AGENDA

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

November 06, 2017

1:00 p.m.

EBD Board Room – 501 Building, Suite 500

I.	*Call to Order*	*Dr. Scott Pace, Chairman*
II.	*Approval of August 7, 2017 Minutes*	*Dr. Scott Pace, Chairman*
III.	*Ocaliva Discussion*	*Dr. Knapple*
IV.	*Second Review of Medications*	*Dr. Geri Bemberg, Dr. Jill Johnson, UAMS*
V.	*New Drugs*	*Dr. Jill Johnson, UAMS*
VI.	*Rebate Review*	*Dr. Rachael McCaleb, UAMS*
VII.	*Board Report*	*Dr. Geri Bemberg, UAMS*

2018 Upcoming Meetings

February 05, 2018

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

Notice: Silence your cell phones and other noise that is disruptive to the meeting. Keep your personal conversations to a minimum.

State and Public School Life and Health Insurance Board
Drug Utilization and Evaluation Committee Minutes
November 6, 2017

The State and Public Life and Health Insurance Board, Drug Utilization and Evaluation Committee (DUEC) met on Monday, November 6, 2017 at 1:00 p.m., in the EBD Board Room, 501 Woodlane, Little Rock, AR.

Voting Members present:
Dr. Scott Pace, Chairman
Dr. Hank Simmons, Vice-Chairman
Laura Mayfield
Mike Boyd
Dr. William Golden
Dr. Kat Neill
Dr. John Kirtley

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

Members absent:
Dr. Appathurai Balamurugan

Chris Howlett, EBD Executive Director, Employee Benefits Division

OTHERS PRESENT
Eric Gallo, Rhoda Classen, Jamie Levinsky, Shay Burleson EBD; Sandra Wilson, Active Health; Jessica Akins, Health Advantage; Ronda Walthall, Wayne Whitley, Arkansas Highway Department; Jon Maguire, GSK; Jim Chapman, ABBVIE; Nikki Coff, Nova Nordisk; Elizabeth Whittington, ACHI; Marc Bagby, Lilly; Sean Seago, Merck; John Brewer, Charlotte Downs, Sanofi Genzyme; Lee Hennigan, Novartis; Dr. GeriBeth Bemberg, Sherry Bryant, Ashley Leach, Claire Benly, Dwight Davis, UAMS; Suzanne Woodall, MedImpact; Marc Watts, ASEA; Beverly Thornton, Collegium Pharma; Richard Ponder, J & J; Whit Knapple, M.D.; Marc Welton, Jonathan Leyoub, Intercept; Marvin “Bud” McConkie, Allergen.

CALL TO ORDER
Meeting was called to order by Dr. Scott Pace, Chairman, and he announced that we do have a quorum today.

APPROVAL OF MINUTES
The request was made by Dr. Pace to approve the August 7, 2017 minutes. He asked the members to take a few minutes to look over the minutes and mention any edits that you might want to suggest. Dr. Kirtley made the motion to approve. Dr. Simmons seconded; all were in favor.

Minutes Approved.

I. Ocaliva Discussion: *Dr. Knapple*

Dr. Pace mentioned that it is not our general practice to invite or allow audience members to come up and present clinical data. This instance is a special circumstance since there is new data available. Ocaliva was approved on an accelerated pathway by the FDA even though there was no new data or significant improvements noted.

Dr. Whit Knapple is a board certified Gastroenterologist in a single specialty group practice in North Little Rock. Arkansas Gastroenterology primarily treats Primary Biliary Cholangitis, PBC, which is a liver disease that can lead to cirrhosis and ultimately lead to liver transplantation. Until recently the only medical therapy was ursodeoxycholic acid. Most individuals responded to this therapy with a significant reduction in their alkaline phosphatase. We know that alkaline phosphatase is a non-invasive marker which indicates responsive therapy and can predict transplant re-survival. Obeticholic acid has been approved by the FDA for individuals intolerant to ursodeoxycholic acid or did not have a therapeutic decrease in their alkaline phosphatase. The goal is to slow or stop cirrhosis of the liver.

Dr. Bemberg wanted Dr. Knapple to address the extra warning from the FDA in 2017 regarding liver failure and death in patients who have used this drug. Dr. Knapple stated that these people had a decompensated liver already, and they were dosed inappropriately and infrequently. The hope is to intervene earlier and prevent the decompensation.

Dr. Kirtley asked about liver related adverse events including sudden worsening of the PBC symptoms. Dr. Knapple responded that the main side effect of this disease is severe pruritus, severe itching, and this group of patients were predisposed to this symptom. They had the decompensated disease to begin with. Dr. Kirtley said there is a whole section on liver related adverse reactions, but it does not give us any indication on how often this happens. Dr. Knapple replied that he did not have the numbers for that. Dr. Kirtley also wanted to know how the medicine is given. Dr. Knapple replied that it is a daily medication given orally, starting at 5mg daily to make sure they can tolerate the drug. Only 10% had to discontinue the drug.

Dr. Golden stated that Dr. Knapple mentioned analysis that had two times the alkaline phosphatase versus the study that had 1.67, and he wanted to know which criteria would be preferable. Dr. Knapple stated that some studies on PBC go as low as 1.5, and this study was 1.67. The meta-analysis was two times upper limit of normal so anywhere from 1.5-2. If it were 2 or less, it would be acceptable. The point of this is the reduction in an alkaline phosphatase because this meta-analysis did prove that it is an acceptable marker to prevent prognosis. Dr. Golden asked if labs have a standard for alkaline phosphatase, and Dr. Knapple responded that there is not an absolute upper limit of normal; each lab has their own upper and lower limit for the blood.

Dr. Kirtley asked Dr. Bemberg if this is considered a specialty drug, and what is the cost and distribution model. Dr. Bemberg responded that it is considered a specialty drug, and we have had a few requests for it. We have not approved it due to lack of clinical data. It is also being looked at in other indications, but the requests have been mainly in PBC. Dr. Kirtley stated it is a small sale non-biologic specialty, and he also asked about the cost. Dr. Johnson responded that for one year it will be $82,000 for 10mg.

Dr. Johnson stated that the drug's package insert states "obeticholic acid has not shown any improvement in survival or disease related symptoms". This committee wants to cover drugs that show a difference in the longevity or quality of a person's life. Clinicaltrials.gov shows there is an ongoing clinical trial currently recruiting that IS measuring clinical endpoints such as death, liver transplant, uncontrolled ascites, hospitalization for variceal bleed, etc. Lastly she stated that the best current evidence (Cochrane Systematic Reviews) states "Based on very low quality evidence, there is currently no evidence that any intervention is beneficial for PBC…and further well-designed randomized clinical trials are necessary".

Dr. Golden asked what is the prevalence of people that have this disease in Arkansas, and Dr. Knapple said 1 per 100,000.

Dr. Kirtley requested that we take this for information and wait for more data. Dr. Golden asked for more literature from Dr. Bemberg. She will get the information to him.

II. 2nd review of Drugs: *by Dr. Jill Johnson, Dr. Geri Bemberg, UAMS*

A. Cerdelga (eliglustat): Dr. Johnson discussed Cerdelga, a drug used for treating Gaucher disease Type 1. The first line of therapy is enzyme replacement therapy. Dr. Johnson recommends to continue exclusion on this drug. The drug is an enzyme inhibitor, there was one clinical trial in which Cerdelga did not sufficiently improve the condition. The endpoints in the trial were nonclinical measurements. No trial measured quality of life or extension of life.

Dr. Simmons made a motion to continue to exclude this. Neill seconded. All in favor.

Dr. Golden asked if this is an improvement in enzyme replacing or difference in enzyme blocking.

Dr. Bemberg stated that the difference is the dosing and not a note of improvement.

Dr. Golden asked about the difference of the cost, and Cerdelga could be as much as $30,000 a month and enzyme replacement therapy is about $19,000 per month depending on weight.

Correction to be made for Board: Cerdelga is $30600/m while imiglucerase enzyme replacement is $38K/m.

Motion Approved.

B. Radicava (edaravone): Dr. Johnson stated that Radicava was previously excluded, but she would like to recommend to have a medical PA for continuation and meet criteria for a new patient.

Dr. Kirtley made a motion to adopt the recommendation with the PA criteria. Dr. Simmons seconded. All in favor.

Motion Approved.

C. Emverm (Mebendazole): Mebendazole chew tabs were released onto the market in the early 2000s. At that time, the price/tablet was under $7 each. The generic products went obsolete in 2011. In early 2016, Emverm was released at $442.80/tablet. There are other options available for Emverm's indications. Recommendation: exclude Emverm.

Dr. Pace asked if the recommendation is to exclude on January 1, 2018, and Dr. Bemberg said she could actually discontinue it now.

Dr. Kirtley made a motion to immediately exclude this drug. Dr. Simmons seconded. All in favor.

Motion Approved.

D. Fluoxetine 60mg: Dr. Bemberg presented on fluoxetine 60mg. Fluoxetine was released by Edgemont Pharmaceuticals in November of 2011. Fluoxetine 60mg is now owned and manufactured by Almatica Pharma, and is recognized by the FDA as a single source brand. Currently, this product is processing at Tier 2 ($40) for Premium and Primary members. Other fluoxetine strengths (10mg, 20mg, 40mg) are marketed as generics and are available in both capsule and tablet, at a much cheaper rate. While there are indications for

which amounts of fluoxetine over 40mg are used, there is no evidence to support the use of a "convenience dose" of 60mg total at the expense of both the member and the plan

Dr. Neill made a motion to exclude the 60mg in ninety days with communication to members about alternate mechanisms to reach this dose. Dr. Simmons seconded. All in favor.

Motion Approved.

E. Isordil (isosorbide dinitrate): Dr. Bemberg stated there is no evidence available demonstrating superiority of Isordil Titradose over currently available formulations of isosorbide dinitrate. Isordil was developed by Wyeth Pharmaceuticals, who at some point sold the rights to the drug to Biovail Pharmaceuticals. Biovail Pharma merged with Valeant Pharmaceuticals in 2010.

Dr. Kirtley made a motion to exclude Isordil effective immediately. Dr. Simmons seconded. All in favor.

Motion Approved.

F. Formulary Cleanup: Dr. Bemberg proposed the exclusions of Nascobal nasal spray, Verdeso foam, Desonate gel, Dexpak, and Cordran tape. All have suitable alternatives.

Formulary Cleanup

Drug	Formulation	Indication	Other Options	Evidence	Price
Nascobal (cyanocobalamin – vit b12)	500mcg/spray nasal spray	Vit B12 deficiency	IM inj – tier 1 Tabs – tier 1	None; UTD notes that "We generally do not use the intranasal formulations because of their variable absorption and higher cost; these formulations may also cause rhinorrhea."[1]	$158.04/dose
Verdeso (desonide)	0.05% foam	Atopic dermatitis	Cream, lotion, ointment (all 0.05%) tier 1	Low potency steroid along with desonide cream and lotion; also several other products[2]	$936.00/100g
Desonate (desonide)	0.05% gel	Atopic dermatitis	Cream, lotion, ointment (all 0.05%) tier 1	Lower-mid potency along with desonide ointment; also several other products[2]	$616.07/60g
Dexpak (dexamethasone)	1.5mg (21) 1.5mg (35) 1.5mg (51)	Multiple indications	Dexamethasone tabs available tier 1	[3]	$9.70/tablet
Cordran (flurandrenolide)	4mcg/sq cm tape	Corticosteroid-responsive dermatoses	Multiple others	Super-high potency steroid along with betamethasone ointment, lotion; also several others	$696.84

Dr. Simmons made a motion to exclude all. Mayfield seconded. All in favor.

Motion Approved.

III. Rebate Review: *by Dr. Rachael McCaleb, UAMS*

Dr. McCaleb reviewed the Botulinum Toxin products and growth hormones.

Botulinum Toxin Summary:

- From the available evidence, there is no proven superiority for a single BTP for treatment of cervical dystonia.
- For the treatment of blephaospasm, after dosage adjustment, Botox and Xeomin are probably equivalent, and Botox and Dysport are possibly equivalent.
- No head-to-head comparison of botulinum toxin products for treatment of spasticity. However, Botox, Xeomin, and Dysport are considered as safe and effective treatment options for spasticity.
- Evidence supports that Myobloc and Botox for primary axillary hyperhidrosis have similar efficacy and safety.
- No head-to-head comparison of botulinum toxin products in chronic migraines. Only able to locate studies evaluating Botox.
- No head-to-head comparison of botulinum toxin products in overactive bladder. Botulinum toxin products are superior to placebo.

Recommendation: EBD Formulary may include up to two covered products (i.e. 1 or 2); all other products will be excluded.

Dr. Pace asked how the patients are administering this right now. Dr. Bemberg replied that the patient is filling it at the pharmacy and taking it to their physician hopefully.

Dr. Simmons made a motion to accept this recommendation. Dr. Kirtley seconded. All were in favor.

Motion Approved.

Growth Hormone Summary:

The currently available growth hormone replacement products are, by definition, similar in their clinical effects. Limited head-to-head data is available. Other than slight pharmaceutical differences, no pharmacologic difference among the agents exists in terms of safety and efficacy.

Recommendations: Include 1 formulary GH product, all others will be excluded from coverage except Serostim® (indicated for HIV wasting in adults) and Zorbtive® (indication for treatment of short bowel syndrome).

Dr. Simmons made a motion to accept this recommendation. Mayfield seconded. All in favor.

Motion Approved.

IV. New Drugs*: by Dr. Jill Johnson and Dr. Jarrod King, UAMS*

Dr. Jill Johnson and Dr. Jarrod King reported on new drugs released July 3, 2017 – September 25, 2017.

A. Recommended Additions

1. Non-specialty Medications

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Humalog Junior Kwikpen	insulin lispro 100units/mL	$42.43/mL	Diabetes	Humalog covered Tier 2 (Rebated)	T2

2. Specialty Medications

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Jadenu Sprinkle	deferasirox 90mg, 180mg, 360mg packets	$42.69 - $170.77/packet	Chronic iron overload	Jadenu tablets - T4PA Exjade 500mg - T4PA	T4PA. Also add all doses of Exjade to formulary.
Rituxan Hycela	rituximab/hyaluronidase 11.7/1400, 13.4/1600 vial	$622.30 - 623.63/vial	CLL, Diffuse large B-cell lymphoma, Follicular lymphoma	Rituxan - PA medical	PA, medical
Renflexis	infliximab-abda 100mg vial	$904.07/vial	Multiple indications	Biosimilar for Remicade. Remicade and Inflectra both covered PA	T4PA with same PA as Remicade; relook at TIMS
Nityr	nitisinone 2mg, 5mg, 10mg tablets	$98.08-$490.42/tablet	Hereditary tyrosinemia type 1	Orfadin capsules & suspension T4PA	Cover T4PA; exclude Orfadin capsules and suspension, code 13.
Nuwiq	antihemophilia FVIII vials	$2.03	Hemophilia	Hemophilia agents T4PA	T4PA
Mylotarg	gemtuzumab ozogamicin 4.5mg	$9,840/vial	Multiple indications	Covered oncology agents at T4PA	PA, medical

B. Recommended Exclusions

1. Non-specialty Medications

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Alzair	Hypromellose spray	$554.15	Allergies		Exclude, code 3
Prednisolone-nepafenac	Prednisolone-nepafenac 1%-0.1% eye drops				Exclude, code 3 & 13
Prednisolone-gatifloxacin	Prednisolone-gatifloxacin 1%-0.5%				Exclude code 3, Exclude Pred Mild code 13
Prednisolone-gatifloxacin-nepafenac	Prednisolone-gatifloxacin-nepafenac 1%-0.5%-0.1%				Exclude, code 3
Mydayis	Dextroamphetamine/amphetamine 12.5mg, 25mg, 37.5mg, 50mg extended release capsules	$10.83/capsule	ADHD	Generic extended release amphetamine salts available T1/RBP (QL) (MAC)	Exclude, code 13
Cotempla XR-ODT	methylphenidate 8.6mg, 17.3mg, 25.9mg XR ODT tab	$12.79/tablet	ADHD	methylphenidate products (IR & ER) available T1 (QL) (MAC)	Exclude, code 13
ArmonAir Respiclick	fluticasone propionate 55mcg, 113mcg, 232mcg inhalers	$188.09-$251.84/inhaler	Asthma for 12 years of age and up	Asmanex, QVAR preferred at T2 (Rebated)	Exclude, code 13
Flolipid	simvastatin 20mg/5mL & 40mg/5mL oral suspension	$2.03-$2.07/mL	Hypercholesterolemia	simvastatin available tier 1 (MAC)	Exclude, code 13
L.E.T.	Lidocaine-epinephrine-tetracaine 4%-0.05%-0.5% gel				Exclude code 3
Pertzye	lipase/protease/amylase 24K-86.25K DR capsules	$7.91/capsule	Pancreatic insufficiency	Other Pertzye strengths excluded; Creon, Pancreaze, Zenpep covered T2	Exclude, code 13. Look for rebate options for single Brand

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Duzallo	lesinurad/allopurinol 200-200mg & 200-300mg tablets	$14.84/tablet	Hyperuricemia associated with gout	allopurinol T1	Exclude, code 1, 13
Carospir	spironolactone 25mg/5mL oral suspension			spironolactone tablets available T1 (MAC)	Exclude code 13
Bevyxxa	betrixaban maleate 40mg & 80mg capsules	$18/capsule	VTE prophylaxis	Xarelto & Eliquis preferred X1 inhibitors at T2 (rebated)	Exclude
Nymalize	nimodipine 30mg/10mL oral solution	$5.38/mL		nimodipine capsules T1	Exclude, code 13; PA generic nimodipine and move to T4
Endari	glutamine 5g powder packets	$22.20/packet			Exclude, code 12
Gocovri	amantadine 68.5mg, 137mg ER caps	$47.50/capsule	Multiple indications	amantadine tablets, capsules, solution covered T1	Exclude, code 13

2. Specialty Drugs

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Panhematin	hemin 350mg vial	$8,677.86/vial	Porphyria		NA Medical; exclude code 12
Nerlynx	Neratinib 40mg tablet	$70/tab	Breast cancer	Covered oncology agents at T4PA	Exclude, code 1 & 8, Relook 10/2018
Benlysta	belimumab 200mg/mL syringe & auto-injector	$1,059/syringe	Systemic lupus erythematosus (SLE)		Exclude, code 1

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Idhifa	enasidenib 50mg, 100mg tablets	$994.88/tablet	Acute myeloid luekemia (AML)	Covered oncology agents at T4PA	Exclude, code 2
Totect	dexrazoxane 500mg vial	$573.75/vial	Prevention of doxorubicin cardiomyopathy; treatment of anthracycline extravasation		Exclude from pharmacy, medical drug, code 12
Besponsa	inotuzumab ozogamicin 0.9mg vial	$22,440/vial	Acute lymphoblastic leukemia (ALL)	Covered oncology agents at T4PA	Exclude code 8, 13
Lynparza	olaparib 100mg, 150mg tablets	$134.82/tablet	Ovarian cancer	Covered oncology agents at T4PA	Exclude, code 1, revisit
Triptodur	triptorelin pamoate 22.5mg vial	$19,200/vial	Multiple indications		Exclude code 13
Jetrea	ocriplasmin/PF 0.125-0.1	$16,900/vial	Vitreomacular adhesion		Exclude, code 9
Aliqopa	copanlisib 60mg vial	$5,040/vial	Follicular lymphoma	Covered oncology agents at T4PA	Exclude code 1, 2, Relook in DCWG Oct 2018

C. Tabled

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Haegarda	C1 esterase inhibitor 2000 unit, 3000-unit vial	$2,256 - $3,384/vial	Hereditary angioedema prophylaxis	Cinryze - T4PA	Send to DCWG
Tremfya	guselkumab 100mg/mL	$11,620.80/syringe	Plaque psoriasis	Several agents available T2PA, T4PA	Table, look at all TIMs
Vosevi	sofobuvir-velpatasvir-voxilaprevir 400mg-100mg-100mg tabs	$1,068/tablet	Chronic hepatitis C	Zepatier preferred T4PA (rebated)	Table

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Mavyret	glecaprevir-pibrentasvir 100mg-40mg tablet	$188.57/tablet	Chronic hepatitis C	Zepatier preferred T4PA (rebated)	Coverage TBD based on rebates, cover only for GT1 NS5A tx experienced patients
Kymriah	tisagenlecleucel	$570,000.00	ALL	Covered oncology agents at T4PA	Refer to DCWG

Dr. Golden motioned to approve the first six of non-specialty drug recommendations. Dr. Niell seconded. All in favor.

Motion Approved.

Dr. Kirtley motioned to approve the rest of the non-specialty recommendations with the exception of Hulamog Junior and the Nimodipine moved to Tier 1 PA. Mayfield seconded. All in favor.

Motion Approved.

Dr. Simmons made a motion to approve all specialty drug recommendations. Dr. Kirtley seconded. All in favor.

Motion Approved.

V. Board Report: *by Dr. Geri Bemberg, UAMS*

Dr. Golden made a comment of the FDA approval and the lack of data, and there is a study coming out that looks at drug patents that were granted from 2005-2015 and found that 74% were released on existing medications. Please note that when you see exclude on several drugs, there are already drugs on the market for conditions.

Meeting Adjourned.

***New Drug Code Key:**

1	Lacks meaningful clinical endpoint data; has shown efficacy for surrogate endpoints only.
2	Drug's best support is from single arm trial data
3	No information in recognized information sources (PubMed or Drug Facts & Comparisons or Lexicomp)
4	**Convenience Kit Policy** - As new drugs are released to the market through Medispan, those drugs described as "kits will not be considered for inclusion in the plan and will therefore be excluded products unless the product is available solely as a kit. Kits typically contain, in addition to a pre-packaged quantity of the featured drug(s), items that may be associated with the administration of the drug (rubber gloves, sponges, etc.) and/or additional convenience items (lotion, skin cleanser, etc.). In most cases, the cost of the "kit" is greater than the individual items purchased separately.
5	**Medical Food Policy** - Medical foods will be excluded from the plan unless two sources of peer-reviewed, published medical literature supports the use in reducing a medically necessary clinical endpoint. A medical food is defined below: A medical food, as defined in section 5(b)(3) of the Orphan Drug Act (21 U.S.C. 360ee(b)(3)), is "a food which is formulated to be consumed or administered eternally under the supervision of a physician and which is intended for the specific dietary management of a disease or condition for which distinctive nutritional requirements, based on recognized scientific principles, are established by medical evaluation." FDA considers the statutory definition of medical foods to narrowly constrain the types of products that fit within this category of food. Medical foods are distinguished from the broader category of foods for special dietary use and from foods that make health claims by the requirement that medical foods be intended to meet distinctive nutritional requirements of a disease or condition, used under medical supervision, and intended for the specific dietary management of a disease or condition. Medical foods are not those simply recommended by a physician as part of an overall diet to manage the symptoms or reduce the risk of a disease or condition, and all foods fed to sick patients are not medical foods. Instead, medical foods are foods that are specially formulated and processed (as opposed to a naturally occurring foodstuff used in a natural state) for a patient who is seriously ill or who requires use of the product as a major component of a disease or condition's specific dietary management.
6	**Cough & Cold Policy** - As new cough and cold products enter the market, they are often simply re-formulations or new combinations of existing products already in the marketplace. Many of these existing products are available in generic form and are relatively inexpensive. The new cough and cold products are branded products and are generally considerably more expensive than existing products. The policy of the ASE/PSE prescription drug program will be to default all new cough and cold products to "excluded" unless the DUEC determines the product offers a distinct advantage over existing products. If so determined, the product will be reviewed at the next regularly scheduled DUEC meeting.
7	**Multivitamin Policy** - As new vitamin products enter the market, they are often simply re-formulations or new combinations of vitamins/multivitamins in similar amounts already in the marketplace. Many of these existing products are available in generic form and are relatively inexpensive. The new vitamins are branded products and are generally considerably more expensive than existing products. The policy of the ASE/PSE prescription drug program will be to default all new vitamin/multivitamin products to "excluded" unless the DUEC determines the product offers a distinct advantage over existing products. If so determined, the product will be reviewed at the next regularly scheduled DUEC meeting.
8	Drug has limited medical benefit &/or lack of overall survival data or has overall survival data showing minimal benefit
9	Not medically necessary
10	Peer -reviewed, published cost effectiveness studies support the drug lacks value to the plan.
11	**Oral Contraceptives Policy** - OCs which are new to the market may be covered by the plan with a zero dollar, tier 1, 2, or 3 copay, or may be excluded. If a new-to-market OC provides an alternative product not similarly achieved by other OCs currently covered by the plan, the DUEC will consider it as a new drug. IF the drug does not offer a novel alternative or offers only the advantage of convenience, it may not be considered for inclusion in the plan.
12	Other
13	Insufficient clinical benefit OR alternative agent(s) available

Edaravone (Radicava®)
30mg/100mL IV infusion

Indication: amyotrophic lateral sclerosis (ALS)
Dosing: Initial cycle: 60mg QD IV infusion x 14 days, followed by a 14-day drug-free period;
Subsequent cycles: 60mg QD x 10 days within a 14-day period, followed by a 14-day drug-free period

Evidence

Confirmatory DB, parallel-group, PC study of efficacy and safety of edaravone (MCI-186) in ALS patients[1]
Phase 3 trial in Japan including pts age 20-75 w/ a dx of 'definite', 'probable' or 'probable lab-supported' ALS according to the revised Airlie House diagnostic criteria; FVC of at least 70%; duration of disease within 3 years; & change in revised ALS functional rating scale (ALSFRS-R) score during the 12-wk pre-observation period of -1 to -4 pts. Pts also had a Japanese ALS severity classification of 1 or 2. Exclusions: reduced respiratory fxn & complaints of dyspnea; complications that may substantially influence evaluation of drug efficacy such as Parkinson's disease, schizophrenia, and dementia; complications that require hospitalization including liver, cardiac, and renal dx; infections that require abx tx; deteriorated general condition; renal dysfxn w/ CrCl of <50mL/min within 28 days before tx; & undergoing cancer tx. Pts were required to remain consistent on tx w/ riluzole.
Pts went through a 12-wk pre-obs period then were randomized to placebo or edaravone using dynamic allocation to minimize the effects of 3 factors (change in ALSFRS-R score, initial sx, & use of riluzole). Study period was 36 wks (including pre-obs) followed by 24 wks of tx. A single tx cycle consisted of 14 days of study drug followed by a 14-day observation period. Subsequent cycles got 10 out of 14 days in admin period.
1`efficacy endpoint was change in ALSFRS-R score. N=206 (placebo (n=104) or edaravone (n=102).
Changes in ALSFRS-R during the 24-week treatment were –6.35+/- 0.84 in the placebo group (n=99) and –5.70+/- 0.85 in the edaravone group (n=100), with a difference of 0.65+/-0.78 (p=0.411). difference of 0.65 ± 0.78 (-0.90, 2.19)
AEs were 88.5% (92/104) in the placebo group and 89.2% (91/102) in the edaravone group.
"In conclusion, the reduction of ALSFRS-R was smaller in the edaravone group than in the placebo group, but efficacy of edaravone for treatment of ALS was not demonstrated." Levels and frequencies of reported adverse events were similar in the two groups.
Placebo grp had 2 deaths (respiratory failure) & the edaravone grp had 3 (2 respiratory disorder & 1 respiratory failure). Investigators determined all deaths were due to the primary dx.

Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a R, DB, PC trial.[2]
Phase 3, R, DB, PG, PC study in Japan. Eligible pts were 20-75 years old w/ a dx of ALS w/ independent living status, decrease in ALSFRS-R score of 1-4 during a 12-wk obs period. Pts had a score of ≥2 on all 12 items of ALSFRS-R; FVC of at least 80%; definite or probably ALS; & duration of dx from the 1st sx (any ALS sx) of ≤2 yrs. Pts were excluded if they had a score of ≤3 on ALSFRS-R for dyspnea, orthopnea, or respiratory insufficiency; hx of spinal sx after onset of ALS; or CrCl of <50ml/min. Riluzole status could not change during the study. 1`efficacy endpoint was change in ALSFRS-R score from baseline to end of cycle 6.
137 pts were enrolled to placebo (n=68) or edaravone (n=69). Change in ALSFRS-R was -5.01 (SE 0.64) in the edaravone grp and -7.50 (0.66) in the placebo grp. Difference in mean ALSFRS-R scores between tx grps at the end of cycle 6 **was 2.49 in favor of edaravone (95% CI 0.99 – 3.98, p=0.0013) [This change represents a 33.2% difference in change in decline for edavarone vs placebo and exceeds the 20% threshold that 90% of surveyed physicians thought to be clinically meaningful.]**

Added value of this study: The safety and efficacy of edaravone were examined in this placebo-controlled, double-blind phase 3 study for patients with ALS who met all of the following criteria identified in post-hoc analyses of the previous phase 3 trial: scores of at least 2 points on all 12 items of ALSFRS-R, forced vital capacity of at least 80%, definite or probable ALS (El Escorial and revised Airlie House diagnostic criteria), and disease duration of 2 years or less. The primary endpoint, change in ALSFRS-R at 24 weeks, was significantly smaller in the patients receiving edaravone, by comparison with placebo. The results of the secondary endpoints Modified Norris Scale (total) and ALS Assessment Questionnaire (ALSAQ-40), also supported the primary result. Implications of all the available evidence In a small, well defined group of patients with early stage ALS, the progression of ALS symptoms was slowed by edaravone. However, the effect of edaravone administration on the long term survival rate, the efficacy of edaravone in a wider population of patients with ALS, and the efficacy in patients with advanced disease were not considered in this study.

ALSFRS-R
48 pt scale that asks the severity of sx in 12 areas: speech, salivation, swallowing, handwriting, cutting food, dressing & hygiene, turning in bed, walking, climbing stairs, dyspnea, orthopnea, & respiratory insufficiency. Also takes into account yrs since onset of sx. 4= best, 0 = worst on the scale. MCID –This survey demonstrated that the majority of clinicians and clinical researchers surveyed believe that a therapy that resulted in a change of 20% or greater in the slope of the ALSFRS-R would be clinically meaningful.
Recommendation & EBRx Outcome 6/21/17: Exclude due to lack of clinical significance of drug.
Recommendation & EBRx Outcome 9/29/17: PA

References:
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2. The Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well-defined patients with amyotrophic lateral sclerosis: a randomized, double-blind, placebo-controlled trial. Lancet Neurol 2017;16:505-12.

Pricing: 30mg/100mL (100mL) - $651.60; $1,303.20/dose; $18,244.80 for the 1st month, $13,032 for subsequent months; **$169,725/year after 1st year.**

Mebendazole (Emverm) 100mg chewable tablet
Jill Johnson, Pharm.D., BCPS 6/8/16; updated by Geri Bemberg, Pharm.D. 11/1/2017

		Drugs	Cost/unit	Cost per course of treatmnt by indication			
				Pinworm[1]	Whipworm	Roundworm	Hookworm
EMVERM	mebendazole 100mg chewable oral tablet	**Emverm** (mebendazole)100mg chewable tablet	AWP = $442.80/tablet	$885.60	$2,656.80	$2,656.80	$2,656.80
		Albenza (albendazole)200mg tablet	AWP = $201.27/tablet (2-tab pack)	$805.08	$1,207.62	$402.54	$402.54
		Pin-X (pyrantel pamoate)[2,3] 144mg/mL suspension; 250mg chewable tablet	MAC = $0.16/mL AWP = $1.12/tablet	$0.36 - $1.84 $2.24 - $8.96	N/A N/A	$0.18 - $0.92[4] $1.12 - $4.484	$0.54 - $2.76[4] $3.36 - $13.444
		Ivermectin[3]3mg tablet	MAC = $4.09/tablet	N/A	$12.27 - $73.62[4]	$4.09 – 24.54[4]	N/A
		1. Cost for 2 courses of treatment, as recommended by the CDC 2. Available OTC 3. Weight-based dosing, based on a patient weight of 15-90 kg 4. Off-label use					

Notes: Mebendazole chew tabs were released onto the market in the early 2000s. At that time, the price/tablet was under $7 each. The generic products went obsolete in 2011. In early 2016, Emverm was released at $442.80/tablet.

Recommendation: exclude Emverm.

Fluoxetine 60mg

Indications: Depression, obsessive-compulsive disorder, bulimia nervosa, etc

Pricing History (following the release of the medication in November of 2011)

Date	Price/Unit	Percentage Increase from Previous Amount	Percentage Increase Since 2012
August 25, 2012	$2.856		
January 3, 2013	$2.976	4.2%	4.2%
April 1, 2013	$3.168	6.5%	10.9%
July 9, 2013	$3.456	9.1%	21%
December 2, 2013	$3.96	14.6%	38.7%
April 17, 2014	$4.608	16.4%	61.3%
July 3, 2014	$5.40	17.2%	89.1%
October 3, 2014	$6.00	11.1%	110.1%
February 14, 2015	$6.864	14.4%	140.3%
July 1, 2015	$7.80	13.6%	173.1%
January 1, 2016	$8.568	9.8%	200%
May 2, 2016	$9.60	12%	236.1%
January 6, 2017	$10.752	12%	276.5%
June 1, 2017	**$11.612**	**8%**	**306.6%**

This drug was released by Edgemont Pharmaceuticals in November of 2011. Fluoxetine 60mg is now owned and manufactured by Almatica Pharma, and is recognized by the FDA as a **single source brand**.

A savings coupon is available on the drug's website to allow for patients to pay $28 or less per month. Currently, this product is processing at Tier 2 ($40) for Premium and Primary members. Other fluoxetine strengths (10mg, 20mg, 40mg) are marketed as generics and are available in both capsule and tablet, at a much cheaper rate.

While there are indications for which amounts of fluoxetine over 40mg are used, there is no evidence to support the use of a "convenience dose" of 60mg total at the expense of both the member and the plan.

Recommendation:
Exclude fluoxetine 60mg, effective January 1, 2018. Members may achieve this dose using a combination of currently available products.

References
1. Lexicomp
2. MedImpact Claims System/First Data Bank
3. www.fluoxetine60.com

Isordil (isosorbide dinitrate)
5mg, 40mg tablets

Indications: angina pectoris (prevention)

Isosorbide dinitrate formulations available

Product	Strengths	Coverage	Price/unit
Isordil Titradose	5mg tab 40mg tab	BPC Tier 2	$9.79 $21.56
Isosorbide dinitrate	5mg tab 10mg tab 20mg tab 30mg tab	Tier 1	$0.99 $1.08 $1.19 $1.31
Isosorbide dinitrate ER	40mg ER tab	Tier 1	$2.37
Dilatrate-SR	40mg ER cap	Excluded	$4.41

No evidence is available demonstrating superiority of Isordil Titradose over currently available formulations.

Isordil 40mg History:

Date	Price/Unit	Percentage Increase from Previous Amount	Percentage Increase since 2005
November 1, 2005	$0.76		
August 2, 2006	$0.82	7.9%	
January 4, 2007	$0.89	8.5%	
June 29, 2007	$0.94	5.6%	
December 21, 2007	$1.09	16%	
March 28, 2008	$1.25	14.7%	
June 2, 2008	$1.43	14.4%	
January 2, 2009	$1.51	5.6%	
July 30, 2009	$1.57	4%	
January 6, 2010	$1.58	0%	
July 15, 2010	$1.66	5.1%	
January 5, 2011	$1.74	4.8%	
August 27, 2011	$1.92	10.3%	
January 17, 2012	$2.01	4.7%	
April 5, 2012	$2.31	14.9%	
September 7, 2012	$2.43	5.2%	
January 4, 2013	$2.68	10.3%	
April 1, 2013	$2.88	7.5%	278.9%
Isordil goes obsolete in September of 2013.			
Isordil is re-released onto the market in October of 2013 (1 week later).			
December 3, 2013	$3.23	12.2%	
February 28, 2014	$3.61	11.8%	
May 1, 2014	$4.11	13.9%	
July 18, 2014	$8.22	100%	
October 1, 2014	$10.69	30%	
November 21, 2014	$11.75	9.9%	
December 22, 2014	$13.50	14.9%	
January 1, 2015	$14.83	9.9%	
March 27, 2015	$16.30	9.9%	
May 29, 2015	$18.75	15%	
July 31, 2015	$21.56	15%	2,736.8%

Isordil was developed by Wyeth Pharmaceuticals, who at some point sold the rights to the drug to Biovail Pharmaceuticals. Biovail Pharma merged with Valeant Pharmaceuticals in 2010.
Late 2015 is when details regarding the outrageous pricing strategy of Valeant Pharmaceuticals emerged into the mainstream media.

Recommendation: EXCLUDE.

Formulary Cleanup

Drug	Formulation	Indication	Other Options	Evidence	Price
Nascobal (cyanocobalamin – vit b12)	500mcg/spray nasal spray	Vit B12 deficiency	IM inj – tier 1 Tabs – tier 1	None; UTD notes that "We generally do not use the intranasal formulations because of their variable absorption and higher cost; these formulations may also cause rhinorrhea."[1]	$158.04/dose
Verdeso (desonide)	0.05% foam	Atopic dermatitis	Cream, lotion, ointment (all 0.05%) tier 1	Low potency steroid along with desonide cream and lotion; also several other products[2]	$936.00/100g
Desonate (desonide)	0.05% gel	Atopic dermatitis	Cream, lotion, ointment (all 0.05%) tier 1	Lower-mid potency along with desonide ointment; also several other products[2]	$616.07/60g
Dexpak (dexamethasone)	1.5mg (21) 1.5mg (35) 1.5mg (51)	Multiple indications	Dexamethasone tabs available tier 1	[3]	$9.70/tablet
Cordran (flurandrenolide)	4mcg/sq cm tape	Corticosteroid-responsive dermatoses	Multiple others	Super-high potency steroid along with betamethasone ointment, lotion; also several others	$696.84

Recommendation: Exclude Nascobal, Verdeso, Desonate, and Dexpak.

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2. Goldstein BG, Goldstein AO. General principles of dermatologic therapy and topical corticosteroid use. Up to Date. Mar 29, 2016. Accessed November 1, 2017.
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DUEC
July 3, 2017 - Sept 25, 2017

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY/AWP	Jill's NOTES	DUEC VOTE	DUEC DATE	IB VOTE	IB DATE	
NON-SPECIALTY DRUGS										
Alzair	Hypromellose spray	$554.15	Allergies		Exclude, code 3		2017 11 06			
Prednisolone-nepafenac	Prednisolone-nepafenac 1%-0.1% eye drops				Exclude, code 3 & 13		2017 11 06			
Prenisolone-gatifloxacin	Prednisolone-gatifloxacin 1%-0.5%				Exclude code 3, Exclude Pred Mild code 13		2017 11 06			
Prednisolone-gatifloxacin-nepafenac	Prednisolone-gatifloxacin-nepafenac 1%-0.5%-0.1%				Exclude, code 3		2017 11 06			
Mydayis	Dextroamphetamine/amphetamine 12.5mg, 25mg, 37.5mg, 50mg extended release capsules	$10.83/capsule	ADHD	Generic extended release amphetamine salts available T1/RBP (QL) (MAC)	Exclude, code 13		2017 11 06			
Cotempla XR-ODT	methylphenidate 8.6mg, 17.3mg, 25.9mg XR ODT tab	$12.79/tablet	ADHD	methylphenidate products (IR & ER) available T1 (QL) (MAC)	Exclude, code 13		2017 11 06			
ArmonAir Respiclick	fluticasone propionate 55mcg, 113mcg, 232mcg inhalers	$188.09-$251.84/inhaler	Asthma for 12 years of age and up	Asmanex, QVAR preferred at T2 (Rebated)	Exclude, code 13		2017 11 06			
Flolipid	simvastatin 20mg/5mL & 40mg/5mL oral suspension	$2.03-$2.07/mL	Hypercholesterolemia	simvastatin available tier 1 (MAC)	Exclude, code 13		2017 11 06			
L.E.T.	Lidocaine-epinephrine-tetracaine 4%-0.05%-0.5% gel				**Exclude code 3**		2017 11 06			
Humalog Junior Kwikpen	insulin lispro 100units/mL	$42.43/mL	Diabetes	Humalog covered Tier 2 (Rebated)	**Cover same as Humalog if same rebate is available.**		2017 11 06			
Pertzye	lipase/protease/amylase 24K-86.25K DR capsules	$7.91/capsule	Pancreatic insufficiency	Other Pertzye strengths excluded; Creon, Pancreaze, Zenpep covered T2	**Exclude, code 13. Look for rebate options for single Brand**		2017 11 06			
Duzallo	lesinurad/allopurinol 200-200mg & 200-300mg tablets	$14.84/tablet	Hyperuricemia associated with gout	allopurinol T1	**Exclude, code 1, 13**		2017 11 06			
Carospir	spironolactone 25mg/5mL oral suspension			spironolactone tablets available T1 (MAC)	**Exclude code 13**		2017 11 06			
Bevyxxa	betrixaban maleate 40mg & 80mg capsules	$18/capsule	VTE prophylaxis	Xarelto & Eliquis preferred X1 inhibitors at T2 (rebated)	**Table**		2017 11 06			
Nymalize	nimodipine 30mg/10mL oral solution	$5.38/mL		nimodipine capsules T1	**Exclude, code 13; PA generic nimodipine**		2017 11 06			
Endari	glutamine 5g powder packets	$22.20/packet			**NA; OTC alternatives**		2017 11 06			
Gocovri	amantadine 68.5mg, 137mg ER caps	$47.50/capsule	Multiple indications	amantadine tablets, capsules, solution covered T1	**Exclude, code 13**		2017 11 06			
SPECIALTY DRUGS										
Jadenu Sprinkle	deferasirox 90mg, 180mg, 360mg packets	$42.69 - $170.77/packet	Chronic iron overload	Jadenu tablets - T4PA Exjade 500mg - T4PA	**T4PA. Also add all doses of Exjade to formulary.**		2017 11 06			
Panhematin	hemin 350mg vial	$8,677.86/vial	Porphyria		**NA Medical; exclude code 12**		2017 11 06			
Rituxan Hycela	rituximab/hyaluronidase 11.7/1400, 13.4/1600 vial	$622.30 - 623.63/vial	CLL, Diffuse large B-cell lymphoma, Follicular lymphoma	Rituxan - PA medical	**NA Medical; exclude on pharmacy side. Add to Rituxan PA by indication**		2017 11 06			
Haegarda	C1 esterase inhibitor 2000 unit, 3000 unit vial	$2,256 - $3,384/vial	Hereditary angioedema prophylaxis	Cinryze - T4PA	Send to DCWG for class review. Katie & Jarrod working on weight table for Cinryze vs Haegarda		2017 11 06			
Tremfya	guselkumab 100mg/mL	$11,620.80/syringe	Plaque psoriasis	Several agents available T2PA, T4PA	**Table, look at all TIMs (Rachael)**		2017 11 06			
Nerlynx	Neratinib 40mg tablet	$70/tab	Breast cancer	Covered oncology agents at T4PA	**Exclude, code 1&8, Relook 10/2018**		2017 11 06			
Renflexis	infliximab-abda 100mg vial	$904.07/vial	Multiple indications	Biosimilar for Remicade. Remicade and Inflectra both covered PA	**T4PA with same PA as Remicade; 11/2017 relook at TIMS**		2017 11 06			
Vosevi	sofobuvir-velpatasvir-voxilaprevir 400mg-100mg-100mg tabs	$1,068/tablet	Chronic hepatitis C	Zepatier preferred T4PA (rebated)	**Table**		2017 11 06			
Mavyret	glecaprevir-pibrentasvir 100mg-40mg tablet	$188.57/tablet	Chronic hepatitis C	Zepatier preferred T4PA (rebated)	**Coverage TBD based on rebates, cover only for GT1 NS5A tx experienced patients**		2017 11 06			
Benlysta	belimumab 200mg/mL syringe & auto-injector	$1,059/syringe	Systemic lupus erythematosus (SLE)		**Exclude, code 1**		2017 11 06			
Idhifa	enasidenib 50mg, 100mg tablets	$994.88/tablet	Acute myeloid luekemia (AML)	Covered oncology agents at T4PA	**Exclude, code 2**		2017 11 06			
Nityr	nitisinone 2mg, 5mg, 10mg tablets	$98.08-$490.42/tablet	Hereditary tyrosinemia type 1	Orfadin capsules & suspension T4PA	**Cover T4PA Nityr, exclude Orfadin capsules and suspension, code 13.**		2017 11 06			
Totect	dexrazoxane 500mg vial	$573.75/vial	Prevention of doxorubicin cardiomyopathy; treatment of anthracycline extravasation		**Exclude from pharmacy, medical drug, code 12**		2017 11 06			

Besponsa	inotuzumab ozogamicin 0.9mg vial	$22,440/vial	Acute lymphoblastic leukemia (ALL)	Covered oncology agents at T4PA	**Exclude code 8, 13**		2017 11 06			
Lynparza	olaparib 100mg, 150mg tablets	$134.82/tablet	Ovarian cancer	Covered oncology agents at T4PA	**Exclude, code 1, revisit next month 10/17.**		2017 11 06			
Nuwiq	antihemophilia FVIII vials	$2.03	Hemophilia	Hemophilia agents T4PA	**T4PA**		2017 11 06			
Kymriah	tisagenlecleucel	$570,000.00	ALL	Covered oncology agents at T4PA	**Exclude, code 8**		2017 11 06			
Triptodur	triptorelin pamoate 22.5mg vial	$19,200/vial	Multiple indications		**Exclude code 13**		2017 11 06			
Jetrea	ocriplasmin/PF 0.125-0.1	$16,900/vial	Vitreomacular adhesion		**Exclude, code 9**		2017 11 06			
Mylotarg	gemtuzumab ozogamicin 4.5mg	$9,840/vial	Multiple indications	Covered oncology agents at T4PA	**PA Medical**		2017 11 06			
Aliqopa	copanlisib 60mg vial	$5,040/vial	Follicular lymphoma	Covered oncology agents at T4PA	**Exclude code 1, 2, Relook 10/2018**		2017 11 06			

Therapeutic Class: Growth Hormones

Rachael McCaleb, PharmD, BCPS

November 2017

Growth hormone (GH), also known as somatotropin (human growth hormone [hGH or HGH]), is a peptide hormone that stimulates growth, cell reproduction, and cell regeneration in humans. Table 1 list current GH agents and Table 2 list current FDA approved indication indications. All of the available GH preparations are available for subcutaneous injection and there are currently no generics available within the class.

Table 1: Growth Hormone (Somatropin) Available

Trade Name (Manufacturer)	Preparation	Trade Name (Manufacturer)	Preparation
Genotropin® (Pharmacia & Upjohn)	Cartridge, powder for reconstitution: 5 mg, 12 mg Cartridge, powder for reconstitution (preservative free): 0.2 mg, 0.4 mg, 0.6 mg, 0.8 mg, 1.0 mg, 1.2 mg, 1.4 mg, 1.6 mg, 1.8 mg, and 2.0 mg	**Saizen®** (Serono)	Cartridge, powder for reconstitution: 8.8 mg Vial, powder for reconstitution: 5 mg (15 IU) and 8.8 mg (26.4 IU)
Humatrope® (Lilly)	Cartridge, powder for reconstitution: 6 mg, 12 mg, and 24 mg Vial, powder for reconstitution: 5 mg	**Serostim®** (Serono)	Vial, powder for reconstitution: 4 mg (12 IU) Vial, powder for reconstitution (preservative-free): 5 mg (15 IU) and 6 mg (18 IU)
Norditropin® (Novo Nordisk)	Prefilled pen (Norditropin® FlexPro®): 5 mg/1.5 mL, 10 mg/1.5 mL, and 15 mg/1.5 mL	**Tev-Tropin®** (Teva Select Brands)	Cartridge, powder for reconstitution: 5 mg
Nutropin® (Genentech)	Prefilled cartridge (Nutropin AQ NuSpin®): 5 mg/2 mL, 10 mg/2 mL, and 20 mg/2 mL Prefilled pen cartridge (Nutropin AQ®): 10 mg/2 mL and 20 mg/2 mL	**Zomacton®** (Ferring Pharmaceuticals)	Vial, powder for reconstitution: 5 mg and 10 mg
Omnitrope® (Sandoz)	Prefilled cartridge: 5 mg/1.5 mL and 10 mg/1.5 mL Vial, powder for reconstitution: 5.8 mg/vial	**Zorbtive®** (Serono)	Vial, powder for reconstitution: 8.8 mg

Table 2: Current FDA Approved Indications

	Genotropin	Humatrope	Norditropin	Nutropin	Omnitrope	Saizen	Serostim	Tev-Tropin	Zomacton	Zorbtive
Pediatrics										
GHD										
Growth failure secondary to Turner syndrome										
Growth failure secondary to Prader-Willi syndrome										
Growth failure secondary to chronic renal insufficiency up to renal transplant										
Growth failure in children born small for gestational age unable to catch-up growth	By 2 y/o	By 2-4 y/o	By 2-4 y/o		By 2 y/o					
Idiopathic short stature (Ht SDS ≤-2.25 and not likely to reach normal adult ht)										
Short stature or growth failure associated with short stature homeobox gene (SHOX) deficiency										
Short stature associated with Noonan syndrome										
Adults										
HIV patients with wasting or cachexia with concomitant antiviral therapy										
GHD who meet the following criteria: - Biochemicla diagnosed adult GHD[a] **AND** - Adult onset **OR** Childhood onset										
Treatment of short-bowel syndrome										

[a] GH stimulation test response w/ peak GH ≤5 mcg/L

Clinical Data:

Overall, treatment with GH therapy is considered to be more effective than no treatment and/or placebo and data suggests that not one specific preparation for each indication is preferred over another. (Deodati, Takeda, lindgren)) Limited availability of head-to-head clinical trials; therefore, it is difficult to determine if one specific preparation of GH is more effective and/or safe than another. Treatment guidelines do not distinguish among the various preparations.

GHD in children:

- Phase III clinical trial comparing Omnitrope (n=44) versus Genotropin (n=45) in eighty-nine treatment-naïve, prepubertal children with GHD for 9 months. (romer)
- Results: similar effects on growth parameters (height and height velocity) were noted

Choice of Preparation Based on Current Clinical Guidelines:

The choice of preparation should be individualized for each patient, taking into consideration therapeutic need and likelihood of adherence to treatment. If more than one preparation is suitable, the least costly should be chosen.

Evidence for Switching GH Preparations:

Little information available regarding effects of switching between GH products. Flodmark et al describe the outcomes of switching children requiring GH treatment from originator GH products to Omnitrope in 102 children in Sweden. The results indicated that the switch did not have any impact on growth velocity in patients overall, or in specific growth disturbances. Similar results were shown in a retrospective cohort study by Rashid and colleagues in the United States [Omnitrope compared to other GH preparations]. Two US surveys determined that majority (92%) of pediatric endocrinologists consider all GH preparations to be equivalent and 90% reported switching GH preparations at least once.

Summary:

The currently available growth hormone replacement products are, by definition, similar in their clinical effects. Limited head-to-head data is available. Other than slight pharmaceutical differences, no pharmacologic difference among the agents exists in terms of safety and efficacy.

Recommendations:

Include 1 formulary GH product, all others will be excluded from coverage except Serostim® (indicated for HIV wasting in adults) and Zorbtive® (indication for treatment of short bowel syndrome).

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Therapeutic Class: Botulinum Toxin Products

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	abobotulinumtoxinA	incobotulinumtoxinA	onabotulinumtoxinA	rimabotulinumB
Trade name	Dysport®	Xeomin®	Botox®	Myobloc®
Manufacturer	Ipsen Biopharmaceuticals	Merz Pharmaceuticals	Allergan	Solstice Neurosciences
Unit/vial	300, 500	50, 100, 200	100, 200	2500, 5000,10,000
FDA Approved Indication	**Cervical dystonia** and upper limb spasticity	Blepharospasm, **cervical dystonia**, and upper limb spasticity	Bladder dysfunction, blepharospasm, **cervical dystonia**, chronic migraine, spasticity (upper/lower limb), strabismus, and primary axillary hyperhidrosis	**Cervical dystonia**

Table 1 – Botulinum toxin products and indications

	Dose Equivalent (units)
abobotulinumtoxinA	2-3
incobotulinumtoxinA	1
onabotulinumtoxinA	1
rimabotulinumB	40

Table 2 – Botulinum toxin products reported dose equivalents

Introduction

Currently four botulinum toxins are FDA approved for a number of different indications. Dysport (abobotulinumtoxinA) is approved for cervical dystonia and upper limb spasticity. Xeomin (incobotulinumtoxinA) is approved for cervical dystonia, blepharospasm, and upper limb spasticity. Botox (onabotulinumtoxinA) is approved for the following indications: bladder dysfunction, blepharospasm, cervical dystonia, chronic migraine, spasticity, and primary axillary hyperhidrosis. Myobloc (rimabotulinumB) is only approved for the treatment of cervical dystonia. With the numerous botulinum toxin products on the market, it may be difficult for providers to differentiate when to favor the use of a single product over another for an indication. The evaluation of head to head comparison trials and reviews is needed in order to make an informed decision when choosing one botulinum preparation over another. This objective of this review is to evaluate the safety and efficacy through the literature on the use of different botulinum toxin preparations in their FDA approved indications.

Clinical Evidence

Cervical dystonia

Cervical dystonia (CD) is a painful condition characterized by involuntary movements of the head[1]. CD is the only indication for which all four botulinum products are approved.

Evidence

The following studies compared multiple botulinum treatment in patients with cervical dystonia. The studies were primarily double blind, randomized studies.[2–6] In addition to being double blind and randomized they were also characterized as parallel group[4,6], non-inferiority[5], multicenter[4], and crossover[2,3] studies. Botox was the primary comparator in each head to head comparison study.

Dysport was compared to Botox in three studies.[2,3,6] Myobloc was compared to Botox in two studies.[4,5] The primary efficacy measures were changes in the Tsui score[3,6] and in the Toronto Western Spasmodic Torticollis Rating Scale[2,4,5]. The Tsui score measures the amplitude of sustained movement, duration of movement, shoulder elevation, and tremor severity in patients with CD.[7] The Toronto Western Spasmodic Torticollis Rating Scale is an accepted measure for CD severity.[8] The length of the studies ranged from 12 weeks[2,6], 16 weeks[3], and 20 weeks[4,5]. The most frequently reported adverse events were dysphagia[2,4,6], dry mouth[2,4,5], neck weakness[2,3], and muscle weakness[3]. Authors concluded that both treatments were safe and effective[5], non-inferior[3], or equivalent[4,6]. One study reported that Dysport had suboptimal efficacy to Botox.[2] No head to head comparisons were found comparing Xeomin to other botulinum products. From the available head to head trials, it can be concluded that Myobloc, Dysport, and Botox treatments can be used to treat CDs safely and effectively. This is consistent with the recommended guidelines.[9]

Blepharospasm

Xeomin and Botox are the two botulinum toxin treatments approved for the treatment of blepharospasm. Blepharospasm is a neurological condition characterized by involuntary contractions of the eyelid. This causes repetitive eyelid closure and can potentially cause blindness due to prolonged eyelid closure.

Evidence

Two randomized trials were found comparing the efficacy and safety of Xeomin and Botox in patients with blepharospasm.[10,11] The primary efficacy measure in both studies was the Blepharospasm Disability Index (BSDI)[12]. Wabbels et al. performed a double-blind, randomized, parallel group study in 2011 comparing these two drugs. 31 patients treated with Botox and 33 patients treated with Xeomin were followed for 8 weeks. The most frequent adverse events reported in this study were periorbital hematoma and headache. There was a non-significant trend toward greater improvement with Botox compared to Xeomin for both BSDI and JRS at weeks 4 and 8.[10] However, a post hoc analysis of responders (n=43) showed that significantly more subjects treated with Botox achieved a four point change in total BSDI, threshold for clinically significant change, at week four compared to subjects treated with Xeomin (13/19 vs 6/24, p=0.006). A more recent study by Saad et al. provided 47 patients with 4 injections of either drug. The authors did not report any adverse events and did not report a significant difference in changes in BSDI scores or patient preference between the treatment groups.[11] The mean units used per eye was higher in Wabbels et al study compared to Saad et al study (26.8-29 vs 20). From these studies it would seem that Botox may be the preferred treatment method over Xeomin, however, both can be safe and effective.

Spasticity

Three botulinum toxin products are approved for the treatment of spasticity. Spasticity is a motor disorder characterized by continuously contracted muscles that in turn cause stiffness and tightness and can affect mobility and speech.[13]

Evidence

No studies or reviews compare Botox, Xeomin, and Dysport head to head. Botox was compared to titzanide, a different treatment option for spasticity, in 2009. 60 patients were followed for 22 weeks. The main adverse event associated with Botox were somnolence, and fatigue. It was concluded that Botox was safer and more effective.[14] Xeomin was compared to placebo in an open label extension of a double blind placebo controlled multicenter study. Injection site pain and muscular weakness were reported by 8 of the 145 patients followed for 69 weeks. Xeomin sustained efficacy and was well tolerated.[15] The third study, a double blind placebo controlled trial, compared Dysport to saline in 55 patients for 24 weeks. All three studies used the Ashworth Scale as an efficacy measure. The Ashworth scale is a validated measure used to detect muscle tone and functionality differences in several flexors.[16] In addition to using the Ashworth scale, the authors comparing Dysport to saline measured caregiver burden. In this study pneumonia and fever were the most frequently reported adverse events.

Dysport was considered safe, decreased caregiver burden, and improved muscle spasticity.[17] All three botulinum toxin treatments should be considered as safe and effective treatment options for spasticity.

Primary Axillary Hyperhidrosis
Primary axillary hyperhidrosis is characterized by abnormally increased underarm sweating. Botox is the only botulinum treatment approved for the treatment of primary axillary hyperhidrosis.

Evidence
A randomized bilaterally paired single subject study compared Botox to Myobloc. The study followed 24 patients for 20 weeks. The primary efficacy measure was a change in Hyperhidrosis Disease Severity Scale (HDSS) score. The HDSS provides a qualitative measure of the severity of the patient's condition based on how it affects their daily activities.[18] Mild pain was the only adverse event reported by one patient. Statistically comparable efficacy in both groups was observed.[19] From this study it seems that despite Botox being the only approved botulinum toxin for the treatment of primary axillary hyperhidrosis, Myobloc may also be an effective and safe treatment for this condition.

Chronic Migraine
Botox is the only botulinum toxin approved for the treatment of chronic migraine. Chronic migraines are characterized by headaches occurring on at least 15 days for at least 3 months and a migraine on at least 8 days out of the month.[20]

Evidence
Diener et al. pooled two phase II and two phase III double blind, placebo-controlled trials assessing the efficacy and safety of Botox vs. placebo. A total of 2436 patients were included in the pooled analysis of which 1997 were included in the Botox treatment arm. The included trials were very similar with a time horizon of approximately 12 weeks. Neck pain and muscle weakness were reported. No other serious adverse events occurred. The authors concluded that Botox was well tolerated and efficacious.[21] An additional phase III randomized study, published in 2016, followed 1236 patients for 48 weeks. The authors compared Botox to a placebo and reported no adverse events. It was concluded that Botox is safe and efficacious in the long-term.[22] From the evidence in these trials, Botox is a safe and effective for the treatment of chronic migraines.

Neurogenic Detrusor Overactivity/Overactive Bladder
Botox is the only botulinum toxin approved for the indication of an overactive bladder.

Evidence
Two studies published in 2016 followed a group of patients diagnosed with overactive bladder syndrome for 6 months comparing Botox to either placebo[23] or sacral neuromodulation therapy[24]. Both studies used the change from baseline mean number of daily urgency urinary incontinence episode as the primary efficacy measure. The first study by Hsiao et al. followed 89 patients, did not report adverse events and found that Botox had an overall success rate of 63.8%.[23] The second study was a multicenter, open label, randomized trial following 364 women comparing Botox to sacral neuromodulation therapy. Urinary tract infection was the most frequently reported adverse events and was observed most frequently in the Botox group. The authors found that Botox had a small yet significant overall improvement over the compared treatment.[24] It seems that Botox is a possibly effective and safe treatment for overactive bladder syndrome. A retrospective cohort study showed that Dysport compared to Botox resulted in a higher risk of self-cauterization.[25] However, it is difficult to draw any sound conclusion from this study given the retrospective study design and potential for bias.

Summary

- From the available evidence, there is no proven superiority for a single BTP for treatment of cervical dystonia.
- For the treatment of blephaospasm, after dosage adjustment, Botox and Xeomin are probably equivalent, and Botox and Dysport are possibly equivalent.
- No head-to-head comparison of botulinum toxin products for treatment of spasticity. However, Botox, Xeomin, and Dysport are considered as safe and effective treatment options for spasticity.
- Evidence supports that Myobloc and Botox for primary axillary hyperhidrosis have similar efficacy and safety.
- No head-to-head comparison of botulinum toxin products in chronic migraines. Only able to locate studies evaluating Botox.
- No head-to-head comparison of botulinum toxin products in overactive bladder. Botulinum toxin products are superior to placebo.

Recommendation

- EBD Formulary may include up to two covered products all other products will be excluded.

Author	Year	Indication	Study Type	Comparison	Sample	Primary Efficacy Measure	Timeline	AE	Efficacy Results
Cervical Dystonia									
Comella et al.	2005	Cervical Dystonia	Randomized, double-blind, parallel-arm, multicenter	Myobloc vs. Botox	139	Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)	20 weeks	Dysphagia and dry mouth	**Equivalent benefit** Change in TWSTRS at wk 4: Myobloc: 10.2 Botox: 9.3 P=0.75 Similar improvements in PGA and SGA at wk 4 PGA: Botox: 2.0; Myobloc: 1.8; *p* =0.05 SGA: Botox: 1.6; Myobloc: 1.4; *p* =0.05 Similar duration of effect: 13 wks for Botox and 11.7 wks for Myobloc (p=0.095)
Pappert et al.	2008	Cervical Dystonia	Randomized, double-blind, noninferiority trial	Myobloc vs. Botox	111	TWSTRS	20 weeks	Mild dry mouth more frequent in Botox	Both safe and effective Treatment difference -2.2 points (90% CI -4.9,0.6) (upper limit of CI below 4 meeting NI criteria) No difference in duration of effect; 13.1 wks Botox and 13.7 wks for Myobloc p=0.833
Odergren et al.	1998	Cervical Dystonia	Double Blind, randomized, parallel group Inclusion: min of 4 previous Botox treatments	Botox and Dysport 1:3	73	Tsui Score	12 weeks	Dysphagia - no significant difference between groups	Similar improvement in both groups No difference in post-treatment Tsui scores between treatments Dysport 4.8(0.3) and Botox 5.0 (0.3); p=0.66 No difference in improvement of Tsui score (secondary outcome)
Yun et al.	2014	Cervical Dystonia	Double Blind, randomized Crossover trial	Botox and Dysport 1:2.5	103	Tsui Score	16 weeks	Neck and muscle weakness - not significantly different	Dysport non inferior to Botox Similar mean change in Tsui score from baseline at 4 wks (Dysport 4.0 vs Botox 4.8 (95% CI, -0.1 to 1.7; p=0.091)
Rystedt et al.	2015	Cervical Dystonia	A Double-Blind, Randomized, Crossover Trial Treatment with Dysport at least 1 yr	Botox and Dysport 1:3 or 1:1.7	46	TWSTRS	12 weeks	Dysphagia, Dry Mouth and neck weakness reported	Median difference in TWSTRS Dysport vs Botox 1:3 was 1.96 p=0.0799 and Dysport vs Botox 1:1.7 was 1.38 p=0.3413
Blepharospasm									
Wabbels et al.	2011	Blepharospasm	Double-blind, randomized, parallel group	Xeomin and Botox	64	Blepharospasm Disability Index (BDSI)	8 weeks	Periorbital hematoma and headache	Botox higher responder threshold (13/19 vs 6/24, p=0.006) and change in and higher BDSI score change (-2.8 vs -1.3, p=0.093)

									Duration of effect was similar for both treatments (13 wks)
Saad et al.	2014	Blepharospasm	Prospective, randomized, double-blinded split face technique	Xeomin and Botox Pervious treatment w/Botox	47	BDSI	4 injections	No AE reported	Equivalent benefit BSDI scores did not reveal any difference compared with baseline (P = 0.8161), nor did it demonstrate an effect of time on BSDI scores (P = 0.6108)
Spasticity									
Simpson et al.	2009	Spasticity	Randomized double blind placebo controlled trial	Botox vs. tizanidine	60	Modified Ashworth Score (MAS)	22 weeks	Somnolence and fatigue	Botox is safer and more effective Botox greater reduction in finger/wrist flexors at 3 wks (p,<.001 vs TZD; p<0.02 vs placebo) and 6 (p=0.001 vs TZD; p=0.08 vs placebo) Botox lower incidence of AE (p,<.001 vs TZD; p=0.001 vs placebo)
Kanovsky et al.	2011	Spasticity	Open Label extension of double blind placebo controlled multicenter study	Xeomin vs. placebo	145	MAS	69 weeks	Injection site pain and muscular weakness	Sustained efficacy and well tolerated
Lam et al.	2012	Spasticity	Double blind placebo controlled trial	Dysport vs. saline	55	Caregiver burden scale and MAS	24 weeks	Pneumonia and Fever	Decrease in burden of care and significant improvement considered safe
Primary Axillary Hyperhidrosis									
Soo et al.	2015	Primary Axillary Hyperhidrosis	Randomized bilaterally paired single-subject study	Botox vs. Myobloc 1:30	24	Hyperhidrosis Disease Severity Scale (HDSS)	20 weeks	Mild pain was reported in 1 patient	Statistically comparable efficacy in both groups No difference in HDSS efficacy at wk 2, 12, and 20
Chronic Migraine									
Lipton et al.	2016	Chronic Migraine	Phase 3 Randomized Study	Botox vs. placebo	1236	Headache Impact Test	48 weeks	None reported	Long-term efficacy compared to placebo
Diener et al.	2014	Chronic Migraine	Pooled analysis of RCT	Botox vs. placebo	2436	Different among analyses	12 week intervals	Neck pain and muscle weakness	Efficacious and well tolerated
Overactive Bladder									
Hsiao et al.	2016	Overactive Bladder Syndrome	RCT	Botox	89	Daily urgency incontinence episodes symptoms	6 months	No safety report	Overall success rate 63.8%
Amundsen et al.	2016	Overactive Bladder Syndrome	Multicenter, open label randomized trial	Botox vs. sacral neuromodulator	364 women	Daily urgency incontinence episodes symptoms	6 months	Urinary tract infection most frequently reported in Botox group	Small yet significant greater level of improvement in Botox group
Ravindra et al.	2013	Non-neurogenic OAB	Retrospective cohort study	Botox vs Dysport	207	Patient-reported global satisfaction			Equivalent in terms of voiding diary parameters, ICIQ questionnaires, patient

				1:2.5 then 1:1.5					reported global satisfaction and duration of effect Significant difference in intermittent self-catheterization Botox 23% vs Dysport 42%; p=0.009 (no difference between different doses of Dysport

Table 3 – Summary of studies evaluating botulinum toxin studies

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