



AGENDA

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

April 6, 2015

1:00 p.m.

EBD Board Room – 501 Building, Suite 500

- I. Call to Order..... Dr. Kat Neill, Chairman*
- II. Approval of February 20, 2015 Minutes Dr. Kat Neill, Chairman*
- III. Delivery Coordination Workgroup.....Dr. David Keisner, UAMS*
- IV. Topical NSAID review.....Dr. Jill Johnson, UAMS*
- V. Second Review of Onfi.....Dr. Jill Johnson, UAMS*
- VI. New Drugs.....Dr. Jill Johnson, UAMS*
- VII. EBD ReportDr. David Keisner, UAMS*

Upcoming Meetings

August 3, 2015

November 2, 2015

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

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

State and Public School Life and Health Insurance Board Clinical and Fiscal Drug Utilization and Evaluation Committee Minutes April 6, 2015

The State and Public Life and Health Insurance Board, Drug Utilization and Evaluation Committee (DUEC) met on Monday April 6, 2015 at 1:00 p.m., in the EBD Board Room, 501 Woodlane, Little Rock, AR.

Voting Members present:

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

Non-Voting Members present:

Dr. Jill Johnson
Connie Bennett
Dr. David Keisner

Members absent:

Dr. Appathurai Balamurugan
Dr. Melodee Harris
Dr. Scott Pace

Lori Eden, Deputy Executive Director, Employee Benefits Division

OTHERS PRESENT

Dwight Davis, Geri Bemberg, UAMS College of Pharmacy; Sherry Bryant, Ethel Whittaker, Stella Greene, EBD; Steve Johnston, N. Nordisk; Charlene Kaiser, Amgen; Takisha Sanders, Health Advantage; Ronda Walthall, AHTD; Jon McGuire, GSK; Bridgett Johnson, Pfizer; Andy Davis, Arkansas Democrat Gazette; Takisha Sanders, Kanita Collins, Health Advantage; Martha Hill, Jim Chapman, Brian Strickland, Gilead; Sam Smothers, Astra Zeneca; Connie Bennett, Catamaran; Treg Long, ACS; Barry Felder, Karyn Langley, Qual Choice; Frances Bauman, Nova Nordisk

CALL TO ORDER

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

APPROVAL OF MINUTES

The request was made by Dr. Neill to approve the February 24, 2015 minutes. Dr. Simmons made the motion to approve. Kirtley seconded. All were in favor.

Minutes Approved.

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

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

Drugs used in the treatment of Cancers and non-cancer drugs were reviewed by the DCWG and a report made to the DUEC on April 6th. Recommendations from this report are outlined below.

	Current Coverage	Proposed Coverage for 2015
<u>Multiple Sclerosis (MS)</u> Lemtrada (alemtuzumab)	New Drug	Medical PA
<u>IVIG</u> Multiple Products	T4 PA Pharmacy/Medical PA	PA Pharmacy products for self Admin. Remove medical PA
<u>Metastatic Melanoma</u> <u>Opdivo (nivolumab)</u>	New Drug	Medical PA

Dr. Kirtley motioned to approved the Delivery Coordination Work Group Report. Dr. Simmons seconded. All were in favor.

Motion Approved

TOPICAL NSAIDs REVIEW: *by, Dr. Jill Johnson, UAMS*

Topical NSAIDs have shown to be as efficacious as oral NSAIDs in the available clinical trials. Topical NSAIDs were reported to have a better safety profile when compared to systemic NSAIDs. Predominantly these results reflect gastrointestinal adverse events such as nausea, dyspepsia, and abdominal pain which are typically manageable. GI bleeds were not addressed in any of the reviewed trials. Use of topical diclofenac for actinic keratosis may not be as effective as topical 5-FU. It is reasonable to NOT cover topical NSAIDs based on the current evidence. In the past six (6) months there have been 773 users.

Drug	Use	Current Coverage	Proposed Coverage
Diclofenac Na transderm. soln 1.5%	OA	Tier 1	Exclude; 90 day communication to members (773 users in past 6 months)
Flector (diclofenac TD Patch) 1.3%	Acute pain	Tier 3	
Pennsaid (diclofenac TD soln) 1.5%, 2%	OA	Tier 3	
Voltaren (diclofenac TD gel) 1%	OA	Tier 3	

Topical Diclofenac Gel 1%	OA	Tier 1	
Diclofenac Na transderm gel 3%	AK	Tier 1	
Solaraze (diclofenac TD gel) 3%	AK	Brand penalty	

Dr. Simmons motioned to exclude for osteoarthritis and acute pain. Provide a 90 day notice to utilizers. Dr. Kirtley seconded. All were in favor.

Motion Approved.

SECOND REVIEW OF ONFI: : by, Dr. Jill Johnson, UAMS

Drug	Use	Current Coverage	Proposed Coverage
Onfi (clobazam)	Lennox-Gastaut Syndrome Uncontrolled drop seizures	Excluded	Tier 3 PA

The Recommendation is to cover on Tier 3 with PA criteria.

Dickerson motioned to approve. Dr.Crumbaugh seconded. All were in favor.

Motion Approved

HEPATATIS C REVIEW: by Dr. Jill Johnson, UAMS

Dr. Johnson reported on information requested from board members. She met with Dr. Duarte, Liver Specialist at UAMS, regarding the current policy. The updated PA criteria are listed below. Updated coverage pathways are included as an addendum. The following modifications to current coverage and PA criteria are recommended.

1. Ensure the patient has CHRONIC hepatitis C. This requires either a HCV AB test and then a viral load 6m later OR two viral loads 6m apart. We only treat CHRONIC hcv. Up to 20% of Hep C infections resolve on their own.
2. Remove esophageal varices and history of variceal bleeding from the list of decompensation manifestations that would lead to denial of therapy (unless listed on a liver transplant list).
3. Allow treatment when comorbidities exist (chronic HBV, autoimmune hepatitis, alcoholic hepatitis, hemochromatosis, Wilson’s disease, alpha1 antitrypsin deficiency) after referral to a gastroenterologist for treatment of concomitant diseases.
4. Include FibroScan and Fibrotest to APRI or FIB-4 as noninvasive tests to ascertain metavir F3 or F4 stage.
5. Allow access to Harvoni for GT1 treatment-naïve, interferon-eligible patients.
6. Following a completed therapy, if the patient experiences a relapse, he/she is eligible for retreatment. However, if treatment is abandoned, the patient would not be eligible to repeat the treatment.

Dr. Golden reported concerns are if the patients are cooperating, and adhering to the therapy. Dr. Golden reported one key question is will the patient follow through the therapy process. Dr. Golden discussed retreatment if the patient is using alcohol or illicit drugs in the six month time frame. Dr. Simmons reported having many years' experience with drug testing is concerned with the expense in terms of retreatment.

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

Dr. Golden motioned to accept Harvoni for eight (8) week treatment. Dr. Simmons seconded. All were in favor.

Motion Approved

Dr. Kirtley motioned to accept the above six (6) Hepatitis C recommendations. Dr. Simmons seconded. All were in favor.

Motion Approved

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

<p>1. The patient must test positive for chronic HCV infection. Two options:</p> <ul style="list-style-type: none"> • HCV antibody \geq6m before a positive HCV RNA (viral load) , OR • 2 HCV RNA levels 6 months apart <p><input type="checkbox"/> The viral load must be documented. _____</p> <p><input type="checkbox"/> The genotype and subtype must be documented. _____</p>	<p>The diagnosis of CHRONIC HCV must be made. 15-25% seroconvert on their own and the patient clears the infection. We only treat chronic HCV infection.</p>
<p>2. The patient must be free of using illicit drugs for the past 6 months.</p> <p><input type="checkbox"/> A patient-signed statement attesting to this is acceptable.</p>	<p>Any positive drug screen for injectable drug use during treatment stops access to the HCV drugs. Reinfection is a risk for IV drug users.</p>
<p>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).</p> <p><input type="checkbox"/> A patient-signed statement attesting to this is acceptable.</p>	
<p>4. If the patient has cirrhosis, there must be NO signs of decompensation (ascites, episodes of spontaneous bacterial peritonitis, hepatic encephalopathy,), unless the patient is currently listed for liver transplant.</p> <p><input type="checkbox"/> The drug profile for the past 1 year must be submitted.</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 with liver disease due to any cause other than HCV infection (chronic hepatitis B infection, autoimmune hepatitis, alcoholic hepatitis, hemochromatosis, Wilson's disease, alpha1 antitrypsin deficiency) should be referred to a gastroenterologist.</p>	
<p>6. The extent of fibrosis may be shown by liver biopsy, FIB-4, APRI, Fibroscan (transient elastography), or Fibrotest to demonstrate the patient has a Metavir score of F3 or F4.</p>	
<p>7. Patients with extrahepatic manifestations of chronic HCV infection are candidates for therapy regardless of corresponding Metavir score as long as they meet the other requirements above.</p>	

8. If the patient was provided HCV eradication therapy and abandoned therapy, they are not eligible for a second course of treatment. If the patient completed but relapsed or had intolerance to the first course of therapy, then they would be eligible for subsequent treatment depending on what is requested and the clinical evidence. <input type="checkbox"/> A review of the drug profile for fills provided in the past for HCV eradication drug therapy. Further explanation by the patient/physician may be required.	
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A. Other questions which must be collected on EVERY patient seeking drug therapy for HCV infection:

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

NEW DRUGS: by Dr. Jill Johnson, UAMS

Recommended Additions:

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	DUEC VOTE
Arnuity	Fluticasone furoate aerosol powder breath act	\$156/100mcg; \$209/200mcg	New fluticasone formulation. Once daily inhaled corticosteroid for maintenance tx of asthma as prophylactic therapy – not indicated for relief of acute bronchospasm	T2 plan options: Flovent HFA: 110 mcg/\$2131, 220 mcg/\$359. Pulmicort Flexihaler 90 mcg/\$165, 180mcg/\$250. QVAR: 40 mcg/\$167, 80 mcg/\$224	Tier 2
INCRUSE ELPT INHALER	umeclidinium BR aero powder breath act	\$270/30 doses	Long-term, once daily maintenance treatment of air flow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	T2 plan options: Spiriva Respimat 60 doses/\$357; Spiriva Handihaler Powder/\$357. Tudorza Press air powder for inhalation: \$336/60 doses	Tier 2
SOOLANTRA CREAM	ivermectin cream	\$330/30gm	Treatment of inflammatory lesions of rosacea	T1 plan option: topical metronidazole gel,cream - \$42/45gm	Tier 3, QL of 30 g tube/30d
SAVAYSA TABS	edoxaban tosylate	\$11.08/tab	Oral anticoagulant for reduction in the risk of stroke and systemic embolism in patients with atrial fibrillation that is unrelated to valvular heart disease and for treatment of DVT and PE in patients intially treated with an injectable anticoagulant		Tier 2, QL
MOVANTIK	naloxegol	\$9.98/tab	Treatment of opioid-induced	Tier 3 plan options for	Cover, Tier3,

	oxalate	(dose= 1 tab/day)	constipation in adults with chronic non-cancer pain	opioid induced constipation: Amitiza/\$9.90 per day. Relistor by subcutaneous injection/\$86 every other day	QL of 1/1, revisit in 6 months (Sept 2015) for price reasons bring to DCWG in Sept 2015.
ZUBSOLV SUB 8.6-2.1	buprenorphin e-naloxone SL tab 8.6-2.1mg	\$12.67/tab	new dosage form	Other ZUBSOLV strengths excluded by plan	TIER 3 PA, QL #62/31. Revisit on 09/25/15.
PAZEO DROPS	olopatadine opgth solution 0.7%	\$179/2.5ml	For ocular allergy itch relief	Tier 1 plan options: azelastine/\$104 per 6 ml; olopatadine/\$78/5ml	Tier 3

Recommended Additions (continued):

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	DUEC VOTE
FLUZONE QUAD INJ	influenza virus vac split quad intradermal pen	\$24.70/pen	flu vaccine		Covered as per immun. policy
BEXSERO INJ	meningococcal Vac B inj in prefiiled syringe		Meningococcal vaccine		Covered as per immun. policy
SPECIALTY DRUGS					
REYATAZ	atazanavir oral powder packet 50mg	\$7.90 each	New dosage formulation. For HIV infection	Reyataz caps covered as specialty tier. 100mg cap = \$21.97	Tier 3 PA, for infants >3m & children weighing 10-25kg, age edit of less than 7 years
VITEKTA	elvitegravir tabs	\$45.06/tab	For use in combination with ritonavir, another protease inhibitor, and other antiretroviral drug (s) to treat HIV in adults who are antiretroviral experienced		Tier 3
EVOTAZ TAB	atazanavir 300mg-cobicistat 150 tab(Reyataz-Tybost)	\$56.14/tab	Treatment of HIV infection	Reyataz covered specialty tier (\$50.69/300mg tab) Tybost 150mg coded as excluded (\$7.20/150mg tab)	Tier 3

PREZCOBIX TAB	darunavir 800mg-cobicistat 150mg(Prezista-Tybost)	\$57.52/tab	Treatment of HIV infection	Prezista covered specialty tier (\$50.32/800mg tab) Tybost 150mg coded as excluded (\$7.20/150mg tab)	Tier 3
COSENTYX INJ AUTO-INJECTOR AND PREFILLED SYRINGE	secukinumab SQ auto-injector ro prefilled syringe	\$4,104/28 day	Human interleukin-17A antagonist indicated for treatment of moderate to severe plaque in adults who are candidates for systemic therapy or phototherapy		Tier 4 PA

Recommended Exclusions:

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	Code
AFREZZA	insulin regular(human) inhalation powder	\$271/box of 90-4unit cartridges (\$0.75/unit)	Inhaled insulin in 4 & 8 unit/cartridge	T2 plan options: Humulin R = \$71/10ml; Novolin R = \$60/10ml. Note: Prices are listed at AWP	13

Recommended Exclusions (continued):

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	Code
RAPIVAB	peramivir inj 200mg/20ml	\$380/20ml vial	Treatment of influenza infection in adults. Dose=600mg IV as a single-dose infused over 15-30 minutes(given within 48 hours of onset of influenza symptoms)		13; make sure excluded on J-codes as well
LIDOVEX CREAM 3.75%	lidocream 3.75%	\$1,297/60 gm tube	Local anesthetics	T1 plan options: lidocaine ointment 5%, lidocaine cream 3%	13
QNASL CHILD SPRAY 40MCG	beclomethasone dipropionate nasal aerosol 40mcg/act	\$164/inhaler	Nasal steroid	Plan options: generic products - azelastine, flunisolide, fluticasone - tier 1. Reference priced: Beconase, Beconase AQ, Flonase, Nasonex, mometasone, Rhinocort AQ, budesonide	13

OBREDON SOLUTION	hydrocodone-guaifenesin soln 2.5-200mg/5ml	\$5.75/5ml	Cold/cough/allergy combination	Tier 1 products available guaifenesin/codeine	13
RYTARY CAPS	carbidopa & levodopa cap CR	\$2.76/cap	Treatment of Parkinson's disease	Tier 1 plan options: carbidopa/levodopa extended release tabs = \$0.93/tab	13
GLYXAMBI	empagliflozin-linagliptin	\$19.20/tab	Treatment of Type 2 diabetes - combination of Jardiance[SGLT2] and Tradjenta[DPP-4 inhibitor]	SGLT2 class excluded. Tradjenta is tier 3 with PA. Costs: Tradjenta - \$13.22/tab, Jardiance = \$13.71/tab	1
DUOPA	carbidopa-levodopa entera suspension	1 box of 7 cartridges = \$1,694	Enteral suspension of carbidopa-levodopa for the treatment of motor fluctuations for people with advanced Parkinson's disease. Duopa is administered using a small, portable infusion pump that delivers carbidopa & levodopa directly into the small intestine for 16 continuous hours via a procedurally placed tube		13

Recommended Exclusions (continued):

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	Code
SOTYLIZE SOLUTION	sotalol oral solution 5mg/ml	\$1.50/ml	Beta-adrenergic blocking agent. Oral solution of sotalol. Prior to approval of oral solution, the tablet form of the product was commonly compounded by pharmacists	sotalol 80mg tab = \$0.45	13
ROSULA	sulfacetamide w/sulfur wash 10-4.5%	\$435/bottle	For acne and seborrheic dermatitis	Tier 1 generic options available	13
ONEXTON GEL	clindamycin - benzoyl peroxide	\$488/bottle	Topical acne product	Other like combinations excluded	13
SPECIALTY DRUGS					
BLINCYTO	blinatumoma b for IV infusion	\$3,814/35mcg	For patients with Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia		1

MIRCERA	methoxy polyethylene glycol-epoetin beta inj	50mcg/\$108 75mcg/\$162 100mcg/\$216	Long-acting erythropoietin receptor activator indicated for treatment of anemia associated with chronic kidney disease. Dosed every 2 weeks.		3
LYNPARAZA	olaparib cap 50mg	\$30/cap. Dose= 400mg by mouth twice a day. \$13,440/448 caps	Monotherapy with deleterious or suspected deleterious germline BRCA mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy		1
IBRANCE CAP	palbociclib	\$11,802 for 21 day supply (125mg/day for 21 days, off 7 days and repeat	Treatment of advanced metastatic breast cancer		1; awaiting OS data
SIGNIFOR LAR INJ	pasireotide for IM ER susp	Available in 20, 40, and 60mg. All strengths \$12,923/vial	Treatment of patients with acromegaly. Initiate therapy with 4mg IM once every 28 days and may be increased to a max of 60mg	Alternatives are octreotide.	13

Not Reviewed/DCWG

BRAND NAME	INGREDIENTS	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	Code
Compound Kits/Bulk Creams/Multivitamin					
CLINOIN CREAM	clindaymcin=tretinonoin-cholesty cream comp kit				4
FP NATURAL LOTION	lotion base				4
DIPENTOCAINE CREAM	diclofenac-gabapentin-lidocaine comp kit				4
BIEST/PROGES CRE	estradiol-estriol-progesterone comp kit				4
PCP 100 KIT	mag cit-bisacodyl-petrolat-PEG-metoclopramide-electrol kit				4
CENOVIA CREAM	hydroquin-fluticas-tretinon cm kit				4
CLARYS CREAM	hydroquin-fluticas-tretinoin crem kit				4
CLINDAP-T CREAM	adapalene-clindamycin cm kit				4
EXTARDOL CREAM	amantadine-gabapentin-diclofenac-baclofen-lido crm kit				4
GAPEAUM CRE BUDIBAC	bulk chemical compound kit				4
INNOPRAX-5 CREAM	amantadine-gabapentin-diclofenac-baclofen-lido kit				4
SUPRACIL CRE	fluorouracil-salicylic cm kit				4
TRISEON CREAM	adapalene-clindamycin - cm kit				4

VALIDERM CRE	calcitriol-fluticasone-tacrolimus cream kit			4	
VERRUNEX	fluorouracil-salicylic cm kit			4	
NOVOCLAIR CRE	tamoxifen-adapalene-diclofenac cm kit			4	
NUVYA	tamoxifen-adapalene-diclofenac cm kit			4	
EMVOREN CRE	diclofenac-amitripty-prilo-lido cm kit			4	
ZYVODOL	diclofenac-amitripty-prilo-lido cm kit			4	
FLUORAC	fluorouracil-diclofenac cm kit			4	
AMITRIPTYLIN CRE	bulk cm			4	
BACLOFEN CRE	bulk cm			4	
OCUVEL	multiple vitamins w/minerals & FA caps		multivitamin	multivitamin policy	7
REVESTA CAP 1MG-5750	folic acid-cholecalciferol cap 1mg-5750 unit	\$829/30 tabs	folic acid/Vit D combo - not listed in Clinical Pharmacology	vitamin/no info	7
POLY-VI-FLOR MIS FS	pediatric multiple vitamins w/fluoride oral strip 1mg	\$248/box of 30 strips	multivitamin strip	vitamin policy	7

Not reviewed Misc:

EPIFIX	amniotic membrane allograft (human)		Surgical supply - not in scope of pharmacy benefits	
ZERBAXA INJECTION	ceftolozane-tazobactam for inj 1-0.5GM	\$99/vial	Combination IV anti-infective for complicated intra-abdominal and complicated urinary tract infections	out of scope and/or DCW
VYVANSE CAPS 10MG	lisdexamfetamine dimesylate cap 10mg		Vyvanse currently T3 with quantity limits and reference priced for members 26 and older. NOTE: new indication for Vyvanse - binge-eating disorder	new strength of covered product. Vyvanse reference priced.
PAIN RELIEF PAD PATCH	lidocaine-menthol patch 5-1%	\$43/patch	Local anesthetics	like products excluded
SCAR PATCH PAD	allantoin-lidocaine-petrolatum patch	\$47/patch	Local anesthetics	like products excluded
PRECEDEX INJ	dexmedetomidine IV solution	n/a	IV administered for sedation induction/maintenance - not in scope of pharmacy benefit	out of scope and/or DCW

Dickerson motioned to accept the report as amended. Dr. Simmons seconded. All were in favor.

Motion Approved

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

Dr. Keisner reported at the previous board meeting the topic of vendor audits were discussed. The board requested input from the DUEC Committee in terms of what should be audited. The following are recommended:

- Brand/Generic fees are applied and priced correctly
- Singular Mac List is applied and priced correctly
- Rebates
- Eligibility
- Deductibles – to ensure they are calculated correctly on the high deductible plan
- “Lesser-than” Logic.
- AWP Discounts
- In-house: step therapy, quantity limits, Prior Authorizations, exclusions, etc.
- Contract Guarantees

ELECTION OF CHAIR AND VICE-CHAIR: *by, Dr. Kat Neill, UAMS*

Dr. Neill announced her term as Chair and Dr. Simmons term as Vice-Chair has expired. Dickerson nominated Dr. Simmons as Chair. Dr. Simmons accepted the position as Chair. Dickerson nominated Dr. Neill as Vice-Chair. Dr. Neill accepted the position of Vice-Chair. Dr. Kirtly motioned for nominations to cease. All were in favor.

Nominations Approved

Meeting Adjourned

	A	B	C	D
1	<u>Delivery Coordination Workgroup Report</u>			
2				
3	<u>Members:</u>			
4	David Keisner PharmD- EBRx			
5	Jill Johnson, PharmD - EBRx			
6	Geri Beth Bemberg PharmD-EBRx managed care resident			
7	Henry Simmons, MD PhD- Medical Director Arkansas Poison Control			
8	Sidney Keisner PharmD- Board Certified Oncology Pharmacist at VA Little Rock			
9	Kati Beth Lewis, PharmD- Clinical Pharmacist at Blue Cross			
10	Stephen Sorsby, MD- Medical Director at Qualchoice / Barry Fielder, PharmD			
11				
12		<u>Current Coverage</u>	<u>Proposed Coverage</u>	
13	<u>Multiple Sclerosis (MS)</u>			
14	Lemtrada (alemtuzumab)	New Drug	Medical PA	
15				
16	<u>IVIG</u>			
17	multiple products	T4 PA pharmacy/Medical PA	PA pharmacy products for self admin. Remove medical PA	
18				
19				
20	<u>Metastatic Melanoma</u>			
21	Opdivo (nivolumab)	New Drug	Medical PA	

Alemtuzumab (Lemtrada)

Ashley Wilson
December 2014

Labeled Indications: relapsing forms of multiple sclerosis (MS)

Comparators:

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

Contraindications: Patients infected with HIV

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

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

Evidence:

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

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

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

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

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

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

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

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

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

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

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

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

Lemtrada (alemtuzumab)

<u>Drug</u>		<u>Year 1</u>	<u>Year 2</u>	<u>Year 3</u>	<u>Year 4</u>	<u>Year 5</u>	<u>Estimated Total 5 year cost for 100 pts</u>
Lemtrada (alemtuzumab)	IV	5 doses \$118,500	3 doses \$71000	20% would receive 3doses 71K	20% would receive 3doses \$71000	20% would receive 3doses \$71000	\$23,210,000
Rebif (interferon beta 1a)	SC 3x/w	\$80,730	\$80,730	\$80,730	\$80,730	\$80,730	\$40,365,000
Betaseron (Interferon b- 1a)	SC QOD	\$78778	\$78778	\$78778	\$78778	\$78778	\$39,389,000
Copaxone (glatiramer)	SC 20mgqd	\$81,176	\$81,176	\$81,176	\$81,176	\$81,176	\$40,588,000
Tysabri (natalizumab)	IV 300mg q4w	\$72,992	\$72,992	\$72,992	\$72,992	\$72,992	\$36,496,000
Gilenya (fingolimod)	PO qd	\$79,939	\$79,939	\$79,939	\$79,939	\$79,939	\$39,969,500

Coles, A.J. et al. *Alemtuzumab more effective than interferon B-1aat 5-year follow CAMMS223 Clinical trial.* 2012. Neurology. 78: 1069-1078

<u>Drug</u>	<u>Cost</u>	
Lemtrada (alemtuzumab)	Year 1 (IV 5 doses) \$118,500	Year 2: (IV 3 doses) \$71,000. Year 3: 80% did not require retreatment
Rebif (interferon beta 1-a)	Yearly cost (SQ 3x/2) \$80,730	
Betaseron (interferon beta-1a)	Yearly cost (SQ qod): \$78,777.95	
Copaxone (glatiramer acetate)	Yearly cost (SQ 20mg daily) \$81,176	Yearly cost (SQ 40mg TIW) \$72,402
Tysabri (natalizumab)	Yearly cost (IV 300mg q4w): \$72,992	
Gilenya (fingolimod)	Yearly cost (PO once daily): \$79,939	
*Lemtrada (alemtuzumab) 12mg/1.2ml: \$23,700	Campath (alemtuzumab): Off the market	

From FiercePharma: “Sanofi Pulls Campath to clear way for higher priced Lemtrada:”

“Campath for leukemia treatment runs \$60,000 per year in the U.S. MS patients need a fraction of the cancer dosage, and so under that pricing scheme, the drug would cost just \$6,000 per year”

“Effective September 4, 2012 Campath will no longer be available commercially, but will be provided through the Campath Distribution Program free of charge.”

Pharmacoeconomic analysis:

<u>Publication</u>	<u>Recommendation</u>	<u>Other info</u>
National Centre for Pharmacoeconomics (NCPE)	"reimbursement of alemtuzumab is recommended. "	"In the incremental analysis of lifetime costs and benefits, alemtuzumab dominated all active comparators in RRMS (i.e. was less costly and more effective)*"
National Institute for Health and Care Excellence (NICE)	"Alemtuzumab is recommended as an option, within its marketing authorization, for treating adults with active relapsing–remitting multiple sclerosis."	The Committee noted that for patients with rapidly evolving severe relapsing-remitting multiple sclerosis, alemtuzumab dominated natalizumab (that is, less expensive and more effective).

*Major drivers of cost-effectiveness in the model are the assumptions that the majority of patients will receive just two annual treatments

Immune Globulin Cost Comparison

Pharmacy Pricing

<u>Product</u>	<u>AWP per gram</u>
Hyqvia kit	\$192/g
Bivigam	\$155/g
Flebogamma	\$101/g
Gammagard	\$149/g
Gammaked	\$145/g
Gammaplex	\$154/g
Gamunex-C	\$122/g
Hizentra	\$181/g
Octagam	\$152/g
Privigen	\$156/g
Garimune NF	\$110/g
Gammagard S/D	\$136/g
Gammagard S/D less IgA	\$190/g

*2014 spend through pharmacy:
\$395,800*

Medical Pricing

Less Cost

Less Variability between products

Prior authorization Requests

Since 9-1-14 there have been 17 PA requests for IVIG, all resulted in approval.

Proposal: Limit IVIG products to medical benefit without PA. PA only pharmacy products to be self-administered.

Opdivo® (nivolumab) 100 mg/10 mL, 40 mg/10 mL Vials

Nghia Tran, PA

February 17, 2015

Labeled Uses: Opdivo® (nivolumab) is indicated for the treatment of patients with unresectable stage III or metastatic stage IV melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor

Comparator Drugs

AWP Cost Comparison for a Month Supply			
Drug	Dosing Regimen	AWP	AWP for a Month Supply (70 kg or BSA: 1.8 m ² Adult)
Opdivo® (nivolumab)	IV: 3 mg/kg once every 2 weeks until disease progression or unacceptable toxicity	<u>IV Solution</u> 100 mg/10 mL (10 mL): \$2,877.60 40 mg/4 mL (4 mL): \$1,151.04	1 mg = \$28.78 420 mg (1 Month) = \$12,085.92
Yervoy® (ipilimumab)	IV: 3 mg/kg every 3 weeks for 4 doses	<u>IV Solution</u> 200 mg/40 mL (40 mL): \$31,025.77 50 mg/10 mL (10 mL): \$7,756.44	1 mg = \$155.13 280 mg (1 Month) = \$43,436.40
DTIC-Dome® (dacarbazine)	IV: 250 mg/m ² /dose days 1-5 every 3 weeks	<u>IV Reconstituted Solution</u> 200 mg (1): \$12.71 100 mg (1): \$11.34	1 mg = \$0.06 600 mg (1 Month/Minimum 1 Dose) = \$38.13 3000 mg (1 Month/Maximum 5 Doses) = \$190.65
Keytruda® (pembrolizumab)	IV: 2 mg/kg once every 3 weeks until disease progression or unacceptable toxicity	<u>IV Reconstituted Solution</u> 50 mg (1): \$2,589.60	1 mg = \$51.79 187 mg (1 Month) = \$9,668.01
Menkinst® (trametinib)	Oral: 2 mg once daily until disease progression or unacceptable toxicity	<u>Tablets</u> 2 mg (30): \$12,085.61 0.5 mg (30): \$3,021.41	\$12,085.61
Tafinlar® (dabrafenib)	Oral: 150 mg twice daily (approximately every 12 hours) until disease progression or unacceptable toxicity	<u>Capsules</u> 75 mg (120): \$10,557.54 50 mg (120): \$7,038.83	\$10,557.54
Zelboraf® (vemurafenib)	Oral: 960 mg twice daily; continue until disease progression or unacceptable toxicity	<u>Tablets</u> 240 mg (120): \$6,510.48	\$13,020.96
Peg-Intron® (peginterferon alfa-2b)	SubQ: Initial: 6 mcg/kg/week for 8 doses; Maintenance: 3 mcg/kg/week for up to 5 years	<u>Subcutaneous Kit</u> 150 mcg/0.5 mL (1): \$1,044.84 120 mcg/0.5 mL (1): \$995.06 80 mcg/0.5 mL (1): \$947.63 50 mcg/0.5 mL (1): \$902.60	Initial Week Dose = \$3,084.74 Initial Month Dose = \$12,338.96

MOA: Opdivo® (nivolumab) is a human immunoglobulin G4 (IgG4) monoclonal antibody that selectively inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor to block the ligands PD-L1 and PD-L2 from binding, resulting in the activation of T-cells and cell-mediated immune responses against tumor cells or pathogens to be recognized as foreign and be eliminated

Severe Adverse Effects: Pneumonitis, colitis, hepatitis, nephritis and renal dysfunction, hypothyroidism, hyperthyroidism, and embryo-fetal toxicity

Drug Interactions: no formal pharmacokinetic drug-drug interaction studies have been conducted

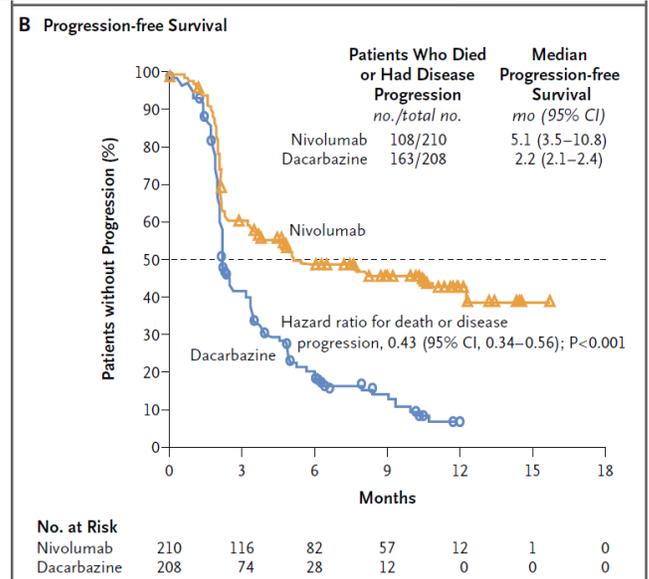
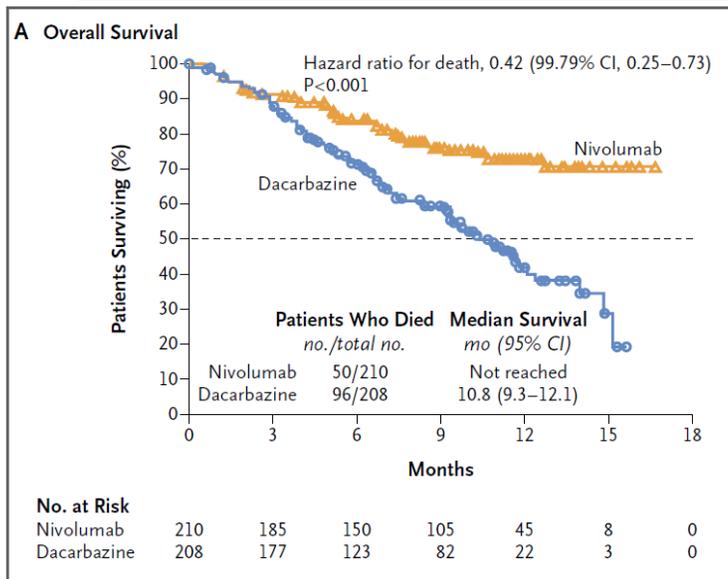
Nivolumab in Previously Untreated Melanoma without BRAF Mutation

- Phase III randomized, double-blind study

- 418 subjects aged 18 to 87 years old who met the following criteria: had confirmed, unresectable, previously untreated stage III of IV melanoma without a BRAF mutation, an Eastern Cooperative Oncology Group performance status score of 0 to 1 (on a scale of 0 to 5), with 0 (no symptoms) and 1 (mild symptoms), and availability of tumor tissue for PD-L1 biomarker analysis

ECOG Performance Status	
Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled and cannot carry on any self-care; totally confined to bed or chair
5	Dead

- 210 subjects received IV infusion of 3 mg of nivolumab per kilogram of body weight every 2 weeks, plus a dacarbazine-matched placebo every 3 weeks; 208 subjects received IV infusion of 1000 mg of dacarbazine per square meter of body-surface area every 3 weeks, plus a nivolumab-matched placebo every 2 weeks
- Dacarbazine was chosen as a comparator because it was a treatment option for patients with melanoma without a BRAF mutation
- Primary efficacy endpoint: overall survival
- Results: At year 1, overall survival rate in the nivolumab group was 72.9% and in the dacarbazine group was 42.1% (hazard ratio for death 0.42; 99.79% CI; P<0.001)
- Secondary endpoint: median progression free-survival was 5.1 months in the nivolumab group and 2.2 months in the dacarbazine group (hazard ratio for death or progression of disease 0.43; 95 CI; P<0.001)



	Adverse Events no. of patients (%)			
	Nivolumab		Dacarbazine	
	Any Grade	Grade 3 or 4	Any Grade	Grade 3 or 4
Adverse event leading to d/c of treatment	14 (6.8%)	12 (5.8%)	24 (11.7%)	19 (9.3%)

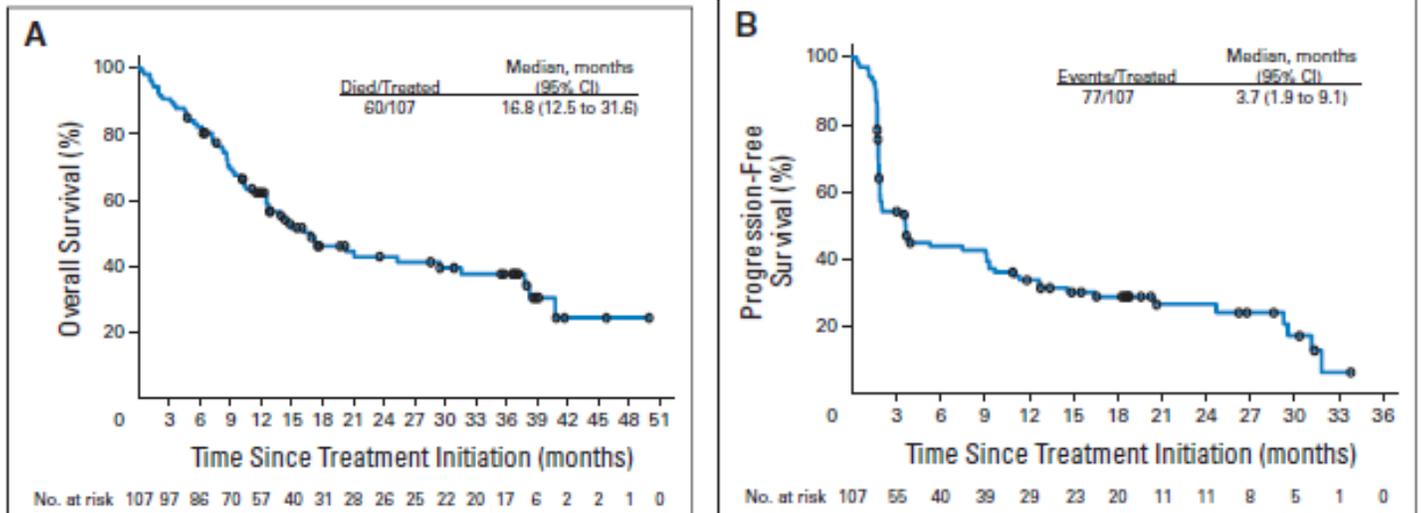
- Funded by Bristol-Myers Squibb Pharmaceutical

Robert C, Long GV, et al. Nivolumab in previously untreated melanoma without BRAF mutation. *N Engl J Med.* 2015 Jan 22;372(4):320-30.

Survival, Durable Tumor Remission, and Long-Term Safety in Patients with Advanced Melanoma Receiving Nivolumab

- Phase I/II dose-escalation, cohort expansion study
- 107 patients were treated at doses from 0.1 to 10 mg/kg in an outpatient setting every two weeks for up to 96 weeks (12 cycles)

- Primary efficacy endpoint: overall survival
- Results: median overall survival was 16.8 months, and the one and two year survival rate was 62% and 43%
- Secondary endpoint: median progression-free survival was 3.7 months



- A/E: fatigue (32%), rash (23%), diarrhea (18%), pruritus (13%), vitiligo (9%), nausea (8%), abdominal pain (8%)
- Funded by Bristol-Myers and Squibb Pharmaceutical and Ono Pharmaceutical

Topalian SL, Sznol M, et al. Survival, durable tumor remission, and long-term safety in patients with advanced melanoma receiving nivolumab. *Journal of Clinical Oncology*. 2014 Apr 1;32(10):1020-30.

NCCN 2.015 Guidelines for Systemic Therapy Options for Advanced or Metastatic Melanoma		
Preferred First-Line Regimens	Alternative Regimens	
<ul style="list-style-type: none"> • Ipilimumab (2A) • Dabrafenib + trametinib (2A) • Pembrolizumab (2A) • Nivolumab^{8,10}(2A) 	<ul style="list-style-type: none"> • Vemurafenib (2A) • Dabrafenib (2A) • Trametinib (2A) • Imatinib (2A) • Dacarbazine (2A) • Temozolomide (2A) 	<ul style="list-style-type: none"> • Albumin-bound paclitaxel (2A) • High-dose IL-2 (2A) • Dacarbazine or temozolomide combination therapy (2B) • Paclitaxel (2B) • Paclitaxel/carboplatin (2B)

⁸While pembrolizumab and nivolumab are indicated for disease progression after treatment with ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor, there is consensus among the NCCN panel that both drugs have a higher response rates and less toxicity compare to ipilimumab, and that both drugs should be included as options for first-line treatment.

¹⁰Nivolumab may cause immune-mediated adverse reactions, including pneumonitis, colitis, hepatitis, nephritis, hypothyroidism, and hyperthyroidism. Depending on the adverse event and the severity of the reaction, discontinuation of therapy and administration of corticosteroids may be required.

Summary:

- Nivolumab had a greater overall survival rate of 30.8% and a greater progression-free survival of 2.9 months than dacarbazine
- Less patients d/c therapy due to a/e in nivolumab compared to dacarbazine
- NCCN recommends nivolumab as first-line therapy for advanced or metastatic melanoma

Recommendation: Include in coverage for patients meeting criteria and requiring a PA

DUEC

Feb, March 2015

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	Consultant NOTES	DUEC DATE	DUEC VOTE	IB DATE	IB VOTE
NON-SPECIALTY DRUGS									
ARNUITY	fluticasone furoate aerosol powder breath act	\$156/100mcg; \$209/200mcg	New fluticasone formulation. Once daily inhaled corticosteroid for maintenance tx of asthma as prophylactic therapy - not indicated for relief of acute bronchospasm	T2 plan options: Flovent HFA: 110mcg/\$231, 220mcg/\$359. Pulmicort Flexihaler 90mcg/\$165, 180mcg/\$250. QVAR: 40mcg/\$167, 80mcg/\$224	Exclude, code 13	2015 04 06			
INCRUSE ELPT INHALER	umeclidinium BR aero powder breath act	\$270/30 doses	Long-term, once daily maintenance treatment of air flow obstruction in patients with COPD, including chronic bronchitis and/or emphysema	T2 plan options: Spiriva Respimat 60 doses/\$357; Spiriva Handihaler Powder/\$357. Tudorza Pressair powder for inhalation: \$336/60 doses	T2	2015 04 06			
AFREZZA	insulin regular(human) inhalation powder	\$271/box of 90-4unit cartridges (\$0.75/unit)	Inhaled insulin in 4 & 8 unit/cartridge	T2 plan options: Humulin R = \$71/10ml; Novolin R = \$60/10ml. Note: Prices are listed at AWP	Exclude, code 13	2015 04 06			
SOOLANTRA CREAM	ivermectin cream	\$330/30gm	Treatment of inflammatory lesions of rosacea	T1 plan option: topical metronidazole gel,cream - \$42/45gm	T3, QL of 30g tube/30d	2015 04 06			
RAPIVAB	peramivir inj 200mg/20ml	\$380/20ml vial	Treatment of influenza infection in adults. Dose=600mg IV as a single-dose infused over 15-30 minutes(given within 48 hours of onset of influenza symptoms)		Exclude, code 13. make sure excluded on J-codes as well	2015 04 06			
LIDOVEX CREAM 3.75%	lidocream 3.75%	\$1,297/60 gm tube	Local anesthetics	T1 plan options: lidocaine ointment 5%, lidocaine cream 3%	Exclude. Other lidocaine creams available in 4% & 5%(5g, 15, 30, 45g tubes). This is \$1231.80/60gtube. The 3% (85g) generic AWP=\$122.52. Smaller tubes 4&5% are \$19-33.	2015 04 06			
QNASL CHILD SPRAY 40MCG	beclomethasone dipropionate nasal aerosol 40mcg/act	\$164/inhaler	Nasal steroid	Plan options: generic products - azelastine, flunisolide, fluticasone - tier 1. Reference priced: Beconase, Beconase AQ, Flonase, Nasonex, mometasone, Rhinocort AQ, budesonide	RP or exclude until comparative trials	2015 04 06			
SAVAYSA TABS	edoxaban tosylate	\$11.08/tab	Oral anticoagulant for reduction in the risk of stroke and systemic embolism in patients with atrial fibrillation that is unrelated to valvular heart disease and for treatment of DVT and PE in patients initially treated with an injectable anticoagulant		Cover Tier 2 w/ others	2015 04 06			
OBREDON SOLUTION	hydrocodone-guaifenesin soln 2.5-200mg/5ml	\$5.75/5ml	Cold/cough/allergy combination	Tier 1 products available guaifenesin/codeine	Exclude, code 13	2015 04 06			
RYTARY CAPS	carbidopa & levodopa cap CR	\$2.76/cap	Treatment of Parkinson's disease	Teir 1 plan options: carbidopa/levodopa extended release tabs = \$0.93/tab	Exclude, code 13	2015 04 06			
GLYXAMBI	empagliflozin-linagliptin	\$19.20/tab	Treatment of Type 2 diabetes - combination of Jardiance[SGLT2] and Tradjenta[DPP-4 inhibitor]	SGLT2 class excluded. Tradjenta is tier 3 with PA. Costs: Tradjenta - \$13.22/tab, Jardiance = \$13.71/tab	Exclude, code 1	2015 04 06			
MOVANTIK	naloxegol oxalate	\$9.98/tab (dose= 1 tab/day)	Treatment of opioid-induced constipation in adults with chronic non-cancer pain	Tier 3 plan options for opioid induced constipation: Amitiza/\$9.90 per day. Relistor by subcutaneous injection/\$86 every other day	Cover, Tier 3, QL of 1/1, revisit in 6 months (Sept 2015) for price reasons, bring to DCWG in Sept 2015.	2015 04 06			

DUOPA	carbidopa-levodopa entera suspension	1 box of 7 cartridges = \$1,694	Enteral suspension of carbidopa-levodopa for the treatment of motor fluctuations for people with advanced Parkinson's disease. Duopa is administered using a small, portable infusion pump that delivers carbidopa & levodopa directly into the small intestine for 16 continuous hours via a procedurally placed tube			2015 04 06			
					Exclude, code 13.				
SOTYLIZE SOLUTION	sotalol oral solution 5mg/ml	\$1.50/ml	Beta-adrenergic blocking agent. Oral solution of sotalol. Prior to approval of oral solution, the tablet form of the product was commonly compounded by pharmacists	sotalol 80mg tab = \$0.45	Exclude, code 13.	2015 04 06			
ZUBSOLV SUB 8.6-2.1	buprenorphine-naloxone SL tab 8.6-2.1mg	\$12.67/tab	new dosage form	Other ZUBSOLV strenghts excluded by plan	T3PA, QL #62/31. Revisit on 9/25/13.	2015 04 06			
PAZEO DROPS	olopatadine opgth solution 0.7%	\$179/2.5ml	For ocular allergy itch relief	Tier 1 plan options: azelastine/\$104 per 6 ml; olopatadine/\$78/5ml	T3.	2015 04 06			
ROSULA	sulfacetamide w/sulfur wash 10-4.5%	\$435/bottle	For acne and seborrheic dermatitis	Tier 1 generic options available	Exclude, code 13.	2015 04 06			
ONEXTON GEL	clindamycin -benzoyl peroxide	\$488/bottle	Topical acne product	Other like combinations excluded	Exclude, code 13.	2015 04 06			
SPECIALTY DRUGS						2015 04 06			
BLINCYTO	blinatumomab for IV infusion	\$3,814/35mcg	For patients with Philadelphia chromosome-negative precursor B-cell acute lymphoblastic leukemia		Exclude, code 1	2015 04 06			
MIRCERA	methoxy polyethylene glycol-epoetin beta inj	50mcg/\$108 75mcg/\$162 100mcg/\$216	Long-acting erythropoietin receptor activator indicated for treatment of anemia assoicated with chronic kidney diesase. Dosed every 2 weeks.		EXCLUDE, code 3	2015 04 06			
LYNPARAZA	olaparib cap 50mg	\$30/cap. Dose= 400mg by mouth twice a day. \$13,440/448 caps	Monotherapy with deleterious or suspected deleterious germline BRCA mutated advanced ovarian cancer who have been treated with three or more prior lines of chemotherapy		Exclude, code 1	2015 04 06			
REYATAZ	atazanavir oral powder packet 50mg	\$7.90 each	New dosage formulation. For HIV infection	Reyataz caps covered as specialty tier. 100mg cap = \$21.97	T3PA, for infants >3m and children weighing 10-25kg, age edit of less than 7 years.	2015 04 06			
VITEKTA	elvitegravir tabs	\$45.06/tab	For use in combination with ritonavir, another protease inhibitor, and other antiretroviral drug (s) to treat HIV in adults who are antiretroviral experienced		Tier 3, no PA.	2015 04 06			
EVOTAZ TAB	atazanavir 300mg-cobicistat 150 tab(Reyataz-Tybost)	\$56.14/tab	Treatment of HIV infection	Reyataz covered specialty tier (\$50.69/300mg tab) Tybost 150mg coded as excluded (\$7.20/150mg tab)	Tier 3, no PA.	2015 04 06			
PREZCOBIX TAB	darunavir 800mg-cobicistat 150mg(Prezista-Tybost)	\$57.52/tab	Treatment of HIV infection	Prezista covered specialty tier (\$50.32/800mg tab) Tybost 150mg coded as excluded (\$7.20/150mg tab)	Tier 3, no PA.	2015 04 06			
IBRANCE CAP	palbociclib	\$11,802 for 21 day supply (125mg/day for 21 days, off 7 days and repeat	Treatment of advanced metastatic breast cancer		Exclude, code 1.Awaiting OS data.	2015 04 06			

COSENTYX INJ AUTO-INJECTOR AND PREFILLED SYRINGE	secukinumab SQ auto-injector ro prefilled syringe	\$4,104/28 day	Human interleukin-17A antagonist indicated for treatment of moderate to severe plaque in adults who are candidates for systemic therapy or phototherapy		T4PA	2015 04 06			
SIGNIFOR LAR INJ	pasireotide for IM ER susp	Available in 20, 40, and 60mg. All strengths \$12,923/vial	Treatment of patients with acromegaly. Initiate therapy with 4mg IM once every 28 days and may be increased to a max of 60mg		Exclude, code 13. Data showed only a slight difference in IGF-1 and GH, and had a high side effect profile, especially with diabetes and hyperglycemia. Alternatives are octreotide.	2015 04 06			
						2015 04 06			
Not Reviewed						2015 04 06			
						2015 04 06			
COMPOUND KITS/BULK Creams						2015 04 06			
CLINOIN CREAM	clindaymcin=tretinonoi n-cholesty cream comp kit					2015 04 06			
FP NATURAL LOTION	lotion base					2015 04 06			
DIPENTOCAINE CREAM	diclofenac-gabapentin-lidocaine comp kit					2015 04 06			
BIEST/PROGES CRE	estradiol-estriol-progesterone comp kit					2015 04 06			
PCP 100 KIT	mag cit-bisacodyl-petrolat-PEG-metoclopramide-electrol kit					2015 04 06			
CENOVIA CREAM	hydroquin-fluticas-tretinon cm kit					2015 04 06			
CLARYS CREAM	hydroquin-fluticas-tretinoin crem kit					2015 04 06			
CLINDAP-T CREAM	adapalene-clindamycin cm kit					2015 04 06			
EXTARDOL CREAM	amantadine-gabapent-diclofenac-baclofen-lido crm kit					2015 04 06			
GAPEAUM CRE BUDIBAC	bulk chemical compound kit					2015 04 06			
INNOPRAX-5 CREAM	amantadine-gabapent-diclofenac-baclofen-lido kit					2015 04 06			
SUPRACIL CRE	fluorouracil-salicyclie cm kit					2015 04 06			
TRISEON CREAM	adapalene-clindaymycin - cm kit					2015 04 06			
VALIDERM CRE	calcitriol-fluticasone-tacrolimus cream kit					2015 04 06			
VERRUNEX	fluorouracil-salicyclie cm kit					2015 04 06			
NOVOCLAIR CRE	tamoxifen-adapalene-diclofenac cm kit					2015 04 06			
NUVYA	tamoxifen-adapalene-diclofenac cm kit					2015 04 06			
EMVOREN CRE	diclofenac-amitripty-prilo-lido cm kit					2015 04 06			

ZYVODOL	diclofenac-amitripty-prilo-lido cm kit					2015 04 06			
FLUORAC	fluorouracil-diclofenac cm kit					2015 04 06			
AMITRIPTYLIN CRE	bulk cm					2015 04 06			
BACLOFEN CRE	bulk cm					2015 04 06			
MISC						2015 04 06			
EPIFIX	amniotic membrane allograft (human)		Surgical supply - not in scope of pharmacy benefits			2015 04 06			
						2015 04 06			
OCUVEL	multiple vitamins w/minerals & FA caps		multivitamin	multivitamin policy		2015 04 06			
FLUZONE QUAD INJ	influenza virus vac split quad intradermal pen	\$24.70/pen	flu vaccine	immunization policy		2015 04 06			
ZERBAXA INJECTION	ceftolozane-tazobactam for inj 1-0.5GM	\$99/vial	Combination IV anti-infective for complicated intra-abdominal and complicated urinary tract infections	out of scope and/or DCW		2015 04 06			
REVESTA CAP 1MG-5750	folic acid-cholecalciferol cap 1mg-5750 unit	\$829/30 tabs	folic acid/Vit D combo - not listed in Clinical Pharmacology	vitamin/no info		2015 04 06			
VYVANSE CAPS 10MG	lisdexamfetamine dimesylate cap 10mg		Vyvanse currently T3 with quantity limits and reference priced for members 26 and older. NOTE: new indication for Vyvanse - binge-eating disorder	new strength of covered product. Vyvanse reference priced.		2015 04 06			
BEXSERO INJ	meningococcal Vac B inj in prefilled syringe		Meningococcal vaccine	immunization policy		2015 04 06			
PAIN RELIEF PAD PATCH	lidocaine-menthol patch 5-1%	\$43/patch	Local anesthetics	like products excluded		2015 04 06			
SCAR PATCH PAD	allantoin-lidocaine-petrolatum patch	\$47/patch	Local anesthetics	like products excluded		2015 04 06			
PRECEDEX INJ	dexmedetomidine IV solution	n/a	IV administered for sedation induction/maintenance - not in scope of pharmacy benefit	out of scope and/or DCW		2015 04 06			
POLY-VI-FLOR MIS FS	pediatric multiple vitamins w/fluoride oral strip 1mg	\$248/box of 30 strips	multivitamin strip	vitamin policy		2015 04 06			

**Arnuity Ellipta (fluticasone furoate) 100mcg, 200mcg/actuation
Inhaled Corticosteroid**

Indications: once daily maintenance treatment of asthma as prophylactic therapy in patients 12 years of age and older. (As a reminder, Flovent HFA & Flovent Diskus are both indicated for age 4 and up.)

Dosing: 100 to 200mcg once daily, with a maximum of 200mcg once daily

Drug Formulation	Package Size	Price	Price/unit	Price/day
Arnuity Ellipta 100mcg	14 actuations	\$73.02	\$5.216	\$5.216
Arnuity Ellipta 100mcg	30 actuations	??		
Arnuity Ellipta 200mcg	14 actuations	\$97.76	\$6.983	\$6.983
Arnuity Ellipta 200mcg	30 actuations	???		
Flovent HFA 44mcg	10.6g (120 act)	\$172.79	\$1.44	\$2.88
Flovent HFA 110mcg	12g (120 act)	\$231.34	\$1.928	\$3.856
Flovent HFA 220mcg	12g (120 act)	\$359.32	\$2.994	\$5.989
Flovent Diskus 50mcg	60 blisters	\$163.86	\$2.731	\$5.462
Flovent Diskus 100mcg	28 blisters	\$100.61	\$3.593	\$7.186
Flovent Diskus 100mcg	60 blisters	???		
Flovent Diskus 250mcg	28 blisters	\$134.71	\$4.811	\$9.622
Flovent Diskus 250mcg	60 blisters	???		

Recommendation: Exclude Arnuity based on pricing. Revisit when data becomes available concerning once daily fluticasone furoate vs twice daily fluticasone propionate.

Umeclidinium (Incruse Ellipta)

Sarah Mangham, P4

01/26/2015

Labeled Uses: Maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

Comparator Drugs: FDA approved for the treatment of COPD.

Brand (generic)	Dose (DPI)	Frequency of Administration	AWP for 30 days supply
Incruse Ellipta (umeclidinium)	One 62.5 mcg inhalation	Once daily	\$269.71
Tudorza Pressair (aclidinium)	One 400 mcg inhalation	Twice Daily	\$256.05
Spiriva Handihaler (tiotropium)	Two inhalations of the contents of one 18 mcg capsule	Once daily	\$357.37

MOA: Umeclidinium is a long-acting muscarinic antagonist. It has similar affinity to the subtypes of muscarinic receptors M1 to M5. It competitively and reversibly inhibits the action of acetylcholine at type M₃ receptors in bronchial smooth muscle causing bronchodilation.

Contraindications: Hypersensitivity to umeclidinium or any component of the formulation. Severe hypersensitivity to milk proteins.

Adverse Reactions: Nasopharyngitis, URTI, cough, arthralgia, abdominal pain, bruising, myalgia, pharyngitis, tachycardia, toothache and atrial fibrillation.

Drug interactions:

Umeclidinium may increase the adverse effects of the following: Neuromuscular blocking agents, opioid analgesics, anticholinergic agents (avoid concomitant use), mirabegron, thiazide diuretics, topiramate, and potassium chloride (avoid concomitant use). Umeclidinium may diminish the effects of the following: Acetylcholinesterase inhibitors, cholinergic agents, and secretin.

Evidence:

Umeclidinium in patients with COPD

- **Design:** A randomized, placebo-controlled study was used to evaluate the efficacy and safety of umeclidinium in patients with moderate to very severe COPD. It compared the use of once daily umeclidinium 62.5 mcg (n=62) and 125 mcg (n= 56) to placebo (n=50) over 12 weeks. 246 subjects were enrolled, but only 168 completed the study.
- **Results:** At day 85, statistically significant (p<0.001) improvements (primary endpoint) in least squares mean (LSM) change from baseline in trough FEV₁ were observed for umeclidinium 62.5 mcg (127 mL, 95% CI 52 to 202 mL) and for 125 mcg (152 mL, 95% CI 76 to 229 mL) compared with placebo. The differences in rescue-treatment use from placebo (secondary endpoint) were also of note, umeclidinium 62.5 mcg (mean -0.7 puffs per day (95% CI -1.3 to -0.1), p=0.025), but not 125 mcg (mean -0.6 puffs per day (95% CI -1.2 to 0.0), P=0.069). The percentage of rescue-free days over 12 weeks increased from baseline for umeclidinium 62.5 mcg (9.0%) and 125 mcg (8.3%) but decreased with placebo (-4.2%).

Roopa Trivedi, Nathalie Richard, et al. Umeclidinium in patients with COPD: a randomised, placebo-controlled study. ERS Journals. Eur Respir J 2014; 43: 72–81. PMID: 23949963

Bronchodilation of umeclidinium, a new long-acting muscarinic antagonist, in COPD patients

- **Design:** This randomized, double blind, placebo-controlled, parallel-group study was used to evaluate the dose response of umeclidinium. Three once daily doses of umeclidinium (125, 250 and 500 mcg) were compared to a placebo for 28 days in 285 patients with COPD having FEV₁ of 35–70% predicted (mean post-bronchodilator FEV₁ = 1.577 (0.450)).
- **Results:** The primary endpoint was a morning trough FEV₁ at Day 29. All strengths of umeclidinium increased trough FEV₁ over placebo from 150 to 168 mL (p < 0.001). The secondary endpoint was a 0–6 h weighted mean FEV₁ from 113 to 211 mL (p < 0.001), and serial FEV₁ at each point in time over 24 h. Reductions in salbutamol use and improvements in FVC were noted for all doses.

Decramera M, Maltais F, Etal. Bronchodilation of umeclidinium, a new long-acting muscarinic antagonist, in COPD patients. ELSEVIR Respiratory Physiology & Neurobiology 185 (2013) 393– 399. PMID: 23026438

Recommendation: I recommend covering Incruse Ellipta due to cost and frequency of administration compared to other LAMAs.

Outcome: Cover drug, tier 2...Revisit pricing in 6 months.

Short acting inhaled insulin (Afrezza)
Sarah Mangham, P4
01/26/2015

Labeled Uses: Afrezza is a short acting inhaled insulin (uses technosphere inhalation technology) indicated to improve glycemic control in adult patients with diabetes mellitus type 1 & 2.

Comparator Drugs:

Brand	How supplied (units/cartridge for Afrezza)	AWP
Afrezza	4 units (#30) 8 units (#60) *total=600 units, #90 cartridges	\$334.31
Afrezza	4 units (#60) 8 units (#30) *total=480 units, #90 cartridges	\$302.80
Afrezza	4 units (#90) *total=360 units, #90 cartridges	\$271.15
Novolin R	10 ml vial (100 units/ml) *total=1000 units	\$131.47
Humulin R	3 ml vial (100 units/ml) *total=300 units	\$39.49

Contraindications: Chronic lung disease (asthma or COPD) due to risk of bronchospasm, during episodes of hypoglycemia, and hypersensitivity to regular insulin or any of the Afrezza excipients.

Adverse Reactions: Acute bronchospasm in patients with chronic lung disease, hypoglycemia, decline in pulmonary function, dry non-productive cough, lung cancer, weight gain, diabetic ketoacidosis, and hypersensitivity reactions.

Drug interactions: Drugs that may increase the risk of hypoglycemia: Quinolone antibiotics, antidiabetic agents, ACEI/ARBs, disopyramide, fibrates fluoxetine, MAOIs, pentoxifylline, salicylates, somatostatin analogs, and sulfonamide antibiotics.

Drugs that may increase or decrease the blood glucose lowering effect of Afrezza: Alcohol, beta-blockers, clonidine, and lithium salts. Pentamidine may cause hypoglycemia, which may sometimes be followed by hyperglycemia.

Evidence:

Efficacy and Safety of Technosphere Inhaled Insulin Compared With Technosphere Powder Placebo in Insulin-Naive Type 2 Diabetes Suboptimally Controlled With Oral Agents

- **Design:** The efficacy, safety, and tolerability of Technosphere insulin (n=61) was compared with Technosphere powder as placebo (n=62) in a double-blind, placebo-controlled, randomized, multicenter, parallel-group study in subjects (n=123) that were insulin-naïve type 2 diabetic with suboptimal control with oral antidiabetics.
- **Results:** Technosphere insulin had a 7.9% greater HgA_{1c} reduction from baseline (primary endpoint) compared to Technosphere placebo (-0.72 vs -0.30%; p=0.003). Postprandial glucose levels (secondary endpoint) were reduced by 56% with Technosphere insulin compared to a 43% reduction by Technosphere placebo. Adverse events such as hypoglycemia, hyperglycemia, and cough were low in both subject groups.

Rosenstock J, Bergenstal R, et al. Efficacy and Safety of Technosphere Inhaled Insulin Compared With Technosphere Powder Placebo in Insulin-Naïve Type 2 Diabetes Suboptimally Controlled With Oral Agents. Diabetes Care, volume 31, number 11, November 2008. PMID: 18678610

Pulmonary function over 2 years in diabetic patients treated with prandial inhaled Technosphere Insulin or usual antidiabetes treatment: a randomized trial

- **Design:** This randomized, open-label study evaluated pulmonary function changes in diabetes patients receiving inhaled Technosphere insulin (TI) or usual antidiabetes treatment (usual care) over a 2 year period at 220 sites. PFTs were prospectively followed in patients with type 1 or 2 diabetes receiving TI (n=730) or usual care (n=824) along with a cohort without diabetes not receiving any care (n=145).
- **Results:** Lung function declined from baseline in all groups, after 24 months TI was non-inferior to usual care for mean FEV₁ change from baseline (primary endpoint). The adjusted mean treatment group difference in change in FEV₁ was 0.037 (0.0119; 95% CI, 0.014 to 0.060). TI was well tolerated, with the most common respiratory event being a mild, transient cough that occurred within minutes of inhalation (secondary endpoint).

Raskin P, Heller S, et al. Pulmonary function over 2 years in diabetic patients treated with prandial inhaled Technosphere Insulin or usual antidiabetes treatment: a randomized trial. Diabetes, Obesity and Metabolism 14: 163–173, 2012. PMID: 21951325

Table 4. Results at Week 24 in an Active-Controlled Study of Mealtime AFREZZA plus Basal Insulin in Adults with Type 1 Diabetes

Efficacy Parameter	AFREZZA + Basal Insulin (N=174)	Insulin Aspart + Basal Insulin (N=170)
HbA _{1c} (%)		
Baseline (adjusted mean [*])	7.94	7.92
Change from baseline (adjusted mean ^{*,†})	-0.21	-0.40
Difference from insulin aspart (adjusted mean ^{*,†})	0.19	
(95% CI)	(0.02, 0.36)	
Percentage of patients achieving HbA _{1c} ≤ 7% [‡]	13.8	27.1
Fasting Plasma Glucose (mg/dL)		
Baseline (adjusted mean [*])	153.9	151.6
Change from baseline (adjusted mean ^{*,†})	-25.3	10.2
Difference from insulin aspart (adjusted mean ^{*,†})	-35.4	
(95% CI)	(-56.3, -14.6)	

* Adjusted mean was obtained using a Mixed Model Repeated Measures (MMRM) approach with HbA_{1c} or FPG as the dependent variable and treatment, visit, region, basal insulin stratum, and treatment by visit interaction as fixed factors, and corresponding baseline as a covariate. An autoregression (1) [AR(1)] covariance structure was used.

† Data at 24 weeks were available from 131 (75 %) and 150 (88%) subjects randomized to the AFREZZA and insulin aspart groups, respectively.

‡ The percentage was calculated based on the number of patients randomized to the trial.

Table used from Afrezza package insert accessed from dailymed on 1/23/2015.

Recommendation: Afrezza should not be covered. There are other available options that are proven to be effective and much more cost effective to outweigh the possible ease of use of inhaled insulin.

Outcome: Exclude.

Ivermectin (Soolantra) 1% Cream
Geri Bemberg, Pharm.D.

Indications: treatment of inflammatory lesions of rosacea

MOA: unknown. Thought to be due to the anti-inflammatory effects of ivermectin, as well as the possible involvement of parasitic mites (*Demodex folliculorum*). By inhibiting the lipopolysaccharide-induced production of inflammatory cytokines and increasing the anti-inflammatory cytokine IL-10, ivermectin is believed to act on rosacea mainly with its anti-inflammatory processes.

Ivermectin in a Cetaphil vehicle.

Drug	Formulation	Dosing Interval	Price/package
Soolantra (ivermectin) 1%	Cream	Once daily	\$330.00/30g
MetroCream (metronidazole) 0.75%	Cream	Twice daily	\$620.88/45g
Rosadan (metronidazole) 0.75%	Cream	Twice daily	\$258.24/45g
Metronidazole 0.75%	Cream	Twice daily	\$319.67/45g
Noritrate (metronidazole) 1%	Cream	Once daily	\$1135.68/60g
Metrogel (metronidazole) 1%	Gel (pump)	Once daily	\$373.68/55g
Rosadan (metronidazole) 0.75%	Gel	Twice daily	\$258.24/45g
Metronidazole 0.75%	Gel	Twice daily	\$170.85/45g
Metronidazole 1%	Gel	Once daily	\$277.26/55g
MetroLotion (metronidazole) 0.75%	Lotion	Twice daily	\$713.64/59mL
Metronidazole 0.75%	Lotion	Twice daily	\$247.14/59mL
Finacea (azelaic acid) 15%	Gel	Twice daily	\$283.34/50g

Effective and evidence-based management strategies for rosacea: summary of a Cochrane systematic review. Zuuren EJ, Kramer SF, Carter BR, et al. Brit Assoc Derm 2011(165):760-781.

Systematic review of 58 randomized controlled trials in people with moderate to severe rosacea were included. Interventions included topical metronidazole, oral antibiotics, topical azelaic cream or gel, topical benzoyl peroxide and/or combined with topical antibiotics, sulphacetamide/sulphur, and others.

Findings: Topical metronidazole, azelaic acid and doxycycline (40mg) appear to be effective and safe for papulopustular rosacea. In some trials, it appears that azelaic acid is more effective than metronidazole, but has more side-effects. A single dose of azelaic acid looks to be as effective as the twice daily dose. However, RCTs on the effectiveness of azelaic acid and metronidazole in maintenance therapy are still required.

There is no clear evidence “demonstrating that any one of these treatments, or any combination of treatments, has a particular advantage in terms of higher remission rates and/or fewer adverse effects.

Efficacy and Safety of Ivermectin 1% Cream in Treatment of Papulopustular Rosacea: Results of Two Randomized, Double-Blind, Vehicle-Controlled Pivotal Studies. Gold LS, Kircik L, Fowler J, et al. J Drugs Dermatol. 2014;13(3)316-323.

Two randomized, double-blind, controlled studies of ivermectin 1% cream or vehicle once daily for 12 weeks were conducted in patients with moderate to severe PPR. Primary efficacy assessments were Investigator’s Global Assessment of disease severity (0-4 taking into account inflammatory lesions, erythema severity. 0= clear, 4=severe) and inflammatory lesions counts.

% of patients with IGA success (clear or almost clear at week 12)		
Treatment arm	Study 1	Study 2
Ivermectin 1%	38.4%	40.1%
Vehicle (cetaphil)	11.6%	18.8%
Difference	26.8%	21.3%

Not yet published, but has been accepted for publication in the British Journal of Dermatology and is currently being edited and typeset. Accepted Aug 12, 2014 Superiority of ivermectin 1% cream over metronidazole 0.75% cream in treating inflammatory lesions of rosacea: a randomized, investigator-blinded trial. Taieb A, Ortonne JP, Ruzicka T, et al.

Phase 3, investigator-blinded, randomized, parallel group study. Eligible patients were those 18 or older with moderate or severe papulopustular rosacea (IGA of 3 or 4) and presenting with 15-70 facial inflammatory lesions. Total of 962 patients were randomized to receive IVM 1% (n=478) once daily or metronidazole 0.75% (n=484) twice daily over 16 weeks. Patients were instructed to apply

to the entire face, and to maintain a consistent lifestyle avoiding rosacea triggers (avoiding known offending environmental factors and foods, and excessive sun exposure.) Primary efficacy assessments were inflammatory lesion counts and Investigator’s Global Assessment (IGA). Also looked at the patient reported Dermatology Life Quality Index (DLQI).*** Both groups were similar at baseline with an average of 32 inflammatory lesions, and the majority having moderate rosacea (83.3% with an IGA of 3).

Results			
Endpoint	Ivermectin	Metronidazole	Difference between groups
Inflammatory lesion count (% reduction from baseline)	83%	73.7%	9.3%
IGA success rate (patients rating clear or almost clear)	84.9%	75.4%	9.5%

13.2% more patients rated at completely clear for ivermectin, and in a subgroup analysis, 19.5% more patients with severe rosacea at baseline achieved success.

DLQI		
Group	Baseline	Change
Ivermectin	6.93	-5.18
Metronidazole	6.05	-3.92

*****DLQI –**

10 questions worth 3 points each, for a maximum score of 30. The higher the score, the more quality of life is impaired. Questions measure topics such as symptoms and feelings, work and school, and personal relationships. Scale as follows:

- 0-1= no effect at all on patient’s life
- 2-5= small effect on patient’s life
- 6-10= moderate effect on patient’s life
- 11-20= very large effect on patient’s life
- 21-30= extremely large effect on patients life

Minimum clinically important difference of the DLQI is a change of 2.2-6.9.

IGA		
Grade	Score	Clinical Description
Clear	0	No inflammatory lesions present, no erythema
Almost clear	1	Very few small papules/pustules, very mild erythema present
Mild	2	Few small papules/pustules, mild erythema
Moderate	3	Several small or large papules/pustules, moderate erythema
Severe	4	Numerous small and/or large papules/pustules, severe erythema

Recommendation:

1. Exclude until further evidence.
2. Approve coverage for papulopustular rosacea after failure of metronidazole and azelaic acid.

References

1. Basra MKA, Fenech R, Gatt RM, Salek MS, Finlay AY. The Dermatology Life Quality Index 1994-2007: a comprehensive review of validation data and clinical results. Br J Dermatol. 2008; 159:997-1035.
2. Superiority of ivermectin 1% cream over metronidazole 0.75% cream in treating inflammatory lesions of rosacea: a randomized, investigator-blinded trial. Taieb A, Ortonne JP, Ruzicka T, et al.
3. Effective and evidence-based management strategies for rosacea: summary of a Cochrane systematic review. Zuuren EJ, Kramer SF, Carter BR, et al. Brit Assoc Derm 2011(165):760-781.
4. Up to Date. Management of rosacea. December 2014

Rapivab® (peramivir) 200 mg/20 mL Vial

Nghia Tran, P4

February 15, 2015

Labeled Uses: treatment of acute uncomplicated influenza within 2 days of onset of symptoms in patients 18 years and older

Dosage and Administration: a single 600 mg dose administered via intravenous infusion for 15 to 30 minutes

Treatment and Prophylaxis for Acute Uncomplicated Influenza				
Antiviral Agent	Use	Recommend For	AWP for Treatment of Acute Uncomplicated Influenza	Dosing Adjustment with Renal Impairment
Rapivab® (peramivir) IV Solution 200 mg/20 mL: \$380.00	Treatment	18 years and older	Single Dose IV 600 mg (60 mL): \$1,140	CrCl \geq 50 mL/minute: No dosage adjustment necessary CrCl 30-49 mL/minute: 200 mg as a single dose CrCl 10-29 mL/minute: 100 mg as a single dose ESRD intermittent hemodialysis: 100 mg as a single dose, administered after dialysis
	Prophylaxis	Not recommended		
Tamiflu® (oseltamivir) Oral Capsules 75 mg (10): \$144.72	Treatment	Any age	75 mg BID for 5 days: \$144.72	CrCl >60 mL/minute: No dosage adjustment necessary CrCl >30 to 60 mL/minute: 30 mg twice daily for 5 days CrCl >10 to 30 mL/minute: 30 mg once daily for 5 days ESRD not undergoing dialysis: use is not recommended
	Prophylaxis	3 months and older		
Relenza® (zanamivir) Aerosol Powder 5 mg/blister (20): \$70.80	Treatment	7 years and older	Two Inhalations (10 mg) BID for 5 days: \$70.80	Adjustment Not Necessary
	Prophylaxis	5 years and older		

MOA: a cyclopentane analogue that selectively inhibits the influenza virus neuraminidase enzyme, preventing the release of viral particles from infected cells

Common Adverse Reactions: diarrhea and nausea

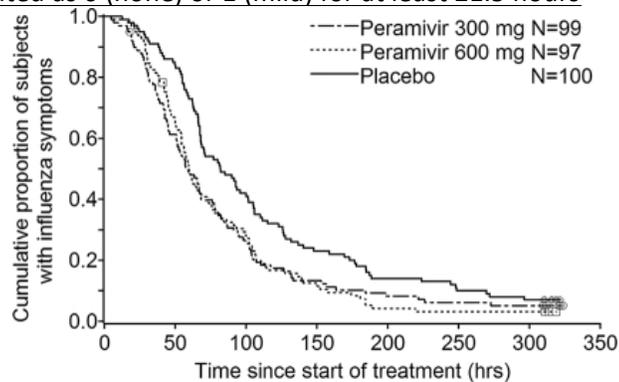
Serious Adverse Reactions: skin/hypersensitivity reactions (erythema multiforme and Stevens-Johnson syndrome), neuropsychiatric events (delirium and abnormal behavior)

Drug Interactions: may reduce the efficacy of live attenuated influenza vaccine (LAIV); avoid use of LAIV within 2 weeks before or 48 hours after administration of peramivir

Efficacy and Safety of Intravenous Peramivir for Treatment of Seasonal Influenza Virus Infection

- Phase II 3-armed, MC, DB, R, PC, outpatient trial
- 300 adult subjects aged 20 to 64 years old who met the following criteria were enrolled: onset of influenza-like illness within the previous 48 hours, fever with an axillary temperature of \geq 38.0°C (100.4°F), at least two moderate to severe symptoms among seven symptoms (headache, muscle or joint pain, feverishness or chills, fatigue, cough, sore throat, and nasal stuffiness) due to influenza, and a rapid antigen test (RAT) result positive for influenza
- 99 subjects received a single IV infusion of 300 mg peramivir; 97 received a single IV infusion of 600 mg peramivir; 100 received placebo (2 subjects withdrew before treatment, 1 subject did was not confirmed to have influenza, 1 subject did not have any symptoms assessment data)
- All subjects were dispensed acetaminophen at enrollment and instructed to take only for symptom relief
- Subjects assessed their symptoms based on Influenza Symptom Severity scale questionnaire: 0 (none), 1 (mild), 2 (moderate), and 3 (severe); questionnaire was asked twice daily on days 1-9 and once daily on days 10-14

- Primary efficacy endpoint: time to alleviation of influenza symptoms at the first time point when all seven influenza symptoms were rated as 0 (none) or 1 (mild) for at least 21.5 hours



- Results: median times to alleviation of symptoms were 59.1 hours for 300 mg IV peramivir (hazard ratio 0.681; adjusted P value 0.0092), 59.9 hours 600 mg IV peramivir (hazard ratio 0.666; adjusted P value 0.0092), and 81.8 hours for placebo
- Safety: most common adverse events were diarrhea and nausea
- Funded by Shinogi Pharmaceutical (BioCryst Pharmaceutical's Partner in Japan)

Kohno S, Kida H, et al. Efficacy and safety of intravenous peramivir for treatment of seasonal influenza virus infection. *Antimicrob Agents Chemother.* 2010;54(11):4568.

Phase III Randomized, Double-Blind Study Comparing Single-Dose Intravenous Peramivir with Oral Oseltamivir in Patients with Seasonal Influenza Virus Infection

- A 3-armed, MC, DB, R, double-dummy, outpatient study
- Aimed to demonstrate noninferiority of peramivir to oseltamivir in reducing the time to alleviation of influenza symptoms with hazard model analysis and a noninferiority margin of 0.170 and a upper limit of 1.170
- 1099 adult subjects 20 years or older with influenza who met the following criteria were enrolled: availability for treatment within 48 hours of onset of influenza symptoms, fever with an axillary temperature of $\geq 38.0^{\circ}\text{C}$ (100.4°F), at least two moderate to severe symptoms among seven symptoms (headache, muscle or joint pain, feverishness or chills, fatigue, cough, sore throat, and nasal stuffiness) due to influenza, and a rapid antigen test (RAT) result positive for influenza
- 364 subjects received a single IV infusion of 300 mg peramivir; 362 received a single IV infusion of 600 mg peramivir; 365 received oseltamivir 75 mg PO BID for 5 days (6 subjects withdrew before treatment and 2 subjects did not have any symptoms assessment data)
- Concomitant use of acetaminophen was allowed
- Subjects assessed their symptoms based on Influenza Symptom Severity scale questionnaire: 0 (none), 1 (mild), 2 (moderate), and 3 (severe); questionnaire was asked twice daily on days 1-8 and once daily on days 9-14
- Primary efficacy endpoint: time to alleviation of influenza symptoms at the first time point when all seven influenza symptoms were rated as 0 (none) or 1 (mild) for at least 21.5 hours
- Results: median times to alleviation of symptoms were 78.0 hours for 300 mg IV peramivir (hazard ratio 0.946, CI 97.5%, 0.793, 1.129), 81.0 hours 600 mg IV peramivir (hazard ratio of 0.970, CI 97.5%, 0.814, 1.157), and 81.8 hours for oseltamivir; both peramivir groups demonstrated noninferiority to oseltamivir
- Safety: incidence of adverse drug reactions 14.0% for 300 mg IV peramivir, 18.1% for 600 mg IV peramivir, and 20% oseltamivir; most common a/e was diarrhea, decreased neutrophil count, and nausea
- Funded by Shinogi Pharmaceutical (BioCryst Pharmaceutical's Partner in Japan) and Green Cross Pharmaceutical

Kohno S, Yen MY, et al. Phase III randomized, double-blind study comparing single-dose intravenous peramivir with oral oseltamivir in patients with seasonal influenza virus infection. *Antimicrob Agents Chemother.* 2011 Nov;55(11):5267-76.

Summary:

- Expensive compared to oseltamivir and zanamivir; clinical trial suggest noninferior to oseltamivir
- Not recommended for pediatric patients and cannot be taken prophylactically for influenza
- One time dose may improve adherence and useful for patients unable to take PO or inhalation

Recommendation: Exclude from pharmacy, cover for only if patient is unable to take PO or inhalation

Edoxaban tosylate (Savaysa®)

Eric Roberts, P4

February 25, 2015

Labeled Uses: Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE); prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation

Dosing: Prophylaxis of stroke and systemic embolism in non-valvular atrial fibrillation - 60 mg once daily

Treatment of DVT and PE – 60 mg once daily after 5 to 10 days of initial therapy with a parenteral anticoagulant

Comparator Drugs:

Drug	Normal Dosing Schedule	AWP for 30 Day Supply
Edoxaban (Savaysa)	60 mg once daily	\$ 332.64
Warfarin (generic)	5 mg once daily	\$ 20.04
Rivaroxaban (Xarelto)	20 mg once daily*	\$ 377.64
Apixaban (Eliquis)	5 mg twice daily**	\$ 377.99
Dabigatran (Pradaxa)	150 mg twice daily	\$ 377.64

* Initial DVT/PE treatment with rivaroxaban: 15 mg twice daily for 21 days followed by 20 mg once daily

** Initial DVT/PE treatment with apixaban: 10 mg twice daily for 10 days followed by 5 mg twice daily

MOA: Selective factor Xa inhibitor

Contraindications:

- Active pathological bleeding

Adverse Drug Events:

- U.S. Boxed Warning: Reduced efficacy in non-valvular atrial fibrillation patients with CrCl > 95 mL/min
- U.S. Boxed Warning: Premature discontinuation of edoxaban increases risk of ischemic events
- U.S. Boxed Warning: Spinal/Epidural hematomas may occur in patients treated with edoxaban who are receiving neuraxial anesthesia or undergoing spinal puncture

Drug Interactions:

 Edoxaban is a substrate of P-glycoprotein

- Avoid concomitant use with anticoagulants, apixaban, dabigatran, omacetaxine, rifampin, rivaroxaban, urokinase or vorapaxar
- Avoid concomitant use with P-glycoprotein inhibitors: quinidine, verapamil and dronedarone, as these will increase edoxaban exposure

Evidence:

Edoxaban versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism

- 12 month, Randomized, double-blind, multi-center, non-inferiority study
- Funded by Daiichi-Sankyo, Inc.
- 8292 participants, ≥ 18 years, with acute, symptomatic DVT involving the popliteal, femoral, or iliac veins or acute, symptomatic PE received either warfarin (dose adjusted to INR between 2.0 and 3.0) or edoxaban 60 mg once daily (30 mg adjusted dose for CrCl 30 to 50 mL/min, body weight of 60 kg or less, or concomitant treatment with potent P-glycoprotein inhibitors) after initial treatment of enoxaparin or unfractionated heparin for at least 5 days.
- Treatment with edoxaban or warfarin was to be continued for at least 3 months in all patients and for a maximum of 12 months. The duration was determined by the treating physician.
- Primary efficacy outcome: incidence of adjudicated symptomatic recurrent venous thromboembolism (defined as a composite of DVT or nonfatal or fatal PE)
- Primary safety outcome: incidence of adjudicated clinically relevant bleeding (defined as a composite of major or clinically relevant non-major bleeding; major bleeding was defined as overt and associated with a decrease in hemoglobin of 2 g per deciliter or more or required a transfusion of 2 or more units of blood, occurred in a critical site, or contributed to death)
- Results: Edoxaban was non-inferior to warfarin with respect to the primary efficacy outcome and caused significantly less bleeding.

Outcome	Edoxaban (N = 4118)	Warfarin (N = 4122)	Hazard Ratio with Edoxaban	P Value
(Modified ITT	# of patients with	# of patients with		

Population)	event (%)	event (%)	(95% CI)	
Primary Efficacy	130 (3.2%)	146 (3.5%)	0.89(0.70-1.13)	p<0.001 (for non-inferiority)
Primary Safety	349 (8.5%)	423 (10.3%)	0.81(0.71-0.94)	p = 0.004 (for superiority)

- To satisfy non-inferiority, the upper boundary of the two-sided 95% confidence interval for the hazard ratio of the primary efficacy end point could not exceed 1.5, which was an estimate that preserved at least 70% of the benefit of warfarin over placebo.

Buller HR, Decousus H, Grosso MA *et al.* *Edoxaman versus Warfarin for the Treatment of Symptomatic Venous Thromboembolism.* N Engl J Med 2013;369:1406-15.

Edoxaban vs. warfarin in atrial fibrillation

- Three group, randomized, double blind, double dummy, multicenter, non-inferiority trial
- Funded by Daiichi-Sankyo, Inc.
- 21,105 patients, ≥ 21 years, with A.Fib. and a CHADS2 score ≥ 2
- Key exclusions: high risk for bleeding, use of dual anti-platelet therapy, other indications for anticoagulation therapy, ACS, coronary revascularization, or stroke within 30 days prior to randomization
- Treatment: Patients received either edoxaban 60mg once daily, edoxaban 30mg once daily, or dose adjusted warfarin (INR 2.0 – 3.0) once daily
- Primary End Points: Efficacy – time to 1st adjudicated stroke or systemic embolic event, Safety – adjudicated major bleeding during treatment as defined by the International Society on Thrombosis and Haemostasis
- Results: Both edoxaban regimens were non-inferior to well-managed warfarin (time in therapeutic range 68.4%) for the prevention of stroke or systemic event. Compared to warfarin, edoxaban was associated with consistently lower, dose-related rates of all types of bleeding, including major bleeding, intracranial bleeding and life-threatening bleeding. The single exception was gastrointestinal bleeding, which occurred more frequently with high-dosed edoxaban but less frequently with low dose edoxaban than it did with warfarin.

End Point	Warfarin (N = 7036)	High-Dose Edoxaban (N = 7035)	High-Dose Edoxaban vs. Warfarin	Low-Dose Edoxaban (N = 7034)	Low-Dose Edoxaban vs. Warfarin
(ITT Population)	# of patients with event (% per year)	# of patients with event (% per year)	Hazard Ratio (95% CI)	# of patients with event (% per year)	Hazard Ratio (95% CI)
Primary Efficacy	337 (1.8%)	296 (1.57%)	0.87(0.73-1.04) p = 0.08	383 (2.04%)	1.13(0.96-1.34) p = 0.10
Primary Safety	524 (3.43%)	418 (2.75%)	0.80(0.71-0.91) p<0.001	254 (1.61%)	0.47(0.41-0.55) P<0.001

- To satisfy non-inferiority, the upper boundary of the one-sided 97.5 confidence interval for the hazard ratio of the primary efficacy end point could not exceed 1.38, which was an estimate that preserved at least 50% of the benefit of warfarin over placebo.

Giugliano R, Ruff C *et al.* *Edoxaban versus Warfarin in Patients with Atrial Fibrillation.* N Engl J Med 2013;369:2093-104.

Summary and Recommendation:

Edoxaban has shown non inferiority to warfarin in both safety and efficacy; however only the ITT population was analyzed. There is a concern related to bleeding adverse events based on low body weight as well as efficacy concerns with a CrCl > 95 mL/min. Based on the efficacy and safety profile of edoxaban, I would recommend covering this medication.

Outcome: T2.

Carbidopa/levodopa (Rytary)
Anti-Parkinson's Agent, Decarboxylase Inhibitor; dopamine Precursor

Indication: treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

Available Strengths:

23.75/95 (23.75mg carbidopa and 95mg levodopa); 36.25/145, 48.75/195, 61.25/245

Dosing:

- Starting dose, levodopa naïve: 23.75mg/95mg TID; may increase to 36.35mg/145mg TID on the 4th day of treatment
- Max daily dose: 612.5mg/2450mg (10 caps 61.25/245 tabs)

Table 1: Conversion from Immediate-Release Carbidopa-Levodopa to RYTARY

Total Daily Dose of Levodopa in Immediate-Release Carbidopa-Levodopa	Recommended Starting Dosage of RYTARY	
	Total Daily Dose of Levodopa in RYTARY	RYTARY Dosing Regimen
400 mg to 549 mg	855 mg	3 capsules RYTARY 23.75 mg / 95 mg taken TID ^a
550 mg to 749 mg	1140 mg	4 capsules RYTARY 23.75 mg / 95 mg taken TID
750 mg to 949 mg	1305 mg	3 capsules RYTARY 36.25 mg / 145 mg taken TID
950 mg to 1249 mg	1755 mg	3 capsules RYTARY 48.75 mg / 195 mg taken TID
Equal to or greater than 1250 mg	2340 mg or	4 capsules RYTARY 48.75 mg / 195 mg taken TID or
	2205 mg	3 capsules RYTARY 61.25 mg / 245 mg taken TID

^a TID: three times a day

Brand	Strength	Price	Price/Day @ Max Dose
Rytary ER Capsule	23.75mg/95mg	\$276 (100) \$662.40 (240)	\$24.84 (3 caps TID)
	36.25mg/145mg	\$276 (100) \$662.40 (240)	\$24.84 (3 caps TID)
	48.75mg/195mg	\$276 (100) \$662.40 (240)	\$24.84 (3 caps TID)
	61.25mg/245mg	\$346.80 (100) \$832.32 (240)	\$34.68 (10 caps)
Sinemet CR (CR tab)	25mg/100mg	\$146.42 (100)	\$11.71 (8 tabs)
	50mg/200mg	\$282.10 (100)	\$22.57 (8 tabs)
Carbidopa/Levodopa ER (CR tab)	25mg/100mg	\$93.90 (100)	\$7.51 (8 tabs)
	50mg/200mg	\$180.50 (100)	\$14.44 (8 tabs)
Sinemet Oral (tab)	10mg/100mg	\$115.94 (100)	\$9.28 (8 tabs)
	25mg/100mg	\$130.92 (100)	\$10.47 (8 tabs)
	25mg/250mg	\$166.81 (100)	\$13.34 (8 tabs)
Carbidopa/levodopa Oral (tab)	10mg/100mg	\$77.23 (100)	\$6.18 (8 tabs)
	25mg/100mg	\$80.02 (100)	\$6.40 (8 tabs)

	25mg/250mg	\$101.97 (100)	\$8.16 (8 tabs)
Carbidopa/levodopa Oral (ODT)	10mg/100mg	\$121.48 (100)	\$9.72 (8 tabs)
	25mg/100mg	\$137.18 (100)	\$10.97 (8 tabs)
	25mg/250mg	\$174.76 (100)	\$13.98 (8 tabs)

Max dose immediate release, ODT: 8 tabs of any strength daily or 200mg of carbidopa and 2000mg of levodopa

Adverse Effects: similar to those seen with other carbidopa/levodopa products: nausea, insomnia, dyskinesia, headache, dizziness, on and off phenomenon, etc.

Evidence:

Randomized trial of IPX066, carbidopa/levodopa extended release, in early Parkinson's disease.

Eligible patients: met the United Kingdom Parkinson's Disease Society Bran Bank Diagnostic Criteria for PD, ≥30 years old at diagnosis, Hoehn & Yahr stage I, II, or III, levodopa naïve (not exposed for >30 days & not within 4 wks of enrollment). Could be stable on anticholinergics, amantadine, and MAO-B inhbs. Mini-mental state exam ≥26 & sum of Unified Parkinson's disease Rating Scale (UPDRS)* Part II & III was ≥18. 381 patients were assigned to placebo, or IPX066 at 145, 245, or 390mg doses of levodopa TID.

Change in UPDRS Parts II + III from baseline to end of study (30 weeks)		
Trial Arm	Baseline UPDRS Part II + III Mean (SD)	Change from Baseline UPDRS Part II + III
Placebo (n=92)	36.3 (11.9)	-0.6
IPX066 145mg TID (n= 87)	36.1 (13.6)	-11.7
IPX066 245mg TID (n= 104)	38.1 (15.6)	-12.9
IPX066 390mg TID (n= 98)	36.3 (13)	-14.9

Pahwa R, Lyons KE, Hauser RA, et al. Randomized trial of UPX066, carbidopa/levodopa extended release, in early Parkinson's disease. *Park and Rel Dis* 20(2014)142-148.

Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomised, double-blind trial

Eligible patients: diagnosis of Parkinson's disease according to UK Parkinson's disease Bran Bank Criteria, ≥30 years old at time of diagnosis, Hoehn & Yahr stage I-IV in the on-state, a mini-mental state exam score of ≥26, treatment with a stable regimen of an IR levodopa formulation for at least 4 weeks before screening, a total daily levodopa dose of at least 400mg & a daily dosing frequency of at least 4 times/day & a 3-day average of at least 2.5h off-time per day on Parkinson's disease diaries at baseline and at visit 2. Concomitant tx w/dopamine agonists, MOA-B inhbs, amantadine, & anticholinergics at stable doses was permitted. 393 patients were randomly allocated in the double-blind maintenance period. 201 received ER carbidopa/levodopa & 192 received IR therapy.

Change from baseline in off-time, percentage of waking day			
Trial arm	Baseline off-time, percentage of waking day	End of study off-time	Change from baseline off-time
ER carbidopa/levodopa (n=201)	36.88%	23.82%	-13.06%
IR carbidopa/levodopa (n=192)	35.99%	29.79%	-6.21%
Mean difference			-5.97%

ER carbidopa/levodopa was associated with a 1.17h greater reduction in daily off-time. It did not, however, result in a significant difference in QOL results.

Hauser RA, Hsu A, Hell S, et al. Extended-release carbidopa-levodopa (IPX066) compared with immediate-release carbidopa-levodopa in patients with Parkinson's disease and motor fluctuations: a phase 3 randomised, double-blind trial. *Lancet Neurol* 2013;12:346-56.

There are no studies currently comparing Rytary to Sinemet CR.

*UPDRS – 199 points maximum, with no defined MCID. For the most part, clinicians consider a 15-30% improvement to be relevant. Looks at 4 major areas:

Part I: Mentation, behavior, mood; Part II: ADL; Part III: Motor examination; Part IV: Complications of therapy (off periods, sleep disturbances, etc.)

Recommendation: Exclude, due to lack of comparative evidence to current regimens.

Empagliflozin-Linagliptin (Glyxambi)

Ashlé D. Reid, P4

March 20, 2015

Labeled Use: Adjunct to diet and exercise to improve glycemic control in adults with T2DM.

Dosing:

Oral (initial): Empagliflozin 10mg/linagliptin 5mg once daily in the morning with or without food; may increase to empagliflozin 25mg/linagliptin 5mg once daily.

Comparators:

AWP Cost for 30-Day Supply

Drug	Minimum Daily Dose	Maximum Daily Dose
Empagliflozin-Linagliptin (Glyxambi)	\$576.00	\$576.00
Empagliflozin (Jardiance)	\$411.38	\$411.38
Linagliptin (Tradjenta)	\$396.77	\$396.77
Alogliptin-Metformin (Kazano)	\$374.36	\$374.36
Linagliptin-Metformin (Jentaducto)	\$396.80	\$396.80
Canagliflozin-Metformin (Invokamet)	\$411.41	\$411.41
Dapagliflozin-Metformin (Xigduo XR)	\$411.53	\$411.53

Contraindications:

- Serious hypersensitivity to empagliflozin, linagliptin, or any component of the formulation
- Severe renal impairment, including end-stage renal disease (ESRD) or dialysis

Adverse Drug Events: Urinary tract infection, hypoglycemia, increased serum cholesterol, increased hematocrit, upper respiratory tract infection, nasopharyngitis

Drug Interactions:

May increase levels/effects of: ACE inhibitors, duloxetine, hypoglycemic agents, insulin, levodopa, risperidone, sulfonylureas

May be increased by: androgens, barbiturates, MAO inhibitors, nicorandil, pegvisomant, P-glycoprotein/ABCB1 inhibitors, quinolone antibiotics, ritonavir, salicylates, SSRIs, teriflunomide

May be decreased by: bosentan, corticosteroids, CYP3A4 inducers, P-glycoprotein/ABCB1 inducers

Evidence:

Initial Combination of Empagliflozin and Linagliptin in Subjects With Type 2 Diabetes

Design: Subjects not receiving anti-diabetes therapy for 12 weeks were randomized to empagliflozin 25 mg/linagliptin 5 mg (n = 137), empagliflozin 10 mg/linagliptin 5 mg (n = 136), empagliflozin 25 mg (n = 135), empagliflozin 10 mg (n = 134), or linagliptin 5 mg (n = 135) for 52 weeks. The primary end point was change from baseline in HbA1C at week 24.

Results: Reductions from baseline in HbA1C with empagliflozin/linagliptin were significantly different versus linagliptin and empagliflozin 10 mg but not versus empagliflozin 25 mg. Empagliflozin-linagliptin was well tolerated.

Lewin A, DeFronzo RA, Patel S, Liu D, Kaste R, Woerle HJ, Broedl UC. Initial combination of empagliflozin and linagliptin in subjects with type 2 diabetes. *Diabetes Care*. 2015 Mar; 38(3):394-402 PMID: 25633662

Recommendation: Due to increased cost and no improvement in diabetes related complications/key endpoints, do not include in coverage.

Outcome: No clinical endpoint data. Exclude.

Naloxegol Oxalate (Movantik)

Ashlé D. Reid, P4

March 20, 2015

Labeled Use: Treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

Dosing:

Oral: 25mg once daily in the morning on an empty stomach. If not tolerated, reduce dose to 12.5mg once daily. D/C if opioid pain medication is discontinued.

Renal Impairment (CrCl<60ml/min): 12.5mg PO once daily; if well tolerated but OIC symptoms continue, may increase to 25mg PO once daily, taking into consideration the increased potential for renal impairment and the increased risk of adverse reactions.

Comparators:

AWP Cost for 30-Day Supply

Drug	Minimum Daily Dose	Maximum Daily Dose
Naloxegol (Movantik) - PO	\$299.52	\$299.52
Methylnaltrexone (Relistor) - SQ	\$2,143.80	\$2,143.80
Lubiprostone (Amitiza) - PO	\$359.47	359.47

Contraindications:

- Serious or severe hypersensitivity reaction to naloxegol or any component of the formulation
- Known or suspected GI obstruction or at increased risk of recurrent obstruction
- Concomitant use with strong CYP3A4 inhibitor

Adverse Drug Events: GI discomfort (abdominal pain, diarrhea, N/V, flatulence), headache, hyperhidrosis (increased sweating)

Drug Interactions: Avoid use with strong CYP3A4 inhibitors (increased effect/toxicity). Avoid use in strong CYP3A4 inducers (decreased effect)

Evidence:

A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation

Design: Four week international, multicenter, randomized, double-blind, placebo-controlled, dose-escalation phase 2 study (n = 207)

Results: Once-daily oral naloxegol improves the frequency of spontaneous bowel movements (SBM) in comparison to placebo and is generally well tolerated in this population of patients with OIC. Significant changes from baseline SBMs were observed during weeks 2-4 with naloxegol vs. placebo. The median change after 4 weeks was statistically significant for the 25mg dose cohort at 3.4 SBM vs. 1.0 SBM with placebo. Median time to first laxation in the 25mg dose cohort was also statistically significantly shorter with naloxegol than placebo (6.6hrs vs 48.6h, 95% CI, P= 0.0012).

Webster L, Dhar S, Eldon M, Masuoka L, Lappalainen J, Sostek M. A phase 2, double-blind, randomized, placebo-controlled, dose-escalation study to evaluate the efficacy, safety, and tolerability of naloxegol in patients with opioid-induced constipation. Pain. 2013 Sep;154(9):1542-50. PMID: 23726675

Naloxegol for Opioid-Induced Constipation in Patients with Noncancer Pain

Design: Twelve week, two identical phase 3, double-blind studies (study 04, n=652; study 05, n=700)

Results: Treatment with naloxegol, as compared with placebo, resulted in a significantly higher rate of treatment response (≥ 3 SBM/wk and an increase from baseline of ≥ 1 SBM for ≥ 9 of 12 weeks and for ≥ 3 of the final 4 weeks), without reducing opioid-mediated analgesia. For both studies, a shorter time to the first post-dose SBM and a higher mean number of days/wk with one or more SBM were observed with 25mg naloxegol vs placebo (P<0.001) and 12.5mg naloxegol vs placebo in study 04. Pain scores and daily opioid use were similar among the placebo, 12.5 naloxegol, and 25mg naloxegol groups.

Chey WD, Webster L, Sostek M, Lappalainen J, Barker PN, Tack J. Naloxegol for opioid-induced constipation in patients with noncancer pain. N Engl J Med. 2014 Jun 19;370(25):2387-96. PMID: 24896818

Recommendation: Include in coverage.

Outcome:

Carbidopa/levodopa enteral suspension (Duopa)
Anti-Parkinson's Agent, Decarboxylase Inhibitor; dopamine Precursor

Indication: treatment of Parkinson's disease, post-encephalitic parkinsonism, and parkinsonism that may follow carbon monoxide intoxication or manganese intoxication.

Available Strengths: 4.63/20 mg/mL

Dosing: Prior to initiation of therapy, convert patient from all forms of levodopa to oral immediate-release carbidopa/levodopa tablets. Patients should receive their routine night-time dosage of oral immediate-release carbidopa/levodopa after discontinuation of daily infusion.

Brand	Strength	Price	Price/Day @ Max Dose
Duopa enteral suspension	4.63/20 mg/mL	\$242.209 (100mL)	\$242.21 (1 cassette/day)
Rytary ER Capsule	23.75mg/95mg	\$276 (100) \$662.40 (240)	\$24.84 (3 caps TID)
	36.25mg/145mg	\$276 (100) \$662.40 (240)	\$24.84 (3 caps TID)
	48.75mg/195mg	\$276 (100) \$662.40 (240)	\$24.84 (3 caps TID)
	61.25mg/245mg	\$346.80 (100) \$832.32 (240)	\$34.68 (10 caps)
Sinemet CR (CR tab)	25mg/100mg	\$146.42 (100)	\$11.71 (8 tabs)
	50mg/200mg	\$282.10 (100)	\$22.57 (8 tabs)
Carbidopa/Levodopa ER (CR tab)	25mg/100mg	\$93.90 (100)	\$7.51 (8 tabs)
	50mg/200mg	\$180.50 (100)	\$14.44 (8 tabs)
Sinemet Oral (tab)	10mg/100mg	\$115.94 (100)	\$9.28 (8 tabs)
	25mg/100mg	\$130.92 (100)	\$10.47 (8 tabs)
	25mg/250mg	\$166.81 (100)	\$13.34 (8 tabs)
Carbidopa/levodopa Oral (tab)	10mg/100mg	\$77.23 (100)	\$6.18 (8 tabs)
	25mg/100mg	\$80.02 (100)	\$6.40 (8 tabs)
	25mg/250mg	\$101.97 (100)	\$8.16 (8 tabs)
Carbidopa/levodopa Oral (ODT)	10mg/100mg	\$121.48 (100)	\$9.72 (8 tabs)
	25mg/100mg	\$137.18 (100)	\$10.97 (8 tabs)
	25mg/250mg	\$174.76 (100)	\$13.98 (8 tabs)

Max dose immediate release, ODT: 8 tabs of any strength daily or 200mg of carbidopa and 2000mg of levodopa

Adverse Effects: similar to those seen with other carbidopa/levodopa products: nausea, insomnia, dyskinesia, headache, dizziness, on and off phenomenon, etc. Also the complications associated with the device.

Evidence: In the Duopa vs placebo trial, all patients were taking some sort of oral medication. Duopa with placebo oral or placebo suspension with oral carbidopa/levodopa. Even with this regimen, Duopa only improved off time by a mean of 1.9 hours. Patients were not allowed access to extended-release products.

Recommendation: Exclude, due to lack of comparative evidence to current regimens. There are other options.

sotalol HCl Oral Solution 5 mg/mL (Sotylize)

Matt Devers

March 2015

Labeled Indications: Documented life-threatening ventricular arrhythmia, Delay in recurrence of atrial fibrillation/atrial flutter

MOA: Has both beta-adrenoreceptor blocking (Vaughan Williams Class II) and cardiac action potential duration prolongation (Vaughan Williams Class III) antiarrhythmic properties.

Comparators:

Medication	Cost
Sotylize Oral Solution (5 mg / mL)	\$1658.88 per month
sotalol HCl 80 mg tablet	\$144.96 per month

Contraindications: Sinus bradycardia (< 50 bpm during waking hours), sick sinus syndrome or 2nd and 3rd degree AV block unless a functioning pacemaker is present; Congenital or acquired long QT syndromes, baseline QT interval > 450 ms; Cardiogenic shock, uncontrolled HF; Creatinine clearance < 40 mL/min; Serum potassium < 4 meq/L; Bronchial asthma or related bronchospastic conditions; Hypersensitivity to sotalol

Warnings/Precautions: QT prolongation and proarrhythmias; Bradycardia/heart block; Sick sinus syndrome; Hypotension; Recent acute MI; Abrupt withdrawal; Renal impairment; Non-allergic bronchospasm; Diabetes; Thyrotoxicosis; Anaphylaxis; Major surgery

Drug Interactions: Digoxin; Calcium-channel blocking agents; Catecholamine-depleting agents; Insulin and oral antidiabetic agents; Beta-2 receptor stimulants; Clonidine; Drugs that prolong QT interval and antiarrhythmic agents; Antacids

Evidence: Approval for Sotylize based on clinical trials for oral sotalol already on the market.

According to Lexicomp,

"A 5 mg/mL sotalol syrup may be made with Betapace, Sorine, or Betapace AF tablets and Simple Syrup containing sodium benzoate 0.1% (Syrup, NF). Place 120 mL Syrup, NF in a 6-ounce amber plastic (polyethylene terephthalate) prescription bottle; add five Betapace, Sorine, or Betapace AF 120 mg tablets and shake the bottle to wet the tablets. Allow tablets to hydrate for at least 2 hours, then shake intermittently over > 2 hours until the tablets are completely disintegrated; a dispersion of fine particles (water-insoluble inactive ingredients) in syrup should be obtained. Note: To simplify the disintegration process, tablets can hydrate overnight; tablets may also be crushed, carefully transferred into the bottle and shaken well until a dispersion of fine particles in syrup is obtained. Label "shake well". Stable for 3 months at 15 degrees Celsius to 30 degrees Celsius (59 degrees Fahrenheit to 86 degrees Fahrenheit) and ambient humidity.

Betapace prescribing information, Bayer HealthCare Pharmaceuticals Inc, Wayne, NJ 2011.

Betapace AF prescribing information, Bayer HealthCare Pharmaceuticals Inc, Wayne, NJ 2011.

Sorine prescribing information, Upsher-Smith, Minneapolis, MN, 2012"

Recommendation: Exclude from coverage as other formulations of the medications exist.

Olopatadine (Pazeo)
Second generation H1 Antagonist

Indication: Treatment of the signs and symptoms of allergic conjunctivitis

Brand	Strength	Dosing	Price
Pazeo	0.7%	One drop once daily	\$171.94 (2.5mL)
Pataday	0.2%	One drop once daily	\$179.10 (2.5mL)
Patanol	0.1%	One drop BID	\$285 (5mL)

Evidence:

Package insert

Pazeo was compared in two randomized, double-masked, placebo-controlled, conjunctival allergen challenge clinical studies in patients with a history of allergic conjunctivitis. In Study 1, patients were randomized to Pazeo, Pataday or vehicle, and in Study 2, patients were randomized to Pazeo, Pataday, Patanol, or vehicle. Patients were evaluated with a ocular itching severity score ranging from 0 (no itching) to 4 (incapacitating itch). A 1 unit difference compared to vehicle is considered a clinically meaningful change in the score.

	Time Point	PAZEO (Olopatadine, (N = 66)	PATADAY (Olopatadine, 0.2%) (N = 68)		Vehicle (N = 68)	
		Mean	Mean	Difference (95% CI)	Mean	Difference (95%
Onset	3 mins	0.36	0.39	-0.02 (-0.31, 0.26)	1.90	-1.54 (-1.82, -1.25)
	5 mins	0.53	0.61	-0.08 (-0.39, 0.22)	2.06	-1.53 (-1.84, -1.22)
	7 mins	0.48	0.61	-0.13 (-0.44, 0.17)	1.97	-1.49 (-1.80, -1.18)
16h	3 mins	0.70	0.87	-0.17 (-0.44, 0.11)	2.20	-1.50 (-1.77, -1.23)
	5 mins	0.79	1.04	-0.24 (-0.55, 0.07)	2.27	-1.48 (-1.79, -1.16)
	7 mins	0.75	0.98	-0.23 (-0.54, 0.08)	2.13	-1.38 (-1.69, -1.07)
24h	3 mins	0.93	1.41	-0.48 (-0.76, -0.20)	2.54	-1.61 (-1.88, -1.33)
	5 mins	1.10	1.52	-0.42 (-0.72, -0.12)	2.62	-1.51 (-1.81, -1.21)
	7 mins	1.09	1.50	-0.41 (-0.72, -0.10)	2.50	-1.41 (-1.72, -1.11)
Study 2						
		(N = 98)	(N = 99)		(N = 49)	
Onset	3 mins	0.38	0.47	-0.09 (-0.28, 0.09)	1.91	-1.53 (-1.76, -1.30)
	5 mins	0.53	0.61	-0.08 (-0.29, 0.12)	1.99	-1.46 (-1.71, -1.22)
	7 mins	0.65	0.61	0.04 (-0.18, 0.26)	1.82	-1.17 (-1.45, -0.90)
24h	3 mins	1.01	1.33	-0.31 (-0.57, -0.06)	2.30	-1.29 (-1.60, -0.97)
	5 mins	1.22	1.48	-0.26 (-0.51, -0.01)	2.37	-1.15 (-1.46, -0.84)
	7 mins	1.25	1.41	-0.16 (-0.42, 0.11)	2.14	-0.89 (-1.22, -0.57)

Topical Clindamycin Products

Julianna Marcus, Jill Johnson

August 25, 2014, rev 4/3/15

Comparison of Products:

Product	Ingredient	Tube size	Price (AWP)	Plan Coverage
Onexton Gel	Clindamycin 1.2%/benzoyl peroxide 3.75%	50 g	\$488	Proposed: exclude
Clindamycin/BP gel 1-5%	clindamycin 1%, benzoyl peroxide 5%	25 g	\$212.68	Tier 1
Clindamycin/BP gel 1.2-5%	clindamycin 1.2 %, benzoyl peroxide 5%	45 g	\$203.21	Tier 1
Clindamycin gel 1%	clindamycin 1%	30 g	\$86.38	Tier 1
Clindamycin solution 1%	clindamycin 1%	60 mL	\$78.35	Tier 1
Clindamycin aerosol 1%	clindamycin 1%	50 g	\$262.18	Tier 1
Clindamycin lotion 1%	clindamycin 1%	60 mL	\$120.18	Tier 1
Clindamycin pads 1%	clindamycin 1%	60	\$46.40	Tier 1
Clindamycin lotion 10mg	clindamycin 10 mg	N/A	N/A	Tier 1
Ziana gel	clindamycin 1.2%, tretinoin 0.025%	30 g	\$400.73	Tier 2
Veltin gel	clindamycin 1.2%, tretinoin 0.025%	30 g	\$252.54	-
Acanya gel	clindamycin 1.2%, benzoyl peroxide 2.5%	50 g	\$444.77	Tier 2
Clindagel 1%	clindamycin 1%	75 mL	\$685.02	Tier 2
BenzaClin gel with pump	clindamycin 1%, benzoyl peroxide 5%	35 g	\$359.59	Tier 2
Benzoyl peroxide gel 10%	benzoyl peroxide 10%	60 g	\$14.20	-
Benzoyl peroxide gel 5%	benzoyl peroxide 5%	60 g	\$13.35	-
Benzoyl peroxide gel 2.5%	benzoyl peroxide 2.5%	60 g	\$19.79	-

*Tier 1= \$15 copay, Tier 2= \$40 copay

Evidence:

Seidler, Elizabeth M. and Kimball, Alexa B. "Meta-analysis comparing efficacy of benzoyl peroxide, clindamycin, benzoyl peroxide with salicylic acid, and combination benzoyl peroxide/clindamycin in acne." *Journal of American Academy of Dermatology* 2010.

- Methods: A meta-analysis designed to compare efficacy of 5% BPO, 1% to 1.2% CL, 5% BPO with SA, and combination BPO/CL was conducted using the Cochrane collaboration in accordance with the PRISMA statement. Inclusion criteria included one end point measuring inflammatory lesion count and/or percent reduction in lesion count, at least one cohort using 5% BPO (either alone or with SA preparation), 1-1.2% CL, or combination BPO/CL, one end point measuring inflammatory lesion count, one end measuring non-inflammatory lesion count, and end points between 2-4 week and/or 10-12 week. Exclusion criteria included single-arm studies, studies examining acne rosacea, any BPO products other than 5% BPO, end points other than lesion reduction, and studies with retinoids in all arms.

Results:

Actual Inflammatory Lesion Count Reduction (2-4 weeks), Actual Non-Inflammatory Lesion Count Reduction*

	5% BPO + SA	Other 5% BPO	1-1.2% CL	BPO/CL	Placebo
# of studies	2	6	5	10	3
# of intent to treat subjects	134	612	359	1658	234
Mean baseline lesion ct	22.2	30.1	26.0	26.5	26.6
Weighted mean reduction [95% CI]	10.52 [10.12, 10.92]	7.95 [6.87, 9.03]	6.55 [5.00, 8.09]	10.23 [9.09, 11.38]	2.36 [-.40-5.12]
Standard deviation	0.58	2.70	3.52	3.70	4.88
Mean baseline lesion ct.*	37.4	52.9	45.0	44.2	47.5
Weighted mean reduction [95% CI]*	16.08 [10.01, 22.15]	7.43 [4.22, 10.64]	4.65 [2.26, 7.04]	10.86 [9.01-12.71]	3.90 [1.40, 6.40]
Standard deviation*	8.76	8.03	5.46	5.98	4.42

Actual Inflammatory Lesion Count Reduction (10-12 weeks), Actual Non-Inflammatory Lesion Count Reduction*

	5% BPO + SA	Other 5% BPO	1-1.2% CL	BPO/CL	Placebo
# of studies	2	10	9(1), 8 (NI)	13	6
# of intent to treat subjects	107	824	651 (I), 547 (NI)	1819	343
Mean baseline lesion ct	22.2	30.1	26.0	26.5	26.6
Weighted mean reduction [95% CI]	11.64 [11.31-11.97]	11.51 [9.87-13.15]	13.07 [10.44-15.70]	14.48 [13.39-15.66]	4.30 [2.35-6.24]
Standard deviation	0.48	5.29	8.04	4.36	4.87
Mean baseline lesion ct*	37.4	52.9	45.0	44.2	47.5
Weighted mean reduction [95% CI]*	19.70 [15.07-24.34]	13.56 [9.14-17.98]	7.15 [4.85-9.46]	18.29 [16.23-20.36]	3.04 [0.58-5.49]
Standard deviation*	6.69	14.27	6.66	7.59	6.14

Recommendation: Do not cover BenzaClin gel with pump. Consider covering Veltin gel (\$252.54 AWP) instead of Ziana gel.

Decision: Exclude Clindagel 1% (generic available). Exclude clindamycin aerosol due to cost (expensive dosage form). Exclude BenzaClin pump and Acanya (similar generics). Exclude Ziana (Tretinoin, clindamycin covered separately.)

blinatumomab (Blinicyto) 35mcg of lyophilized powder in a single-use vial

Abbey Merry, P4

1/26/15

Labeled Uses: Treatment of Philadelphia chromosome-negative (Ph-) relapsed or refractory B-cell precursor acute lymphoblastic leukemia (ALL)

Comparator Drugs:

	Per vial	Cycle	Per cycle
Blinatumomab	\$3,814.28 - 35 mcg vial	28mcg x28days, then 14 days break, up to 5 cycles	\$106,799.84
Cytarabine, idarubicin	\$24.00 - 100mg/mL (20mL) vial, \$600.00 10mg/10mL (10mL) vial	Cytarabine 3.0g/m ² x5days and idarubicin 40mg/m ² on day 3	\$4,262.28 ¹
Nelarabine	\$831.78 - 5mg/mL (50mL) vial	1500mg.m ² on days 1,3, & 5, repeat every 21days	\$27,448.74 ²
	1. 1st cycle cost is \$95,357.00	2. based on BSA 1.73m ²	

MOA: a bispecific CD19-directed CD3 T-cell engager that binds to CD19 expressed on the surface of cells of B-lineage origin and CD3 expressed on the surface of T cells. It activates endogenous T cells by connecting CD3 in the T-cell receptor (TCR) complex with CD19 on benign and malignant B cells. Blinatumomab mediates the formation of a synapse between the T cell and the tumor cell, upregulation of cell adhesion molecules, production of cytolytic proteins, release of inflammatory cytokines, and proliferation of T cells, which result in redirected lysis of CD19+ cells.

Contraindications: Known hypersensitivity to blinatumomab or to any component of the formulation

Adverse Reactions: pyrexia, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, tremor, rash, and constipation

Drug Interactions: No formal drug interaction studies have been conducted. The highest drug-drug interaction risk is during the first 9 days of the first cycle and the first 2 days of the second cycle in patients who are receiving concomitant CYP450 substrates, particularly those with a narrow therapeutic index

Safety and activity of blinatumomab for adult patient with relapsed or refractory B-precursor acute lymphoblastic leukemia: a multicenter, single-arm, phase 2 study

Design: n=189 with Ph- primary refractory or relapsed leukemia were enrolled in a MC, single-arm, open-label phase 2 study. Blinatumomab was given 9 mcg/day for first 7 days then 28 mcg/day by continuous IV infusion over 4 weeks every 6 weeks up to 5 cycles. Primary endpoint was complete remission (CR) or CR with partial hematological recovery or peripheral blood counts (CRh) within 2 cycles.

Results: After 2 cycles 63 patients had achieved CR and 18 patients had achieved CRh. Grade 3 adverse events were febrile neutropenia (25%), neutropenia (16%), anemia (14%), neurological toxicities (13%), pneumonia (9%), thrombocytopenia (8%), hyperglycemia (8%), leukopenia (8%), elevated alanine aminotransferase (7%), hypokalemia (7%), and pyrexia (7%). Blinatumomab has showed antileukemic activity in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia with negative prognostic factors. The median estimated relapse-free time was 5.9 months and overall survival times was 6.1 months.

Topp MS, Gokbuget N, et al. Safety and activity of blinatumomab for adult patient with relapsed or refractory B-precursor acute lymphoblastic leukemia: a multicenter, single-arm, phase 2 study. *Lancet Oncology*. 16(1): 57-66.

Phase II Trial of the Anti-CD19 Bispecific T Cell-Engager Blinatumomab Shows Hematologic and Molecular Remissions in Patients With Relapsed or Refractory B-Precursor Acute Lymphoblastic Leukemia

Design: n=36 with relapsed or refractory B-precursor ALL participated in a single-arm study. Patients received 4-week continuous infusion followed by 2-week treatment-free period. Primary endpoint was complete remission (CR) or CR with partial hematological recovery (CRh).

Results: Twenty-five patients achieved CR or CRh. The median overall survival was 9.8 months and relapse-free survival was 7.6 months. The most common adverse effect was pyrexia with 75% of patients experiencing grade 1 or 2 and 6% of patients experiencing grade 3. Other adverse effects were nervous systems disorders (6 patients) and cytokine release syndrome (2 patients). Data supports further investigation in a larger confirmatory study.

Topp MD, Gokbuget N, et al. Phase II trial of the anti-CD19 bispecific T cell-engager blinatumomab shows hematological and molecular remissions in patients with relapsed or refractory B-precursor acute lymphoblastic leukemia. *Clinical Oncology*. 2014; 32:4134

NCCB,org Guidelines for Chemotherapy in Relapsed/Refractory ALL 2.2014:

1. Clofarabine-containing regimens (2A)
2. Cytarabine-containing regimens (2A)
3. Alkylator combination regimens (2A)
4. Nelarabine (2A)
5. Augmented hyper-CVAD (2A)
6. Vincristine aulfate liposome injection (2A)
7. Blinatumomab (2A) – product preparation & administration must be strictly followed to minimize errors

Recommendations: Exclude from coverage.

Outcome: Exclude, code 1 (no clinical endpoints).

Olaparib (Lynparza)
50mg oral capsules
Jill Johnson, Pharm.D., BCPS
3/4/15

FDA-approved for advanced ovarian cancer. Note: should be administered only to patients with deleterious or suspected deleterious germline BRCA mutations, as detected by an approved test.

NCCN.org 1.2015:

Evidence:

Lederman J, Harter P, Gourley C, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. N Engl J Med. 2012;366(15):1382-92.

Phase 2 trial, R, DB, PC, to evaluate maintenance treatment with olaparib, randomly assigned to olaparib 400mg BID or placebo. 1` endpt was PFS, 2`endpt OS. Median PFS 8.4m vs 4.8m from randomization on completion of chemotherapy. AEs were more commonly reported with olaparib: nausea 68% vs 35%, fatigue 49% vs 38%, vomiting 32% vs 14%, anemia 17% vs 5% most of which were grade 1 or 2. An interim analysis of OS when 38% of patients had dies showed no significant difference between groups (HR with olaparib, 0.94; 95%CI 0.63 to 1.39; p=0.75).

PI:

Single-arm study in patients w/ deleterious or suspected deleterious germline BRCA-mutated advanced cancers (Study 1). N=137 treated with ≥ 3 prior lines of CTX. All pts received 400mg BID until disease progression or intolerable toxicity. ORR and duration of response were assessed. 93% were ECOG 0 or 1.

	N=137
ORR (95%CI)	34% (26, 42)
CR	2%
PR	32%
Med DOR (months), 95%CI	7.9, 5.6-9.6

Recommendation:

Exclude. To date, there are no known OS benefits of olaparib. The AE profile is worse than placebo. If appealed, will ask for peer-reviewed publication supporting an improvement in OS or QOL for approval.

Outcome:

Atazanavir sulfate (Reyataz) oral powder packet 50mg
Antiretroviral, Protease Inhibitor

Indications: Must be taken with ritonavir and food and should not be used in children who weigh less than 10 kg or who weight 25 kg or more

Atazanavir formulations available			
Formulation	Strength	Price	Price/unit
Capsules	150mg	\$1535.23 (60)	\$25.587/cap
Capsules	200mg	\$1535.23 (60)	\$25.587/cap
Capsules	300mg	\$1520.72 (30)	\$50.691/cap
Powder Packet	50mg	\$237.14 (30)	\$7.905/packet

Dosing: Infants ≥ 3 months and children weighing 10kg to <25kg

- 10 to <15kg: atazanavir 200mg (4 packets) **plus** ritonavir 80mg once daily (**\$31.62/day**)

- 15 to <25kg: atazanavir 250mg (5 packets) **plus** ritonavir 80mg once daily (**\$39.525/day**)

Mix with food (applesauce or yogurt), beverage (milk or water), or formula. If mixed with water, food must be also given at the same time. Consume all of the powder within one hour of preparation and administer ritonavir immediately following.

Recommendation: Cover for infants ≥ 3 months and children weighing 10kg to <25kg, with an age edit of less than 7.

Elvitegravir (Vitekta)

Laura Harvey

3/30/15

Labeled Use: HIV-1 infection, in combination with an HIV protease inhibitor co-administered with ritonavir and with other antiretroviral drug(s) in antiretroviral treatment-experienced adults

Dosing: Administered with concomitant darunavir and ritonavir, fosamprenavir and ritonavir, or tipranavir and ritonavir: 150 mg once daily

Administered with concomitant atazanavir and ritonavir or lopinavir and ritonavir: 85 mg once daily

Comparator Drugs: Integrase Inhibitors

	Dose	Price per dose	AWP Cost for 30 day supply
Elvitegravir (Vitekta)	85mg once daily	\$45.07	\$1352.05 (30)
	150mg once daily	\$45.07	\$1352.05 (30)
Dolutegravir (Tivicay)	50mg once daily	\$52.72	\$1581.68 (30)
Raltegravir (Isentress)	Chewable: 25mg BID	Chewable: \$1.51	Chewable: \$90.35 (60)
	100mg BID	\$6.02	\$361.37 (60)
	Pack: 100mg BID	Pack: \$6.02	Pack: \$361.37 (60)
	Tablets: 400mg BID	Tablets: \$24.09	Tablets: \$1445.34 (60)
Elvitegravir, Cobicistat, Emtricitabine, Tenofovir (Stribild)	150-150-200-300 mg once daily	\$98.29	\$2948.70 (30)
Abacavir, Dolutegravir, Lamivudine (Triumeq)	600-50-300 mg	\$88.29	\$2648.84 (30)

MOA: Integrase Inhibitor – Integrase is an HIV-1 encoded enzyme that is required for viral replication. Inhibition of integrase prevents the integration of HIV-1 DNA into host genomic DNA, blocking the formation of the HIV-1 provirus and propagation of the viral infection.

Contraindications: none

Adverse Reactions: diarrhea, headache, depression, fatigue, immune reconstitution syndrome, skin rash

Drug Interactions: antacids, bosentan, carbamazepine, contraceptives, CYP 3A4 Inducers, dabrafenib, dererasirox, dexamethasone (systemic), efavirenz, fosphenytoin-phenytoin, itraconazole, ketoconazole (systemic), mitotane, nevirapine, oxcarbazepine, phenobarbital, rifabutin, rifampin, rifapentine, siltuximab, St. John's Wort, tocilizumab, voriconazole, warfarin

Evidence:

Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study

Design: Randomized, double-blind, double-dummy, phase 3 study was conducted at 234 sites in 13 countries. Eligible patients had plasma HIV RNA of 1000 copies/mL or greater, any CD4 cell count, and resistance to or 6 months' experience with at least two classes of antiretroviral drugs. Participants received an open-label background regimen of a fully active, ritonavir-boosted protease inhibitor and a second agent.

Patients were randomly allocated (1:1) by computer with a block size of four to receive either elvitegravir 150mg once daily (n=361; 85 mg dose if given with atazanavir, or lopinavir with ritonavir) or raltegravir 400 mg twice daily (n=363). Placebo tablets were given to mask the difference in daily dosing. The primary endpoint was achievement and maintenance of virological response (HIV RNA <50 copies per mL) through week 48. Non-inferiority was pre-specified with a margin of 10%.

Results: Ten patients allocated elvitegravir and 12 assigned raltegravir were excluded from the analysis (either for protocol violations or because they did not receive treatment). 207 (59%) of 351 patients allocated elvitegravir achieved virological response compared with 203 (58%) of 351 assigned raltegravir (treatment difference 1.1%, 95% CI -6.0 to 8.2), meeting the criterion for non-inferiority (p=0.001). Three patients allocated elvitegravir had serious adverse events related to study drugs compared with seven assigned raltegravir; two and eight patients died, respectively. More individuals assigned elvitegravir reported diarrhoea up to week 48 (p=0.023), and more patients assigned raltegravir had grade 3 or 4 rises in alanine aminotransferase (p=0.020) or aspartate aminotransferase (p=0.009). Since elvitegravir can be given once a day compared with twice a day for raltegravir, elvitegravir might improve patients' adherence.

Molina J, LaMarca A, et al. *Efficacy and safety of once daily elvitegravir versus twice daily raltegravir in treatment-experienced patients with HIV-1 receiving a ritonavir-boosted protease inhibitor: randomised, double-blind, phase 3, non-inferiority study.* The Lancet Infectious Diseases. 2012. (12)27-35.

The role of dolutegravir in the management of HIV infection

Design: The utility of dolutegravir in HIV-infected, treatment-naïve individuals has been examined in three randomized, multicenter Phase III trials to establish safety, efficacy, and tolerability (SPRING-2, SINGLE, FIAMINGO). In each of the initial three trials, patients were stratified by baseline viral load 100,000 copies/mL or 100,000 copies/mL. There are currently three published studies examining the use of dolutegravir in HIV-infected, treatment experienced patients. The SAILING study currently has published 48-week results and compares dolutegravir to raltegravir in antiretroviral experienced patients who are INSTI naïve. The VIKING and VIKING 3 trials were conducted in antiretroviral and INSTI experienced patients who had evidence of INSTI resistance.

Results: Notable findings in the treatment-naïve clinical studies showed non-inferiority to raltegravir in reaching viral load, 50 copies/mL at 48 and 96 weeks in the SPRING-2 study, superiority to tenofovir/emtricitabine/efavirenz to reaching viral load, 50 copies/mL at 48 and 96 weeks in the SINGLE study, and superiority to darunavir/ritonavir based regimens to reaching viral load, 50 copies/mL at 48 weeks in the FLAMINGO study. Primary outcomes of the treatment-experienced clinical studies include dolutegravir being superior to raltegravir in reaching viral load, 50 copies/mL at 48 weeks in the SAILING study, achievement of viral load, 400 copies/mL by day 11 on dolutegravir monotherapy in 78% on once daily dolutegravir and 96% on twice daily dolutegravir in the VIKING study, and achievement of viral load, 50 copies/mL at 24 weeks in 69% when dolutegravir added to failing regimen in the VIKING 3 study. Lack of significant drug interactions, minimal adverse effects, and the availability of a single tablet regimen make dolutegravir a valuable and viable option for both patients and providers.

Miller M, Liedtke M, et al. *The role of dolutegravir in the management of HIV infection.* Infection and Drug Resistance. 2015. (8)19-29.

Recommendation: Include in coverage with PA:

1. Diagnosis of HIV
2. HAART experienced (not initial treatment)
3. Evidence of raltegravir resistance or intolerance

Outcome:

Atazanavir-cobicistat (Evotaz)

Brooks Tune, P4

3/30/15

Labeled Use: Treatment of HIV Type-1 infection for either treatment-experienced or treatment-naïve adult patients. For use in combination with other antiretroviral medications.

Comparator Drugs: FDA approved for HIV Type-1 infection.

	Price (AWP)	Daily Dose	Price per Daily Dose	HHS Rating (Treatment Naïve) ^Ω
atazanavir-cobicistat (Evotaz)	\$1,684.44 (30 tabs)	1 tab, 300mg-150mg TDD	\$56.15	N/A
darunavir-cobicistat (Prezcobix)	\$1,725.79 (30 tabs)	1 tab, 800mg-150mg TDD	\$57.53	N/A
elvitegravir-cobicistat-emtricitabine-tenofovir (Stribild)	\$2,948.70 (30 tabs)	1 tab, 150mg-150mg-200mg-300mg TDD	\$98.29	A,I (only if CrCl > 70 mL/min)
lopinavir-ritonavir (Kaletra)	\$977.22 (120 tabs)	2 tabs BID, 800mg-200mg total daily dose	\$32.57	B,I (in combination with ABC/3TC or TDF/FTC)

(Ω) Rating of Recommendations: A = Strong; B = Moderate; Rating of Evidence: I = Data from randomized controlled trials; ABC = abacavir; 3TC = lamivudine; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine, TDD is total daily dose.

MOA: Atazanavir (protease inhibitor) inhibits the cleavage of viral precursors, leading to noninfectious, undeveloped virions. Cobicistat inhibits the enzymatic activity of cytochrome P450 3A subtypes, increasing the serum concentrations of enzyme substrates.

Contraindications: Co-administration with ranolazine, colchicine (with impaired hepatic function), simvastatin, lovastatin, triazolam, PO midazolam, dronedarone, lurasidone, alfuzosin, ergot derivatives, sildenafil (in treatment of PAH), rifampin, pimozide, cisapride, nevirapine, indinavir, or St John's wort. Do not use with tenofovir disoproxil fumarate if CrCl < 70 mL/min. Not recommended for patients with end-stage renal disease on hemodialysis.

Adverse Reactions: New or worsening kidney dysfunction, toxic skin eruptions or Stevens-Johnson syndrome, immune reconstitution syndrome, hyperbilirubinemia, cardiac conduction abnormalities, abnormal fat deposition, hemophilia, new-onset diabetes mellitus, cholelithiasis and nephrolithiasis, and hepatotoxicity.

Drug Interactions: See Contraindications. CYP3A Inducers (Evotaz levels are decreased by phenytoin, dexamethasone, primidone, efavirenz, phenobarbital, and carbamazepine.) CYP3A Inhibitors (Evotaz levels are increased by itraconazole, clarithromycin, idelalisib, simeprevir, delavirdine, enfuvirtide, posaconazole, and other strong CYP3A inhibitors.) Serum levels of atazanavir are decreased as gastric pH increases. Evotaz levels are reduced if administered with antacids, H₂ antagonists, or proton-pump inhibitors. Evotaz is also not recommended in combination therapy with elvitegravir or additional protease inhibitors because these agents require elevated pharmacokinetic levels, and combined optimal dosing recommendations have not been determined.

Package Insert Disclaimer: Use of Evotaz was not examined in patients less than eighteen years of age.

Evidence: Evotaz product prescribing information (Jan 2015)

Department of Health and Human Services (HHS): Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (May 2014)

Randomized, double-blind, controlled trial

Design: HIV-1 treatment-naïve patients with CrCl > 70 mL/min were randomized 1:1. One arm received atazanavir-cobicistat 300mg-150mg daily along with tenofovir DF 300mg and emtricitabine 200mg daily. The comparison arm received atazanavir-ritonavir 300mg-100mg daily along with tenofovir DF 300mg and emtricitabine 200mg daily. Patients were stratified by HIV-1 RNA levels (≤ or > 100k copies/mL).

Results: At week 48 of treatment, virologic results were compared (HIV-1 RNA < 50 copies/mL). Eighty-five percent of patients from cobicistat arm (n=344) achieved less than 50 copies/mL. Eighty-seven percent of patients from ritonavir arm (n=348) achieved less than 50 copies/mL. The treatment difference was -2.2% (95% CI = -7.4%, 3.0%).

Recommendation: Limited evidence, cost-effective alternatives. Do not cover.

Outcome: T3, no pa.

darunavir-cobicistat (Prezcobix)

Brooks Tune, P4

3/30/15

Labeled Use: Treatment of HIV Type-1 infection for either treatment-experienced or treatment-naïve adult patients. For use in combination with other antiretroviral medications.

Comparator Drugs: FDA approved for HIV Type-1 infection.

	Price (AWP)	Daily Dose	Price per Daily Dose	^Ω HHS Rating (Treatment Naïve)
darunavir-cobicistat (Prezcobix)	\$1,725.79 (30 tabs)	1 tab, 800mg-150mg total daily dose	\$57.53	N/A
atazanavir-cobicistat (Evotaz)	\$1,684.44 (30 tabs)	1 tab, 300mg-150mg total daily dose	\$56.15	N/A
elvitegravir-cobicistat- emtricitabine- tenofovir (Stribild)	\$2,948.70 (30 tabs)	1 tab, 150mg-150mg- 200mg-300mg total daily dose	\$98.29	A,I (only if CrCl > 70 mL/min)
lopinavir- ritonavir (Kaletra)	\$977.22 (120 tabs)	2 tabs BID, 800mg-200mg total daily dose	\$32.57	B,I (in combination with ABC/3TC or TDF/FTC)

(^Ω) Rating of Recommendations: A = Strong; B = Moderate

Rating of Evidence: I = Data from randomized controlled trials

ABC = abacavir; 3TC = lamivudine; TDF = tenofovir disoproxil fumarate; FTC = emtricitabine

MOA: Darunavir (protease inhibitor) inhibits the cleavage of viral precursors, leading to noninfectious, undeveloped virions. Cobicistat inhibits the enzymatic activity of cytochrome P450 3A subtypes, increasing the serum concentrations of enzyme substrates.

Contraindications: Co-administration with ranolazine, colchicine (with impaired hepatic function), simvastatin, lovastatin, triazolam, PO midazolam, dronedarone, lurasidone, alfuzosin, ergot derivatives, sildenafil (in treatment of PAH), rifampin, pimozide, cisapride, or St John's wort. Do not use with tenofovir disoproxil fumarate if CrCl < 70 mL/min.

Adverse Reactions: New or worsening liver dysfunction, severe rash or toxic epidermal necrolysis, abnormal fat deposition, hemophilia, new-onset diabetes mellitus, decreased CrCl/renal function, and sulfonamide allergy.

Drug Interactions: See Contraindications. CYP3A Inducers (Prezcobix levels are decreased by phenytoin, dexamethasone, primidone, efavirenz, phenobarbital, and carbamazepine.) CYP3A Inhibitors (Prezcobix levels are increased by itraconazole, clarithromycin, idelalisib, simeprevir, tenofovir, etravirine, delavirdine, enfuvirtide, and other strong CYP3A inhibitors.) Prezcobix is also not recommended in combination therapy with elvitegravir or additional protease inhibitors because these agents require elevated pharmacokinetic levels, and combined optimal dosing recommendations have not been determined.

Package Insert Disclaimers: A different CYP 3A enzyme inhibitor (ritonavir) was used in combination with darunavir for clinical development and referenced for determination of dosing efficacy. Prezcobix is not for use in darunavir-resistant infections. Use of Prezcobix was not examined in patients less than eighteen years of age.

Evidence: Prezcobix product prescribing information (Jan 2015)

Department of Health and Human Services (HHS): Guidelines for the Use of Antiretroviral Agents in HIV-1-Infected Adults and Adolescents (May 2014)

Recommendation: Limited evidence, cost-effective alternatives. Do not cover.

Outcome: T3, no PA.

palbociclib (Ibrance)

Matt Devers

March 2015

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

MOA: Inhibits cyclin-dependent kinase (CDK) 4 and 6. CDK4/6 are downstream of signaling pathways which lead to cellular proliferation. In vitro, palbociclib reduced cellular proliferation of ER-positive breast cancer cell lines by blocking progression of the cell from G1 into S phase of the cell cycle.

Guidelines: In Stage IV breast cancers that are ER-positive, The National Comprehensive Cancer Network recommends failure of three back-to-back hormone regimens before attempting treatment with a chemotherapeutic agent.

NCCN Guidelines For Patients (NCCN Guidelines), Stage IV Breast Cancer (version 1.2014).
http://www.nccn.org/patients/guidelines/stage_iv_breast/index.html#30 (Accessed on March 23, 2015).

Comparators:

Medication	Cost
Ibrance (palbociclib) 75 mg tablet	\$11820 per cycle (3 weeks on/1 week off)
letrozole 2.5 mg tablet	\$543.44 per month
tamoxifen 20 mg tablet	\$113.65 per month
Faslodex Intramuscular (fulvestrant) 250 mg/5mL	\$6511.14 per month
Androxy 10 mg tablet (fluoymesterone)	\$346.70 per month
paclitaxel IV 300 mg/50 mL (50 mL)	\$152.40 per cycle (every 3 weeks)
capecitabine 500 mg tablet	\$4689.02 per cycle (every 3 weeks)

Contraindications: None

Toxicities/Adverse Reactions: Neutropenia, Infections, Pulmonary Embolism, Embryo-Fetal Toxicity

Drug Interactions: Strong CYP3A4 inhibitors, Strong CYP3A4 inducers, CYP3A4 substrates with narrow therapeutic indexes

Evidence:

The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study.

Design: Open-label, randomized phase 2 clinical trial, 165 patients (postmenopausal women with advanced estrogen receptor-positive and HER2-negative breast cancer who had not received any systemic treatment for their advanced disease were eligible) were enrolled in 2 separate cohorts that accrued sequentially: in cohort 1, patients were enrolled on basis of estrogen receptor-positive and HER2-negative status, but patients in cohort 2 were required to have cancer with amplification of cyclin D1, loss of p16, or both. Patients were randomly assigned at a 1:1 ratio to receive letrozole 2.5 mg daily or letrozole 2.5 mg daily plus palbociclib 125 mg daily for 3 weeks, followed by an off-week over 28 day cycles. Accrual to cohort 2 ended after an interim analysis of cohort 1 and statistical analysis was changed to a combine analysis of both cohorts. The study is ongoing but closed to accrual.

Results: At the time of analysis, progression-free survival events favored the palbociclib + letrozole group (41) over the letrozole group (59). Median progression-free survival also favored the palbociclib + letrozole group (20.2 months) over the letrozole group (10.2 months). Adverse events occurred at a much higher rate in palbociclib + letrozole group; Grade 3-4 neutropenia (54% versus 1%), leukopenia (19% versus 0%), fatigue (4% versus 1%). Serious adverse events that occurred in more than one patient in the palbociclib plus letrozole group were pulmonary embolism (4%), back pain (2%), and diarrhea (2%). 13% of patients in the palbociclib + letrozole left the study due to adverse events versus 2% in the letrozole group.

Finn RS, Crown JP, Lang I, Boer K, Bondarenko IM, Kulyk SO, et al. The cyclin-dependent kinase 4/6 inhibitor palbociclib in combination with letrozole versus letrozole alone as first-line treatment of oestrogen receptor-positive, HER2-negative, advanced breast cancer (PALOMA-1/TRIO-18): a randomised phase 2 study. *Lancet Oncol.* 2015;16:25–35. doi: 10.1016/S1470-2045(14)71159-3.

Recommendation: Exclude from coverage until more data are available.

Secukinumab (Cosentyz)

Laura Harvey

3/30/15

Labeled Use: Plaque psoriasis - Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Dosing: 300 mg SubQ once weekly at weeks 0, 1, 2, 3, and 4 followed by 300 mg every 4 weeks. Some patients may only require 150 mg per dose.

Comparator Drugs:

	Pharmacologic Category	Dose	Price for Tx Initiation	Price for monthly maintenance therapy	Annual Price
Secukinumab (Cosentyx) SubQ	IL-17 Inhibitor	Initial: 300mg once weekly at weeks 0, 1, 2, 3, & 4 Maintenance: 300mg every 4 weeks. (*Some patients may only require 150mg/dose.)	Initial: \$20,520 (150mg/ml x2 =1 dose \$4104=2 autoinjector/pre-filled syringes =1 dose)	Maintenance: \$49,428	Total: \$69, 768
Adalimumab (Humira) SubQ	TNF Blocking Agent	Initial: 80mg as a single dose Maintenance: 40mg every other week beginning 1 week after initial dose	Initial: \$3496.38	Maintenance: \$45,452.94	Total: \$48,949.32
Etanercept (Enbrel) SubQ	TNF Blocking Agent	Initial: 50mg twice weekly x 3 months Maintenance: 50mg once weekly (*starting doses of 25 or 50 mg once weekly have also been used successfully)	Initial: \$20,982 (50mg twice weekly x 12 weeks)	Maintenance: \$34,970	Total: \$55,952
Infliximab (Remicade) IV	TNF Blocking Agent	Initial: 5 mg/kg at 0, 2, and 6 weeks Maintenance: 5 mg/kg every 8 weeks	Based on 80kg Initial: \$13,366.68 (100mg) (1) \$1113.89 400mg (\$4455.56)x 3	Based on 80kg Maintenance: \$26,733.36 (\$4455.56 x 6)	Based on 80kg Total: \$40,100.04
Ustekinumab (Stelara) SubQ	IL-12/IL-23 Inhibitor	≤100 kg: Initial: 45 mg at 0- and 4 weeks Maintenance: 45 mg every 12 weeks >100 kg: Initial: 90 mg at 0- and 4 weeks Maintenance: 90mg every 12 weeks	≤100 kg: Initial: \$18,386.78 >100 kg: Initial: \$36,773.48	≤100 kg: Maintenance: \$36,773.56 >100 kg: Maintenance: \$73,546.96	≤100 kg: Total: \$55,160.34 >100 kg: Total: \$110,320.44

MOA: Secukinumab is a Human IgG1 monoclonal antibody that selectively binds to the interleukin-17A (IL-17A) cytokine and inhibits its interaction with the IL-17 receptor. IL-17A is a naturally occurring cytokine involved in normal inflammatory and immune responses. Secukinumab inhibits the release of proinflammatory cytokines and chemokines.

Contraindications: Serious hypersensitivity reaction to secukinumab or any component of the formulation

Adverse Reactions: infection, nasopharyngitis, urticarial, diarrhea, candidiasis, rhinitis, rhinorrhea

Drug Interactions: BCG, belimumab, coccidioides immitis skin test, denosumab, Echinacea, leflunomide, natalizumab, pimecrolimus, roflumilast, sipuleucel-T, tacrolimus (topical), tofacitinib, trastuzumab, vaccines (live and inactivated)

Evidence:*Secukinumab in Plaque Psoriasis – Results of Two Phase 3 Trials*

Design: In two phase 3, double-blind, 52-week trials, ERASURE (Efficacy of Response and Safety of Two Fixed Secukinumab Regimens in Psoriasis) and FIXTURE (Full Year Investigative Examination of Secukinumab vs. Etanercept Using Two Dosing Regimens to Determine Efficacy in Psoriasis), 738 patients (in the ERASURE study) and 1306 patients (in the FIXTURE study) were randomly assigned to subcutaneous secukinumab at a dose of 300mg or 150mg (administered once weekly for 5 weeks, then every 4 weeks), placebo, or (in the FIXTURE study only) etanercept at a dose of 50mg (administered twice weekly for 12 weeks, then once weekly). The objective of each study was to show the superiority of secukinumab over placebo at week 12 with respect to the proportion of patients who had a reduction of 75% or more from baseline in the psoriasis area-and-severity index score (PASI 75) and a score of 0 (clear) or 1 (almost clear) on a 5-point modified investigator's global assessment (coprimary end points).

Results: The proportion of patients who met the criterion for PASI 75 at week 12 was higher with each secukinumab dose than with placebo or etanercept: in the ERASURE study, the rates were 81.6% with 300 mg of secukinumab, 71.6% with 150 mg of secukinumab, and 4.5% with placebo; in the FIXTURE study, the rates were 77.1% with 300 mg of secukinumab, 67.0% with 150 mg of secukinumab, 44.0% with etanercept, and 4.9% with placebo (P<0.001 for each secukinumab dose vs. comparators). The proportion of patients with a response of 0 or 1 on the modified investigator's global assessment at week 12 was higher with each secukinumab dose than with placebo or etanercept: in the ERASURE study, the rates were 65.3% with 300 mg of secukinumab, 51.2% with 150 mg of secukinumab, and 2.4% with placebo; in the FIXTURE study, the rates were 62.5% with 300 mg of secukinumab, 51.1% with 150 mg of secukinumab, 27.2% with etanercept, and 2.8% with placebo (P<0.001 for each secukinumab dose vs. comparators). The rates of infection were higher with secukinumab than with placebo in both studies and were similar to those with etanercept.

Langley R, Elewski B, et al. Secukinumab in Plaque Psoriasis – Results of Two Phase 3 Trials. *The New England Journal of Medicine*. 2014; 371:326-38.

Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE)

Design: This phase III trial randomized subjects with moderate to severe plaque psoriasis to secukinumab 300 mg, 150 mg or placebo self-injection once weekly to Week 4, then every 4 weeks. Co-primary end points at Week 12 were $\geq 75\%$ improvement in Psoriasis Area and Severity Index (PASI 75) and clear/almost clear skin by investigator's global assessment 2011 modified version (IGA mod 2011 0/1). Secondary end points included autoinjector usability, assessed by successful, hazard-free self-injection and subject-reported acceptability on Self-Injection Assessment Questionnaire.

Results: Week 12 PASI 75 and IGA mod 2011 0/1 responses were superior with secukinumab 300 mg (86.7% and 73.3%, respectively) and 150 mg (71.7% and 53.3%, respectively) vs. placebo (3.3% and 0%, respectively) (P < 0.0001 for all). All subjects successfully self-administered treatment at Week 1, without critical use-related hazards. Subject acceptability of autoinjector was high throughout 12 weeks. Adverse events were higher with secukinumab (300 mg, 70.0%; 150 mg, 63.9%) vs. placebo (54.1%), with differences largely driven by mild/moderate nasopharyngitis. Week 12 PASI 75 and IGA mod 2011 0/1 responses were superior with secukinumab 300 mg (86.7% and 73.3%, respectively) and 150 mg (71.7% and 53.3%, respectively) vs. placebo (3.3% and 0%, respectively) (P < 0.0001 for all). All subjects successfully self-administered treatment at Week 1, without critical use-related hazards. Subject acceptability of autoinjector was high throughout 12 weeks.

Paul C, Lacour J.P, et al. *Efficacy, safety and usability of secukinumab administration by autoinjector/pen in psoriasis: a randomized, controlled trial (JUNCTURE)* *Journal of the European Academy of Dermatology and Venereology*. 2014. DOI: 10.1111/jdv.12751

Recommendation: Include in coverage with PA.

1. Diagnosis of chronic plaque psoriasis (not pustular, erythrodermic, or guttate psoriasis)
2. Moderate to severe psoriasis defined by:
 - PASI score ≥ 12 **and**, (*see table below)
 - IGA mod 2011 score of ≥ 3 **and**, (*See scale below)
 - BSA affected by plaque-type psoriasis of $\geq 10\%$
3. Candidate for systemic therapy, defined as having chronic plaque-type psoriasis considered inadequately controlled by:
 - Topical treatment
 - i. Topical corticosteroid cream or ointment
 - Phototherapy
 - i. narrow-band UVB light exposure (treatment of choice, three times weekly)
 - ii. Goeckerman regimen (when unresponsive to UV light may use crude coal tar for many hours in addition to exposure to UVB)

- Previous systemic therapy
 - i. Methotrexate in doses up to 25 mg once weekly orally
 - ii. Cyclosporine 2.5mg/kg twice daily for 6 weeks
 - iii. TNF inhibitors
 1. etanercept 50 mg twice weekly subcutaneously × 12 weeks, then once weekly
 2. infliximab, 5 mg/kg once weekly intravenously at weeks 0, 2, and 6
 3. adalimumab 40 mg every 2 weeks
 - iv. IL-12/IL-23 Inhibitor: Infliximab
 1. ≤100 kg: Initial: 45 mg at 0- and 4 weeks, Maintenance: 45 mg every 12 weeks
 2. >100 kg: Initial: 90 mg at 0- and 4 weeks Maintenance: 90mg every 12 weeks

Example of PASI score

	Head & Neck	Upper ext.	Trunk	Lower ext.
Erythema (0-4)	4	4	4	4
Scale (0-4)	4	4	4	4
Induration (0-4)	4	4	4	4
Sum (E+I+S)	12	12	12	12
Body surface area (1-6)	6	6	6	6
Sum x Area	72	72	72	72
Area multiplier	0.1	0.2	0.3	0.4
Sum x Area	7.2	14.4	21.6	28.8
PASI total	72			

- 0=none
- 1=slight
- 2=moderate
- 3=severe
- 4=very severe

*PASI score can range from a lower value of 0, corresponding to no signs of psoriasis, up to a theoretic maximum of 72.

The IGA mod 2011 rating scale

Score	Short Description	Detailed Description
0	Clear	No signs of psoriasis. Post-inflammatory hyperpigmentation may be present.
1	Almost Clear	Normal to pink coloration of lesions; no thickening; no to minimal focal scaling.
2	Mild	Pink to light red coloration; just detectable to mild thickening; fine scaling
3	Moderate	Dull bright red, clearly distinguishable erythema; clearly distinguishable to Moderate thickening; moderate scaling.
4	Severe	Bright to deep dark red coloration; severe thickening with hard edges; severe Coarse scaling covering almost all or all lesions.

Outcome:

**Pasireotide (Signifor LAR)
Somatostatin Analog**

Indications: Treatment of patients with acromegaly who have had an inadequate response to surgery and/or for whom surgery is not an option

Note: This is the reconstituted suspension IM injection. There is also subcutaneous solution, Signifor, for Cushing disease.

Drug	Dosing	Price
Pasireotide (Signifor LAR)	Initial 40 mg q 28 days, if GH &.or IGF-1 levels are not normalized after 3 months, increase to a max of 60 mg. Decrease by 20mg increments if adverse reactions or IFG-1 levels decrease to less than lower limit of normal.	\$12923.08 (1) q 28 months
Octreotide	<u>Subq, IV:</u> Initial 50mcg TID; titrate to achieve desired growth hormone levels, usual effective dose 100-200 mcg TID, can range 300-1500mcg/day. <u>IM depot injection:</u> Patients must be stabilized on subq for at least 2 weeks before switching to the long acting-depot. 20 mg IM intragluteally q 4 weeks for 3 months, then adjust.	<u>Subq, IV: (generic)</u> \$28.44-126/day, \$796.32-3528/28 days <u>IM depot (Sandostatin):</u> \$3668.38/28 days
Lanreotide (Somatuline Depot)	Initial: subq 90 mg q 4 weeks for 3 months, adjust dose based on clinical response, GH levels, and/or IGF-1	\$5013.60/28 days

Evidence:

Pasireotide versus octreotide in acromegaly: A Head-to-Head Superiority Study

358 patients with medically-naïve acromegaly were enrolled in a randomized, double-blind study.

Patients were randomized to pasireotide 40mg/28days (n=176) or octreotide 20mg/28 days (n=182) for 12 months, with an option to titrate at months 3 and 7. Primary outcome was proportion of patients with biochemical control (GH<2.5 mcg/L and normal IGF-1) at month 12.

Results: Biochemical control was achieved by 31.3% of pasireotide patients and 19.2% of octreotide patients, p=0.007. In pasireotide and octreotide patients respectively, 38.6% and 23.6% (p=0.002) achieved normal IGF-1, and 48.3% and 51.6% achieved GH goals. 31.0% of pasireotide and 22.2% of octreotide who did not achieve biochemical control did not receive the recommended dose increase.

Adverse effects with pasireotide vs octreotide were mild-to-moderate diarrhea (39.3% vs 45.0%), cholelithiasis (25.8% vs 35.6%), headache (18.5% vs 25.6%), and hyperglycemia (28.7% vs 8.3%). 14 (8.0%) on pasireotide and 6 (3.3%) on octreotide discontinued treatment due to ADE.

Recommendation: Exclude due to other medical treatment options for acromegaly. Pasireotide comes with a high price tag and a significant adverse effect profile, with little benefit to the patient. Even in the areas where it appears to be better and/or superior, closer examination of the data shows that the actual values of GH and IGF-1 differ very little between octreotide and pasireotide.