; Bridgett Johnson, Pfizer; Bruce Valentine, Acorda; Steve Althoff, MTI; Andy Davis, Arkansas Democrat Gazette; Mary Lawrence, Jack Fanagher

CALL TO ORDER

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

APPROVAL OF MINUTES

The motion was made by Dr. Neill to approve the April 7, 2014 minutes. Dickerson made the motion to approve. Hadley seconded. All were in favor.

Minutes Approved.

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

Drugs used in the treatment of Cancers and non-cancer drugs were reviewed by the DCWG and a report made to the DUEC on August 4th. Recommendations from this report are outlined below.

	Current Coverage	Proposed Coverage for 2015
<p><u>Metastatic Melanoma Treatment options:</u> Zelboraf (Vemurafenib) Tafinlar (dabrafenib) Mekinist (trametinib) Yervoy (ipilimumab) Tafinlar (dabrafenib) + Mekinist (trametinib) combined</p> <p>Dr. Golden motioned to approve the proposed coverage. Dr. Kirtley seconded. All were in favor. Motion Approved.</p>	<p>T4PA excluded T4PA Medical, no PA required Excluded</p>	<p>T4PA T4PA T4PA EBRx PA Excluded</p>
<p><u>Metastatic Prostate Cancer Treatment Options</u> Zytiga (abiraterone) Xtandi (enzalutamide) Jevtana (cabazitaxel) Provenge (sipuleucel-T) Xofigo (radium 223) Docetaxel</p> <p>Dr. Hadley motioned to approve. Dr. Pace seconded. All were in favor. Motion Approved.</p>	<p>T4PA T4PA Medical, No PA required Medical, No PA required Medical, No PA required Medical, No PA required</p>	<p>T4PA T4PA excluded excluded EBRx PA Medical, No PA require</p>
<p><u>Hodgkins Lymphoma/Anaplastic large T cell Lymphoma</u> Adcetris (brentuximab)</p> <p>Dr. Hadley motioned to approve. Dickerson seconded. All were in favor. Motion Approved.</p>	<p>Medical, No PA required</p>	<p>EBRx PA</p>

	Current Coverage	Proposed Coverage for 2015
<p><u>Chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL)</u> Imbruvica (ibrutinib) Arzerra (ofatumumab)</p> <p>Dr. Kirtley motioned to approved. Dr. Pace seconded. All were in favor. Motion Approved.</p>	<p>Excluded Medical, no PA required</p>	<p>T4PA EBRx PA</p>
<p><u>Hereditary Angioedema</u> Cinryze</p>	<p>Medical, no PA required</p>	<p>EBRx PA</p>

Berinert Kalbitor Firazyr Dr. Kirtley motioned to approve. Dickerson seconded. All were in favor. Motion Approved.	Medical, no PA required Excluded Excluded	Medical, no PA required Excluded Excluded
<u>New Drugs</u> Zykadia (ceritinib)-ALK positive NSCLC Xalkori (crizotinib) Cyramza IV (advanced stomach cancer/gastroesophageal junction adenocarcinoma). Dr. Kirtley motioned to approve. Dr. Golden seconded. All were in favor. Motion Approved.	Not yet reviewed T4PA Not yet reviewed	Exclude Exclude Exclude

2015 FORMULARY EXPLANATION & 2015 REFERENCE PRICE CHANGES: *by Dr. David Keisner, UAMS*

2015 Formulary Explanation: *Dr. David Keisner, UAMS*

Dr. Keisner reported there will no longer be a Gold, Silver, and Bronze Plans. The 2015 Plans are Premium, Classic, and Basic. There will be a pharmacy out-of-pocket for the Premium Plan. Reference price Med's will not count toward's the out-of-pocket max. For the Classic and Basic plans (pharmacy co-insurance plans), medications listed as reference priced are considered a non-covered benefit, and the member will pay the entire cost of the medication. This amount will not count toward the member's OOP maximum. Members have the option of the covered Tier 1 generic alternative(s) or to appeal to EBRx for coverage.

Revised Reference Pricing Coverage 2015 <i>Drug</i>	<i>Dr. David Keisner, UAMS</i> <i>Coverage for 2015</i>
The medication zolpidem ER, Temazepam 7.5 mg and 22.5 mg commonly used to treat insomnia, will be referenced priced on the premium plan and will be a non-covered med on the classic and basic plans. Zolpidem immediate release , temazepam 15 mg and 30 mg will remain covered under Tier 1.	Dr. Golden motioned to exclude Flurazepam for new users. Dr. Hadley seconded. All were in favor. Motion Approved.
Oxybutynin extended release, commonly used to treat overactive bladder, will be reference priced on the Premium plan and will be a non-covered medication on the classic and basic plans. Oxytrol Patches, commonly used to treat overactive bladder, will be excluded from all plans. There is also a new over-the-counter (OTC) preparation of Oxytrol patches available. Please note OTC products are not a covered benefit. Oxybutynin	Dr. Pace motioned to exclude Oxytrol Patches. Dr. Simmons seconded. All were in favor. Motion Approved.

immediate release will remain covered under Tier 1.	
Nasacort AQ and triamcinolone nasal, commonly used to treat allergic rhinitis, will be excluded from all plans. Azelastine, flunisolide, and fluticasone nasal will remain covered at Tier 1. There is also a new OTC preparation of Nasacort available. Please note OTC products are not a covered benefit.	Dr. Pace motioned to exclude Nasacort AQ and triamcinolone products. Dr. Simmons seconded. All were in favor. Motion Approved.
Dr. Simmons motioned to add Zolpidem ER and Temazepam 7.5 & 22.5 mg to the referenced priced structure. OTC Oxytrol Patches not covered. Recommend to the Board to cover the immediate release product with a dosage of 3x daily. Dickerson seconded. All were in favor. Motion Approved.	

Dr. Keisner reported specialty meds should not be allowed more than a thirty (30) day supply distribution from any source. Controlled substances are also in this category. However, Claims adjudication has allowed more than a thirty (30) day supply.

Dr. Pace reported under no circumstances should there be over a thirty (30) day supply dispensed which includes mail order fill. The DUEC Committee affirmed this coverage decision.

Dr. Johnson reported in some circumstances the committee has only voted for a fifteen (15) day supply to be filled.

Dr. Pace recommended Dr. Keisner complete an audit of how many specialty prescriptions were filled for more than a thirty (30) day supply.

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

Dr. Johnson recommends Sovaldi to be covered with a PA. Please see attachment.

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	

<p>> 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)</p>	
<p>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).</p>	<p>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.</p>
<p>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, alpha 1 antitrypsin deficiency, cholangitis)</p>	<p>These patients were excluded from the clinical trials.</p>
<p>6. Cirrhosis must be shown by liver biopsy and be metavir score F3 or F4. Alternatively, the FIB-4 score or the APRI score will suffice for stating cirrhosis in lieu of liver biopsy.</p>	

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

<p>1. Is the patient currently on the liver transplant list?</p>	
<p>2. Has the patient previously received any treatment for HCV infection? If so, what regimen and duration?</p>	
<p>3. Has the patient tested positive for HIV?</p>	<p>There are no data in HCV treatment-experienced HIV patients.</p>

Dr. Golden motioned to accept Dr. Johnson's recommendations. Sovaldi (sofosbuvir) will be covered T4PA. Olysio (simeprevir) is excluded. However, in six (6) months the committee will review updated information and guidelines. In addition, it is recommended that therapy will be processed through case management and requests for PA be initiated by a Hepatologist or GI Specialist. Dr. Hadley seconded. All were in favor.

Motion Approved.

2ND REVIEW OF DRUGS: *by Dr. Jill Johnson, UAMS*

Current Coverage	Recommendation
Provigil	Cover: Continue same PA criteria
Tivicay	Cover: Remove PA criteria
Nuvigil 200 mg	Cover: Continue same PA criteria

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

Johnson reported on new drugs. The review covered products released March 17, 2014 – May 31, 2014.

BRAND Name	GENERIC name	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	CODE*
AVEED	Testosterone Undecanoate	\$990/750mg	Testosterone undecanoate IM injection in oil for treatment of low testosterone. Dose 750 mg IM given at initiation of therapy, at 4 weeks. Then every 10 weeks thereafter	Testosterone cypionate	Exclude 13
Hetlioz 20 mg caps (Specialty Drug)	tasimelteon	\$8,432/30 days	Treatment of non-24-hour sleep wake disorder.	none	Exclude 13
Xartemis XR Tabs 7.5 325 mg	Osycodone w/acetaminophen controlled release tab	\$2.76/tab	New formulation of oxycodone/acetaminophen in an extended release tab	Immediate release oxycodone/acetaminophen tab = \$1 less	Exclude
Orenitram Tabs	Treprostinil diolamine controlled release tab	\$7,020/60-2.5mg tabs	Extended release – treatment of pulmonary arterial hypertension.	Other oral specialty drugs for PAH and AWP for 30 day supply.	Exclude
Otezla Tabs	apremilast	\$2,250/60 tabs	Treatment of adults with active psoriatic arthritis.	Other specialty drugs for psoriatic arthritis administered by subcutaneous injection and AWP/month..	T4 PA

Myalept INJ 11.3 mg (metreleptin) Specialty Drug	metreleptin	1 vial = \$1,766	To treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy.	None	Exclude
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New Drugs (continued):

Hemangeol soln 4.25 mg/ml (propranolol oral soln)	Propranolol hcl solution	\$450/120ml	Treatment of proliferating infantile hemangioma requiring systemic therapy.	First and only pediatric formulation of propranolol.	Exclude 13
Zenzedi (dextroampheta mine sulfate 15, 20, 30mg)	Dextroampheta mine sulfate	\$5.95/tab	New table formulation with 2 new strengths of dextroamphetamine	Exclude – unless cost is a factor and thee is a benefit to having this.	Exclude
Q-tabs 1 mg (levomefolate glucosamine tab 1 mg (folate equivalent)	Levomefolate glucosamine 1mg	\$4.64/tab	Folice acid, vitamin 89	Folic acid 1mg tabs </40.50/tab(tier 1)	Exclude 13
Sitavig 50 mg buccal tab	Acyclovir buccal tablet		Treatment of recurrent herpes labialis (cold sores) in immunocompetent adults.	No other buccal tabs.	Exclude code 13
Zontivity Tabs (vorapaxar)	Vorapaxar sulfate	\$320/30 days	To reduce the risk of heart attack, stroke, cardiovascular death, and need ofr procedures to restore the blood flow to the heart in patients with previous heart attacks or blockages in arteries to the legs.	First-in-class oral PAR 1 inhibitors	Exclude code 12
Grastek Subling Tab 2800 BAU Specialty Drug	Timothy grass plllen allergen extract	\$297/30 days	Treatment of grass pollen – induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test in vitro testing for pollen	None	Exclude
Ragwitek Subling Tabs Specialty Drug	Short raweed pollen allergen extract	\$297/30 days	Treatment of allergic rhinitis with or without conjunctivitis that is induced by short ragweed pollen in adults age 18-65.	None	Exclude

Oralair SL 300 IR Specialty Drug	Grass mixed pollen extract	\$360/30 days	Treatment of allergic rhinitis (hay fever) with or without conjunctivitis that is induced by certain grass pollen for people 10-65 years.	None	Exclude
Entyvio Inj 300 mg Specialty Drug	Vedolizumab	\$5,782/300 mg	For adults patients with moderately to severely active ulcerative colitis or Crohn's disease.	Humira 40 mg subj injection every other week/\$3,002;Cimzia 400 mg subj injection every 4 weeks/\$3,322.	Tabled Code 7
Prena1 Chewable and Redichew Rx CHW	Prenatal Vitamin		Prenatal Vitamins	Multiple generics (tier 1)	Exclude Code 7
Select-OB-CHW	Prenatal Vitamins		Prenatal Vitamins	Multiple generics (tier 1)	Exclude Code 7
Products Administered IV:					
Nitronal IV Solution	Nitroglycerin	N/A	Not in the scope of Pharmacy benefits.		N/A medical

Compounding Kits:

Vancomycin oral solution kit					May add depend on cost
Cyclobenzaprine Cream kit					Exclude
Tramadol Cream 8% kit					Exclude

Dr. Kirtley requested additional information on compound kits to present to the board for review and recommendation. Dr. Neil recommended table the compound kits until further information is received.

Dr. Hadley motioned to adopt the recommended changes and exclusions and the previous motions. Dr. Simmons seconded. All were in favor.

Motion Approved.

EBD REPORT: *by Lori Eden, EBD Chief Operations Officer*

There was not an EBD Report presented.

Meeting Adjourned.

	A	B	C
1	<u>Delivery Coordination Workgroup Report August 4, 2014</u>		
2			
3		<u>Current Coverage</u>	<u>Proposed Coverage</u>
4	<u>Metastatic Melanoma Treatment options</u>		
5	Zelboraf (Vemurafenib)	T4PA	T4PA
6	Tafinlar (dabrafenib)	excluded	T4PA
7	Mekinist (trametinib)	T4PA	T4PA
8	Tafinlar + Mekinist	Combo excluded	Combo excluded
9	Yervoy (ipilimumab)	Medical, no PA required	EBRx PA
10			
11	<u>Metastatic Prostate Cancer Treatment Options</u>		
12	Zytiga (abiraterone)	T4PA	T4PA
13	Xtandi (enzalutamide)	T4PA	T4PA
14	Jevtana (cabazitaxel)	Medical, no PA required	excluded
15	Provenge (sipuleucel-T)	Medical, no PA required	excluded
16	Xofigo (radium 223)	Medical, no PA required	EBRx PA
17	docetaxel	Medical, no PA required	medical, no PA required
18			
19	<u>Hodgkins Lymphoma/Anaplastic large T cell Lymphoma</u>		
20	Adcetris (brentuximab)	Medical, no PA required	EBRx PA
21			
22	<u>Chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL)</u>		
23	Imbruvica (ibrutinib)	excluded	T4PA
24	Arzerra (ofatumumab)	Medical, no PA required	EBRx PA
25			
26	<u>Hereditary Angioedema</u>		
27	Cinryze	Medical, no PA required	EBRx PA
28	Berinert	Medical, no PA required	Medical, no PA required
29	Kalbitor	Excluded	Excluded
30	Firazyr	Excluded	Excluded
31			
32	<u>New Drugs</u>		
33	Zykadia (ceritinib)- ALK positive NSCLC	not yet reviewed	exclude
34	Xalkori (crizotinib)	T4PA	exclude
35	Cyramza IV (advanced stomach cancer/gastroesophageal junction adenocarcinoma)	not yet reviewed	exclude

Metastatic Melanoma Treatment Options

	Vemurafenib¹ (960 mg po bid)	Dabrafenib³ (150 mg po bid)	Trametinib⁴ (2 mg po daily)	Trametinib + dabrafenib⁵ Phase II trial (monotherapy doses)	Ipilimumab⁶ (3 mg/kg IV every 3 weeks x 4 doses)
Current Coverage	T4PA	excluded	T4PA	Exclude Combo	Medical, No PA required
Proposed Coverage	T4PA	T4PA	T4PA	Exclude Combo	EBRx PA
Comparison	Dacarbazine	Dacarbazine	Dacarbazine or paclitaxel	Dabrafenib	gp100 vaccine (considered placebo)
Previous lines of tx allowed	None	None (except IL-2)	0 or 1 (but no BRAF inh or ipi)	No restriction stated	≥1
Response rate (%)	48	50	22	76	37.5
PFS (mo)	5.3 ^a	5.1	4.8	9.4	2.86 ^b
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)	<u>HR 0.54</u> (95% CI, 0.32 to 0.92)	At 12 months: 79% alive (vs. 70%; p not reported)	10.1 mo vs. 6.4 mo [HR 0.66 (95% CI, 0.51-0.87)]

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

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

Considerations:

- Overall survival benefit not demonstrated for dabrafenib as monotherapy or in combination with trametinib. Complicated by crossover rate, and not a primary endpoint so not powered to find a difference in overall survival. Also may see difference with more prolonged follow up.
- Trametinib monotherapy probable place in therapy is if there is a contraindication to BRAF inhibitor. Contraindicated if pt has disease progression on vemurafenib or dabrafenib
- Ipilimumab: only drug available (besides IL-2) that may give a durable response
- Trametinib+dabrafenib study: Phase II randomized (n=108); Phase III trial ongoing (per clinicaltrials.gov)
- Phase I study of combination therapy with vemurafenib and ipilimumab was closed early due hepatotoxicity
- Sequencing of ipilimumab and BRAF inhibitor:
 - Symptomatic: use BRAF inhibitor first
 - Asymptomatic: unclear

Metastatic Melanoma Treatment Options

TOXICITY

BRAF INHIBITORS

GENERAL:

cutaneous squamous cell carcinoma
rash
alopecia
arthralgias
headache
weakness
fatigue
uveitis

VEMURAFENIB:

QT prolongation
photosensitivity
peripheral facial palsy
severe radiation dermatitis

DABRAFENIB:

pyrexia
hyperglycemia

TRAMETINIB

rash
hypertension
acneiform dermatitis
diarrhea
edema
fatigue

LESS COMMON:
decreased ejection fraction (7%)
interstitial lung disease
retinal detachment
retinal vein occlusion

DABRAFENIB + TRAMETINIB

Compared with dabrafenib alone:

Fewer cutaneous toxicities (including squamous cell carcinoma)
More pyrexia and chills
More nausea/vomiting

References:

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

Toxicity data obtained from clinical trials and LexiComp.

Metastatic Prostate Cancer Treatment Options

	Abiraterone¹ (1000 mg po daily plus prednisone 5 mg bid)	Abiraterone² (1000 mg po daily plus prednisone 5 mg bid)	Enzalutamide³ (160 mg po daily)	Cabazitaxel⁴ (25 mg/m ² q3w plus prednisone 5 mg bid)	Sipuleucel-T⁵	Radium 223⁶ (given q4w x 6 doses)	Docetaxel^{7,8} (75 mg/m ² IV q3w plus prednisone 5 mg bid)
Current Coverage	T4PA	T4PA	T4PA	Medical, No PA required	Medical, No PA required	Medical, No PA required	Medical, No PA required
Proposed coverage	T4PA	T4PA	T4PA	exclude	exclude	PA	Medical, No PA required
Comparison	Placebo + prednisone	Placebo + prednisone	Placebo	Mitoxantrone + prednisone	Placebo	Placebo	mitoxantrone (plus prednisone)
Place in therapy (per study)	Asymptomatic/ minimally symptomatic mCRPC ^a with no prior chemo	mCRPC with prior docetaxel	mCRPC with prior docetaxel	mCRPC with prior docetaxel	Asymptomatic/ minimally symptomatic mCRPC; no visceral mets	Symptomatic mCRPC with two bone mets and no visceral mets	mCRPC (no prior chemotherapy allowed)
Tumor response rate (%)	36 vs. 16%	14 vs. 3%	29 vs. 4%	14.4 vs. 4.4%	Not an endpoint; [time to radiographic disease progression: 14.6 vs. 14.4 mo (p=0.63)]	Not an endpoint [time to first symptomatic skeletal event ^c : 15.6 vs. 9.8 mo (p<0.001)]	35 vs. 22%
PSA response rate (%)	62 vs. 24%	29 vs. 6%	54 vs. 2%	39.2 vs. 17.8%	Not a prespecified endpoint	Not an endpoint	45 vs. 32%
Median overall survival	median not reached vs. 27.2 mo [HR 0.75 (95% CI, 0.61-0.93)] ^b	14.8 vs. 10.9 mo [HR 0.65 (95% CI, 0.54-0.77)]	18.4 vs. 13.6 mo [HR 0.63 (95% CI, 0.53-0.75)]	15.1 vs. 12.7 mo [HR 0.7 (95% CI, 0.59-0.83)]	25.8 vs. 21.7 mo [HR 0.78 95% CI, 0.61 to 0.98]]	14.9 vs. 11.3 mo [HR 0.70 (95% CI, 0.58–0.83)]	19 vs. 16.3 mo [HR 0.79 (95% CI, 0.67 to 0.93)]

a mCRPC: metastatic castration resistant prostate cancer

b p=0.01 → study's prespecified significant p value set at p ≤ 0.0001

Metastatic Prostate Cancer Treatment Options

c symptomatic skeletal event defined as use of radiation therapy to relieve skeletal symptoms, new symptomatic pathologic vertebral or nonvertebral bone fractures, spinal cord compression, or tumor-related orthopedic surgical intervention

Considerations:

-All should only be used for metastatic disease.

References:

1. Ryan CJ et al. N Engl J Med 2013;368:138-48.
2. De Bono JS et al. N Engl J Med 2011;364:1995-2005.
3. Scher HI et al. N Engl J Med 2012;367: 1187-1197
4. De Bono JS et al. Lancet 2010; 376: 1147–54
5. Kantoff PW et al. N Engl J Med 2010;363:411-22.
6. Parker C et al. N Engl J Med 2013;369:213-23.
7. Tannock IF et al. N Engl J Med 2004;351:1502-12.
8. Berthold DR et al. J Clin Oncol 2004;26:242-245.

Brentuximab vedotin (Adcetris®)

Current Coverage	Medical. No PA required.
Proposed Coverage	Medical. Add PA requirement.

Pharmacology

- Monoclonal antibody directed at CD30
- Monomethyl auristatin E (MMAE) is released inside the cell disrupting the microtubule network

Classical Hodgkin Lymphoma (HL)

- After failure of autologous stem cell transplant (ASCT)

OR

- After failure of at least two previous multi-agent chemotherapy regimens in patients who are not candidates for ASCT

Relapsed/Refractory Hodgkin Lymphoma¹	
Patients included	n = 102 Relapsed/refractory disease after SCT (auto only) Median number of prior regimens: 3.5 *FDA-approved indication also includes pt who are not candidate for SCT AND who have failed ≥ 2 or more therapies.
Dosing	1.8 mg/kg IV over 30 minutes (max 180 mg) every three weeks x up to 16 doses *FDA-approved indication initially limited dosing to 16 cycles, but this limitation was removed from labeling
Median number of cycles given	9
Objective Response	75%
Complete Response	34%
Median duration of response	6.7 mo
Median duration of response (CR pt only)	20.5 mo
Median PFS, months	5.6 mo
Median PFS (CR pt only)	21.7 mo
Median overall survival	40.5 mo at 3 years f/u (updated per abstract data) ²

*SCT = stem cell transplant; NE = not estimable; PFS = progression free survival

-There is a phase II trial of brentuximab after allogeneic SCT (response rate 50%)³

-Data published in abstract form show dosing beyond 16 doses to be safe⁴

- For relapsed HL, overall response rates with chemotherapy generally are 70-80% with CR rates 11-54%³

-NCCN guideline recommends use per FDA indication

Anaplastic large cell lymphoma (ALCL) [subset of peripheral T cell lymphomas]

- After failure of at least one previous multi-agent chemotherapy regimen

Systemic Anaplastic Large Cell Lymphoma⁵	
Patients included	n = 58 Recurrent ALCL after at least one prior therapy Median # of prior regimens: 2
Dosing	1.8 mg/kg IV over 30 minutes (max 180 mg) every three weeks x up to 16 doses
Objective response	86%
Complete response	57 %
Median duration of response	12.6 mo
Median duration of response for patients with CR	13.2 mo
Median progression-free survival, months	13.3 mo

*Median overall survival not reached at time of analysis

-Abstract data show dosing beyond 16 doses to be safe⁴

FDA-Approved Treatments for Relapsed/Refractory peripheral T cell lymphomas⁶				
	Chemotherapy n = 98	Pralatrexate n = 111	Romidepsin n = 130	Brentuximab vedotin n = 58
PTCL-NOS, AILT, or ALCL	100%	80%	90%	100 (all ALCL)
Overall response rate	40-50%	29% (CR 2%)	38% (CR 11%)	86% (CR 57%)
Median PFS (mo)	3.7	3.5	4	13.3
Median DOR (mo)	NR	10.1	16.6	12.6
Median OS (mo)	6.5	14.5	NR	NR

NR = not reported,

PFS = progression free survival, DOR = duration of response, OS = overall survival, PTCL-NOS = peripheral T cell lymphoma, AILT = angioimmunoblastic T cell lymphoma

References

1. Younes A, et al. Results of a pivotal phase II study of brentuximab vedotin for patients with relapsed or refractory hodgkin's lymphoma. *Journal of Clinical Oncology* 30(18):2183-89, 2012.
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Relapsed or refractory chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL)

	Current Imbruvica Coverage:	Excluded
	Proposed Coverage:	T4PA
	Ibrutinib vs. Ofatumumab n = 391	Other regimens for relapsed/refractory CLL/SLL patients who are not candidates for purine analogue
Patients	-Relapsed/refractory CLL/SLL -≥1 prior therapy (median: 2-3) -not candidate for purine analogue	<u>Bendamustine/Rituximab:</u> Phase II: OR/CR: 59%/9% Phase III: vs. Rituximab/chlorambucil: OR/CR: 89%/11% vs. 83%/4%
Dosing	Ibrutinib 420 mg po daily until disease progression Ofatumumab (IV) Week 1: 300 mg Weeks 2-7: 2000 mg weekly Then 2000 mg q4wk x 4 doses [total duration: 24 wks]	<u>High dose methylprednisolone/Rituximab:</u> OR/CR: 78-93%/14-36% Median PFS 7-15 mo Median OS 20 mo [infectious complications: 30%]
Median f/u	9.4 mo	<u>Alemtuzumab:</u> OR/CR: 33-49%/2% Median OS: 16-19 mo [very immunosuppressive]
PFS (mo)	Median not reached vs. 8.1 [HR 0.22 (95% CI, 0.15-0.32)]	<u>Alemtuzumab/Rituximab:</u> OR/CR: 53%/18%
Response rate (%)	Partial response: -42.6 vs. 4.1% (p=0.005) -excludes ibrutinib pt with PR with lymphocytosis (20% of all pt) Stable disease: -32 vs. 78% *Above per independent assessment. Response rates higher for investigator assessment	<u>Lenalidomide:</u> OR/CR: 32-47%/7-9% [OR 13% for pt with del(17p)] <u>Lenalidomide+R:</u> OR/CR: 66%/12%
Overall survival	[HR 0.43 (95% CI, 0.24-0.79)] At 12 mo, survival rate: 90 vs. 81%	
Notes	-At time of analysis 57 pt (30%) of ofatumumab pt had crossed over to ibrutinib. Above OS data censored. Uncensored data had similar OS outcome.	

Toxicity	Severe: similar rates between groups Other: Ibrutinib associated with more diarrhea, nausea, arthralgia, blurred vision and slightly higher rates of heme effects. More infusion reactions with ofatumumab.	
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CLL=chronic lymphocytic leukemia

SLL=small lymphocytic leukemia

PFS=progression free survival

OR=overall response rate

CR=complete response rate

Agents for the Treatment of Hereditary Angioedema: A Review of the Evidence and a Proposal (6/6/14)

Jordan Brazeal, Pharm.D., October 31, 2012, addendum Jill Johnson June 6, 2014

Drug Name	Current Coverage	Proposed Coverage
human C1 inhibitor (Cinryze®)	Medical. No PA	Medical. Add PA
human C1 inhibitor (Berinert®)	Medical. No PA	Medical. No PA
ecallantide (Kalbitor®)	Excluded	Exclude
icatibant (Firazyr®)	Excluded	Exclude

Hereditary angioedema (HAE), or inherited C1 inhibitor deficiency, is a rare genetic disorder characterized by recurrent episodes of angioedema that most often affect the skin or mucosal tissues of the upper respiratory or gastrointestinal tracts. This disorder may be the result of a deficiency in C1 inhibitor (Type I) or a dysfunction in C1 inhibitor (Type II). Although the swelling is limited in most cases even without treatment, edema of the larynx can cause fatal asphyxiation.⁶

Three new treatment options are available for patients with HAE: human C1 inhibitor (Berinert®, Cinryze®), ecallantide (Kalbitor®), and icatibant (Firazyr®). These agents have been the subject of various clinical trials, evaluating their use in acute treatment and prophylaxis of HAE crises. HAE is a rare disorder, yet the treatment options can be costly to an insurance plan. The intent of this review is to provide a well-defined prior authorization pathway.

The FDA-approved dosing for each agent is described in the table below.¹⁰⁻¹³

Drug Name	FDA-approved Indication	Dosing	Cost (AWP) on 6/6/14
human C1 inhibitor (Cinryze®)	Routine prophylaxis against HAE attacks	I.V.: 1000 units every 3-4 days	500units=\$2943 8-10 doses/month=\$47088-\$58,860
human C1 inhibitor (Berinert®)	Treatment of abdominal, facial, or laryngeal HAE attacks	I.V.: 20 units/kg	500units=\$2897 2 attacks/m in 85kg patient: 1700units/dose, twice monthly=8vials/month=\$23176
ecallantide (Kalbitor®)	Treatment of acute attacks of HAE	SubQ: 30 mg; may repeat an additional 30 mg within 24 hours	10mg/mL X 3=1 dose; may repeat w/in 24h. Assume 2 attacks/month with repeat tx in 24h. 6 syringes/episode; 12 syringes/month. 10mg/mL=\$4452. One episode=30mg=\$13356. If repeat in 24h, the episode = \$26712. Twice monthly=\$53424
icatibant (Firazyr®)	Treatment of acute attacks of HAE	SubQ: 30 mg/dose; may repeat one dose every 6 hours if response is inadequate or symptoms recur (max: 3 doses/ 24hours)	30mg/mL syringe=\$9606 3 doses/24h=\$28818 Twice/m=\$57636

Search Methods. Trials were searched through Ovid™ MEDLINE, Cochrane Database of Systematic Reviews, and International Pharmaceutical Abstracts. The search terms [angio\$] and [ecallantide] or [icatibant] or ([human] or [recombinant] or [c1]) were used to find articles; these search terms were limited to “title” and yielded 407 trials. These results were limited to English language, human subjects, and randomized-controlled trials (RCT) to yield 23 trials. An attempt was also made to limit the original 403 articles to systematic reviews or meta-analyses, but the resultant hit was “0.” Of the 23 RCTs, 14 were selected for use in this article. The data for each article will be used to describe the clinical evidence for each agent, below.

Human C1 Inhibitor (Berinert or Cinryze). Since patients with HAE have either a deficient or defunct C1 inhibitor, the purpose of human C1 inhibitor therapy is to replenish that supply and bring the HAE attack under control. Currently, human C1 inhibitor is available under two proprietary names: Berinert® and Cinryze®, each FDA-approved for different indications (see table above); there are no generic products available at this time. Berinert® has been evaluated for use in acute HAE attacks in 4 RCTs totaling 288 patients^{4,8,18,19} and 2 open-label trials in 66 patients.^{5,7} Berinert® and Cinryze® been evaluated for use as routine prophylaxis against HAE attacks in 2 RCTs totaling 30 patients^{17,18} and one open-label trial in 6 patients.⁷ One RCT assessed the thrombogenicity of Berinert®.¹

For the treatment of acute HAE attacks, efficacy has been evaluated through a number of endpoints, including time to symptomatic relief (primary efficacy endpoint in 4 RCTs), time to complete resolution of symptoms, number of patients with improved HAE symptoms, and percentage of patients experiencing unequivocal relief in 4 hours. The efficacy of Berinert® to provide onset of symptomatic relief ranged from 0.5 hours to 7.62 hours ($P < 0.05$ in all cases) in placebo-controlled trials. One RCT assessed the use of Cinryze® in acute attacks. This trial, by Zurow et al., found a statistically significant difference in the primary endpoint of time from administration to unequivocal relief of symptoms, but failed to maintain that difference after 4 hours post-administration when compared to placebo.¹⁸

For use prophylactically, Berinert® and Cinryze® have been evaluated in 3 studies. One study of Berinert®, due to its poor design and small sample size, failed to show a difference in the primary endpoint at 2 hours post-infusion.¹⁷ Another study of Berinert® was an open-label, single-arm trial.⁷ The final study, a randomized crossover trial, evaluated Cinryze® in 24 patients. This trial demonstrated a significant reduction versus placebo in the number of HAE attacks over the study duration (24 weeks) with a number-needed-to-treat (NNT) of 2.¹⁸

The adverse event profile of human C1 inhibitor is relatively mild. Overall, treatment-emergent adverse events (TEAE) occurred more frequently in placebo groups than in treatment groups. The most common TEAEs with C1 appear to be headache and nausea. Thrombotic events have been reported with the use of C1; however, the study by Bakhtiari et al. concluded that usage of C1 does not increase risk of thrombotic events.¹

Ecaltantide. Ecaltantide (Kalbitor®) is a kallikrein inhibitor that exerts its pharmacological action by preventing conversion of kininogen to bradykinin, thereby reducing the vascular permeability and angioedema associated with HAE.¹³ Ecaltantide has been evaluated for use in treatment of acute HAE attacks in 4 RCTs totaling 376 patients.^{2,9,15,16} Its efficacy has been observed through various endpoints, including change in baseline Mean Symptom Complex Severity (MSCS) score 4 hours post-administration, percentage of patients reporting significant improvement 4 hours post-administration, Treatment Outcome Score (TOS) 4 hours post-administration, and proportion of patients achieving TOS. The EDEMA4 trial, by Levy et al., demonstrated a significant difference versus placebo in MSCS scores (-0.8 vs. -0.4; $P = 0.01$) and proportion of patients achieving TOS after 4 hours (44% vs. 21%; $P = 0.02$; $NNT = 4.34$) in a sample size of 96 patients.⁹ In the study by Schneider et al., ecaltantide I.V. demonstrated a difference versus placebo in patients reporting a significant improvement in symptoms 4 hours post-administration; however, this difference was only significant with the ecaltantide I.V. 40 mg/m² group (72.5% vs. 25.0%; $P = 0.02$; $NNT = 2.11$).¹⁵ The study by Cicardi et al. showed a significant improvement of ecaltantide in TOS 4 hours post-administration versus placebo (50.0 vs. 0.0; $P = 0.004$). This trial included 160 patients.²

Adverse events were similar in all trials between placebo and treatment groups. The most commonly-reported TEAEs with ecallantide were headache and fatigue. The prophylactic use of ecallantide has not been evaluated in a RCT to date.

Icatibant. Icatibant (Firazyr®) is a selective bradykinin B₂ receptor antagonist. Activation of the B₂ receptor by bradykinin results in localized swelling, inflammation, and pain; and is thought to be an essential pathophysiological component of acute HAE attacks. Icatibant, therefore, inhibits the action of bradykinin and prevents the angioedema associated with HAE. Its effectiveness in the treatment of acute HAE attacks has been studied in 3 RCTs – 2 placebo-controlled and 1 active-controlled (tranexamic acid 3 mg) – totaling 228 patients.^{3,14} Versus placebo, icatibant has demonstrated a significant reduction in subject-assessed time to 50% reduction in symptom severity (2.0 hours vs. 19.8 hours; P<0.001).¹⁴ In the FAST-1 trial by Cicardi et al., icatibant **did not achieve statistical difference versus placebo in median time to clinically significant relief of index symptoms (2.5 hours vs. 4.6 hours; P=0.14).** Through post-hoc analysis, the authors proposed that the use of rescue medication in the placebo group may have skewed the results in favor of placebo.³ In the FAST-2 trial, icatibant demonstrated significant difference versus tranexamic acid in the primary endpoint of median time to clinically significant relief of index symptom (2.0 hours vs. 12.0 hours; P<0.001). Moreover, the proportion of patients reaching this endpoint in 4 hours was also statistically different between groups (80% vs. 31%; P<0.001; NNT=2.04).³

Overall, adverse events with icatibant occur more frequently than with other HAE treatment options. In the trials, 97% of patients experienced an injection site reaction with icatibant. Pyrexia and dizziness, in much smaller event rates, were also frequent. The prophylactic use of icatibant has not been evaluated in a RCT to date.

Summary of Evidence. As of **June 2014**, no systematic review or meta-analysis of the data for these agents has made its way to the medical literature. Furthermore, due to the discrepancy in efficacy endpoints across trials for these agents, indirect comparison is not feasible. No head-to-head trials for any of these agents are available.

For prevention of HAE attacks, the data lie with Cinryze®, as it is the only agent that has been subjected to at least one rigorous study and demonstrated a statistically significant difference versus placebo.

For treatment of acute HAE attacks, all three agents appear to be efficacious to some extent. Most of the data are with Berinert®, although Kalbitor® and Firazyr® have demonstrated superiority over placebo and active-control, respectively. Based on side effect profiles, it would appear that Berinert® and Kalbitor® would be preferable to Firazyr®, as adverse events were not reported as commonly for the former two than for the latter. Nevertheless, there is no difference in life-threatening or otherwise detrimental adverse effects among the three, so grounds for a formal preference are not judged to exist. **(Based on the FAST-1 and -2 trials, icatibant was not superior to placebo (FAST-1) but was better than tranexamic acid (FAST-2). Indirectly, tranexamic acid showed a longer recovery than did placebo which would lead me (Jill) to avoid TE in favor of placebo and not necessarily towards icatibant. The place in therapy of icatibant for HAE and leading to an endpoint has not been sufficiently established.)**

The following 2 pages contain tables within which pertinent data for the trials discussed herein are presented.

Study	Design	Duration	No. of pts	Ages	Inclusion criteria	Exclusion criteria	Dosing	1 st outcome measured	Other outcomes measured	1 st Results	Other Results	NNT
Beriner[®] (Human C1 Inhibitor)												
Bakhtiar et al. 2012 (Treatment)	RCT	unknown	?	?	HAE	unknown	50-100u/kg	aPTT; levels of: prothrombin fragment 1+2, thrombin-antithrombin complex, D-dimer, plasmin-antiplasmin	unknown	prolonged aPTT	?	?
Craig et al. 2009 (Treatment)	PC, DB	12 weeks post-attack	125	6-72	type I or II HAE, 26 y/o, attack within 5 hrs	acquired AE, tx with FFP, habitual use of narcotics	10 - 20 u/kg	Time from start of tx to onset of symptom relief	Proportion of pts with worsened intensity of HAE symptoms	20:0.5h, 10:1.2h, P: 1.5h (p=0.0025, NS)	20:4.7%, P: 31.0% (p=0.0014)	3.8
Craig et al. 2011 (Treatment)	OLE of Craig et al. 2009	24 months	57, 1085 attacks	10-53	Prior enrollment in Craig et al. 2009	Non-enrollment in Craig et al. 2009	20 u/kg	Time from start of tx to onset of symptom relief	Pr-reported time to complete resolution of HAE symptoms	0.46h	15.5h	N/A
Waytes et al. 1996- Prophylaxis arm	R, PC	Two 17-d periods sep. by 3 wks	6	?	Dx of HAE w/Cl < 30%, > 5 HAE attacks in prev. yr, lack of response to SOT	?	25 u/kg	Functional C1 levels	C4 levels	2h post-infusion, no difference	2h post-infusion, no difference	N/A
Kunschak et al. 1998 (Treatment)	R, DB, PC, ITT	at least 12 mos.	22	15-60	HAE w/Cl < 30%, > 5 HAE attacks in prev. yr, lack of response to androgens	concurrent androgen therapy, drug abuse	25 u/kg	Time from start of tx to onset of symptom relief	Pr-reported time to complete resolution of HAE symptoms	T: 7.62h, P: 15.35h (p=0.007)	T: 23.98h, P: 34.58h (p=0.09)	N/A
Zuraw et al. 2010 (Treatment)	R, DB, PC	Attack onset + f/u in 3 mos.	70	17-66	HAE, 212 y/o, C1-Inh < 50% of normal	Narcotic/anti-emitic use	50, 100 u/kg	Time from start of tx to onset of symptom relief	Time to VAS < 20 mm for defining site	100: 66m, 50: 122m, P: 495m (p<0.001 and p=0.013)	100: 266m, 50: 247m, P: 1210m (p<0.001 and P=0.001)	N/A
Hofstra et al. 2011 (Treatment study)	OL	10-15 attacks	9-18 attacks	25-56	HAE type I or II, age 21-6 yrs, AAE	Pregnancy or lactation, heparin use in prev. 2 days, narc use	1000 units IV w/ in 5h of attack	Time-to-relief	Time-to-resolve	2.0h	21.3h	N/A
Hofstra et al. 2011 (Prophylaxis study)	OL	16 weeks	6, 31 attacks	31-58	HAE type I or II, age 21-6 yrs, AAE, prophylactic AE therapy	Pregnancy or lactation, heparin use in prev. 2 days, narc use	1000 units Q5-7 days	number, type, duration, severity of attacks	extra doses of C1-inh	31 attacks, 10 severe, 16 moderate, 3 mild, 2 unknown	29 extra doses	N/A
Cynryze[®] (Nanofiltered Human C1 Inhibitor)												
Zuraw et al. 2010 (Treatment Study)	R, PC, DB	Attack onset + f/u in 3 mos.	71 (68 in ITT)	36.2 avg.	HAE (low C4, normal C1q, low CI), ≥ 6 y/o	low C1q, h/o B-cell cancer, anti-C1Ab, pregnancy, narc addition	1000 units	Time from administration to unequivocal relief of sx at defining site	% of pts with onset of unequivocal relief within 4h of tx	T: 2h, P: >4h (p=0.02)	T: 60%, P: 43% (p=0.06)	5.89
Zuraw et al. 2010 (Prophylaxis Study)	R, DB, crossover	24 weeks (crossover)	24	34.5 avg.	HAE (low C4, normal C1q, low CI), ≥ 6 y/o	low C1q, h/o B-cell cancer, anti-C1Ab, pregnancy, narc addition	1000 units Q3-4 days	number of HAE attacks during tx period	Average severity, duration of attacks, # of OL inj. of C1inh, # days of swelling	T: 6.26, P: 12.73 (p<0.001)	# of pts req. OL inj. of C1inh = T: 11 (50%), P: 22 (100%)	2

Study	Design	Duration	No. of pts	Ages	Inclusion criteria	Exclusion criteria	Dosing	1 ^o outcome measured	Other outcomes measured	1 ^o Results	Other Results
Kalbitor® (Kallikrein Inhibitor)											
Leyv et al. EDEM44 (treatment)	R, DB, PC, ITT	7 days after attack	96	37.5 avg.	HAE, ≥10 y/o	?	30 mg SC	Change from baseline in MSCS score 4h after dosing	TOS 4h after dosing; proportion of pts achieving TOS	T: -0.8, P: -0.4 (P=0.01)	T: 44%, P: 21% (P=0.02)
Schneider et al. 2007 (treatment)	R, DB, PC	4 weeks after infusion	48	?	HAE, ≥10 y/o	Serious illness, concurrent infection, SCR > 10% ULN, LFTs 2 2X ULN, pregnant or breast-feeding	5, 10, 20, 40 mg/m ² IV	% of pts reporting significant improvement at 4h after drug administration	none	T: 72.5%, P: 25.0% (P=0.0169)	Time to beginning of improvement: T: 30.5min, P: 71.5min
Sheffer et al. 2011 (treatment)	R, DB, PC	?	72	?	?	?	30 mg SC	TOS 4h after drug administration	Change from baseline in MSCS score 4h after dosing	?	?
Cicardi et al. 2010 (treatment)	R, DB, PC	90 days after attack	160	35.4 avg.	HAE, ≥10 y/o	pregnancy, breast-feeding	30 mg SC	TOS 4h after drug administration	Change from baseline in MSCS score 4h after dosing	T: 50.0, P: 0.0 (P=0.004)	T: 165.0min, P: >24h min (P=0.14)
Firazyr® (Selective Bradykinin B₂ Receptor Antagonist)											
Lumry et al. 2011 (treatment)	R, DB, PC	attack onset + f/u for 24 weeks	98	36 avg.	HAE, ≥18 y/o, CI-1 inh <50% of normal	eMaterials (not included in trial)	30 mg SC	Subject-assessed time to 50% reduction in symptom severity by VAS	Median time to onset of primary symptom relief, etc.	T: 2.0h, P: 19.8h (P<0.001)	T: 1.5h, P: 18.5h (P < 0.001)
Cicardi et al. FAST-1 (treatment)	R, DB, PC	attack onset + f/u for 24 weeks	56	34 avg.	HAE, ≥18 y/o, CI-1 inh <50% of normal	Dx other than HAE concomitant illness, pregnancy or lactation	30 mg SC	Median time to clinically significant relief of index symptom	Proportion of pts reaching 1 ^o endpoint in 4 hrs	T: 2.5h, P: 4.6h (P=0.14)	T: 67%, P: 46% (P=0.18)
Cicardi et al. FAST-2 (treatment)	R, DB, AC	attack onset + f/u for 24 weeks	74	40 avg.	HAE, ≥18 y/o, CI-1 inh <50% of normal	Dx other than HAE type I or II, serious concomitant illness, pregnancy or lactation	T: 30 mg SC, P: tran-examic acid 3 mg X 2d	Median time to clinically significant relief of index symptom	Proportion of pts reaching 1 ^o endpoint in 4 hrs	T: 2.0h, P: 12.0h (P<0.001)	T: 80%, P: 31% (P<0.001)

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Ramucirumab (Cyramza)

-Recombinant monoclonal antibody that binds to and blocks activation of vascular endothelial growth factor receptor-2.

-FDA approved for use as a single agent for the treatment of patients with advanced or metastatic, gastric or gastroesophageal junction adenocarcinoma with disease progression on or after prior treatment with fluoropyrimidine- or platinum-containing chemotherapy.

-No standard options for 2nd line therapy. Regimen chosen based on prior therapy received and performance status.

-Preferred 2nd line agents (per NCCN):

Docetaxel
Irinotecan
Paclitaxel

-Patients (n=66) treated with docetaxel OR irinotecan had improved OS compared with best supportive care (5.3 vs. 3.8 mo; P=0.007). Response rate 11% (all partial responses).¹

-Paclitaxel similar efficacy to irinotecan²

	Ramucirumab vs. placebo³ (n=355)	Ramucirumab + paclitaxel vs. paclitaxel alone (n=665) [abstract data only]⁴
Patients	-Gastric or gastro-esophageal junction adenocarcinoma -Metastatic/unresectable, locally recurrent disease -progression of disease after first line therapy -ECOG 0-1	-Gastric or gastro-esophageal junction adenocarcinoma -Metastatic/unresectable, locally recurrent disease -progression of disease after first line therapy
Dosing	8 mg/kg IV q2w until disease progression or unacceptable toxicity	Ramucirumab: same as monotherapy trial Paclitaxel: 80 mg/m ² weekly (3 weeks on, 1 week of)
Overall survival (primary)	5.2 vs 3.8 mo [HR 0.776, 95% CI 0.603-0.998; p=0.047]	9.63 vs. 7.36 mo [HR 0.807, 95% CI 0.678-0.962; p=0.0169]
PFS	2.1 vs. 1.3 mo [HR 0.483, 95% CI 0.376-0.620; p<0.0001]	4.4 vs. 2.86 mo [HR 0.635, 95% CI 0.536-0.752; p<0.0001]
Response rate	Complete response: <1% vs. 0% Partial response: 3% vs. 3% Stable disease: 45% vs. 21%	Overall response rate: 28% vs. 16%
Median duration of tx	8 weeks vs. 6 weeks	Not reported
Quality of Life at 6 weeks	Improved QOL: 10% vs. 4% Stable QOL: 24% vs. 9% Worsened QOL: 12% vs. 9%	Not reported
Toxicities	Hypertension: 16% vs. 8% Grade 3 or higher AE: 57% vs. 58%	-More hypertension in combination group. -More neutropenia in combination group, but similar rates of febrile neutropenia between groups.

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Ceritinib (Zykadia)

-Oral inhibitor of ALK (anaplastic lymphoma kinase) tyrosine kinase

-FDA approved for use as a single agent for treatment of ALK-positive metastatic non-small cell lung cancer (NSCLC) who have progressed on or are intolerant to crizotinib

-Ceritinib given accelerated approval based on tumor response and duration of response

-2-7% of NSCLC patients are ALK positive (usually adenocarcinoma histology, never smoker, male, younger)

-For metastatic, ALK-positive NSCLC, crizotinib is recommended for first-line therapy. Second line therapy options (before ceritinib available) included chemotherapy.

-Standard second line chemotherapy

*pemetrexed or docetaxel monotherapy: in second-line setting for ALK negative patients, response rate <10%; median survival ~8 mo; median progression free survival ~3 mo¹

-May also use platinum doublet that is used in first line setting for ALK negative patients

*cisplatin or carboplatin plus another agent

	Ceritinib n=163 [data taken from PI and FDA medical review]^{2,3}
Patients	-ALK-positive NSCLC -progressed on crizotinib or intolerant to crizotinib -ECOG performance status 2 or less
Dosing	750 mg PO once daily
Overall survival	Median not reached
PFS (median)	6.74 mo
Response rate	<u>Investigator assessment:</u> Overall: 54.6 (partial 53.4%) Duration of response(median): 7.4 mo <u>Independent reviewer assessment:</u> Overall: 43.6% (partial 41.1%) Duration of response(median): 7.1 mo
Time to response	6.1 WEEKS

References:

1. Hanna N et al. J Clin Oncol 22:1589-1597.
2. Zykadia [package insert] East Hanover, NJ Novartis;2014. www.accessdata.fda.gov. Accessed July 3, 2014.
3. FDA Medical review. www.accessdata.fda.gov. Accessed July 3, 2014.

Xalkori (crizotinib)

- Oral inhibitor of ALK (anaplastic lymphoma kinase) tyrosine kinase
- FDA approved (accelerated approval) for ALK-positive non-small cell lung cancer, metastatic
- For metastatic, ALK-positive NSCLC, crizotinib is recommended for first-line therapy.

	Crizotinib
Current PA Criteria	-Locally advanced or metastatic non small cell lung cancer -ALK positive as detected by FDA approved test -ECOG 0-3 or Karnofsky score >60
Dosing	250mg BID AWP (\$239.7 per unit)
Overall survival	No significant improvement with crizotinib as compared with chemotherapy. Confounded by the high crossover rate.
PFS (median)	7.7 months vs 3.0 months in the chemo group (p<0.001)
NICE (national institute for Health Care and Excellence) Recommendation:	"Crizotinib does not provide enough benefit to patients to justify its high cost"
QALY analysis form Journal of clinical oncology:	"Among patients with known EML4-ALK-positive advanced NSCLC first line crizotinib therapy provided 0.379 additional QALY's cost an additional \$95,043 compared with standard care and produced an ICER of \$250,632 per QALY gained. The major driver of cost effectiveness was drug price"

Shaw, Alice T et al. *Crizotinib versus Chemotherapy in Advanced ALK Positive Lung Cancer*. New England Journal of Medicine 368;25. June 2013

Djalalov, S. et al. *Cost effectiveness of EML4-ALK Fusion Testing and First-Line Crizotinib Treatment for Patients with Advanced ALK-Positive Non-Small-Cell Lung Cancer*. Journal of Clinical Oncology. Vol 32, Number 10. April 2014

Revised Reference Pricing 2015

For the premium plan (the pharmacy copay plan) the amount a member pays for drugs labeled as “reference priced” will not be allocated to the out-of-pocket maximum. For example, if the plan pays \$0.30 per pill for a referenced price drug and the drug cost is \$4.00 per pill, or \$120 per month, the plan will pay \$9 for the month supply and the member will be required to pay the remaining \$111. The \$111 is considered a non-covered benefit. The non-covered benefit amount (\$111) will not be applied to the member’s OOP maximum (ie; deductible or coinsurance limits).

For the classic and basic plans (the pharmacy coinsurance plans) medications listed as reference priced are considered a non-covered benefit and the member will pay the entire cost of the medication. This amount will not count towards the member’s OOP maximum (ie; deductible or coinsurance limits). Members will still have the option of the covered Tier 1 generic alternative(s) or to appeal to EBRx for coverage.

	Tier 1	Tier 2	Tier 3	Tier 4
Antihyperlipidemic-HMG (Statins)	atorvastatin, lovastatin, pravastatin, simvastatin	Crestor 40mg*(PA)		
	*(RP) Reference Priced Antihyperlipidemic-HMG (Statins): Plan pays \$0.30 per unit. Member is responsible for remaining cost.	Altoprev, Crestor 5mg, crestor 10mg, Crestor 20mg Lescol, Lescol XL, Lipitor, Mevacor, Pravachol, Zocor		
Angiotensin II Rec Antagonist (ARB)/Direct Renin Inhibitor (DRI)	losartan/HCTZ, irbesartan/HCTZ, valsartan/HCTZ, irbesartan, losartan			
	(RP) Reference Priced Angiotensin Receptor Blockers (ARB): Plan pays \$0.81 per unit. Member is responsible for remaining cost.	Amturnide, Atacand, candesartan(NG) , Atacand HCT, candesartan cilexetil/HCTZ, Avalide, Avapro, Azor, Benicar, Benicar HCT, Cozaar, Diovan, Diovan HCT, Edarbi, Edarbyclor, Exforge, Exforge HCT, Hyzaar, Micardis, telmisartan*(NG) , Micardis HCT, Tekturna, Tekturna HCT, Teveten, Teveten HCT, Twynsta, telmisartan/amlodipine*(NG)		

Antidepressant (SNRIs)	venlafaxine, venlafaxine XR capsule			
	*(RP) Serotonin norepinephrine reuptake inhibitors (SNRIs): Plan pays \$0.75 per unit. Member is responsible for remaining cost.	Cymbalta, duloxetine, Effexor XR, venlafaxine extended release tablets		
Antidepressants (SSRIs)	sertraline, fluoxetine, paroxetine, citalopram, fluvoxamine			
	*(RP) Selective serotonin reuptake inhibitors (SSRIs): Plan pays \$0.30 per unit. Member is responsible for remaining cost.	Lexapro, escitalopram, Luvox CR, fluvoxamine ER, Paxil ER, paroxetine ER, Pexeva		
Sedative Hypnotics	temazepam 15mg, temazepam 30mg, triazolam, zolpidem			
	*(RP) Reference Priced Sedatives/Hypnotics: Plan pays \$0.15 per unit. Member is responsible for remaining cost.	Ambien, Ambien CR, zolpidem ER, Lunesta, Rozerem, Sonata, zaleplon, temazepam 7.5mg, temazepam 22.5mg		
Proton Pump Inhibitors	omeprazole 10mg, omeprazole 20mg, omeprazole 40mg, pantoprazole 20 & 40 mg		Zegerid powder packets	
	*(RP) Reference Priced Proton Pump Inhibitors: Plan pays \$0.30 per unit. Member is responsible for remaining cost.	Aciphex, Dexilant, lansoprazole, Nexium, omeprazole/sodium bicarb capsule, Prevacid, Prevacid 24hr <i>OTC</i> , Prilosec, Prilosec <i>OTC</i> , omeprazole <i>OTC</i> , Protonix, Zegerid capsule		
Overactive Bladder Agents	oxybutynin immediate release			
	*(RP) Reference Priced Overactive Bladder Agents: Plan pays \$0.51 per unit. Member is responsible for remaining cost.	Detrol, tolterodine, Detrol LA, tolterodine (extended release), Ditropan, Ditropan XL, Enablex, Sanctura, trospium, Sanctura XR, trospium ER, Vesicare, oxybutynin extended release		

	azelastine, flunisolide, fluticasone			
Nasal Products	*(RP) Reference Priced Nasal Steroids: Plan pays up to \$26.00 for a one month supply. Member is responsible for remaining cost.	Beconase, Beconase AQ, Flonase, Nasonex, mometasone, Nasacort AQ, triamcinolone, Rhinocort AQ, budesonide		
ADHD Medications	amphetamine salts*(QL), dextroamphetamine*(QL), methylphenidate*(QL), methylphenidate ER*(QL), modafinil*(PA)*(QL), pemoline*(QL), amphetamine - dextroamphetamine SR*(QL)	Nuvigil*(PA, QL), Strattera*(QL)	Adderall XR*(QL), Concerta*(QL), Daytrana*(QL), Dexedrine*(QL), Focalin*(QL), Focalin-XR*(QL), Metadate CD*(QL), ER*(QL), Provigil* (PA), Ritalin Tablet, LA*(QL), SR, Vyvanse*(QL)	
	*(RP) Long Acting Amphetamines: Plan pays \$2.50 per unit. Member is responsible for remaining cost.	Long Acting Amphetamines are reference priced for members 26 years of age or older; *Quantity Limits will still apply to reference priced long acting amphetamines. Adderall XR*(QL), amphetamine salts*(QL) extended release, Dexedrine*(QL), dextroamphetamine*(QL) extended release, Vyvanse*(QL)		
Fibromyalgia	gabapentin			
	*(RP) Fibromyalgia agents: Plan pays \$0.35 per unit. Member is responsible for remaining cost.	Lyrica		
Osteoporosis- Calcium Regulators	alendronate, calcitonin nasal spray	Miacalcin Injection		Forteo*(PA)
	*(RP) Reference Priced Calcium Regulators: Plan pays up to \$0.10 per pill/unit. Member is responsible for remaining cost.	Actonel, Atelvia, Boniva, ibandronate		

DUEC Materials
Jill Johnson, Pharm.D., BCPS
UAMS College of Pharmacy

August 4, 2014

Hepatitis C
EBRx Prior Authorization Criteria
7/18/2014—PRELIMINARY, revised
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 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)	These patients were excluded from the clinical trials.
6. Cirrhosis must be shown by liver biopsy and be metavir score F3 or F4. Alternatively, the FIB-4 score or the APRI score will suffice for stating cirrhosis in lieu of liver biopsy. (Holmberg SD, et al. Clinical Infectious Diseases 2013;57(2):240-6)	

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

GT1	Sofosbuvir	Simeprevir
GT1 treatment naïve, noncirrhosis, interferon eligible	Not covered. No comparative data with other triple therapy. Other triple therapy is available.	Not covered. No comparative data with other triple therapy. Other triple therapy is available.
	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.	Boceprevir & telaprevir triple therapy is effective. Unknown which of the 3 is more effective. Must have Q80K negativity for simeprevir. QUEST-1 & -2.

	Sofosbuvir: Study 1910. In HIV+ population showed sofosPR is effective. Lawitz, Lalezari, et al. Comparative sofosbuvirPR vs PR trial. 0% cirrhotics. High PR response rate. Lepidasvir+sofos. Afdhal, et al. Ledipasvir+sofos has efficacy. No SOC control arm.	
GT1 treatment naïve, noncirrhosis, interferon-INeligible	Not covered. Await newer therapies.	Not covered. Await newer therapies.
	Sofosbuvir: PHOTON-1 (via PI) showed sofos +R to be effective. No control arms. Lepidasvir+sofos. Afdhal, et al. Ledipasvir+sofos has efficacy. No SOC control arm.	
GT1 treatment naïve, compensated cirrhosis <u>AND</u> listed for liver transplant, interferon-eligible	Covered for 12 w combined w/ PR. Basis: shorter duration for stage 4 cirrhotics than other triple therapies.	Not covered.
GT1 treatment naïve, compensated cirrhosis BUT NOT listed for liver transplant, interferon-eligible	Not covered. Other triple therapy is available.	Not covered. Other triple therapy is available.
	Boceprevir: Poordad, et al, showed BPR was effective. Had 7-11% cirrhotics. Telaprevir: Jacobson, et al. showed telaprevir is effective. Had 6-7% cirrhotics. NEUTRINO Lepidasvir+sofos. Afdhal, et al. Ledipasvir+sofos has efficacy. No SOC control arm. Had 16% cirrhotics.	QUEST-1 & -2. Had up to 10% cirrhotics. Unknown which of the 3 DAAs is more effective. Must have Q80K negativity for simeprevir. Boceprevir: Poordad, et al, showed BPR was effective. Had 7-11% cirrhotics. Telaprevir: Jacobson, et al. showed telaprevir is effective. Had 6-7% cirrhotics.
GT1 treatment naïve, compensated cirrhosis, interferon-INeligible	Not covered.	Not covered.
	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.	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 Prior nonresponders to PR, noncirrhosis	Not covered. No comparative data with other triple therapy. Other triple therapy is available.	Not covered. No comparative data with other triple therapy. Other triple therapy is available.
	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. Still investigational.	From PI: PROMISE showed simeprevir works better than PR. No comparisons to triple tx.
GT1 Prior nonresponders to PR, cirrhosis	Not covered.	Not covered.
		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)
GT1 Prior nonresponder to BPR or TPR, noncirrhosis	Not covered. Time for other emerging regimens and to await further evidence in this population	Not covered.
		No data.
GT1 Prior relapsers after PR, noncirrhosis	Not covered. No comparative data with other triple therapy. Other triple therapy is available.	Not covered. No comparative data with other triple therapy. Other triple therapy is available.
GT1 Prior relapsers after PR, compensated cirrhosis	Not covered. Other therapy is covered.	Not covered. PR4BPR32 is effective.
	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.
GT1, treatment experienced, coinfectd w/ HIV	Not covered.	Not covered.
	No data.	No data.
GT2		
GT2 treatment naïve, with or w/o compensated cirrhosis	Not covered.	Not covered.
	FISSION (GT2, tx-naïve) compared SR12 to PR24 but used higher R dose in the SR12 group, creating a confounder where we can't tell if it was a function of the R dose. Previous data (Osinusi a, et al. Jama 2013;310(8):804-11, showed R dose matters. PHOTON (HIV+ population) provides evidence of efficacy; n=26), however, it did not have a control arm to compare to. Unknown whether PR if more effective.	
GT2 treatment(PR)-experienced	Covered with ribavirin for 12 weeks	Not covered.
	FUSION (19% of included pts) showed efficacy. No comparative arm. VALENCE (although Valence became a descriptive trial only after a mid-trial protocol amendment.)	
GT2 treatment naïve, unable to take interferon, noncirrhotic	Not covered. Time to await emerging drugs.	Not covered.

	FUSION (19% of included pts) showed efficacy. POSITRON (all w/ inability to take interferon) showed SR12 effective. Nothing to compare to.	
GT2 treatment naïve, unable to take interferon, compensated cirrhotic	Covered with ribavirin for 12 weeks.	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		
GT3 treatment naïve, with or without compensated cirrhosis if able to take interferon	Not covered.	Not covered.
	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.	
GT3 treatment naïve, NONcirrhotic, unable to take interferon	Not covered. Time to await emerging drugs.	Not covered. Time to await emerging drugs.
	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.	
GT3 treatment-experienced, compensated cirrhosis, interferon INeligible	Covered with ribavirin X24 weeks	Not covered.
	FUSION & POSITRON; the alternative is PR and these patients are either interferon-experienced or ineligible for it.	
GT4		
GT4, interferon eligible, treatment naïve, NONcirrhotics	Not covered. Await emerging drugs	Smeprevir with PR is NOT covered.
	NEUTRINO showed 96% for GT4, however, noncirrhotics have time to await emerging drugs.	
GT4, interferon eligible, treatment naïve, compensated cirrhosis	Cover with PR X12w.	NA
	NEUTRINO. Not as much time to wait.	
GT4, interferon ineligible	Not covered.	Not covered.
	Evidence is in abstract form only from April 2014 EASL meeting. Ruane PJ, et al.	Awaiting trial results per AASLD guidelines.
GT5		
GT5	Not covered.	Not covered.
	NEUTRINO included an N=1 GT5 patient.	
GT6		

GT6	Not covered.	Not covered.
	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

***Cirrhosis refers to F3 or F4 and requires a liver biopsy or APRI or FIB-4 test.

Second Review of Drugs
Armodafinil (Nuvigil)
Jill Johnson, Pharm.D. , BCPS
8/4/14

Currently EBD covers modafinil and armodafinil with prior authorization:

Provigil 200mg per day max/ Nuvigil 250mg per day max:

- | |
|--|
| <ol style="list-style-type: none">1. Must have diagnosis of one of the following:<ol style="list-style-type: none">1. Narcolepsy diagnosed by sleep specialist or neurologist2. Adjunctive treatment of obstructive sleep apnea/hypopnea syndrome and compliant on CPAP3. Shift work sleep disorder4. Fatigue related to multiple sclerosis5. Excessive daytime sleepiness for Parkinson's Disease |
|--|

If any of the above criteria are met, approve PA for 1 year.

As of 7/10/14, one article (Ann Surg 2012;255:222-227) on hypersomnia in a group of physicians showed no improvement in the performance of basic procedural tasks or in tests of clinical psychomotor performance. In all patients a review of current medications should be reviewed for the possibility of eliminating the causative drugs (sedatives, anticholinergic drugs) before adding additional medications.

Proposal: Continue with the above listed PA criteria for EBD.

Dolutegravir (Tivicay)
DUEC Re-review
Jill Johnson, Pharm.D., BCPS
8/4/14

Currently: EBD prior authorizes dolutegravir.

Proposal: Remove PA on dolutegravir based on an article that supports better virologic activity than raltegravir in treatment experienced patients. (Cahn P, Posniak AL, Mingrone H, Shuldyakov A, et al. Dolutegravir versus raltegravir in antiretroviral-experienced, integrase-inhibitor-naive adults with HIV: week 48 results from the randomised, double-blind, non-inferiority SAILING study. Lancet 2013; 382: 700-08.) Also the latest guidelines from the NIH.gov on initial antiretroviral regimens recommends it first-line together with abacavir+lamivudine or with tenofovir+emtricitabine as an option if starting an integrase inhibitor as first-line therapy. Many physicians will NOT start here and give NNRTI-based or PI-based therapy as first line therapy. However, the NIH recommends it amongst 1st line therapy.

EBD New Drugs 3/17/14 through
05/31/2014

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	EBRx NOTES	DUEC VOTE	DUEC DATE	IB VOTE	IB DATE	Connie Notes
AVEED inj 750mg/3ml	TESTOSTERONE UNDECANOATE	\$990/750mg	Testosterone undecanoate IM injection in oil for treatment of low testosterone. Dose 750mg IM given at initiation of therapy, at 4 weeks, then every 10 weeks thereafter	Testosterone cypionate 200mg/ml(\$23) and testosterone enanthate 200mg/ml(\$17) . Dose = 50-400mg IM every 2-4 weeks	Exclude, 13	8/4/14				Catamaran requires the patient to be free of any contraindications to therapy, and confirmation of diagnosis by a low-for-age serum testosterone level
HETLIOZ 20MG CAPS (SPECIALTY DRUG)	tasimelteon	\$8,432/30 days	Treatment of non-24-hour sleep wake disorder. Dose: 20mg daily prior to bedtime.	none	Exclude, 13	8/4/14				Catamaran PA/QL requires verification of FDA-approved indication and the presence of total blindness. QL of 1/day
XARTEMIS XR TABS 7.5 325MG	oxycodone w/acetaminophen controlled release tablet 7.5-325mg	\$2.76/tab	New formulation of oxycodone/acetaminophen in an extended release tablet for moderate/severe pain	immediate release oxycodone/acetaminophen tab = \$1 or less (Tier 1) Percoet (tier 3) - \$8.99/tab	Exclude, 13	8/4/14				
ORENITRAM TABS (SPECIALTY DRUG)	treprostinil diolamine controlled release tab	\$7,020/60 - 2.5mg tabs	Extended release formulation of treprostinil for the treatment of pulmonary arterial hypertension. Dose = 0.25mg by mouth two times a day and increase by 0.25mg or 0.5mg every 3-4 days, as tolerated to achieve optimal response	Other oral specialty drugs for PAH and AWP for 30 day supply: Adcirca 40mg/day=\$2,278; Adempas 2.5mg tid = \$9,000; Letairis 10mg/d=\$8,271; Revatio 20mg tid=\$2,750; Tracleer 250mg/day=\$8,874	Exclude due to failure to reach the 41.8m threshold for improvement in 6MWT. Please see handout.	8/4/14				
OTEZLA TABS (SPECIALTY DRUG)	apremilast	\$2,250/60 tabs	Treatment of adults with active psoriatic arthritis. Dose=30mg orally twice a day	Other specialty drugs for psoriatic arthritis administered by subcutaneous injection and AWP/month: Humira 40mg every other week=\$3,002; Enbrel 50mg weekly=\$3,092. Remicade given by IV infusion every 8 weeks is based on weight (5mg/kg) =\$1,061/100mg vial	T4PA, Criteria prior use of 2 DMARDs w/ inadequate response, not to be used with biologic (until trial data available) HTH trial pending vs biologic.	8/4/14				GPI 6670001500B720 - Otezla Starter Pak. Catamaran PA requires use in adult patients with active psoriatic arthritis. Requires trial or inadequate response, contraindication or intolerance to methotrexate.
MYALEPT INJ 11.3MG (metreleptin)(SPECIALTY Drug)	metreleptin	1 vial = \$1,766	Subcutaneous injection as an adjunct to diet as replacement therapy to treat the complications of leptin deficiency in patients with congenital or acquired generalized lipodystrophy. Dose: once daily subcutaneous injection which is dosed based on body weight and gender in both adult and pediatric populations.	none- MYALEPT is the first drug approved for the treatment of metabolic abnormalities associated with lipodystrophy in combination with dietary modification.	Exclude. The only measured outcomes to date are A1C, fasting glucose, and TGs. Administered daily or bid SC. The safety and effectiveness of Myalept, an analog of leptin made through recombinant DNA technology, were evaluated in an open-label, single-arm study that included 48 patients with congenital or acquired generalized lipodystrophy who also had diabetes mellitus, hypertriglyceridemia, and/or elevated levels of fasting insulin. The trial showed reductions in HbA1c (a measure of blood sugar control), fasting glucose, and triglycerides. Anti-drug antibodies with neutralizing activity to leptin and/or Myalept may develop, which could result in severe infections or loss of treatment effectiveness. T-cell lymphoma has been reported in patients with acquired generalized lipodystrophy, both treated and not treated with Myalept, so healthcare professionals should carefully consider the benefits and risks of treatment with Myalept in patients with significant hematologic abnormalities and/or acquired generalized lipodystrophy. Myalept is contraindicated in patients with general	8/4/14				Lipodystrophy is an orphan disease, and it is estimated that only a few thousand patients in the world have this disease, although robust epidemiologic data is not available. Usually diagnosed within early childhood or adolescence. Catamaran PA requires use in patients with congenital or acquired generalized lipodystrophy. In addition to the FDA-approved indication the program requires the patient have a metabolic abnormality that is refractory to current standards of care for lipid and diabetic management, and prescription written by or in consultation with an endocrinologist.
HEMANGEOL SOLN 4.25mg/ml (propranolol oral soln)	propranolol hcl solution	\$450/120ml	Alcohol free, paraben free and sugar free oral solution of propranolol indicated for the treatment of proliferating infantile hemangioma requiring systemic therapy.	First and only pediatric formulation of propranolol	Exclude, Code 13. Generic propranolol solution with 0.6% alcohol was not thought to amount to a clinical difference vs a 0.5% generic solution considering the volume, per EBRx medical director.	8/4/14				

ZENZEDI (dextroamphetamine sulfate 15, 20, 30mg)	dextroamphetamine sulfate	\$5.95/tab	new table formulation with 2 new strengths of dextroamphetamine	Other ZENZEDI strengths excluded by plan. Generic dextroamphetamine range from \$1 - \$2 per tablet	exclude unless cost is a factor and there is a benefit to having this. Otherwise, the 5 and 10mg generic IR tabs are available and are MAC'd.	8/4/14				
Q-tabs 1mg (levomefolate glucosamine tab 1mg (folate equivalent)	levomefolate glucosamine 1mg (folate equivalent)	\$4.64/tab	folic acid, vitamin B9	Folic acid 1mg tabs < \$0.05/tab(tier 1)	Exclude, code 13	8/4/14				
SITAVIG 50MG buccal tab (acyclovir)	acyclovir buccal tablet		Treatment of recurrent herpes labialis (cold sores) in immunocompetent adults. 50mg buccal tablet as a single-dose to the upper gum.	No other buccal tabs. Other generic tier 1 formulary products: acyclovir 400mg tid x 10 days/\$71;famciclovir 250mg tid x10 days/\$189;valacyclovir 2gm x 2 doses/\$58	Exclude, code 13. Their use for oral cold sores reduced the duration of outbreak by 1/2 day vs placebo. No comparisons against active drug are available.	8/4/14				Recommend a quantity limit of 2 tabs/30 days for treatment up to 2 episodes per month.
ZONTIVITY TABS (vorapaxar)	vorapaxar sulfate	\$320/30 days	To reduce the risk of heart attack, stroke, cardiovascular death, and need for procedures to restore the blood flow to the heart in patients with a previous heart attack or blockages in the arteries to the legs. Dose = 1 tab(2.08mg/day).	Firt-in-class oral PAR-1 inhibitors	Exclude 12, harm outweighs benefit; need way to identify those who stand to benefit without the risk. Handout.	8/4/14				
GRASTEK SUBLING TAB 2800 BAU (SPECIALTY DRUG)	timothy grass pollen allergen extract	\$297/30 days	Sublingual allergen extract for treatment of grass pollen-induced allergic rhinitis with or without conjunctivitis confirmed by positive skin test in in vitro testing for pollen-specific IgE antibodies for Timothy grass or cross-reactive grass pollens. Approved for use in persons 5 through 65. Dose = 1 tab/day First dose given in doctor's office	none	Exclude. Curr Opin Otolaryngol Head Neck Surg 2014, 22:211-215 is a systematic review (June 2014) that shows subcutaneous immunotherapy (SCIT) is better than SLIT for symptom control, rescue med use and AEs in indirect comparisons. SL. Use: Hypersensitivity to Timothy grass or cross-reactive grass pollens (e.g., Sweet Vernal, Orchard, Perennial Rye, Kentucky Blue Grass, Meadow Fescue, and Redtop) should be confirmed by positive skin test or in vitro testing for pollen-specific IgE antibodies prior to administration. Age 5-65. Initiate 12 w prior to grass pollen season; continue for 3 years. Dose is 1 tab (2800 bioequivalent allergy units (BAU)). Also must have 1st dose in the office and have access to epi autoinjector.	8/4/14				Specialty product available through BrivoRx but they may also be obtained through normal distribution channels. Catamaran PA requires use in patients with pollen-induced allergic rhinitis with or without conjunctivitis. Requires patient have no contraindications or exclusions to therapy, prescription is written by or in consultation with an allergist or immunologist, and trial or inadequate response, contraindication or intolerance to an intranasal corticosteroid and an antihistamine. QL 1/day
RAGWITEK SUBLING TABS (ragweed pollen extract) (SPECIALTY DRUG)	short raweed pollen allergen extract	\$297/30 days	Sublingual immunotherapy approved for the treatment of allergic rhinitis with or without conjunctivitis that is induced by short ragweed pollen in adults age 18-65. Dose is 1 tab daily. First dose given in doctor's office	none	Exclude. Curr Opin Otolaryngol Head Neck Surg 2014, 22:211-215 is a systematic review (June 2014) that shows subcutaneous immunotherapy (SCIT) is better than SLIT for symptom control, rescue med use and AEs in indirect comparisons.	8/4/14				Specialty product available through BrivoRx but they may also be obtained through normal distribution channels. Catamaran PA requires use in patients with pollen-induced allergic rhinitis with or without conjunctivitis. Requires patient have no contraindications or exclusions to therapy, prescription is written by or in consultation with an allergist or immunologist, and trial or inadequate response, contraindication or intolerance to an intranasal corticosteroid and an antihistamine. QL 1/day
ORALAIR SL 300 IR (SPECIALTY DRUG)	grass mixed pollen extract	\$360.00 / 30 DAYS	Sublingual allergen extract for treatment of allergic rhinitis (hay fever) with or without conjunctivitis that is induced by certain grass pollens for people 10 through 65 years. First doise given in MD office, where the patient can be oserved for potential adverse reactions. Dose - one tablet daily.	none	Exclude. Curr Opin Otolaryngol Head Neck Surg 2014, 22:211-215 is a systematic review (June 2014) that shows subcutaneous immunotherapy (SCIT) is better than SLIT for symptom control, rescue med use and AEs in indirect comparisons.	8/4/14				Limited distribution product available through specialty pharmacies including BrivoRx. Catamaran PA requires use in patients with pollen-induced allergic rhinitis with or without conjunctivitis. Requires patient have no contraindications or exclusions to therapy, prescription is written by or in consultation with an allergist or immunologist, and trial or inadequate response, contraindication or intolerance to an intranasal corticosteroid and an antihistamine. QL 1/day

ENTYVIO INJ 300MG (SPECIALTY DRUG) - integrin receptor antagonist	vedolizumab	\$5,782/300MG	For adults patients with moderately to severely active ulcerative colitis or Crohn's disease who have had a inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. Dose = 300mg IV at zero, two, and six weeks, then every eight weeks thereafter.	Humira(40mg subq injection every other week/\$3,002;Cimzia 400mg subq injection every 4 weeks/\$3,322. Remicade dose based on weight and administered by IV infusion/\$1062 for 100mg vial. All specialty drugs.	T4PA. (See Handout)	8/4/14				
ESCAVITE D CHEWABLE	pediatric multiple vitamin w/FL-FE		Pediatric multiple vitamins	multiple generics (tier 1)	Exclude, code 7	8/4/14				
PRENA1 CHEWABLE AND REDICHEW RX CHW	prenatal vitamin		Prenatal vitamins	multiple generics (tier 1)	Exclude, code 7	8/4/14				
SELECT-OB CHW	prenatal vitamin		Prenatal vitamins	multiple generics (tier 1)	Exclude, code 7	8/4/14				
						8/4/14				
						8/4/14				
PRODUCTS ADMINISTERED IV						8/4/14				
NITRONAL IV SOLUTION	nitroglycerin	N/A	Not in the scope of pharmacy benefits		Add; may be N/A medical	8/4/14				
						8/4/14				
						8/4/14				
COMPOUNDING KITS						8/4/14				
Vancomycin oral solution compounding kit					May add depending on cost	8/4/14				
Cyclobenzaprine Top Cream compounding kit					Exclude	8/4/14				
Tramadol Cream 8% compounding kit					Exclude	8/4/14				

Aveed (testosterone undecanoate injection)

Labeled Uses: deficiency or absence of endogenous testosterone

Contraindications:

Aveed should not be used in any of the following patients:

- Men with carcinoma of the breast or known or suspected carcinoma of the prostate, hypersensitivity to testosterone or any ingredients, women who are pregnant

Comparators:

Aveed	\$330 per unit (750mg)/10 weeks	10 week supply
Testosterone cypionate (similar to pricing for enanthate ester)	\$59.10-\$118.20/10 weeks	Dose recommended range from 50mg weekly to 200mg q 2 weeks
AndroGel Pump 1.62%	~\$1132.50-\$2038.50/10 week supply	2-4 pumps per day

Esters 50-100mg q week or 100-200q 2 weeks

Oil (Testosterone Cypionate Intramuscular)

100 mg/mL (10 mL): \$59.10

200 mg/mL (10 mL): \$112.85

Oil (Testosterone Enanthate Intramuscular)

200 mg/mL (5 mL): \$84.95

Gel (AndroGel Pump Transdermal)

12.5 MG/ACT (1%) (75 g): \$233.66

20.25 MG/ACT (1.62%) (75 g): \$453.23

Gel (AndroGel Transdermal)

20.25 MG/1.25GM (1.62%) (1.25 g): \$15.16

25 mg/2.5 g (2.5 g): \$15.16

40.5 MG/2.5GM (1.62%) (2.5 g): \$15.58

50 mg/5 g (5 g): \$15.58

Evidence:

Pharmacokinetics and Safety of Long-Acting Testosterone Undecanoate Injections in Hypogonadal Men: An 84-Week Phase III Clinical Trial

Design: multicenter, open-label, US-based study of the efficacy (pharmacokinetics) and safety of treatment with 750 mg TU in 3 mL of castor oil by deep IM injections at week 0 (baseline), week 4, and every 10 weeks thereafter through 9 injections in 130 patients.

Results: C_{trough} averages ranged from 309.6 to 389.8 ng/dL over the 64 weeks. C_{max} mean of 890ng/dL. The most commonly reported AEs were acne (6.2%), injection site pain (5.4%), increase in serum PSA to above 4 ng/mL (5.4%), and increased hemoglobin and hematocrit (2.3%). Two patients died (one of myocardial infarction, the other of cardiac arrest; neither event was judged by the investigator to be at least possibly related to study medication). Total of 37.7% of patients experienced at least one ADE possibly related to treatment.

Christina Wang^{1,*}, Mark Harnett², Adrian S. Dobs³ and Ronald S. Swerdloff.

Pharmacokinetics and Safety of Long-Acting Testosterone Undecanoate Injections in Hypogonadal Men: An 84-Week Phase III Clinical Trial. Journal of Andrology. Volume 31, Issue 5, pages 457–465, September-October.2010

Dosage/Administration:

Inject Aveed deeply into the gluteal muscle following the usual precautions for intramuscular administration

The dose of Aveed is 3 mL (750 mg) injected intramuscularly, followed by 3 mL (750 mg) injected after 4 weeks, then 3 mL (750 mg) injected every 10 weeks thereafter. Must be administered by healthcare professional in a clinic setting. Observation after administration for 30 minutes is required.

Adverse Reactions/Warnings:

Monitor patients with benign prostatic hyperplasia (BPH) for worsening of signs and symptoms of BPH

Exogenous administration of androgens may lead to azoospermia

Edema with or without congestive heart failure may be a complication in patients with preexisting cardiac, renal, or hepatic disease

Sleep apnea may occur in those with risk factors

Monitor prostatic specific antigen (PSA), hemoglobin, hematocrit, and lipid concentrations periodically

The most commonly reported adverse reactions ($\geq 2\%$) are acne, injection site pain, prostatic specific antigen (PSA) increased, estradiol increased, hypogonadism, fatigue, irritability, hemoglobin increased, insomnia, and mood swings

REMS Criteria:

POMS and anaphylaxis: certified healthcare professional must administer

Provider and patient education

30 minute observation after each injection

Recommendation:

PA: Confirmed hypogonadism from 3 separate morning testosterone levels $< 300\text{ng/dL}$ with signs and symptoms.

Hetlioz™ (tasimelteon)
Prepared by: Laken K. Lawrence
UAMS P4 Student Pharmacist, April 2014

Overview¹

Tasimelteon is indicated for the treatment of non-24-hour sleep-wake disorder (non-24). Note that efficacy was established in totally blind patients with non-24-hour sleep-wake disorder. Tasimelteon is indicated for adults. There are no unlabeled uses or contraindications. The comparator drugs are ramelteon (Rozerem®) and non-prescription melatonin.

Dosing and Current Pricing¹

Oral: 20 mg once daily at the same time each night before bedtime

- 20 mg Hetlioz™ oral capsules #30 = \$8423.10
- 8 mg Rozerem® oral tablets #30 = \$251.62

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

Significant Toxicities/ADEs¹

- Headache, ALT increased, nightmare/abnormal dreams, URTI, UTI

Drug Interactions¹

- Strong CYP1A2 inhibitors (e.g., fluvoxamine)
- Strong CYP3A4 inducers (e.g., rifampin)

Supporting Evidence

*Study 1 (full text unavailable, data taken from review article)*²

- SET (safety and efficacy of tasimelteon) trial
- Double-blind, multicenter, placebo controlled, N=84, ages 21-84
- Sponsored by Vanda Pharmaceuticals Inc.
- Randomized to receive 20 mg 1 hour before bedtime (N=42) or placebo (N=42) for 6 months
- Used urinary 6-sulfatoxymelatonin (aMT6s) and cortisol timing to measure for entrainment
- Patients with entrained circadian clock was significantly higher in tasimelteon than placebo (aMT6s, $p = 0.0171$ and cortisol timing $p = 0.0313$)
- Proportion of patients with clinical response (defined as entrainment plus score ≥ 3 on the Non-24 Clinical Response Scale) was significantly higher with patients taking tasimelteon ($p < 0.05$) than placebo
- Significant improvements in the Clinical Global Impression of Change and in the measures of total nighttime sleep, daytime nap duration, and midpoint of sleep timing relative to placebo ($p < 0.05$)
- Further statistical analyses unavailable due to lack of published data

¹ Lexi-Comp Online™, Lexi-Drugs Online™, Hudson, Ohio: Lexi-Comp, Inc.; April 10, 2014.

² Dhillon, S.; Clarke, M. "Tasimelteon: First Global Approval" *Drugs*, 2014, 74, 505-511.

Study 2 (full text unavailable, data taken from review article)²

- RESET (randomized withdrawal study of safety and efficacy of tasimelteon) trial
- Double-blind, multicenter, placebo controlled, N=20, ages 28-70, all blind
- Sponsored by Vanda Pharmaceuticals Inc.
- All subjects had to have responded to the SET trial in the tasimelteon group
- Randomized to receive 20 mg once daily (N=10) or placebo (N=10) for 2 months
- Used urinary 6-sulfatoxymelatonin (aMT6s) and cortisol timing to measure for entrainment
- Patients who continued receiving tasimelteon maintained entrainment of their aMT6s (in 90 versus 20% of patients; $p = 0.0026$) and cortisol (in 80 versus 20%; $p = 0.0118$) circadian rhythms.
- Tasimelteon recipients also had significantly longer (by 67.2 min) total nighttime sleep in the worst quartile nights and significantly shorter (by 59.4 min) duration of daytime sleep than placebo recipients (both $p < 0.05$).
- Midpoint of sleep timing for both nighttime and daytime sleep increased significantly ($p = 0.0108$) by 36 min with tasimelteon relative to placebo
- Further statistical analyses unavailable due to lack of published data

Drug Monograph

While the package insert does report clinical studies, these studies were not statistically analyzed due to reporting of “most symptomatic” nights/days only, thus creating bias.³

Recommendations

Based on the lack of published clinical trials, absence of trials comparing tasimelteon to ramelteon, and the clinical benefit of only approximately 1 hour of shifted sleep from day to night, the high cost of tasimelteon cannot be justified at this time. I recommend excluding this drug until further benefits can be proven.

³ Hetlioz™ [package insert]. Washington, D.C.: Vanda Pharmaceuticals Inc; 2014.

Xartemis XR (oxycodone/acetaminophen)

Sarah Dinsmore

FDA approved uses: management of acute pain severe enough to require opioid treatment and for which alternative treatment options are inadequate.

Dosing: 2 tablets every 12 hours

Cost Comparison:

Drug	Dosing	Cost per pill	Cost per day
Xartemis XR (7.5mg oxycodone)	2 tabs every 12 hrs	\$2.76	\$11.00
OxyContin 15mg	1 tablet every 12 hrs	\$4.20	\$8.20
Oxycodone/APAP IR (7.5mg/500mg)	1 tablet every 4 hours	\$1.06	\$6.18

Contraindications: Known hypersensitivity to oxycodone, acetaminophen, or any other component of this product, significant respiratory depression, acute or severe bronchial asthma or hypercarbia, or known or suspected paralytic ileus

Drug Interactions:

- Concurrent use of other CNS depressants may cause respiratory depression, hypotension, and profound sedation or coma.
- XARTEMIS XR may enhance the neuromuscular blocking action of skeletal muscle relaxants and produce an increased degree of respiratory depression.
- Monoamine oxidase inhibitors may intensify the effects of opioids causing anxiety, confusion and significant depression of respiration or coma.
- The CYP3A4 isoenzyme plays a major role in the metabolism of XARTEMIS XR; drugs that inhibit CYP3A4 activity may cause decreased clearance of oxycodone which could lead to an increase in oxycodone plasma concentrations.
- Mixed agonist/antagonist analgesics may reduce the analgesic effect of oxycodone and may precipitate withdrawal symptoms in these patients.
- Anticholinergics may increase risk for urinary retention and severe constipation.

Evidence:

A randomized, double-blind, placebo-controlled study of the efficacy and safety of MNK-795, a dual-layer, biphasic, immediate-release and extended-release combination analgesic for acute pain

- Design: A multicenter, randomized, double-blind, placebo-controlled, parallel-arm, multiple-dose clinical trial with a total of 303 patients whom have undergone a unilateral first metatarsal bunionectomy. They were randomized (1:1) to receive four doses (two tablets q12h) of Xartemis XR or placebo.
- Results: A total of 329 patients were enrolled, of whom 266 (OC/APAP ER, n=135; placebo, n=131) completed the study. The mean (SE) SPID48 was 114.9 (7.6) in the OC/APAP ER group and 66.9 (7.6) in the placebo group (P<0.0001). SPID and TOTPAR values were significantly greater with OC/APAP ER than with placebo over all time periods analyzed, and the median times to perceptible, meaningful, and confirmed pain relief were significantly shorter. More patients showed a greater than 30% reduction in pain intensity scores with OC/APAP ER than with placebo at all times after 0.5 hours. OC/APAP ER was generally well tolerated.

Singla N, Barrett T, Sisk L, Kostenbader K, Young J, Giuliani M. A randomized, double-blind, placebo-controlled study of the efficacy and safety of MNK-795, a dual-layer, biphasic, immediate-release and extended-release combination analgesic for acute pain. *Curr Med Res Opin.* 2014 Mar;30(3):349-59. doi: 10.1185/03007995.2013.876979. Epub 2014 Jan 10.

Recommendation: Do not cover. There is no data that shows Xartemis XR works any better than OxyContin.

Orenitram (treprostinil)

FDA approved uses: Treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise capacity.

Dosing: Starting dose: 0.25 mg BID. Titrate by 0.25 mg or 0.5 mg BID or 0.125 mg TID, not more than every 3 to 4 days as tolerated. Maximum dose is determined by tolerability.

Cost Comparison:

Drug	Dosing	Cost
Remodulin (1mg/ml or 10mg/ml)	Initial: 1.25ng/kg/min Max : 40ng/kg/min	1mg/ml (20ml) vial \$1474.00 10mg/ml (20ml) vial \$12,740.00
Tyvaso (0.6mg/ml)	Initial: 18mcg 4 times daily Max: 14mcg 4 times daily	Starter kit: 0.6mg/ml \$627.20 Refill: 0.6mg/ml \$557.91
Orenitram (0.125-2.5)	Initial:0.25 twice daily	0.25mg (#100) \$1,170.00

Contraindications: Severe hepatic impairment (Child Pugh Class C).

Drug Interactions:

- Blood pressure lowering drugs (e.g., diuretics, antihypertensive agents, or vasodilators): Risk of hypotension
- When co-administered with strong CYP2C8 inhibitors the initial dose is 0.125 mg BID with 0.125 mg BID dose increments every 3 to 4 days.

Evidence:

Efficacy and Safety of Oral Treprostinil Monotherapy for the Treatment of Pulmonary Arterial Hypertension: A Randomized, Controlled Trial

- Design: 349 patients (intent-to-treat population) not receiving endothelin receptor antagonist or phosphodiesterase type-5 inhibitor background therapy were randomized (treprostinil, n=233; placebo,n=116). The primary analysis population (modified intent-to-treat) included 228 patients (treprostinil, n=151; placebo,n=77) with access to 0.25-mg treprostinil tablets at randomization. The primary end point was change from baseline in 6-minute walk distance at week 12. Secondary end points included Borg dyspnea index, clinical worsening, and symptoms of PAH.
- Results: The week 12 treatment effect for 6-minute walk distance (modified intent-to-treat population) was 23.0 m ($P=0.0125$). For the intent-to-treat population, 6-minute walk distance improvements were observed at peak (26.0 m; $P=0.0001$) and trough (17.0 m; $P=0.0025$) plasma study drug concentrations. Other than an improvement in the combined 6-minute walk distance/Borg dyspnea score, there were no significant changes in secondary end points. Oral treprostinil therapy was generally well tolerated; the most common adverse events (intent-to-treat) were headache (69%), nausea (39%), diarrhea (37%), and pain in jaw (25%).

Jing ZC¹, Parikh K, Pulido T, Jerjes-Sanchez C. Efficacy and safety of oral treprostinil monotherapy for the treatment of pulmonary arterial hypertension: a randomized, controlled trial. *Circulation*. 2013 Feb 5;127(5):624-33. doi:10.1161/CIRCULATIONAHA.112.124388

Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial

- Design: A 16-week, multicenter, double-blind, placebo-controlled study in 310 patients with PAH compared bid administration of oral treprostinil (n=157) with placebo (n=153). The primary end point was change in 6-min walk distance at week 16. Secondary efficacy end points were World Health Organization functional class, Borg dyspnea score, dyspnea-fatigue index, signs and symptoms of PAH, and clinical worsening.
- Results: One hundred thirty-two patients (84%) receiving oral treprostinil and 138 (90%) receiving placebo completed the study. The mean \pm SD dose of oral treprostinil at week 16 was 3.1 \pm 1.9 mg bid. The Hodges-Lehmann placebo-corrected median difference in 6MWD at week 16 was 10.0 m (95% CI, -2 to 22 m; P

=.089). There were no significant changes in secondary end points. The most common adverse events associated with oral treprostinil were headache (71%), diarrhea (55%), nausea (46%), flushing (35%), and jaw pain (25%).

Tapson VF, Jing ZC, Xu KF. Oral treprostinil for the treatment of pulmonary arterial hypertension in patients receiving background endothelin receptor antagonist and phosphodiesterase type 5 inhibitor therapy (the FREEDOM-C2 study): a randomized controlled trial. Chest. 2013 Sep;144(3):952-8. doi: 10.1378/chest.12-2875.

Recommendation: Do not cover. Evidence shows that Orenitram is only effective in treatment naïve patients and it only improves 6MWD. There has been no head-to-head studies with the other treprostinil products.

Otezla (apremilast)

MOA:

Otezla is the first PDE-4 inhibitor to treat active psoriatic arthritis in adults.

Labeled Uses:

Treatment of psoriatic arthritis

Comparators:

Otezla (apremilast)	\$2250/month (60 tablets)	\$37.50 per 30mg tab
Inflixumab	~\$2134-\$3201/per month (65-110kg weight)	\$1067 per 100mg (5mg/kg q 8 weeks)
Methotrexate	Up to ~\$35.00 per month	7.5-25mg per week depending on response

Toxicities/Adverse Effects:

Adverse reactions reported in at least 2% of patients taking Otezla. Diarrhea (7.7, 1.6); nausea (8.9, 3.1); headache (5.9, 2.2); upper respiratory tract infection (3.9, 1.8); vomiting (3.2, 0.4); nasopharyngitis (2.6, 1.6); upper abdominal pain (2.0, 0.2).

Drug Interactions:

CYP450 Inducers (rifampin, phenobarbital, carbamazepine, phenytoin)

Evidence:

Treatment of psoriatic arthritis in a phase 3 randomized, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor.

Design: 24-week placebo-controlled phase of PALACE 1, 501 patients were randomized to placebo, apremilast 20mg BID, or apremilast 30mg BID. Patients currently on DMARDS (methotrexate, sulfasalazine, and/or leflunamide) continued therapy in the study. Primary endpoint was proportion of patients achieving ARC20 at week 16.

Results: At week 16, significantly more apremilast 20mg BID (31%) and 30mg BID (40%) patients achieved ARC20 versus placebo (19%). (p<0.001) Most common adverse effects were GI and no major adverse effects were observed.

Kavanaugh A, Mease PJ, Gomez-Reino JJ, et al. *Ann Rheu Dis* Published Online First: April 10, 2014.

Recommendation:

Tier 3 with PA: prior use of 2 DMARD agents with inadequate response, not to be used with biologic (further studies needed). Trial Currently underway (to be completed in 2015) comparing apremilast to biologic agent.

**Propranolol Oral Solution 4.28 mg/mL
(Hemangeol)**

Shannan Carroll
June 26, 2014

Labeled Use: proliferating infantile hemangioma requiring systemic therapy
Initiate treatment at ages 5 weeks to 5 months.
Propranolol is now considered first-line therapy.^{2,3}

Comparator Drugs:

Drug	Maintenance Dose	Cost	Inactive Ingredients
Hemangeol (oral propranolol 4.28mg/mL) (alcohol, paraben, and sugar free)	1.7 mg/kg BID X 6 months	120 ml = \$450 1 mg ~ \$0.88 (Dispense in original container and discard after 2 months of opening)	strawberry/vanilla flavorings, hydroxyethylcellulose, saccharin sodium, citric acid monohydrate, water
generic oral propranolol 20 mg/5 mL or 40 mg/5 mL		<u>20 mg/5 mL</u> 500 mL = \$53.47 1 mg ~ \$0.03 <u>40 mg/5 mL</u> 500 mL = \$76.40 1 mg ~ \$0.02	flavorings, citric acid, disodium edetate, methylparaben , propylene glycol, propylparaben , saccharin sodium, sorbitol , water, 0.6% alcohol (30 µL/5mL)
IV propranolol solution 1 mg/mL		1 mL = \$9.85 1 mg = \$9.85	citric acid monohydrate

Excipient Information: FDA recommends concentrations of alcohol in OTC medications for children under 6 to be ≤ 0.5% and in children from 6 to 11 to be ≤ 5%.¹ Alcohol in children can be neurotoxic and cause hypoglycemia, lethargy, and respiratory depression. Parabens have been associated with hypersensitivities.

Contraindications: premature infants with corrected age <5 weeks, infants weighing <2 kg, asthma or history of bronchospasm, heart rate <80 beats per minute, greater than first degree heart block, decompensated heart failure, blood pressure <50/30 mmHg, pheochromocytoma

Warnings and Precautions: hypoglycemia, bronchospasm, bradycardia, hypotension

Adverse Reactions: (>10%) sleep disorders, aggravated respiratory tract infections, diarrhea, vomiting

Drug Interactions: CYP2D6, CYP1A2 or CYP2C19 inhibitors increase propranolol plasma concentration, CYP1A2 inducers and CYP2C19 inducers decrease propranolol plasma concentration, corticosteroids may increase risk of hypoglycemia

Evidence:

According to the package insert a randomized, double-blind, placebo-controlled study was conducted in 460 infants with proliferating infantile hemangiomas (IH). Patients ranged from 5 weeks to 5 months of age at initiation. Five arms of the trial included four Hemangeol regimens (1.2 or 3.4 mg/kg/day in twice daily divided doses for 3 or 6 months; n=99-103 per group) and placebo (n=55). Similar characteristics were noted between all regimens. Overall, 2/55 patients (4%) on placebo and 61/101 patients (60%) on Hemangeol 3.4 mg/kg/day for 6 months had complete or nearly complete resolution of their hemangioma at Week 24 (p <0.0001). Treatment discontinuation occurred in 58% of patients randomized to placebo, 25-30% of patients randomized to Hemangeol for 3 months (mainly after the switch to placebo), and 7-9% of patients randomized to Hemangeol for 6 months mainly due to inefficacy. There were no significant differences in response by age (35-90 days / 91-150 days), sex, or hemangioma site. 10% of patients on 3.4 mg/kg/day of Hemangeol for 6 months with resolution required retreatment due to recurrence of hemangiomas.

References:

1. U.S. Food and Drug Administration. (2010, December 15). Rulemaking History for OTC Drug Products Containing Alcohol. Retrieved from <http://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/over-the-counterotcdrugs/statusofotcrulemakings/ucm070023.htm>
2. Metry, DW. Management of Infantile Hemangiomas. In: UpToDate, Levy, ML (Ed), UpToDate, Waltham, MA (Accessed on June 18, 2014.)
3. Mathes E.F., Frieden I.J. (2012). Chapter 126. Vascular Tumors. In Goldsmith L.A., Katz S.I., Gilchrest B.A., Paller A.S., Leffell D.J., Wolff K (Eds), *Fitzpatrick's Dermatology in General Medicine, 8e*. Retrieved June 18, 2014 from <http://accessmedicine.mhmedical.com.libproxy.uams.edu/content.aspx?bookid=392&Sectionid=41138845>.
4. Hemangeol ® [package insert]. Pierre Fabre Pharmaceuticals, Inc., Parsippany, NJ. March 2014. www.hemangeol.com. Accessed June 18, 2014.

Recommendation: Cover in children up to 1 year of age.

EBRx Outcome: Do not cover.

**Dextroamphetamine sulfate (Zenzedi)
Central Nervous System Stimulant (C II)**

June 26, 2014

FDA approved uses: Treatment of narcolepsy and attention-deficit/hyperactivity disorder (ADHD) in pediatric patients ages 3 to 16 years.

Narcolepsy is a neurological disease that affects the control of sleep and wakefulness. The treatment of choice for narcolepsy is: modafinil, armodafinil, methylphenidate, dextroamphetamine, or amphetamine-dextroamphetamine.

ADHD is a disorder of inattention. The symptoms of ADHD are hyperactivity, impulsiveness, and inattentiveness. Stimulants, which are controlled substances, are available in short-, intermediate-, and long-acting formulation. The exact mechanism of action is unknown. However, stimulants affect the dopaminergic and noradrenergic system, causing the release of catecholamines.

Dosing: 15 mg tablet, 20 mg tablet and 30 mg tablet, *immediate-release tablets*.

Contraindications: Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, or glaucoma.

Warning/ Precautions: Cardiovascular events: [U.S. Boxed Warning]: Use has been associated with serious cardiovascular events including sudden death in patients with pre-existing cardiac abnormalities or other serious heart problem. Abuse potential: [U.S. Boxed Warning]: Potential for drug dependency exists; prolonged use may lead to drug dependency.

Drug Interactions: Analgesics (Opioid): Amphetamines may enhance the analgesic effect of Analgesics (Opioid). Antacids: May decrease the excretion of Amphetamines. MAO Inhibitors: May enhance the hypertensive effect of Amphetamines. .

References: 1. Vedolizumab. Lexi-Drugs Online. Lexi-Comp, Inc., Copyright 1978-2014. Accessed on the UAMS library website on 6/20/14. 2. Vedolizumab, Clin-eguide Online. Wolters Kluwer Health. Copyright 2014. Accessed on the UAMS library website on 6/20/14.

Recommendation: Cover with prior authorization only Zenzedi that is clinically indicated for ADHD in pediatric patients between ages of 3 to 16 years old. Do not cover Zenzedi when is recommended for Narcolepsy.

Outcome from EBRx: Exclude unless cost is a factor.

Cost Comparison:*Dextroamphetamine*

Drug	Dosing	Cost	Narcolepsy max 60mg/day	ADHD max 40 mg/day
Zenzedi	15 mg tablet	\$5.9	\$23.6 4 tablets	
Zenzedi	20 mg tablet	\$5.9	\$17.7 3 tablets	\$11.8 2 tablets
Zenzedi	30 mg tablet	\$5.9	\$11.8 2 tablets	
Dextroamphetamine Sulfate	5 mg tablets	\$2.90	\$34.8 12 tablets	\$23.2 8 tablets
Dextroamphetamine Sulfate	10 mg tablet	\$3.15	\$18.9 6 tablets	\$12.6 4 tablets

Methylphenidate

Drug	Dosing	Cost	Narcolepsy max 60mg/day	ADHD max 40 mg/day
Ritalin	5 mg tablet	\$0.78	\$9.36 12 tablets	\$6.24 8 tablets
Ritalin	10 mg tablet	\$1.12	\$6.72 6 tablets	\$4.48 4 tablets
Ritalin	20 mg tablet	\$1.61	\$4.83 3 tablets	\$3.22 2 tablets

Dextroamphetamine and Amphetamine

Drug	Dosing	Cost	Narcolepsy max 60mg/day	ADHD max 40 mg/day
Amphetamine-Dextroamphetamine	15 mg tablet	\$1.71	\$6.84 4 tablets	
Amphetamine-Dextroamphetamine	20 mg tablet	\$1.71	\$5.13 3 tablets	\$3.42 2 tablets
Amphetamine-Dextroamphetamine	30 mg tablet	\$1.71	\$3.42 2 tablets	

**Vorapaxar 2.08 mg Tablets
(Zontivity)**

Shannan Carroll
June 26, 2014

Labeled Use: to reduce thrombotic cardiovascular events in patients with a history of MI or established PAD as an adjunct to another antiplatelet drug

Comparator Drugs:

Drug	Maintenance Dose	Cost	Monthly Cost
vorapaxar	1 tablet daily	\$10.69 (1)	\$320.70
aspirin	1 tablet daily	81 mg: \$3.85 (120) 325 mg: \$2.90 (100)	81 mg: \$0.96 325 mg: \$0.87
clopidogrel	75 mg once daily (with or without aspirin)	75 mg: \$208.80 (30)	\$208.80
prasugrel	10 mg once daily in combination with 81 mg aspirin	5 mg: \$237.89(24) 10 mg: \$297.36 (30)	\$297.36

Mechanism of Action: protease-activated receptor-1 (PAR-1) antagonist inhibiting thrombin-induced platelet aggregation

Contraindications: history of stroke, TIA, or intracranial hemorrhage due to increased risk of ICH

Adverse Reactions: increased risk of bleeding (BBW)

Drug Interactions: metabolized by CYP3A4; avoid concomitant use with strong CYP3A4 inducers and inhibitors

Evidence:

Vorapaxar in the Secondary Prevention of Atherothrombotic Events

- Design: Randomized, double-blind, placebo-controlled study conducted in 32 countries at 1,032 sites. Patients with a history of atherosclerosis, defined as an MI or ischemic stroke within 2 weeks to 12 months or established PAD, were randomly assigned to either the vorapaxar (n=13,225) or placebo arm (n=13,224) by a hierarchical stratification system. All additional medications, including other antiplatelets, were managed by clinicians on an individual basis. The primary efficacy end point was a composite of cardiovascular death (all deaths assumed cardiovascular unless clearly not), MI, stroke, or recurrent ischemia leading to urgent coronary revascularization. The major secondary endpoint was CV death, MI, or stroke. The primary and secondary end points were swapped during the trial, during blinded treatment, when the results of the TRACER trial were published. The primary safety end point was a GUSTO defined moderate or severe bleed. GUSTO defines a moderate bleed as one that requires a blood transfusion but does not lead to hemodynamic instability and a severe bleed as one that causes hemodynamic compromise and requires intervention or an ICH. Two years into the trial, all patients with a history of stroke were taken off either vorapaxar or placebo after the DSMB reported a correlation between patients on vorapaxar with a history of stroke and intracranial hemorrhage.

- Results: There was a statistically significant decrease in the composite primary efficacy end point with vorapaxar (-1.2%, p<0.001) and the secondary end point (-1.2%, p=0.001). A composite of CV death or MI showed a significant decrease (-0.9%, p=0.002) as well as MI alone (-0.9%, p=0.001). There was no statistical difference in CV death, stroke, or urgent coronary revascularization as independent end points. The primary safety end point showed a statistically significant increase in bleeds in patients receiving vorapaxar (1.7%, p<0.001). There was also a statistically significant increase in ICH (0.5%, p<0.001). NNT = 84; NNH = 59. In a subgroup analysis, patients with no history of stroke (n=20,699) still showed a significant increase in ICH (0.2%, p=0.049) and moderate or severe bleeds (1.5%, P<0.001). Considering only patients with no history of stroke, NNT= 77 and NNH = 67. Patients with no history of stroke still had significant incidences of ICH (0.2%, p=0.049). In a subgroup analysis of patients with a qualifying MI (n= 17,779), there was significance for both the primary efficacy (-1.6%, p<0.001) and safety endpoints (1.3%, p<0.001). In this subgroup only, NNT = 63 and NNH = 77. Of patients qualifying for MI, 98.1% were also receiving aspirin in both arms and 77.9% and 78.4% were receiving a thienopyridine in the vorapaxar and placebo arms respectively. In patients with PAD, 87.8% and 88.2% of patients were receiving aspirin in the vorapaxar and placebo arms respectively, while 36.8% in each arm were receiving a thienopyridine. Of the stroke qualifiers, 81.2% and 80.7% were receiving aspirin and 23.6% and 23.7% were receiving theinopyridine in the vorapaxar and placebo arms respectively.

Morrow DA, Braunwald E, et al. "Vorapaxar in the Secondary Prevention of Atherothrombotic Events." *N Engl J Med* 2012; 366:1404-1413. DOI: 10.1056/NEJMoa1200933

Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes

- Design: Randomized, double-blind, placebo-controlled study conducted in 37 countries and more than 818 sites. 12,944 patients with non-ST-segment elevation acute coronary syndrome (NSTEMI ACS) were assigned in a 1:1 method to receive either vorapaxar (40 mg loading dose then 2.5 mg daily) or placebo. The primary efficacy end point was a composite of CV death, MI, stroke, recurrent ischemia with rehospitalization, or urgent coronary revascularization. The secondary end point was a composite of CV death, MI, or stroke. A GUSTO moderate or severe bleed was the primary safety end point.
- Results: The trial was stopped 6 months early by the DSMB as the target number of primary end points had been reached. There was no statistically significant reduction in the primary end point (-1.4%, p=0.07) but there was a significant reduction in the secondary end point (-1.7%, p=0.02). MI reduction was the major factor contributing to this difference. The primary safety end point was significantly increased in the vorapaxar group (2%, p<0.001). Subgroups of severe bleeding (1.3%, p<0.001) and ICH (0.9%, p<0.001) were significantly increased with increasing risk over time.

Tricoci P, Huang Z, et al. "Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes." *N Engl J Med* 2012; 366:20-33 DOI: 10.1056/NEJMoa1109719

Recommendation: Do not cover. Even after excluding patients with a prior history of stroke, benefits do not outweigh the risks.

EBRx Outcome: Do not cover.

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

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

FDA Approved indications:

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

Dosage & Administration:

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

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

Place in therapy:

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

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

Warnings & Precautions:

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

Adverse Reactions:

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

Interactions:

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

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

CDAI – Crohn’s Disease Activity Index

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

Mayo Scoring System for Ulcerative Colitis

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

Evidence**Crohn’s Disease**

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

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

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

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

Ulcerative Colitis

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

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

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

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

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

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

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

<h2>To TNF Antagonists</h2>	<ul style="list-style-type: none"> - S/s of persistent, active disease despite a hx of ≥ 1 4-wk induction regimen of 1 of the following: <ul style="list-style-type: none"> - Infliximab: 5 mg/kg IV, 2 doses at least 2 wk apart - Adalimumab: 1 80mg SC dose followed by 1 40mg dose ≥ 2 wk apart (CD only) - Certolizumab pegol: 400mg SC, 2 doses ≥ 2 wk apart (CD only) <u>OR</u> - Recurrence of sym during scheduled maintenance dosing after prior clinical benefit (D/C despite clinical benefit does not qualify) <u>OR</u> - Hx of intolerance of at least 1 TNF antag (including, but not limited to, inf-related rxn, demyelination, CHF, & inf)
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Patients who enrolled in the study did not respond or were intolerant to ≥ 1 corticosteroid, immunosuppressive, or TNF antag; US patients must have failed either immunosuppressive or TNF antag therapy (not corticosteroids only)

**Proposed EBRx PA Criteria for vedolizumab (Entyvio)
Gerri Bemberg, Pharm.D.
July 22, 2014**

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

Ulcerative Colitis	
Initial request to identify responders.	
1. Does the patient have a diagnosis of Ulcerative Colitis?	<input type="checkbox"/> Yes <input type="checkbox"/> No
2. Has the patient failed treatment with, or is dependent on corticosteroids, as defined by the following:	<input type="checkbox"/> Yes <input type="checkbox"/> No

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

Revision History		
Date	What happened	Pharmacist
7/22/14	Created criteria	GBB