AGENDA

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

December 2, 2016

1:00 p.m.

EBD Board Room – 501 Building, Suite 500

I.	*Call to Order*	*Dr. Hank Simmons, Chairman*
II.	*Approval of August 1, 2016 Minutes*	*Dr. Hank Simmons, Chairman*
III.	*Second Review of Drugs*	*Dr. Jill Johnson & Dr. Geri Bemberg, UAMS*
IV.	*New Drugs*	*Dr. Jill Johnson, UAMS*
V.	*Opioid Considerations*	*Dr. Dwight Davis, UAMS*
VI.	*Anticoagulant Rebate Review*	*Dr. Rachael McCaleb, UAMS*
VII.	*EBD Report*	*Dr. Geri Bemberg, UAMS*

2017 Upcoming Meetings

February 6, 2017, April 3, 2017, August 7, 2017, November 6, 2017

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
December 2, 2016

The State and Public Life and Health Insurance Board, Drug Utilization and Evaluation Committee (DUEC) met on Monday, December 2, 2016 at 1:00 p.m., in the EBD Board Room, 501 Woodlane, Little Rock, AR.

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

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

Members absent:
Dr. William Golden
Dr. Appathurai Balamurugan

Chris Howlett, EBD Executive Director, Employee Benefits Division

OTHERS PRESENT

Dwight Davis, Rachael McCaleb, Nick Green, UAMS College of Pharmacy; Sherry Bryant, Ethel Whittaker, Shay Burleson, Cecilia Walker, Eric Gallo, EBD; Marc Watts, ASEA; Charlene Kaiser, Amgen; Takisha Sanders, Health Advantage; Ronda Walthall, Wayne Whitley, AHTD; Jon McGuire, GSK; Bridgett Johnson, Pfizer; Takisha Sanders, Health Advantage; Jim Chapman, ABBVIE; Suzanne Woodall, MedImpact; Stephen Carroll, Allcare Specialty; Frances Bauman, Nova Nordisk; Sean Teague, Merck; Amanda Quick, ASBP; Elizabeth Whittington, ACHI; Mark Bayley, Lilly; Bud McCankic, Allergan; Sam Smothers, Astra Zeneca

CALL TO ORDER

Meeting was called to order by Dr. Hank Simmons, Chairman.

APPROVAL OF MINUTES

Simmons asked for a motion to approve the August 2, 2016 minutes. Dr. Pace motioned for adoption of the minutes. Dr. Kirtley seconded; all were in favor.

Minutes Approved.

I. 2nd review of Drugs: by Dr. Geri Bemberg and Dr. Jill Johnson, UAMS

A. Formulary Cleanup: Dr. Geri Bemberg

Drug Name	Indication	Cost	Utilizing Members	Current Tier	Proposed Tier
Xyrem (sodium oxybate)	Narcolepsy with cataplexy	$4,455.60/180mL ($24.75/mL) (was $10.90/mL in Feb 2012)	5	T2 PA	T4PA
Afinitor (everolimus)	Multiple cancers	$493.39 - $516.11/tablet	4	T3 PA	T4PA
Lupron Depot-Ped (leuprolide)	Precocious puberty	$1,511.45 - $9,066.84	3	T1, T2, T4	T4
Lupron Depot (leuprolide)	Multiple cancers	$1,256.40 - $5988.80	19	T2 (45mg excluded)	T4
Eligard (leuprolide)	Multiple cancers	$542.03 - $2,168.11	0	T2 (45mg excluded)	T4
Alcortin A (Iodoquinol & hydrocortisone)	Dermatoses	$9,561.60 (48g tube or #24 -2g packets)	1	T3	EXCLUDE

Drug	Category	Current Tier	Proposed Tier
Amlodipine/valsartan	ARBs	RBP	Tier 1
Telmisartan	ARBs	RBP	Tier 1
Zaleplon	Sedatives	RBP	Tier 1

Dr. Kirtley motioned to approve as presented. Dr. Neill seconded. All were in favor, motion approved.

B. Flu Mist: Dr. Geri Bemberg

Dr. Bemberg recommended that due to the Advisory Committee on Immunizations Practices' (ACIP) position on the lack of efficacy of Flu Mist, that the medication be excluded from the plan for the 2017 benefit year and revisited for the 2018 plan year.

Dr. Kirtley motioned to exclude Flu Mist for 2017. Dr. Pace seconded. All were in favor, motion approved.

C. Sodium Hyaluronate Injections for the Knee: Dr. Geri Bemberg

Brand	Price	Dosing	Price per treatment	Current Coverage
Synvisc	16mg/2mL (2mL): $497.58 (current) $432 (PFS) (2014)	16mg (2mL) q week x 3 wks	$1,492.73 ($1,296 in 2014) for 3 wks	Excluded
Monovisc	88mg/4mL (4mL): $1,417.82 (current) $1,170 (PFS) (2014)	88mg (4mL) once	$1,417.82 $1,170 (2014)	Covered PA
Euflexxa	20mg/2mL (2mL): $407.91 (current) $369.98 (2014)	20mg (2mL) q wk x 3 wks	$1,223.73 for 3 wks	Excluded
Gel-One	30mg/3mL (3mL): $1,170 - $1,228.80	30mg (3mL) once	$1,170 - $1,228.80	Covered PA
Gelsyn-3	16.8mg/2mL (2mL): $414	16.8mg (2mL) q wk x 3 wks	$1,242 for 3 wks	Excluded
GenVisc 850	25mg/2.5mL (2.5mL): $276.36	25mg (2.5mL) q wk x 5 wks (some may benefit from 3 wks)	$829.08 for 3 wks $1,381.80 for 5 wks	Excluded
Hyalgan	20mg/2mL (2mL): $228 (current) $216 (2014)	20mg (2mL) q wk x 5 wks (some may benefit from 3 wks)	$684 ($648 in 2014) for 3 wks $1,140 ($1,080 in 2014) for 5 wks	Excluded
Hymovis	24mg/3mL (3mL): $320	24mg (3mL) q wk x 2 wks	$640 for 2 wks	TBD
Orthovisc	15mg/mL (2mL): $463.50 (current) $383.96 (2014)	30mg (2mL) q wk x 3-4 wks	$1,390.50 ($1,151.88 in 2014) for 3 wks $1,854 ($1,535.84 in 2014) for 4 wks	Excluded
Supartz	25mg/2.5mL (2.5mL): $241.80	25mg (2.5mL) q wk x 5 wks (some may benefit from 3 wks)	$1209 for 5 wks $725.40 for 3 wks	Excluded DISCONTINUED
Supartz FX	25mg/2.5mL (2.5mL): $276.36	25mg (2.5mL) q wk x 5 wks (some may benefit from 3 wks)	$829.08 for 3 wks $1,381.80 for 5 wks	Excluded
Synvisc-One	48mg/6mL (6mL): $1,492.73 (current) $1,296 (2014)	48mg (6mL) once	$1,492.73 $1,296 (2014)	Covered PA

*All prices reflect AWP from MedImpact's claim system, Lexicomp, and restat

**2014: When looking at Hyalgan, its initial AWP in Sept 2011 was $156/vial, now in 2014 (latest AWP update was in April), price is $216/vial. Safe to assume that applies across the board on all intra-articular hyaluronates.

2016: Please see above for price increase when appropriate. Hyalgan, the drug mentioned in 2014, has now increased to $228/vial

Recommendation: In 2014, this plan excluded series-injection Sodium Hyaluronate products. In April of 2016, BCBS changed their coverage criteria for their commercial plans to stop covering the medications. Now, this plan is being asked to consider excluding any hyaluronate product for intra-articular injection of the knee due to lack of evidence demonstrating efficacy compared to normal saline.

Dr. Pace motioned to exclude. Dr. Kirtley seconded. All were in favor, motion approved.

D. Xuriden: Dr. Jill Johnson

Dr. Johnson asked the committee to reconsider coverage of Xuriden due to lack of concrete evidence for the indication of HOA. After discussion, it was decided to leave Xuriden covered Tier 4 PA, as decided in the previous DUEC meeting.

The committee decided to continue current coverage. No vote taken.

II. New Drugs: by Dr. Jill Johnson, UAMS

Dr. Jill Johnson reported on new drugs. The review covered products released February 1, 2016 – May 23, 2016.

A. Recommended Additions

1. Nonspecialty Medications

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Coly-Mycin-S Otic	Neomycin-Colistin-HC-thonzonium Br Otic Suspension	$209.41	Otic infections	Ciprodex-Tier 3; Cipro-HC-T2; neomycin/polymyxin/HC – T1	Cover, Tier 2
Cetylev	Acetylcysteine 500mg, 2.5g effervescent tablet	$21.70/tablet	Acetaminophen overdose		Cover, Tier 3
Emend	Aprepitant 125mg oral suspension	$339.61/mL	Nausea and vomiting associated w/ chemo or postop	Emend capsules covered T2 w/ QL	Cover, Tier 2 w/ QL

2. Specialty Medications

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Idelvion	Coagulation Factor IX (Recomb) for inj 250, 500, 1000, 2000 units	$5.10/unit	Hemophilia B (congenital factor IX deficiency)	Other hemophilia products covered T4 PA	Cover, Tier 4 PA
Truvada	Emtricitabine-Tenofovir 100-150, 133-200, 167-250mg tablets	$58.66 tablet	HIV, Preexposure prophylaxis, etc.	HIV covered T4. Other Truvada strength covered at T4.	Cover, Tier 4
Afstyla	Antihemophillic Factor Recomb for inj 250,500, 1000, 2000, 3000 units	$1.98/unit	Hemophillia A	Other hemophilia products covered T4 PA	Cover, Tier 4 PA

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Orfadin	Nitisinone 4mg/ml suspension	$19,617.12/90 ml	Hereditary tyrosinemia type 1	Orfadin capsules T4 (AWP $5,999.33-$29,996.48/60 caps)	Cover, Tier 4 PA. PA all other dosage forms.
Tivicay	Dolutegravir 10mg, 25mg	11.38-$28.45/tab	HIV Treatment	HIV covered T4. 50mg Tivicay covered T4 ($56.91/tab)	Cover, Tier 4
Hydroxyprogesterone	Hydroxyprogesterone Carproate IM in Oil 1.25g/5ml	$2,310.69	Preterm birth	Makena (AWP $873.54/ml) is excluded (compound covered)	Cover, Tier 4 PA.
Orencia Clickjet	Abatacept	$1,,083.56	Rheumatoid Arthritis	Rebated category. Orencia covered at non-preferred T4PA	Cover, Tier 4 PA.
Epclusa	Sofosbuvir/velpatasvir	$1,068/tablet	Hepatitis C	Rebated category	Cover, Tier 4 PA
Vonvendi	Von Willebrand Factor 650, 1300 unit	$2.38/unit	Von Willebrand disease	T4 PA	Cover, Tier 4 PA

Dr. Kirtley motioned to adopt the Specialty and Non-Specialty additions. Dr. Pace seconded. All were in favor, motion approved.

B. Recommended Exclusions

1. Nonspecialty Medications

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Xaquil XR	Levomefolate glucosamine 30mg CR tablet	$1.44/tablet			Exclude, code 5
Papaverine-Phentolamine-alprotadil	Papaverine-Phentolamine-alprotadil 12-1-10, 30-1-20/ml	$23.76	Erectile Dysfunction	ED meds covered w/QL at T2 & T3	Exclude code 13
Bevespi	Glycopyrrolate/Formoterol	$389.44	COPD	Rebate category	Exclude
Loprox	Ciclopirox/Skin cleanser No. 40 0.77%	$327.05	Tinea pedis, tinea corporis, tinea cruris	Generic ciclopirox cream0.77% 30g tube covered tier 1 (AWP $56.50)	Exclude, Code 13
Xiidra	Lifitegrast 5% solution	$8.53/ml	Dry eye disease	Diclofenac tabs available T1, omeprazole available T1	Exclude code 13

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Lidotral	Lidocaine 3.88% cream	$1,586.55	Topical anesthetic	Multiple products available at T1	Exclude, Code 13
Otovel	Ciprofloxacin-Fluocinolone 0.3-0.0255	$237.60	Acute otitis media in patient with tympanostomy tubes	Ciprodex – tier 3; Cipro-HC – T2; neomycin/polymyxin/HC – T1	Exclude code 13; POS Msg plan covers Ciprodex
Byvalson	Nebivolol-valsartan 5mg-80mg tablet	$4.384/tablet	Hypertension	Generic beta blockers covered T1 (MAC), Bystolic T3 ARBs RBP, valsartan available T1(MAC)	Exclude code 13
Qbrelis	Lisinopril 1mg/ml oral solution	$3.95/ml	Hypertension	Gen ACEI available TR1 (MAC)	Exclude, Code 13
Zurampic	Lesinurad 200 mg tablet	$14.00/tablet	Hyperuricemia associated with gout	Allopurinol, colchicine T1 (MAC); Uloric T3 PA	Exclude code 1
Relistor	Methylnaltrexone 150mg tablet	$20/tablet	Opioid-induced constipation	Relistor inj T3, Linzess T3PA, Amitiza T3PA, Movantik T3QL	Exclude, code 13. Also exclude Relistor Inj. Add PA to Movantik.
Targadox	Doxycycline Hyclate 50mg	$15/tablet	Tetracycline antibiotic	Doxycycline generic products available T1 (MAC)	Exclude, code 13

2. Specialty Medications

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Rynoderm	Urea Cream 37.5%	$2,717.88	Hyperkeratotic conditions	Generic urea creams available in various strengths	Exclude, code 13. Also exclude Rx 39%, 45%, 47%, and 50% new users. Grandfather the 2 EBD users using 50% product. POS message: "Use 40%".
Ocaliva	Obeticholic Acid 5mg, 10mg tablets	$228/tablet	Primary biliary cholangitis	Multiple pain medications covered	Exclude code 1
Lazanda	Fentanyl Nasal Spray 300mcg/actuation	$829.22	Breakthrough cancer pain in adults	Multiple pain medications covered at different tiers	EBD already excluded Lazanda 5/12/12

BRAND NAME	GENERIC NAME	PRICING (AWP)	INDICATION	SIMILAR THERAPIES ON FORMULARY	DUEC VOTE
Probuphine Implant	Buprenorphine HCl Subdermal Implant	$1,485.00	11/7/16 =F18+	Buprenorphine SL tabs T1 (MAC), buprenorphine-naloxone CL tabs T1 (MAC); Suboxone file covered T2PA	Exclude, Code 13.
Zinbryta	Daclizumab 150mg/ml	$8,200.00	Multiple Sclerosis	Multiple MS meds covered T4PA	Exclude, code 13
Viekira XR	Ombitasvir-Paritaprevir-ritonavir-dasabuvir XR tab	$396.76/tablet	Hepatitis C	Rebate category.	Exclude, code 13

Dr. Kirtley motioned to adopt the Specialty and Non-Specialty additions. Dr. Pace seconded. All were in favor, motion approved.

III. Opioid Considerations: *by Dr. Dwight Davis*

Dr. Davis reported on updates to the CDC guidelines on opioid use. He also gave a snapshot of what EBD's current utilization looks like for members with 12 or more controlled medications in a 3 month period. After much discussion, the committee decided to hold a special opioid specific DUEC in January to further discuss the best way to address new and current utilizers.
The committee voted to follow BCBS's mandate to have all prescribers be enrolled in the PDMP.

Dr. Neill motioned that EBD follow BCBS's mandate to have all new prescribers enrolled in the PDMP by the date predetermined by BCBS. Dr. Simmons seconded. All were in favor, motion approved.

IV. Target Specific Oral Anticoagulants: *by Dr. Rachael McCaleb, UAMS*

Dr. McCaleb provided a class review of Target Specific Oral Anticoagulants.
Recommendations: EBD Formulary may include up to two covered TSOACs. All other products will be excluded. Also, price protection for the life of the contract should be required.

Dr. Kirtley motioned to accept the recommendations. Mr. Boyd seconded. All were in favor, motion approved.

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

Dr. Bemberg reported the Board approved all changes except for the exclusion of PPI's. As a result, PPI's will continue to be covered. Migraine meds will begin reference pricing on 1/1/17.

Dr. Bemberg reported on the following rebates:

- Insulins went into effect 9/1/16
    - Covered Insulin Products: Humulin (R,N, 70/30), Humalog, Lantus, Toujeo
    - Excluded Insulin Products: Novolin (R,N, 70/30), Novolog, Levemir, Apidra
- Targeted Immune Modulators went into effect 10/1/16
    - Preferred agents: Enbrel, Humira

    - Others remain on the formulary at a non-preferred tier.
- ICS/LABA inhalers went into effect 10/1/16
    - Covered: ProAir Respiclick
    - Excluded: Advair Diskus 250-50 and 500-50, Advair HFA, Breo Ellipta
    - Advair 100-50 (Diskus) will still be available for those 4-11
- ICS inhalers went into effect 11/1/16
    - Covered: Asmanex, QVAR, Generic budesonide updraft
    - Excluded: Aerospan, Alvesco, Arnuity, Flovent, Pulmicort brand
- LAMA inhalers went into effect 11/1/16
    - Covered: Spiriva
    - Excluded: Incruse, Tudorza
- LAMA/LABA inhalers went into effect 11/1/16
    - Covered: Stiolto
    - Excluded: Anoro

Respectfully submitted,

Dr. Hank Simmons,
Chair, DUEC

***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

Sodium hyaluronate (Synvisc, Monovisc)
Antirheumatic; Ophthalmic Agent, Viscoelastic; Skin and Mucous Membrane Agent
Geri Bemberg, Pharm.D.

Comparators in trial arms	Primary Outcome	Secondary Outcomes	Patient Baseline Characteristics	Primary Outcome Results	Author's Conclusions	G.Bemberg notes
6 mL Hylan G-F 20 vs 6 mL PBS (single injection)[1]	Change from BL over 26 wks in WOMAC A (0-4 pt scale)	WOMAC A1 & C, PGA, COGA	253 pts (K-L grade II or III) **patients were more severe in placebo grp**	Difference of -0.15 btw grps @26 wks on a 4 pt WOMAC scale (favoring Hylan)	"statistically significant, clinically relevant pain relief…with a modest difference vs. placebo"	No clinically significant difference, didn't meet power in Hylan grp
2.5 mL GO-ON (intermediate MW) vs 2 mL Hyalgan (low MW) 1 inj q week x 3 wks [2]	6 month change in the WOMAC pain subscale (normalized to 100 pt scale)	Total index, physical fxn & stiffness subscales, global knee pain, LFI, ICOAP, PGA, etc	437 pts (K-L grade II or III) **patients more severe in Go-ON grp, but reported more symptoms in Hyalgan grp**	Difference of -4.5 btw grps @ wk 26 **out of 100** pts (favoring GO-ON)	"Tx w/3-weekly inj of intermediate MW HA may be superior to low MW HA on knee OA symptoms over 6 months"	Not clinically significant
3 mL Gel-200 vs 3 mL PBS (single injection)[3]	WOMAC pain @ wk 13	OMERACT-OARSI	379 patients (K-L grade I, II, or III) **patients not as sick as other trials, worse off in Gel-200 grp**	Difference of 6.39 mm between groups out of 100, favoring Gel-200	"…tx with Gel-200 offers statistically sig & clinically meaningful improvements both in pain & physical fxn.."	
Home exercise BID vs 2.5 mL HA inj once weekly x 5 weeks, then monthly until 24 week total.[4]	VAS (100 pt scale), JKOM (100 pt scale), OMERACT-ARSI	Data categorized for logistic regression analysis	102 patients (all females, mean age 70.4)	No significant difference btw grps on any primary outcome.	See below	
2 mL Euflexxa vs 2 mL PBS weekly x 3 weeks[5]	VAS (100 pt scale) @ wk 26 following 50 ft walk test	OARSI responder index, WOMAC subscales	588 pts w/ mod to severe pain on VAS, K-L grade II or III	Least square means diff of -6.6 mm btw grps	Euflexxa resulted in sig pain relief at 26 weeks compared to PBS	
2 mL Hyalgan vs 2 mL saline q week x 5 weeks[6]	Time to recurrence over 1 yr	LFI, 50 m VAS, paracetamol consumption, pt's global assessment, Nottingham health profile, joint effusion & # responders	337 pts (LFI of 10 or more) – mod to severe	No significant difference btw grps	Did not improve pain, fxn, paracetamol consumption or other efficacy parameters 3, 6, 9 or 12 months after tx.	
2.5 mL 1% Na Hyal vs 2.5mL saline. 4 tx cycles of 5 weekly inj each. Follow up 6 months after 1st & 2nd, 1 yr after 3rd & 4th [7]	OARSI responder criteria[7]*	Clinical response according to OMERACT-OARSI, each component of OMERACT-OARSI, & use of rescue meds	306 pts K-L grade II or III **(pts were worse in HA)**	80.5% responders in HA vs 65.8% responders in placebo	Repeated cycles of IA HA improve knee OA sx during in-btw cycle period, & exert a carryover effect for at least 1 yr	

PBS= buffered physiological NaCl solution; WOMAC= Western Ontario & McMaster Universities Osteoarthritis Index; PGA= patient global assessment; COGA= clinical observer global assessment; K-L= Kellgren-Lawrence; LFI= Lequesne algofunctional index score; ICOAP= intermittent & constant osteoarthritis pain index; OMERACT-OARSI= Outcome Measures in Rheumatology Clinical Trials & Osteoarthritis Research Society International; VAS= Visual analogue scale; JKOM= Japanese Knee Osteoarthritis Measure

1. Chevalier X, Jerosch J, et al. Single, intra-articular treatment with 6 ml hylan G-F 20 in patients with symptomatic primary osteoarthritis of the knee: a randomized, multicenter, double-blind, placebo controlled trial. Ann Rheum Dis 2010;69:113-119.

- Baseline characteristics: Hylan grp (51.2% grade II, 48.8% grade III), Placebo (39.2% grade II, 60% grade III, 0.8% grade IV)

Primary efficacy endpoint – WOMAC A (pain) change over 26 weeks (ITT population)					
	Baseline mean	**26-week mean**	**Estimated change**	**Estimated diff btw grps**	**P value**
Hylan G-F 20 (n=124)	2.30	1.43	-0.84	-0.15	0.047
Placebo (n=129)	2.25	1.59	-0.69		

Minimum clinically important improvement in OA = 12-18% improvement in WOMAC A from baseline. Hylan group had a 31.3% improvement, placebo had 29.3% improvement.

2. Berenbaum F, Grifka J, et al. A randomized, double-blind, controlled trial comparing two intra-articular hyaluronic acid preparations differing by their molecular weight in symptomatic knee osteoarthritis. Ann Rheum Dis 2012; 71:1454-1460.

- Baseline characteristics: GO-ON grp (46% grade II, 54% grade III), Hyalgan grp (54% grade II, 46% grade III)

Mean changes from Baseline to Week 26 in the ITT population				
	GO-ON (n=217)	**Hyalgan (n=209)**	**Difference**	**P value**
WOMAC pain	-22.9 (-25.7 to -20.1)	-18.4 (-21.3 to -15.5)	-4.5 (-8.5 to -0.5)	0.021

"The statistically sig ITT differences btw treatments after 6 mnths were 4.5 and 6.4 mm, respectively, ie, below the minimum perceptible clinical improvement, usually set at approximately 10 mm[22] and that was used to define the non-inferiority margin of 9 mm in this trial. Therefore, the clinical relevance of this statistical superiority is uncertain and it cannot be excluded that it is due to chance."

3. Strand V, Baraf HSB, et al. A multicenter, randomized controlled trial comparing a single intra-articular injection of Gel-200, a new cross-linked formulation of hyaluronic acid, to phosphate buffered saline for treatment of osteoarthritis of the knee. Osteo and Cartilage 20 2012; 350-356.

- Baseline characteristics: Gel-200 grp (8.5% grade I, 38.1% grade II, 53.4% grade III), PBS grp (14.1% grade I, 36.7% grade II, 49.2% grade III)

Mean Improvements from Baseline in WOMAC pain subscores		
Week	**Estimated difference**	**P value**
Week 3	8.12 (3.47, 12.68)	0.001
Week 6	8.12 (2.73, 13.50)	0.003
Week 9	5.77 (0.26, 11.29)	0.04
Week 13	6.39 (2.15, 12.05)	0.037

4. Kawasaki T, Kurosawa H, et al. Therapeutic home exercise versus intraarticular hyaluronate injection for osteoarthritis of the knee: 6-month prospective randomized open-labeled trial. J Orthop Sci 2009; 14:182-191.

- Patients were all females over 50 with primary OA, selected according to clinical and radiographic criteria of the American College of Rheumatology.

Intergroup analysis of changes from baseline to the 24th week		
Variable	**HA group (n=42)**	**Exercise group (n= 45)**
VAS	-20.46 ± 36.04	-21.29 ± 27.60
JKOM	-16.12 ± 20.69	-12.82 ± 15.97
ROM	3.49 ± 8.79	5.21 ± 7.65

- Author's conclusions: "Taking into account the cost, convenience, and invasiveness to patients, exercise is thought to have some advantage over intraarticular injection of hyaluronate for the therapy of OA of the knee."

5. Altman RD, Rosen JE, et al. A double-blind, randomized, saline-controlled study of the efficacy and safety of EUFLEXXA for treatment of painful osteoarthritis of the knee, with an open-label safety extension (The FLEXX Trial). Semin Arthritis Rheum 39:1-9.

Group	**Change from baseline in VAS**	**Median % reduction**
EUFLEXXA	-25.7 ± 28.9 mm	53%
PBS	-18.5 ± 32.5 mm	38%

6. Jorgensen A, Stengaard-Pedersen K, et al. Intra-articular hyaluronan is without clinical effect in knee osteoarthritis: a multicenter, randomized, placebo-controlled, double-blind study of 337 patients followed for 1 yr. Ann Rheum Dis 2010;69:1097-1102.

- Time to recurrence defined as time from the start of improvement until recurrence of the LFI. Start of improvement was baseline LFI decreased by at least 1 & recurrence was when the LFI increased by at least 1 pt over baseline.
- ITT population: Mean time to recurrence: Hyaluronan – 172 days
  Placebo – 204 days
- A large portion of patients in each grp (53% in hyaluronan, 59% in placebo) were censored as exact time unknown, mostly due to still in remission at the end of the trial.

7. Navarro-Sarabia F, Coronel P, et al. A 40-month multicenter, randomized placebo-controlled study to assess the efficacy and carry-over effect of repeated intra-articular injections of hyaluronic acid in knee osteoarthritis: the AMELIA project. Ann Rheum Dis 2011;70:1957-1962.

- Baseline characteristics: K-L: HA (70.6% grade II, 29.4% grade III), Placebo (74.5% grade II, 25.5% grade III)

* Responder if: pain or physical fxn score decreased at least 50% & at least 20 mm on VAS, or if 2 of the following 3 were recorded: a decrease in physical fxn of at least 20% or at least 10 mm on VAS, a decrease in physical fxn of at least 20% & at least 10 mm on VAS, or an increase in the score of the PGA by at least 20% & at least 10 mm on VAS.

Primary & Secondary outcomes ITT population				
		HA (n= 149)	**Placebo (n=152)**	**P value**
Responders OARSI 2004 @ end of Follow-up		120 (80.5%)	100 (65.8%)	0.004
Responders OARSI 2004 @ each cycle assessment	7 months	106 (71.1%)	103 (67.8%)	0.525
	14 months	114 (76.5%)	99 (65.1%)	0.03
	21 months	116 (77.9%)	103 (67.8%)	0.049
	27 months	116 (77.9%)	103 (67.8%)	0.049
	34 months	121 (81.2%)	99 (65.1%)	0.002

- No difference in the amt of rescue medication consumed between grps (408.8mg/day vs 451.4 mg/day)
- Adverse event rate was the same in both, with overall frequency of 83% (allergic rxn, pain at inj site, bleeding at inj site, arthralgia, etc)

8. Tiel J, Reijman M, et al. Delayed Gadolinium-Enhanced MRI of Cartilage (dGEMRIC) shows no change in cartilage structural composition after viscosupplementation in patients with early-stage knee osteoarthritis. PLoS One 8(11):e79785.

20 pts (K-L I-II) were followed before and 14 wks after 3 weekly HA inj with pain scales and 6 cartilage regions on dGEMRIC. All KOOS subscales & NRS pain improved significantly 14 weeks after JA, outcomes of dGEMRIC (based on T1 relaxation time) did not change sig after HA compared to baseline in any of the analyzed regions. Questionable as to if changes weren't seen on dGEMRIC because HA may slow down the progression of OA vs not improving at all.

9. Bellamy N, Campbell J, et al. Viscosupplementation for the treatment of osteoarthritis of the knee. Cochrane Database of Systematic Reviews 2006, Issue 2. Art. No: CD005321.

"The analyses suggest that viscosupplements are comparable in efficacy to systemic forms of active interventions, with more local reactions but fewer systemic ADE, & that HA products have more prolonged effects than IA corticosteroids. Overall, the aforementioned analyses support the use of the HA class of products in the treatment of knee OA."

Kellgren-Lawrence
Grade 0: no radiographic features of OA are present
Grade 1: doubtful joint space narrowing (JSN) & possible osteophytic lipping
Grade 2: the presence of definite osteophytes & possible JSN on anteroposterior weight-bearing radiograph
Grade 3: multiple osteophytes, definite JSN, sclerosis, possible bony deformity
Grade 4: large osteophytes, marked JSN, severe sclerosis & definitely bony deformity

Lequesne algofunctional index

0: none	8-10: severe
1-4: mild	11-13: very severe
5-7: moderate	≥14: extremely severe

Uridine Triacetate Oral Granules Packets (Xuriden and Vistogard)
Andrew Mullings, PharmD; Jill Johnson, PharmD, BCPS
3/31/2016, 9/27/16 revised

Product Summary: Uridine triacetate is a form of uridine which is indicated in the treatment of patients with hereditary orotic aciduria (HOA) under the brand Xurdien. It is also indicated in patients with fluorouracil overdose or overexposure as it is a direct chemical antagonist against fluorouracil toxicity under the brand Vistogard.

Agent	Cost Per Unit (AWP)	Cost of Treatment (AWP)
Xuriden	$750 per 2 g packet	$2250 - $3750 cost per month
Vistogard	$3,750 per 10 g packet	$75,000 cost of treatment course

Evidence in the Treatment of Patients with Hereditary Orotic Aciduria (Xurdien)

- Note: Orotic aciduria is a rare inborn error of pyrimidine metabolism that is recessively inherited. This disorder is characterized by an onset in early infancy, growth failure, developmental delay, hypochromic anemia, and excessive urinary excretion of orotic acid, an intermediary of uridine synthesis (per UpToDate). Also associated with nephrolithiasis.

Methods: The HOA clinical program for uridine consisted of a single-arm, open-label, baseline controlled, prospective (n=4) clinical trial conducted. The trial was 6 weeks in duration and was followed by an extension which is ongoing; efficacy data up to 6 months were submitted, and provided evidence of durability of effect for this duration. The '1 efficacy analyses were patient-specific, in that they evaluated the stability of the hematologic parameters that constituted the main manifestation of HOA in each individual patient prior to enrollment. As such, because each patient had a different hematological manifestation, the primary endpoints were different among patients and included neutrophil count, total WBC (one patient each), and RBC MCV (two patients). The secondary efficacy endpoints were shared by all 4 patients were urine orotic acid and orotidine concentrations.

Results: Treatment w/ uridine increased retic counts and improved anemia w/in 2-3w. Reductions in urinary orotic acid can be seen w/in 1-2w of initiating uridine replacement, but full normalization does not always occur. Info on non-hematological manifestations (e.g. failure to thrive) is more limited. Dose info on treating non-hematological manifestations (e.g. failure to thrive) is more limited. **Dose is 150-300mg once daily.**

Evidence in the Treatment of Patients with Fluorouracil overdose or Overexposure (Vistogard)
Methods: 135 patients at excess risk of 5-FU toxicity due to overdose or accidental fluorouracil ingestion (n = 111); or DPD (dihydropyrimidine dehydrogenase) deficiency and/or who showed rapid onset of severe toxicities (n = 24) have been treated with uridine triacetate under emergency IND or expanded access protocols. Patients were to receive uridine triacetate granules (**10g q6h for 20 doses**) up to 96h after the termination of 5-FU therapy. Clinical endpoints included survival compared with historical controls, time to resumption of chemotherapy, and safety.

Results:A total of 130/135 (96%) patients treated with uridine recovered fully (within 30 days after receiving uridine triacetate), including rapid reversal of cardiotoxicity (EKG abnormalities, chest pain, etc) and neurotoxicity (altered mental status, ataxia, etc). **No patient who received uridine within 96 h after stopping 5-FU died. Comparatively, 38 of the 47 historical controls (81%) with 5-FU overexposure died.** Of the 106 overdose patients with a diagnosis of cancer, **40 (37.7%) resumed chemotherapy within 30 days (median 20.0 days post-5-FU)**, highly indicative of rapid recovery from toxicity. Mild, infrequent adverse events (diarrhea/nausea/vomiting) were attributed to uridine.

Recommendation: Due to lack of concrete evidence for the indication of HOA, exclude Xurdien. Despite lack of head to head comparative data, Vistogard is a valuable option in the treatment of 5-FU toxicity and coverage criteria barriers may lead to adverse outcomes such as rehospitalization so should be covered without restriction. Concern for off-label utilization of Vistogard for HOA is a possibility.
Outcome: Tier 4 PA both products ; 9/27/16 EBRx Revised recommendation excludes Xuriden for HOA.

1. Xuriden FDA Summary Review 2016.
2. Ma, Wen Wee, et al. "Clinical trial experience with uridine triacetate for 5-fluorouracil toxicity." ASCO Annual Meeting Proceedings. Vol. 34. No. 4_suppl. 2016

Rev November 2016
Bemberg March 2014

Sodium hyaluronate (Synvisc, Monovisc)
Antirheumatic; Ophthalmic Agent, Viscoelastic; Skin and Mucous Membrane Agent
Geri Bemberg, Pharm.D.

Other brands for osteoarthritis: Euflexxa, Gel-One, Gelsyn-3, Genvisc 850, Hyalgan, Hymovis, Orthovisc, Supartz, Synvisc-One

Other brand names: Amvisc, Amvisc Plus, Bionect, Hygel, Hylase Wound, Juvederm Ultra, Juvederm Ultra Plus, Juvederm Ultra Plus XC, Juvederm Ultra XC, Juvederm Voluma XC, Perlane, Perlane-L, Provisc, Restylane, Restylane-L, Restylane Lyft, Restylane Silk

Labeled Indications:

Intra-articular injection: treatment of pain in osteoarthritis in knee in patients who have failed nonpharmacologic tx or simple analgesics (Euflexxa, Gelsyn-3, Genvisc 850, Hyalgan, Hymovis, Monovisc, OrthoVisc, Supartz, Synvisc, Synvisc-One) or NSAIDs (Gel-One)

Intradermal:

Correction of moderate to severe facial wrinkles or folds: (Juvederm Ultra, Juvederm Ultra Plus, Juvederm Ultra Plus XC, Juvederm Ultra XC, Perlane, Perlane-L, Restylane, Restylane-L, Restylane Lyft)

Correction of perioral rhytids in adults >2: (Restylane Silk, Juvederm Volbella XC)

Subcutaneous/supraperiosteal: Correction of age-related volume deficit (deep [subcutaneous &/or supraperiosteal] injection) for cheek augmentation in the mid-face in adults >21 yrs (Juvederm Voluma XC, Restylane Lyft)

Ophthalmic:

Surgical aid in cataract extraction (Amvisc, Amvisc Plus, Provisc)
Intraocular lens implantation (Amvisc, Amvisc Plus, Provisc)
Corneal transplant (Amvisc, Amvisc Plus)
Glaucoma filtration (Amvisc, Amvisc Plus)
Retinal attachment surgery (Amvisc, Amvisc Plus)

Submucosal: Lip augmentation in adults >21 yrs (Restylane, Restylane-L, Restylane Silk, Juvederm Ultra XC, Juvederm Volbella XC)

Topical cream, gel: Management of skin ulcers and wounds (Bionect, Hylase Wound)

Place in treatment for osteoarthritis

- In knee OA after patient has failed nonpharmacologic treatments such as exercise and self-management programs and weight loss for those with BMI ≥ 25, and pharmacologic treatments such as NSAIDs (oral and topical). Debatable on if they are on the same treatment step as intraarticular corticosteroids or last line after them.

Intra-articular Administration: inject directly into the knee joint

Brand	Price	Dosing	Price per treatment	Current Coverage
Synvisc	16mg/2mL (2mL): $497.58 (current) $432 (PFS) (2014)	16mg (2mL) q week x 3 wks	$1,492.73 ($1,296 in 2014) for 3 wks	Excluded
Monovisc	88mg/4mL (4mL): $1,417.82 (current) $1,170 (PFS) (2014)	88mg (4mL) once	$1,417.82 $1,170 (2014)	Covered PA
Euflexxa	20mg/2mL (2mL): $407.91 (current) $369.98 (2014)	20mg (2mL) q wk x 3 wks	$1,223.73 for 3 wks	Excluded
Gel-One	30mg/3mL (3mL): $1,170 - $1,228.80	30mg (3mL) once	$1,170 - $1,228.80	Covered PA
Gelsyn-3	16.8mg/2mL (2mL): $414	16.8mg (2mL) q wk x 3 wks	$1,242 for 3 wks	Excluded
GenVisc 850	25mg/2.5mL (2.5mL): $276.36	25mg (2.5mL) q wk x 5 wks (some may benefit from 3 wks)	$829.08 for 3 wks $1,381.80 for 5 wks	Excluded
Hyalgan	20mg/2mL (2mL): $228 (current) $216 (2014)	20mg (2mL) q wk x 5 wks (some may benefit from 3 wks)	$684 ($648 in 2014) for 3 wks $1,140 ($1,080 in 2014) for 5 wks	Excluded
Hymovis	24mg/3mL (3mL): $320	24mg (3mL) q wk x 2 wks	$640 for 2 wks	TBD
Orthovisc	15mg/mL (2mL): $463.50 (current) $383.96 (2014)	30mg (2mL) q wk x 3-4 wks	$1,390.50 ($1,151.88 in 2014) for 3 wks $1,854 ($1,535.84 in 2014) for 4 wks	Excluded
Supartz	25mg/2.5mL (2.5mL): $241.80	25mg (2.5mL) q wk x 5 wks (some may benefit from 3 wks)	$1209 for 5 wks $725.40 for 3 wks	Excluded DISCONTINUED
Supartz FX	25mg/2.5mL (2.5mL): $276.36	25mg (2.5mL) q wk x 5 wks (some may benefit from 3 wks)	$829.08 for 3 wks $1,381.80 for 5 wks	Excluded
Synvisc-One	48mg/6mL (6mL): $1,492.73 (current) $1,296 (2014)	48mg (6mL) once	$1,492.73 $1,296 (2014)	Covered PA

*All prices reflect AWP from MedImpact's claim system, Lexicomp, and restat

**2014: When looking at Hyalgan, its initial AWP in Sept 2011 was $156/vial, now in 2014 (latest AWP update was in April), price is $216/vial. Safe to assume that applies across the board on all intra-articular hyaluronates.

2016: Please see above for price increase when appropriate. Hyalgan, the drug mentioned in 2014, has now increased to $228/vial

Outcome of 2014 DUEC: Cover single injection hyaluronates with PA. Exclude the rest.

2016 Considerations: As of April 2016, BCBS no longer covers any hyaluronate for osteoarthritis of the knee. This change was made due to the lack of "scientific evidence of effectiveness in improving health outcomes." As our current coverage differs from that of our medical carrier, this is being brought back to the attention of the committee for further consideration.

References

1. Hochberg MC, Altman RD, April KT, et al. American College of Rheumatology 2012 Recommendations for the Use of Nonpharmacologic and Pharmacologic Therapies in Osteoarthritis of the Hand, Hip, and Knee. Arth Care & Resear. April 2012;64(4):465-474.
2. American Academy of Orthopedic Surgeons. Treatment of Osteoarthritis of the Knee. EBM Guideline 2nd Edition. May 18, 2013.
http://www.aaos.org/research/guidelines/treatmentofOsteoarthritisoftheKneeGuideline.pdf

Target Specific Oral Anticoagulants

University of Arkansas for Medical Sciences College of Pharmacy
Evidence Based Prescription Drug Program
Rachael McCaleb, PharmD
November 2016

Generic name	Trade name	Manufacturer	Strength
Direct Thrombin Inhibitor			
Dabigatran	Pradaxa®	Boehringer Ingelheim	75, 110[a], and 150 mg capsules
Factor Xa Inhibitor			
Rivaroxaban	Xarelto®	Janssen	10, 15, 20 mg tablet
Apixaban	Eliquis®	Bristol-Myers Squibb	2.5 and 5 mg tablet
Edoxaban	Savaysa®	Daiichi Sankyo	15, 30, and 60 mg tablet

[a] 110 mg capsule only approved for postoperative (TKR/THR) thromboprophylaxis indication

FDA approved indication

Drug (Generic)	Stroke prevention in nonvalvular AF	VTE treatment	VTE prophylaxis (post hip/knee)	VTE prophylaxis (medical)	Reduce risk of recurrence of VTE
Dabigatran	**X**	**X**	**X**		**X**
Rivaroxaban	**X**	**X**	**X**		**X**
Apixaban	**X**	**X**	**X**		**X**
Edoxaban	**X**	**X**			

AF = atrial fibrillation; VTE = venous thromboembolism

Pharmacokinetic Parameters

	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Half-life	12-17 hrs	5-9 hrs (11-13 hrs in elderly)	12 hrs	10-14 hrs

Dosage Considerations:

- Dabigatran: Patients with CrCl <30 mL/min were not included in trials [except for AF <15 mL/min excluded]. PI does not provide dosing recommendations in these patients [CrCl <30 mL/min].
  - HD – no recommendations
- Rivaroxaban: Patients with CrCl <30 mL/min were not included in trials [except for AF <15 mL/min excluded]. PI does not provide dosing recommendations in these patients [CrCl <30 mL/min].
  - HD – avoid use
- Apixaban: Dose reduction recommendations provided for AF indication.
  - HD – can use
- Edoxaban: Dose reductions recommendations provide for CrCl <50 mL/min. Avoid use in CrCl <15mL/min.
  - For AF indication, avoid use in CrCl >95 mL/min.

Evidence:

- Stroke prevention in nonvalvular AF
- VTE Treatment
- VTE Prophylaxis (post total knee replacement and total hip replacement)
- Extended Treatment of VTE

1.) Stroke prevention in nonvalvular AF

Indirect Comparison Using Warfarin as Single Common Comparator, on the Basis of the RE-LY, ROCKET-AF, and ARISTOTLE Trials

		Odds ratio (95% CI)			
		APIX vs. D150	**APIX vs. RIVA**	**D150 vs. RIVA**	**RIVA vs. D150**
Stroke/SE	Mantha et al.	1.22 (0.91-1.62)	0.9 (0.71-1.16)	-	**1.35 (1.02-1.78)**
	Lip et al.	1.22 (0.91-1.62)	0.9 (0.71-1.13)	**0.74 (0.56-0.97)**	-
Ischemic Stroke	Mantha et al.	1.2 (0.86-1.67)	1.02 (0.75-1.38)	-	1.19 (0.85-1.65)
	Lip et al.	1.21 (0.88-1.67)	0.98 (0.72-1.33)	0.81 (0.58-1.13)	-
Hemorrhagic Stroke	Mantha et al.	1.93 (0.92-4.07)	0.88 (0.48-1.59)	-	**2.2 (1-4.84)**
	Lip et al.	1.96 (0.94-4.08)	0.86 (0.48-1.57)	**0.44 (0.2-0.96)**	-
Myocardial infarction	Mantha et al.	0.68 (0.45-1.03)	1.1 (0.74-1.62)	-	**0.62 (0.42-0.93)**
	Lip et al.	0.69 (0.46-1.05)	1.09 (0.74-1.6)	**1.57 (1.05-2.33)**	-
All-cause death	Mantha et al.	1.01 (0.85-1.2)	0.97 (0.83-1.15)	-	1.04 (0.87-1.24)
	Lip et al.	1.01 (0.85-1.2)	1.05 (0.84-1.3)	1.04 (0.82-1.3)	-
Major Bleeding	Mantha et al.	**0.74 (0.61-0.91)**	**0.68 (0.55-0.83)**	-	1.10 (0.90-1.34)
	Lip et al.	**0.74 (0.61-0.91)**	**0.66 (0.54-0.81)**	0.89 (0.73-1.09)	-
Intracranial Bleeding	Mantha et al.	1.02 (0.62-1.68)	0.64 (0.40-1.03)	-	1.58 (0.94-2.63)
	Lip et al.	1.05 (0.63-1.76)	0.63 (0.39-1.01)	0.60 (0.35-1.01)	-
Gastrotestinal Bleeding	Mantha et al.	**0.59 (0.41-0.83)**	**0.60 (0.43-0.83)**	-	0.99 (0.72-1.34)
	Lip et al.	**0.59 (0.42-0.83)**	NA	NA	-

Absolute Differences in Events per 1000 Patients Treated (Baker and Phung)

	Absolute Difference in events per 1000 patients treated (95% CI)		
Outcome	**APIX vs. DABI**	**DABI vs. RIVA**	**APIX vs. RIVA**
Stroke/SE	-5 (-12 to 3)	-6 (-14 to 3)	-1 (-9 to 7)
Ischemic Stroke	4 (-3 to 10)	**-9 (-16 to -1)**	-5 (-11 to 2)
Hemorrhagic Stroke	1 (-2 to 5)	-3 (-6 to 1)	-1 (-5 to 2)
All-cause Death	1 (-11 to 13)	-3 (-14 to 8)	-2 (-11 to 8)
Major Bleeding	-11 (-21 to 0)	-6 (-14 to 3)	**-16 (-26 to -7)**
Gastrointestinal Bleeding	**-12 (-18 to -5)**	0 (-8 to 8)	**-11 (-18 to -5)**

Summary:

- No significant difference in efficacy between dabigatran and apixaban for the prevention of stroke or systemic embolism in patients with non-valvular atrial fibrillation
    - Apixaban is associated with less major bleeding than dabigatran and rivaroxaban
    - Apixaban resulted in fewer gastrointestinal bleeds than dabigatran and rivaroxaban
- Rivaroxaban is less effective than dabigatran in the prevention of stroke or systemic embolism and hemorrhagic stroke in patients with non-valvular atrial fibrillation
- Differences in study design and patient populations between the pivotal trials limit the ability of making indirect comparisons between the TSOACs
    - Only a head-to-head direct comparison of the different TSOACs would fully answer the question of efficacy/safety differences between the new drugs for stroke prevention in AF.

2.) VTE Treatment

Effects of the new oral anticoagulants in comparison with warfarin evaluated by and across drug classes

Review	Drugs	# of Trials	Relative Risk (95% CI)		
			Recurrent VTE	VTE/PE Death	All-Cause Death
Adam et al. 2012	DABI RIVA	3	0.95 (0.71-1.27)	1.00 (0.48-2.10)	0.97 (0.72-1.3)
Kakkos et al. 2014	DABI RIVA APIX EDOX	9	0.89 (0.75-1.05)	1.30 (0.57-2.96)	0.98 (0.84-1.14)
van der Hulle et al. 2014	DABI RIVA APIX EDOX	5	0.88 (0.74-1.05)	1.02 (0.39-5.96)	0.97 (0.83-1.14)
Gomez-Outes et al. 2014	DABI RIVA APIX EDOX	6	0.91 (0.79-1.06)	0.98 (0.67-1.44)	0.98 (0.84-1.14)

Kang, N., & Sobieraj, D. M. (2014). Indirect treatment comparison of new oral anticoagulants for the treatment of acute venous thromboembolism.*Thrombosis research*, *133*(6), 1145-1151.

- Systematic review of RCT (n=6) that evaluated TSOACs use for treatment of acute VTE
  - RECOVER, RECOVER-II, AMPLIFY, Hokusai-VTE, EINSTEIN-DVT, and EINSTEIN-PE
- Results:
  - TSOACs did not differ significantly in the risk of mortality, recurrent VTE, recurrent PE or DVT
  - Differences in major bleeding risk

Indirect comparison	Relative risk (95% CI)
RIVA vs DABI	0.73 (0.41-1.30)
RIVA vs. APIX	1.80 (0.91-3.57)
RIVA vs. EDOX	0.65 (0.39-1.10)
DABI vs. APIX	**2.47 (1.21-5.07)**
DABI vs. EDOX	0.90 (0.51-1.57)
EDOX vs. APIX	**2.47 (1.40-5.39)**

Drug	# w/major bleed	Total #	% w/major bleed
DABI[a]	35	2553	1.37
RIVA[b]	40	4150	0.96
APIX[c]	15	2691	0.56
EDOX[d]	56	4118	1.36

a RECOVER & RECOVER II
b EINSTEIN DVT & PE
c AMPLIFY
d Hokusai-VTE

Summary:

- Results from systematic reviews of TSOACs as a class suggest that the TSOACs are comparable to adjusted dose VKAs in preventing recurrent VTE with a tendency of less bleeding and no difference in mortality
- Data suggests apixaban to be the safer [major bleeding] than some other TSOACs [dabigatran and edoxaban]

3.) VTE Prophylaxis (post total knee replacement (TKR) and total hip replacement (THR))

Indirect comparisons between rivaroxaban, dabigatran, and apixaban (Gomez)

	Relative risk (95% CI)		
Outcomes	**RIVA vs. DABI**	**RIVA vs. APIX**	**APIX vs. DABI**
Symptomatic venous thromboembolism	0.68 (0.21 to 2.23)	0.59 (0.26 to 1.33)	**0.73 (0.57 to 0.94)**
Clinically relevant bleeding	1.12 (0.87 to 1.44)	**1.52 (1.19 to 1.95)**	1.16 (0.31 to 4.28)
Major bleeding	1.37 (0.79 to 2.39)	1.59 (0.84 to 3.02)	0.86 (0.41 to 1.83)
Net clinical endpoint	0.95 (0.61 to 1.48)	0.96 (0.66 to 1.40)	0.99 (0.61 to 1.61)

Risk Differences for TSOAC vs. TSOAC (Indirect) for Primary VTE Prophylaxis in TKR and THR per Systematic Review (Gomez)

	Absolute Difference in events per 1000 patients treated (95% CI)		
Indirect Comparisons	**Symptomatic VTE**	**Clinically relevant bleeding**	**Major bleeding**
RIVA vs. DABI	-3 (-11 to 4)	5 (-7 to 16)	4 (-2 to 11)
RIVA vs. APIX	-4 (-9 to 1)	**18 (7 to 28)**	5 (-2 to 12)
APIX vs. DABI	1 (-7 to 8)	**-13 (-24 to -2)**	0 (-8 to 7)

Summary:

- The TSOACs have been shown to be at least as effective as enoxaparin 40 mg once daily for VTE prophylaxis in patients undergoing TKR and THR
- Rivaroxaban tended to be associated with the lowest risk for symptomatic venous thromboembolism
- Apixaban had the lowest risk of clinically relevant bleeding
- No difference in net clinical benefit between the TSOACs
- No direct comparison studies with the TSOACs limits the ability to determine differences in efficacy and safety between the different TSOACs

4.) Extended Treatment of VTE

Kakkos SK, Kirkilesis GI, Tsolakis IA. Efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. Eur J Vasc Endovasc Surg. 2014;48:565-75.

- Meta-analysis that included 3 RCT on secondary prevention of VTE (EINSTEIN-extension, AMPLIFY-EXT and RE-SONATE)
- Results:
    - Compared to placebo, TSOACs significantly reduced the risk of recurrent VTE (RR 0.17; 95% CI 0.12-0.24), including reductions in DVT and PE
        - At the expense of increased non-major clinically relevant bleeding (RR 2.35; 95% CI 1.65-3.35)
    - The overall net clinical benefit favored the TSOACs

SUMMARY:

Differences in efficacy and safety between the TSOACS for stroke prevention in AF, VTE prophylaxis in TKR and THR, acute VTE treatment, and extended VTE treatment is difficult to fully answer secondary to lack of head-to-head direct comparison.

Based on indirect comparisons (systematic reviews and meta-analysis), there does not appear to be major differences in efficacy between the TSOACs. However, data suggests apixaban to be the safer [major bleeding] than some other TSOACs.

RECOMMENDATION:

- EBD Formulary may include up to two covered TSOACs all other products will be excluded
- Require price protection for the life of the contract

Summary of TSOAC Phase 3 Trials

	Stroke Prevention in Nonvalvular AF	VTE prophylaxis in TKR	VTE prophylaxis in THR	Acute VTE treatment	Extended VTE treatment
Dabigatran	RE-LY	RE-MOBILIZE RE-MODEL	RE-NOVATE RE-NOVATE II	RE-COVER RE-COVER II	RE-MEDY RE-SONATE
Rivaroxaban	ROCKET AF	RECORD-3 RECORD-4	RECORD-1 RECORD-2	ENSTEIN DVT ENSTEIN PE	ENSTEIN Continued Treatment
Apixaban	ARISTOTLE AVERROES	ADVANCE-1 ADVANCE-2	ADVANCE-3	AMPLIFY	AMPLIFY-EXT
Edoxaban	ENGAGE AF-TIMI	----	----	Hokusai-VTE	----

References:

Gomez-Outes A, Terleira-Fernandez AI, Suarez-Gea ML, et al. Dabigatran, rivaroxaban, or apixaban versus enoxaparin for thromboprophylaxis after total hip or knee replacement: systematic review, meta-analysis, and indirect treatment comparisons. *BMJ*. 2012;344:e3675

Baker, W. L., & Phung, O. J. (2012). Systematic review and adjusted indirect comparison meta-analysis of oral anticoagulants in atrial fibrillation.*Circulation: Cardiovascular Quality and Outcomes*, *5*(5), 711-719.

Adam SS, McDuffie JR, Ortel TL, et al. Comparative effectiveness of warfarin and new oral anticoagulants for the management of atrial fibrillation and venous thromboembolism. Ann Intern Med. 2012;157:796-807.

Lip GYH, Larsen TB, Skjoth F, et al. Indirect comparisons of new oral anticoagulants for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2012;60:8:738-46.

Mantha S and Ansell J. An indirect comparison of dabigatran, rivaroxaban, and apixaban for atrial fibrillation. Thromb Haemost. 2012;108:476-84.

Kakkos SK, Kirkilesis GI, Tsolakis IA. Efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. Eur J Vasc Endovasc Surg. 2014:http://dx.doi.org/10.1016/j.ejvs.2014.05.001.

Gomez-Outes A, Terleira-Fernandez, Lecumberri R, et al. Direct oral anticoagulants in the treatment of acute venous thromboembolism: a systematic review and meta-analysis. Thromb Res. 2014: http://dx.doi.org/10.1016/j.thromres.2014.06.020.

van der Hulle T, Kooiman J, Den Exter PL, et al. Effectiveness and safety of novel oral anticoagulants as compared with vitamin K antagonists in the treatment of acute symptomatic venous thromboembolism: a systematic review and meta-analysis. J Thromb Haemost. 2014;12:320-8.

DUEC
May 30, 2016 Medispan - 8/29/16 New Drug File

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									
Coly-Mycin-S Otic	Neomycin-Colistin-HC-thonzonium Br Otic Suspension	$209.41	Otic infections	Ciprodex - Tier 3; Cipro-HC - T2; neomycin/polymyxin/HC - T1	T1, exclude cortisporin TC		11/7/16		
Xaquil XR	Levomefolate glucosamine 30mg CR Tablet	$1.44/tablet			Medical food; exclude, code 5.		11/7/16		
Cetylev	Acetylcysteine 500mg, 2.5g effervescent tablet	$21.70/tablet	Acetaminophen OD		T3		11/7/16		
Papaverine-Phentolamine-alprotadil	Papaverine-Phentolamine-alprotadil 12-1-10, 30-1-20/mL	$23.76	Erectile Dysfunction	ED meds covered w/QL at T2 & T3	Exclude, code 13		11/7/16		
Bevespi	Glucopyrrolate/Formoterol 9-4.8mcg	$389.44	COPD	Rebate category	table pending rebates; excluded 10/18/16 lost bid		11/7/16		
Loprox	Ciclopirox/Skin cleanser No. 40 0.77%	$327.05	Tinea pedis, tinea corporis, tinea cruris	Generic ciclopirox cream 0.77% 30g tube covered tier 1 (AWP $56.50)	Exclude, code 13		11/7/16		
Xiidra	Lifitegrast 5% solution	$8.53/mL	Dry eye disease		Exclude, code 13		11/7/16		
Emend	Aprepitatnt 125mg oral suspension	$339.61/mL	Nausea and vomitting associated with chemo or postop	Emend capsules covered w/QL T2	T2 QL to equal same limit as caps		11/7/16		
Lidotral	Lidocaine 3.88% cream	$1,586.55	Topical anesthetic	Multiple products available at T1	Exclude, code 13		11/7/16		
Otovel	Ciprofloxacin-Fluocinolone 0.3-0.025%	$237.60	Acute otitis media in patient with tympanostomy tubes	Ciprodex - Tier 3; Cipro-HC - T2; neomycin/polymyxin/HC - T1	Exclude, code 13; POS Msg "plan covers ciprodex"		11/7/16		
Byvalson	Nebivolol-valsartan 5mg-80mg tablet	$4.384/tablet	Hypertension	Generic beta blockers covered T1 (MAC), Bystolic T3 ARBs RBP, valsartan available T1(MAC)	Exclude, Code 13		11/7/16		
Qbrelis	lisinopril 1mg/mL oral solution	$3.95/mL	Hypertension	Gen ACEi available T1 (MAC)	Exclude, Code 13		11/7/16		
Zurampic	Lesinurad 200mg tablet	$14/tablet	Hyperuricemia associated with gout	Allopurinol, colchicine T1 (MAC); Uloric T3PA	Exclude, code 1		11/7/16		
Relistor	Methylnaltrexone 150mg tablet	$20/tablet	Opioid-induced constipation	Relistor inj T3, Linzess T3PA, Amitiza T3PA, Movantik T3QL	exclude, code 13; revisit in 1 y		11/7/16		
Targadox	Doxycycline Hyclate 50mg	$15/tablet	Tetracycline antibiotic	Doxycycline generic products available T1 (MAC)	exclude, code 13		11/7/16		
SPECIALTY DRUGS									
Idelvion	Coagulation Factor IX (Recomb) for Inj 250, 500, 1000, 2000 units	$5.10/unit	Hemophilia B (congenital factor IX deficiency)	Other hemophilia products covered T4 PA	Specialty Tier; PA criteria: Hemophilia B		11/7/16		
Rynoderm	Urea Cream 37.5%	$2,717.88	Hyperkeratotic conditions	generic urea creams available in various strengths	Exclude 37.5% (this one); also exclude Rx 39%, 45%, 47% new users. Grandfather the 2 EBD users using 50% product. POS message: "Use 40%".		11/7/16		

Ocaliva	Obeticholic Acid 5mg, 10mg tablets	$228/tablet	Primary biliary cholangitis		Exclude, code 1		11/7/16		
Truvada	Emtricitabine-Tenofovir 100-150, 133-200, 167-250mg tablets	$58.66/tablet	HIV, Preexposure prophylaxis, etc	HIV covered T4. Other Truvada strength covered at T4.	specialty tier		11/7/16		
Lazanda	Fentanyl Nasal Spray 300mcg/actuation	$829.22	Breakthrough cancer pain in adults	Multiple pain medications covered at different tiers	EBD already excluded Lazanda 5/12/12.		11/7/16		
Probuphine Implant	Buprenorphine HCl Subdermal Implant	$1,485.00	11/7/16+F18+	Buprenorphine SL tabs T1 (MAC), buprenorphine-naloxone CL tabs T1 (MAC); Suboxone film covered T2PA	Discuss		11/7/16		
Afstyla	Antihemophilic Factor Recomb for Inj 250, 500, 1000, 2000, 3000units	$1.98/unit	Hemophilia A	Other hemophilia products covered T4 PA	T4PA Add to Hemophilia PA		11/7/16		
Orfadin	Nitisinone 4mg/mL suspension	$19,617.12/90 mL	Hereditary tyrosinemia type 1	Orfadin capsules T4 (AWP $5,999.33-$29,996.48/60caps)	T4PA all dosage forms		11/7/16		
Tivicay	Dolutegravir 10mg, 25mg	$11.38-$28.45/tab	HIV treatment	HIV covered T4. 50mg Tivicay covered T4 ($56.91/tab)	T4		11/7/16		
Hydroxyprogesterone	Hydroxyprogesterone Carproate IM in Oil 1.25g/5mL	$2,310.69	Preterm birth	Makena (AWP $873.54/mL) is excluded (compound covered)	T3PA, exclude Makena brand, exclude compounded		11/7/16		
Orencia Clickjet	Abatacept	$1,083.56	Rheumatoid Arthritis	Rebated category. Orencia covered at non-preferred T4PA	T4PA		11/7/16		
Epclusa	Sofosbuvir/velpatasvir	$1,068/tablet	Hepatitis C	Rebated category.	T4PA		11/7/16		
Vonvendi	Von Willebrand Factor 650, 1300 unit	$2.38/unit	von Willebrand disease	T4 PA	T4PA		11/7/16		
Zinbryta	Daclizumab 150mg/mL	$8,200.00	Multiple Sclerosis	Multiple MS meds covered T4PA	Exclude, code 13		11/7/16		
Viekira XR	Ombitasvir-Paritaprevir-ritonavir-dasabuvir XR tab	$396.76/tablet	Hepatitis C	Rebate category.	Exclude, code 13		11/7/16		

Colistin 0.3% with neomycin 0.33%, hydrocortisone 1%, and thonzonium 0.05% (Coly-Mycin S Otic)

Autumn Swindle, PharmD, PGY1, UAMS

FDA indication: treatment of superficial and susceptible bacterial infections of the external auditory canal, mastoidectomy, and fenestration cavities

Pharmacologic category: antibiotic/corticosteroid/surfactant, otic

- Colistin: polypeptide antibiotic which penetrates into and disrupts the bacterial cell membrane
- Neomycin: aminoglycoside (AG) which inhibits protein synthesis
- Hydrocortisone: corticosteroid
- Thonzonium: surface active agent that helps medication pass through dead cells and pus inside the ear by dispersion and penetration of the debris

Dosing: safe for use in patients ≥ 1 year old

- Calibrated dropper: 5 drops into affected ear 3-4 times/day
- Dropper bottle: 4 drops in affected ear 3-4 times/day
- Do not use for longer than 10 days; prolonged treatment may result in overgrowth of nonsusceptible organisms

Contraindications: hypersensitivity to any component and/or aminoglycosides; herpes simplex, vaccinia, varicella

AEs: Irritation, Neomycin sensitization: itching, edema, and failure to heal, Ototoxicity: increased risk in patients with longstanding otitis media or tympanic perforation (rare)

Cost:

- Coly-Mycin S (5mL bottle): $209.41
- Cortisporin TC (10mL bottle): Not available

Evidence:

Vivek Kaushik, Tass Malik, Shakeel R Saeed, et al. Interventions for acute otitis externa. *Cochrane Database of Systematic Reviews* 2010, Issue 1. Art. No.: CD004740. DOI: 10.1002/14651858.CD004740. pub2

19 RCTs, N=3382 participants were included. Three meta-analyses were possible. The overall quality of studies was low. *Pseudomonas aeruginosa* or *Staphylococcus aureus* are the most likely pathogens that should always be covered empirically when treating otitis externa.

Topical antibiotics are 1st line and commonly contain an AG (neomycin, gentamicin) or a fluoroquinolone (FQ) (ciprofloxacin, ofloxacin). Topical AGs are potentially ototoxic when used in the presence of a perforated tympanic membrane, whereas topical FQs are not. If the tympanic membrane is known to be intact and the middle ear and mastoid are closed, the use of a potentially ototoxic preparation presents no risk of ototoxic injury.

- Topical antimicrobials containing steroids were significantly more effective than placebo drops: OR 11 (95% CI 2.00 to 60.57; one trial).
- In general, no clinically meaningful differences were noted in clinical cure rates b/w the various topical interventions.
- One notable exception involved a trial of high quality which showed that acetic acid was significantly less effective vs antibiotic/steroid drops in terms of cure rate at 2 and 3wks (OR 0.29 (95% CI 0.13 to 0.62) and OR 0.25 (95% CI 0.11 to 0.58) respectively).
- One trial of low quality comparing FQ with non-FQ antibiotics did not find any difference in clinical cure rate.
- Given that most topical treatments are equally effective, it would appear that in most cases the preferred choice of topical treatment may be determined by other factors, such as risk of ototoxicity, risk of contact sensitivity, risk of developing resistance, availability, cost and dosing schedule. Factors such as speed of healing and pain relief are yet to be determined for many topical treatments and may also influence this decision.

Recommendation: Add Coly-Mycin S to formulary

EBRx Outcome: Place Colymycin-S at T1. Look at cost of it in 7/2016. Revision: Colymycin-S is the only product available now. AWP $209 (10/27/16).

Acetylcysteine (Cetylev) 500mg, 2.5g effervescent tablets (lemon-mint flavor)
Jill Johnson, Pharm.D., BCPS
10/26/2016

FDA indication: as an antidote for acetaminophen overdose indicated to prevent or lessen hepatic injury after ingestion of a potentially hepatotoxic quantity of acetaminophen in patients with acute ingestion or from repeated supratherapeutic ingestion.

Dosing:
Obtain an APAP level at least 4 hours after ingestion. If the time of APAP ingestion is unknown:

- Administer a loading dose (LD, 140mg/kg) of acetylcysteine immediately
- Obtain an APAP concentration to determine the need for continued treatment

If the APAP concentration cannot be obtained or is unavailable or uninterpretable within the 8 hour time interval after ingestion or there is clinical evidence of APAP toxicity:

- Administer a LD of acetylcysteine immediately and continue treatment for a total of 17 doses, 70mg/kg repeated q4h

IF the patient presents more than 8 hours after ingestion and the time of acute APAP ingestion is known:

- Administer a LD of acetylcystein immediately
- Obtain APAP concentration to determine need for continued treatment

If the patient presents <8h after ingestions and the time of acute APAP ingestion is known and the APAP concentration is known:

- Use the Rumack-Matthew nomogram to determine whether or not to initiate treatment with acetylcycteine

Product	Cost (AWP) 10/26/16	Max doses (#17) in a 70kg patient	Cost of max dosing	Proposed
Cetylev oral 2.5g (20)	$433.96 ($21.70ea)	140mg/kg=9,800mg LD then 70mg/kg=4900 mg X17	LD $86.80 MD 43.40X17= $737.80 Total: $824.60	T3
Cetylev oral 500mg (20)	$86.80 ($4.34ea)		LD $86.80 MD $43.40X17=$737.80 Total: $824.60	T3
Acetylcysteine 10% Solution for inhalation/oral	$12.60 (10mL)		98mL=123.48 49mLX17=1049.58 Total: 1173.06	T1
Acetylcysteine 20% Solution for inhalation/oral	$14.58 (10mL)			
Acetylcysteine IV 200mg/mL (30mL)	$225.60			
Acetadote IV 200mg/mL (30mL)	$207.70			

10% solution is 100mg/mL

Papaverine-Phentolamine
Papaverine-Phentolamine-Alprostidil
Jill Johnson, Pharm.D., BCPS
8/22/16

UpToDate (Accessed 8/22/16):

Self-injection with vasoactive drugs for ED is considered 2nd line therapy.

Penile self-injection — Intracavernosal injection therapy with alprostadil (prostaglandin E1), and papaverine have been used for purposes of inducing erection (figure 4 and table 2B). In the United States, prostaglandin E1 is the only FDA-approved drug for penile self-injection. In other countries, a combination of vasointestinal peptide (VIP) and phentolamine are marketed as Invicorp (table 2B). Some clinicians prefer compounded mixtures of phentolamine and papaverine (Bimix); prostaglandin E1 is sometimes added as a third component (Trimix).

Compounded penile injections of Trimix are commonly utilized penile injections mainly due to excellent efficacy, cost, and finer ability to titrate the dose. It should be noted that compounded penile injections are considered off-label use. All penile injections, whether compounded or commercially available, increase the risk for penile plaque development and patients should be counseled about this potential risk.

The sympathetic nervous system normally maintains the penis in a flaccid or non-erect state. Vasoactive drugs, when injected into the corpora cavernosa, inhibit or override sympathetic inhibition and act as direct smooth muscle vasodilators. The relaxation of the smooth muscle trabeculae within the penile erectile bodies leads to an increase in blood flow to the penis. The increased inflow of blood engorges the penile corpora cavernosa sinusoidal spaces with sufficient pressure to compress the emissary veins that normally drain blood from the penis. The combination of accelerated arterial inflow and impeded venous outflow from the corpora cavernosa creates an erection (figure 5).

Considerable education is required for men to become facile with penile self-injection. Men are trained in sterile methods and the proper technique for inserting an insulin syringe with a 26 to 30 gauge 1/2 inch needle through the shaft of the penis and injecting the vasoactive agent into one corporeal body (figure 4). The cross circulation of the penile corpora allows medication injected into one penile corporeal body to diffuse over to the contralateral side so that a full, firm erection can be expected within a few minutes after intrapenile installation of the drug [105,106].

In a study of 683 men using alprostadil penile self-injections over a 6m period, 87% of the 471 who completed the study were satisfied with results (as were 86% of their partners) [107]. Penile pain, which occurred in 50%, was the SE most often cited by men who DCd therapy.

No dose for papaverine or phentolamine for ED is listed in Lexicomp.
Alprostadil is marketed as Caverject, dosed at 40-60mcg per use; no more than 2 doses in 24 hours.

Kit (Caverject Impulse Intracavernosal)
10 mcg (1): $70.56, 20 mcg (1): $90.87
Kit (Edex Intracavernosal)
10 mcg (1): $127.19; 20 mcg (1): $164.30; 40 mcg (1): $224.38
Pellet (Muse Urethral)
125 mcg (1): $67.86; 250 mcg (1): $71.03; 500 mcg (1): $76.00; 1000 mcg (1): $82.08
Solution (Alprostadil Injection)
500 mcg/mL (1 mL): $48.71
Solution (Prostin VR Injection)
500 mcg/mL (1 mL): $130.02
Solution (reconstituted) (Caverject Intracavernosal)
20 mcg (1): $90.17; 40 mcg (1): $118.94

Xiidra® (lifitegrast)
Prepared by: Mary Leath
UAMS P3 Student Pharmacist, August 2016

FDA-Approved Indication
Lifitegrast is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

Mechanism of Action
Lifitegrast binds to the integrin lymphocyte function-associated antigen-1 (LFA-1), a cell surface protein found on leukocytes and blocks the interaction of LFA-1 with its cognate ligand intercellular adhesion molecule-1 (ICAM-1). ICAM-1 may be overexpressed in corneal and conjunctival tissues in DED. The interaction between LFA-1 and ICAM-1 may add to the formation of an immunological synapse ending in T-cell activation and movement to T-cell tissues. *In vitro* studies show that lifitegrast may inhibit T-cell adhesion to ICAM-1 and may inhibit secretion of inflammatory cytokines in human peripheral blood mononuclear cells. The exact MOA of lifitegrast in DED is not known.

Dosage Form and Dosing Information
Lifitegrast is a white to off-white powder that is soluble in water. Xiidra is an ophthalmic solution containing 5% of lifitegrast and it comes in single use container. Instill one drop of Xiidra into each eye twice daily. Contact lenses should be taken out and reinserted 15 minutes after the administration of Xiidra.

Dosing in Special Population
Pregnant: No available data to inform any drug associated risks.
Lactating: Systemic exposure to lifitegrast from ocular administration is low and there is no data on the presence of lifitegrast in human milk, effects on infant or milk production.
Pediatric: Not established
Geriatric: No overall differences between elderly and younger adult patients.

Drug Interactions
None noted.

Storage
Xiidra comes in a carton of 60 single use containers, with each single use container supplied in a foil pouch. Xiidra can be stored at room temperature (68-77^0 F) in the original foil pouch.

Adverse Effects
5-25% of patients reported instillation site irritation, dysgeusia, and reduced visual acuity. While 1-5% of patients reported blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

Price

Medication	AWP (30 Days)	AWP (Single Dose)
LIfitegrast Ophthalmic Solution 5% (Xiidra)	$511.80	$8.53
Cyclosporine Ophthalmic Emulsion 0.05% (Restasis)	$511.80	$8.53
Artificial Tears:		
Dakrina Ophthalmic Solution 2.7-2%	$6.90	
FreshKote Ophthalmic Solution 2.7-2%	$33.30	
GenTeal Tears Ophthalmic Solution 0.1-0.2-0.3%	$7.20	
HypoTears Ophthalmic Solution 1-1%	$9.54	

Clinical Trials
Shire Mediated Clinical Trial: The safety and efficacy of lifitegrast was assessed via four 12 week, randomized (1:1), multi-center, double-masked, vehicle-controlled studies that included a total of 1181 patients. The primary objectives were effects on symptoms of dry eye disease via an eye dryness score and effects on signs of dry eye disease via inferior fluorescein corneal staining score. Three of the four studies did show a favor for lifitegrast over placebo for both objectives.
Sonata: The safety of lifitegrast was demonstrated via a multicenter, randomized (2:1 lifitegrast to placebo respectively), prospective, double-masked, placebo-controlled phase 3 study to span 360 days in 332 adults with a history dry eye disease. The main objective to this study was the percentage and severity of treatment-emergent adverse events (TEAEs). The secondary objective dealt with ocular safety measures. 53.6% of the patients taking lifitegrast and 34.2% of patients taking placebo experienced ≥1 ocular TEAEs.

Participant Flow		
	Placebo	Lifitegrast
Analyzed	n=111	n=220
Completed Study	n=92	n=170
Discontinued Study	n=19	n=51
Discontinued Study due to Adverse Events	n=9 (9%)	n=27 (16%)

OPUS-1: The efficacy and safety of lifitegrast was assessed via a prospective, randomized (1:1), double-masked, placebo-controlled, parallel arm, multicenter clinical trial that lasted 84 days with 588 adult subjects with a history of dry eye disease. The primary objective of the study was to measure the efficacy of the medication via the mean change from baseline via the inferior corneal staning score (ICSS), while the co-primary subjective of this study measure efficacy via mean change in

baseline via the visual-related function subscale score of the Ocular Surface Disease Index (VR-OSDI). With supportive measures via corneal fluorescein staining scores(superior, central, total cornea), conjunctival lissamine scores(nasal, temporal, and total conjunctiva), and symptom scores.

Efficacy Measures	Baseline	Statistical Significance on Day 84
ICSS	Lifitegrast: 1.84 Placebo: 1.82	P=0.0007
VR-OSDI	Lifitegrast: 0.86 Placebo: 0.93%	P=0.7894
Fluorescein Corneal Staining-Superior	Lifitegrast: 1.82 Placebo: 1.79	P=0.0392
Fluorescein Corneal Staining-Central	Lifitegrast: 1.18 Placebo: 1.22	P=0.7346
Fluorescein Corneal Staining-Total	Lifitegrast: 4.84 Placebo: 4.83	P=0.0148
Lissamine Conjunctival Staining-Nasal	Lifitegrast: 2.05 Placebo: 1.90	P=0.0039
Lissamine Conjunctival Staining-Temporal	Lifitegrast: 1.71 Placebo: 1.68	P=0.1066
Lissamine Conjunctival Staining-Total	Lifitegrast: 3.58 Placebo: 3.74	P=0.0086

OPUS-2: The efficacy and safety of lifitegrast was assessed via a prospective, randomized (1:1), double-masked, placebo-controlled, multicenter clinical trial that lasted 84 days with 718 adult subjects with a history of dry eye disease. The co-primary objectives measured efficacy via an eye dryness score by a visual analogue score (VAS) and via an inferior corneal fluorescein staining score. The secondary objectives of the study measured efficacy via an ocular discomfort score, eye discomfort score by VAS, total corneal fluorescein staining and nasal lissamine staining. The safety was determined by the occurrences of treatment-emergent adverse effects, which the lifitegrast patient group experienced more of these TEAEs.

Measurement	Change from Baseline	Statistical Significance on Day 84
Eye Dryness Score (VAS)	Lifitegrast: -35.30 Placebo: -22.75	P<0.0001
Inferior Corneal Staining	Lifitegrast: -0.73 Placebo: -0.71	P=0.6186
Ocular Discomfort Score	Lifitegrast: -0.91 Placebo: -0.57	P=0.0005
Eye Discomfort Score (VAS)	Lifitegrast: -26.46 Placebo: -16.73	P<0.0001
Total Corneal Fluorescein Staining	Lifitegrast: -1.62 Placebo: -1.49	P=0.3711
Nasal LIssamine Staining	Lifitegrast: -0.25 Placebo: -0.27	P=0.6982

OPUS-3: The efficacy and safety of lifitegrast was assessed via a prospective, randomized (1:1), double-masked, placebo-controlled, multicenter clinical trial that lasted 84 days with adult subjects with a history of dry eye disease. The primary objective of this study was to measure the efficacy via an eye dryness score. Due to the recentness of this trial, only the topline results have been released. The study showed that lifitegrast did decreased the eye dryness score with a greater effect than placebo (P=0.0007).

Conclusion

Lifitegrast seems to have efficacy in treating the signs and symptoms of dry eye disease, but this medication does have some adverse effects such as instillation site irritation, dysgeusia, and reduced visual acuity. Lifitegrast has also not been compared to other ophthalmic products with the same indication.

Recommendation to EBRx: Exclude. There are more cost effective options available.

Outcome of EBRxP&T: Exclude, code 13

References

Donnenfeld, Eric D., et al. "Safety of Lifitegrast Ophthalmic Solution 5.0% in Patients With Dry Eye Disease: A 1-Year, Multicenter, Randomized, Placebo-Controlled Study." *Cornea* 35.6 (June 2016): 741-748.

Lexi-Comp Online™, Lexi-Drugs Online™, Hudson, Ohio: Lexi-Comp, Inc.; August 2016.

Lifitegrast Package Insert. Shire US, Inc. Lexington, MA. Revised: July 2016.

Sheppard, John D., et al. "Lifitegrast Ophthalmic Solution 5.0% for Treatment of Dry Eye Disease." *American Academy of Ophthamology* 121:2 (February 2014): 475-483.

Tauber, Joseph, et al. "Lifitegrast Ophthalmic Solution 5.0% versus Placebo for Treatment of Dry Eye Disease." *American Academy of Ophthamology* 122:12 (December 2015): 2423-2431.

Lidocaine Topical

Geri Bemberg, Pharm.D., J Johnson

Brand	Generic	Strength	Package Size	Price	Price/unit	Coverage to date (8/25/15)
CREAMS						
AneCream External		4%	15g	$19.20	$1.28/g	T1
AneCream5 External		5%	15g	$24.00	$1.60/g	T1
Lidocaine HCl External		3%	85g	$122.52	$1.44/g	T1
Lidopin		3.25%	28g	$837.20	$29.90/g	Excluded
Lidopin		3.25%	85g	$997.90	$11.74/g	Excluded
LMX 4 External		4%	15g	$26.56	$1.77/g	Brand Penalty
LMX 5 External		5%	15g	$33.01	$2.20/g	Brand Penalty
RectiCare External		5%	30g	$21.60	$0.72/g	T1
Lidotral		3.88%	85g	AWP $1586.55	$17.63/g (9/22/16AWP)	
DEVICE						
Zingo Intradermal		0.5mg	1	$26.40	$26.40	Excluded
GEL						
Lidocin		3%	120g	$1212.9996	$10.10833/g	Excluded
Lidocin		3%	240g	$2425.9992	$10.10833/g	Excluded
Glydo External		2%	6mL	$7.14	$1.19/mL	T1
Lidocaine HCl External		2%	5mL	$7.80	$1.56/mL	T1
Tecnu First Aid External		0.2-2.5%	56.7g	$6.00	$0.10/g	Excluded
Topicaine 5 External		5%	30g	$19.50	$0.65/g	T2
Topicaine External		4%	30g	$15.72	$0.52/g	T2
KIT						
AneCream External		4%	1	$33.00	$33.00	T1
LMX 4 Plus External		4%	1	$48.07	$48.07	Brand Penalty
LOTION						
Lidocaine HCl External		3%	177mL	$69.95	$0.395/mL	T1
OINTMENT						
Lidocaine External		5%	35.44g	$300.00	$8.465/g	T1
PATCH						
Lidocaine External		5%	30	$280.81	$9.36/patch	PA T1

Lidoderm External		5%	1	$10.40	$10.40/patch	PA T1
Lidothol Pad	Lidocaine/ Menthol	4.5%/5%				
Lidothol Pad	Lidocaine/ Menthol	4.5%/5%				
SOLUTION						
Lidocaine HCl External		4%	50mL	$9.16	$0.18/mL	T1
Lidocaine HCl Mouth/Throat		4%	4mL	$15.60	$3.90/mL	T1
LTA 360 Kit Mouth/Throat		4%	4mL	$6.49	$1.62/mL	T1
Xylocaine External		4%	50mL	$21.64	$0.43/mL	Brand Penalty
Brand	**Generic**	**Strength**	**Package Size**	**Price**	**Price/unit**	**Coverage to date (8/25/15)**

David's notes: Most (if not all) generic topical Lidocaine is T1. I Show Aflexeryl-LC pad (Lidocaine Menthol patch 4/1%) is our most expensive product at T2. Lidenza patch is also costly at T2. Looks like we need to include Lidocaine/Menthol products in our review as there are a few others. This is a huge category where it may be best to pick 1-2 generic products and exclude "all others".

Ciprofloxacin 0.3% (0.75mg)/fluocinolone 0.025% (0.0625mg) (Otovel) otic solution 0.25mL single dose vials
Jill Johnson, Pharm.D.
9/22/16

FDA approved for treatment of acute otitis media with tympanostomy tubes due to susceptible isolates of Staph aureus, Strep pneumo, H Flu, Moraxella catarrhalis, and Pseudomonas aeruginosa in pediatric patients 6 months or older. (Not indicated in adults)

Dose: 0.25mL into affected ear BID for 7 days.

				Dosing	AWP (9/22/16)
Otovel Otic Solution	Fluocinolone 0.025%	Ciprofloxacin 0.3%	0.25mL single dose vials (14s) PF	BID X 7d	$237.58
Ciprodex otic suspension	Dexamethasone 0.1%	Ciprofloxacin 0.3%	7.5mL	BID X 7d	$231.42
Cipro HC Otic Suspension	Hydrocortisone 1%	Ciprofloxacin 0.2%	10mL	BID X 7d	$312.78
Coly-Mycin S Otic Suspension	Hydrocortisone acetate 10mg	Colistin 3mg, neomycin 3.3mg	10mL	4 drops 3-4X/d X up to 10d	$209.41
Cortisporin-TC Otic Suspension	Hydrocortisone 1%	Colistin 3mg, neomycin 3.3mg	10mL		Discontinued $209.41
Neomycin sulfate/polymyxin B sulfate/hydrocortisone Otic solution (various)	Hydrocortisone 1%	Neomycin 3.5mg, polymyxin B 10000 units	10mL	3 drops 3-4x/d	Not sure if discontinued; no cost info
Neomycin sulfate/Polymyxin B sulfate/Hydrocortisone Otic suspension (various)	Hydrocortisone 1%	Neomycin 3.5mg, polymyxin B 10000 units	10mL	3 drops 3-4x/d	Not sure if discontinued; no cost info

References:

1. Dohar, Joseph, et al. "Topical ciprofloxacin/dexamethasone superior to oral amoxicillin/clavulanic acid in acute otitis media with otorrhea through tympanostomy tubes." *Pediatrics*118.3 (2006): e561-e569.

This trial showed Ciprodex otic BID X7d is superior to Augmentin 90mg/kg/d q12h X 10d in children with AOM with otorrhea through tympanostomy tubes.

2. Otovel PI:

- I could find no peer-reviewed published clinical trials in Pub Med with fluocinolone and ciprofloxacin.
- PI: 2 phase 3 MC, R, DB, active-controlled, parallel group trials. N=662 peds pts (6m-12y) with AOMT. 1` endpt was cessation of otorrhea.

Results:

Trial 1			
	Otovel N=112	Cipro N=109	Fluo N=110
% with cessation of otorrhea by Day 22	88 (78.6%)	73 (67.0%)	53 (48.2%)
Median time to cessation (days)	3.75	7.69	Not estimable
P-value vs Otovel		<0.001	<0.001
Trial 2			
% with cessation of otorrhea by day 22	87 (78.4%)	77 (68.8%)	47 (43.5%)
Median time to cessation (days)	4.94	6.83	Ne
P-value vs Otovel		0.028	<0.001

9/27/16 Proposal to EBRx P&T: T3.

Nebivolol 5mg and valsartan 80mg tablet (Byvalson®)

Prepared by: Mary Leath, UAMS P3 Student Pharmacist

9/27/16

FDA-Approved Indication

Byvalson is indicated as initial hypertension therapy or for pts not controlled on valsartan 80mg or nebivolol ≤10mg daily. (Max dose of nebivolol monotherapy is 40mg daily.)

Mechanism of Action

Nebivolol: highly selective inhibitor of $beta_1$-adrenergic receptors; at doses ≤10 mg it preferentially blocks $beta_1$-receptors. It also produces an endothelium-derived NO-dependent vasodilation resulting in a reduction of systemic vascular resistance.
Valsartan: produces direct antagonism of the angiotensin II (AT2) receptors. It displaces AT2 from the AT1 receptor and produces its blood pressure lowering effects by antagonizing AT1-induced vasoconstriction, aldosterone release, catecholamine release, arginine vasopressin release, water intake, and hypertrophic responses.

Dose: 1 daily

Black Box Warning: Fetal Toxicity

Price

Medication	AWP (30 Days) 9/22/16	AWP (per day)
Byvalson 5 mg/80 mg	$131.40	$4.38
Bystolic 5 mg	$131.40	$4.38
Diovan 80 mg	$224.40	$7.48
Valsartan 80 mg	$139.50	$4.65
Losartan 100mg	$92.46	$3.08
Metoprolol 50 tartrate	$33.30 (60)	$2.22 (MAC'd)

Clinical Trials

From PI:

Safety trial: Allergen USA, Inc. Clinical Trial: The safety of Byvalson was evaluated during the first 4 weeks of an 8 week placebo-controlled trial with a total of 1,664 patients, with 807 receiving Byvalson in an open-label safety study. The overall incidence of adverse effects in the first 4 weeks were similar between the Byvalson, placebo, and individual components (nebivolol 5mg and valsartan 80 mg) groups. Discontinuation rates were 2% for patients treated with Byvalson, 3.2% for patients treated with placebo, and 1% for patients treated with the individual components. 621 of the original 807 continued Byvalson for 180 days, and 476 of the 807 continued Byvalson for 360 days.

Conclusion

Byvalson is a beta adrenergic blocker and an angiotensin II receptor blocker indicated for the treatment of hypertension made up of two individual components, nebivolol and valsartan. Both of these drugs have show efficacy for treating hypertension separately.

Recommendation: Exclude, code 13. (less costly alternatives available)

OUTCOME of EBRx committee: Exclude, code 13.

References

Byvalson Package Insert, Allergen USA, Inc. Irvine, CA. Revised: 06/2016.
Lexi-Comp Online™, Lexi-Drugs Online™, Hudson, Ohio: Lexi-Comp, Inc.; September 2016.
www.Byvalson.com

Lisinopril Oral Solution 1mg/mL (Qbrelis)
Jill Johnson, Pharm.D.
9/22/16

FDA approved for:

- treatment of hypertension in adults and pediatric patients 6 y and older
- reduction of signs and symptoms of systolic heart failure
- reduction of mortality in treatment of hemodynamically stable patients within 24 hours of acute MI

Evidence:
PI:

Hypertension: there were 2 dose response studies; patients were treated with lisinopril 20-80mg daily. In another study, pediatric patients <50kg were treated with 0.625, 2.5mg, or 20mg of lisinopril while patients >50kg received 1.25, 5, or 40mg lisinopril.

Heart failure: 2, 12 week studies compared lisinopril up to 20mg QD to digitalis and diuretics alone. A large (n=3000) survival study (ATLAS Trial) compared 2.5 and 35mg lisinopril in systolic heart failure patients and showed the higher dose of lisinopril had outcomes at least as favorable as the lower dose.

Acute MI: the GISSI-3 study was a MC, controlled, R, unblended trialin 19,394 pts w/ AMI designed to examine the effects of short term (6 w) treatment w/ lisinopril, nitrates, their combination, or no therapy on 6w mortality. Randomized to lisinopril 5mg, then 10mg. Some received 2.5mg.

Cost:

		AWP (9/22/16)	20mg equivalent (AWP cost)	Monthly cost for 20mg daily dose (AWP cost)
Qbrelis	1mg/mL (150mL)	$592.80 (3.952/mg)	79.07/dose	$2372.10
Lisinopril (MACd)	2.5mg	0.64 ea		
	5mg	0.96 ea		
	10mg	0.99 ea		
	20mg	1.06 ea	1.06/dose	$31.80
	30mg	1.51 ea		
	40mg	1.55 ea		$23.25 (scored)

Tablets are not on the Do Not Crush list. They are scored.

Instructions to extemporaneously prepare a suspension available on Lexi-Comp:

Extemporaneously Prepared

A 1 mg/mL lisinopril oral suspension may be made with tablets and a mixture of Bicitra and Ora-Sweet SF. Place ten 20 mg tablets into an 8 ounce amber polyethylene terephthalate (PET) bottle and then add 10 mL purified water and shake for at least 1 minute. Gradually add 30 mL of Bicitra and 160 mL of Ora-Sweet SF to the bottle and gently shake after each addition to disperse the contents. Store resulting suspension at ≤25°C (77°F) for up to 4 weeks. Label bottle "shake well" (Prinivil prescribing information, 2013; Thompson, 2003).

A 1 mg/mL lisinopril oral suspension may be made with tablets and a 1:1 mixture of Ora-Plus® and Ora-Sweet®. Crush ten 10 mg tablets in a mortar and reduce to a fine powder. Add small portions of the vehicle and mix to a uniform paste; mix while adding the vehicle in incremental proportions to **almost** 100 mL; transfer to a graduated cylinder; rinse mortar with vehicle, and add quantity of vehicle sufficient to make 100 mL. Store in amber plastic prescription bottles; label "shake well". Stable for 13 weeks at room temperature or refrigerated (Nahata, 2004).

A 1 mg/mL lisinopril oral suspension also be made with tablets, methylcellulose 1% with parabens, and simple syrup NF. Crush ten 10 mg tablets in a mortar and reduce to a fine powder. Add 7.7 mL of methylcellulose gel and mix to a uniform paste; mix while adding the simple syrup in incremental proportions to **almost** 100 mL; transfer to a graduated cylinder; rinse mortar with vehicle, and add quantity of vehicle sufficient to make 100 mL. Store in amber plastic prescription bottles; label "shake well". Stable for 13 weeks refrigerated or 8 weeks at room temperature (Nahata, 2004).

A 2 mg/mL lisinopril syrup may be made with powder (Sigma Chemical Company, St. Louis, MO) and simple syrup. Dissolve 1 g of lisinopril powder in 30 mL of distilled water. Mix while adding simple syrup in incremental proportions in a quantity sufficient to make 500 mL. Label "shake well" and "refrigerate". Stable for 30 days when stored in amber plastic prescription bottles at room temperature or refrigerated. **Note:** Although no visual evidence of microbial growth was observed, the authors recommend refrigeration to inhibit microbial growth (Webster, 1997).

9/27/16 Proposal to EBRx P&T: Exclude, code 13.

Lesinurad (Zurampic®)
Sam Wolf – P3
9/27/16

FDA-approved indication: treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels w/a xanthine oxidase inhibitor

MOA: reduces serum uric acid levels by inhibiting URAT1 and OAT4 w/IC50 values of 7.3 and 3.7 uM respectively.
Dosage Form and Dosing: 200 mg blue tablet taken once daily in combination with a xanthine oxidase inhibitor. Max daily dose of 200 mg.
Adverse Reactions: Renal events including increased creatinine, renal failure, and nephrolithiasis. No renal adjustment dosing is indicated.

N (%)	Placebo + XOI N=516	Lesinurad 200mg + XOI N=511	Lesinurad 400mg + XOI N=510
Creatinine increased	12 (2.3%)	22 (4.3%)	40 (7.8%)
Renal failure	11 (2.1%)	6 (1.2%)	18 (3.5%)
Nephrolithiasis	9 (1.7%)	3 (0.6%)	13 (2.5%)

AWP (9.22.16) Cost: 30 tablets: $420 AWP; 1 tablet: $14

Clinical Trials:
Fleischmann: Efficacy demonstrated with a phase 1B, multicenter, open-label, multiple dose study of patients w/a sUA > 8 mg/dL following a 14 day wash-out with colchicine to prevent flare ups. Febuxostat 40 or 80 mg was administered on days 1-21 with lesinurad 400 mg on days 8-14 and increased to 600 mg on days 15-21. F/U period was days 22-28. Initial treatment with febuxostat resulted in reduction of sUA by 56-67%. When febuxostat administered with 400 or 600 mg of lesinurad, 100% of subjects achieved an sUA < 6 mg/dL. *study only included men and no one was blinded*

SAD/MAD: Safety was demonstrated through a R, DB, PC, sequential, ascending-dose (SAD) study in which patients received a SAD (5-600 mg) or a multiple ascending dose (MAD) in both fasting/fed states. At even the highest dose (600 mg) the incidence of AE was very low. No subjects D/C due to AEs during SAD. With MAD AEs were low with the highest number being reported with 200 mg when taken with food. Most common reported AE was treatment-related diarrhea. *given lesinurad alone*

PI: Efficacy shown in a 3 multicenter, double-blind, placebo-controlled trial in adult patients with hyperuricemia and gout in combination with a xanthine oxidase inhibitor, allopurinol or febuxostat. All studies were done over 12 months and patients received colchicine or NSAIDs for prophylaxis of flare ups. Study 1 and 2 enrolled patients on allopurinol dose of at least 300 mg with a sUA >6.5 mg/dL and at least 2 flare ups in last 12 months.

In each of the 3 pivotal studies, lesinurad in combo with a XOI, the gout flare rates from the end of Month 6-end of month12 were not statistically different b/w lesinurad 200mg + allopurinol or febuxostat compared with allopurinol or febuxostat alone. In study 3, the proportion of pts who experienced a complete resolution of >1 target tophus was not statistically different b/w lesinurad 200mg in combo w/ febuxostat compared with febuxostat alone.

Study	Timepoint	Pts (%) achieving sUA target (<6mg/dL)		Difference in proportion (95% CI)
		Plac + allop	Lesinurad 200 + allop	Lesinurad 200mg + plac
Study 1 N=603	Month 6	28%	54%	0.26 (0.17, 0.36)
Study 2 N=610	Month 6	23%	55%	0.32 (0-.23, 0.41)

Conclusion: Zurampic shows efficacy in reducing sUA levels when combined with allopurinol or febuxostat in patients with hyperuricemia.

Recommendation: Exclude due to data showing no statistically significant reduction in gout flares despite the addition of this drug to XOIs (allop or febuxostat), the drug did not cause a statistically significant reduction in gout flares.

References:

1. Zurampic. “Zurampic Package Insert.” September 2016. Accessed online at: https://www.zurampic.com/
2. Fleischmann, Roy, et al. "Pharmacodynamic, pharmacokinetic and tolerability evaluation of concomitant administration of lesinurad and febuxostat in gout patients with hyperuricaemia."*Rheumatology* 53.12 (2014): 2167-2174.
3. Shen, Zancong, et al. "Pharmacokinetics, pharmacodynamics, and safety of lesinurad, a selective uric acid reabsorption inhibitor, in healthy adult males." *Drug design, development and therapy* 9 (2015): 3423.

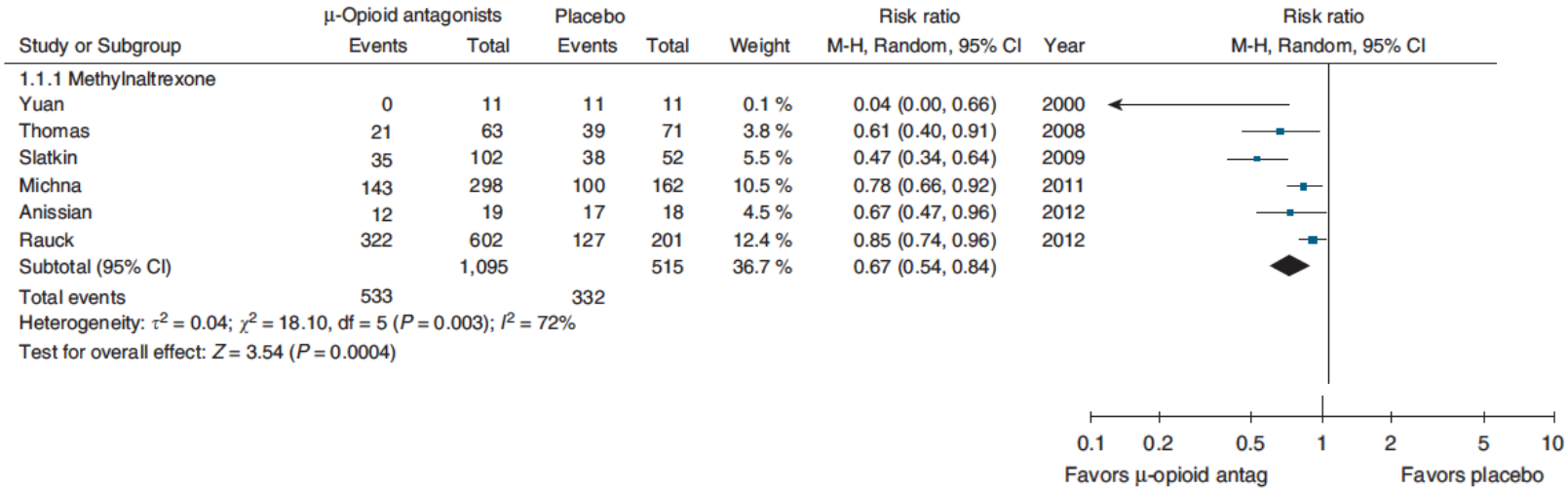
EBRx Outcome: Exclude

IBS/Opioid-induced Constipation/Chronic Idiopathic Constipation Drugs
Methylnaltrexone, linaclotide, lubiprostone, naloxegol
Jill Johnson, Pharm.D., BCPS
9/22/16

			OIC w/ advanced illness	OIC w/ CNCP	CIC in adults	IBSc in adults	IBSc in women ≥18yo	Dose	AWP cost (9/22/16)	Current Utilizers (1Q2016) # members	Plan cost 2016Q1	Current EBD coverage	Proposed EBD coverage
Relistor	methylnaltrexone	8mg/0.4mL, 12mg/0.6mL	•	•				8 or 12mg SC QD	$120 (0.4mL)	4	6344.82	T3	
"	"	150mg tab		•				450mg po QD	?? (#90)	(new drug)			Exclude; revisit in 1 year
Linzess	Linaclotide	145, 290mg cap			•	•		145 or 290mg QD	$387.37 (30) $387.37 (30)	92	36021.14	T3PA	
Amitiza	Lubiprostone	8, 24mcg cap			•		•	8 or 24mcg BID	$396.32 (60) $396.32 (60)	42	13825.69	T3PA	
Movantik	Naloxegol	12.5, 25mg tab		•				12.5 or 25mg QD	$345.64 (30) $345.64 (30)	30	8027.05	T3QL 1/1	
										168	**$64,218.70**		

CIC=chronic idiopathic constipation, IBS=irritable bowel syndrome with constipation, OIC=opioid induced constipation, CNCP=chronic non-cancer pain

[1]RR of failure to respond (failure to achieve ≥3 spontaneous bowel movements/week) to therapy vs placebo:



References:

1. Ford, Alexander C., Darren M. Brenner, and Philip S. Schoenfeld. "Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis." *The American journal of gastroenterology* 108.10 (2013): 1566-1574.

Doxycycline Hyclate (Targadox)
Jill Johnson, Pharm.D.
9/27/16

COST:

Doxycycline Hyclate			
		AWP cost (9/22/16)	Dosing eq to 100mg BID X10d
TargaDOX tab	50mg	$900 (60)	$600
Acticlate	75mg, 150mg	$1908 (60), $1908 (60)	
Doryx DR tab	50mg, 150mg (DSC), 200mg	50mg $1565.28 (120)	
Doryx MPC DR tab	120mg	$900 (60)	
Doxycycline tab(generic)	20mg, 100mg	$118.98 (100), $3073 (500)	$122.92
Doxycycline DR tab	50mg, 75mg, 100mg, 150mg, 200mg	$1407.19 (120), $613.45 (60), $1314.83 (100), $1759.94 (100), $2605.18 (60)	
Doxycycline cap	50mg 100mg	$112.66 (50), $307.35 (50)	$122.94
Morgidox cap	50mg 100mg	100mg $517.22 (30)	$344.81
Morgidox Kit w/cleanser	50mg, 100mg, 100mg X2	100mg $517.22 (1)	
Ocudox w/eyelid cleans/spray kit			
Vibramycin syrup	50mg/5mL	$449.38 (473mL); $0.95/mL; 4.75/5mL	$190.01
Doxycycline Monohydrate			
Adoxa	50mg, 75mg, 100mg, 150mg	$929 (100), $1277.12 (100), $798.90 (50), $3376.06 (60)	$639.12
Adoxa Pak 1/100		$306.20 (31)	
Doxycycline tab	50mg, 75mg, 100mg, 150mg	$335.71 (100), $498.35 (100), $24602 (50), $274.17 (30)	$99.60
Doxycycline cap	50mg, 75mg, 100mg, 150mg	$145.10 (100), $1691.98 (100), $118.45 (50), $1479.01 (60)	$94.76
Doxycycline susp	25mg/5mL	$26.50 (60mL)	
Vibramycin suspension	25mg/5mL	$36.80 (60mL)	
Mondoxyne NL oral cap	50, 75mg, 100mg	$576 (60), $720 (60), $576 (60)	$192
Monodox cap	75mg, 100mg	$2331 (100), $1166 (50)	$233.20
Oracea DR cap	40mg	$725.64 (30)	
Doxycycline DR cap	40mg	$653.07 (30)	

9/27/16 Proposal to EBRx P&T: Exclude TargaDox, code 13.

Factors for Hemophilia

Brand		Dosing	Supplied As	Unit Cost	Vial Cost
Factor IX Human					
AlphaNine SD		15 to 30 units/kg/dose twice weekly* 25 to 40 units/kg/dose twice weekly* 40 to 100 units/kg/dose 2 to 3 times weekly*	500 units 1000 units 1500 units	$1.58 $1.58 $1.58	$790 $1,580 $2,370
Mononine		15 to 30 units/kg/dose twice weekly* 25 to 40 units/kg/dose twice weekly* 40 to 100 units/kg/dose 2 to 3 times weekly*	250 units 500 units 1000 units	$1.20 $1.20 $1.52	$300 $600 $1,520
Factor IX Recombinant					
BeneFIX			250 units 500 units 1000 units 2000 units	$1.64 $1.64 $1.64 $1.64	$410 $820 $1,640 $3,280
Ixinity			500 units 1000 units 1500 units	$1.78 $1.78 $1.78	$890 $1,780 $267
Rixubis		40 to 60 (80 in children) units/kg twice weekly; may titrate dose depending upon age, bleeding pattern, and physical activity			
Factor IX Recombinant factore IX-Fc fusion (fusion of factor IX to a monomeric human immunoglobulin Fc domain (rFIXFc); t 1/2 =54-90h					
Alprolix		50 units/kg once weekly or 100 units/kg once every 10 days; adjust dose based on individual response	500 units 1000 units 2000 units 3000 units	$3.42 $3.42 $3.42 $3.42	$1,710 $3,420 $6,840 $10,260
Factor IX Recombinant, Albumin Fusion Protein—for Hemophilia B (congenital factor IX def); t1/2=102h					
Idelvion		25 to 40 (55 in children) units/kg once every 7 days; if well controlled may switch to 50 to 75 units/kg once every 14 days.	250 units 500 units 1000 units 2000 units	$5.10 $5.10 $5.10 $5.10	$1,275 $2,550 $5,100 $10,200
Factor VIII and Von Willebrand Factor					
Alphanate		15 to 30 units/kg/dose twice weekly (Peds) 25 to 40 units/kg/dose twice weekly (Peds) 40 to 100 units/kg/dose 2 to 3 times weekly (Peds)	250 units 500 units 1000 units 1500 units 2000 units	$1.38 $1.38 $1.38 $1.38 $1.38	
Humate-P			250/600 500/1200 1000/2400	1.40 1.40	
Wilate			500-500 1000-1000	1.56 1.56	
Factor VIII (Recombinant)					
Advate		20 to 40 units/kg every other day (3 to 4 times weekly). Alternatively, an every-third-day dosing regimen may be used to target factor VIII trough levels of ≥1%	250 units 500 units 1000 units 2000 units 3000 units	$1.82 $1.82 $1.82 $1.82 $1.82	$455 $910 $1,820 $3,640 $5,460

			4000 units	$1.82	$7,280
Afstyla Kit		20-50 IU/kg 2 to 3 times weekly	250 units 500 units 1000 units 2000 units 3000 units	1.98 1.98 1.98 1.98 1.98	$495 $990 $1980 $3960 $5940
Eloctate		50 units/kg every 4 days; may adjust within the range of 25 to 65 units/kg at 3- to 5-day intervals based on patient response	250 units 500 units 750 units 1000 units 1500 units 2000 units 3000 units	$2.38 $2.38 $2.38 $2.38 $2.38 $2.38 $2.38	$595 $1,190 $1,785 $2,380 $3,570 $4,760 $7,140
Helixate		25 units/kg 3 times weekly	250 units 500 units 1000 units 2000 units 3000 units	$1.76 $1.76 $1.76 $1.56 $1.76	$440 $880 $1,760 $3,120 $5,280
Kogenate		25 units/kg 3 times weekly	250 units 500 units 1000 units 2000 units 3000 units	$1.75 $1.75 $1.75 $1.75 $1.75	$438 $875 $1,750 $3,500 $5,250
Kovaltry		20 to 40 units/kg 2 or 3 times weekly			
Novoeight		20 to 50 units/kg 3 times weekly or 20 to 40 units/kg every other day	250 units 500 units 1000 units 1500 units 2000 units 3000 units	$1.98 $1.98 $1.98 $1.98 $1.98 $1.98	$495 $990 $1,980 $2,970 $3,960 $5,940
Nuwiq		30 to 40 units/kg every other day	250 units 500 units 1000 units 2000 units	$2.03 $2.03 $2.03 $2.03	$508 $1,015 $2,030 $4,060
Recombinate			220-400 401-800 801-1240 1241-1800 1801-2400	1.82	
*Xyntha**		Treatment experienced patients: 25 to 35 units/kg 3 times weekly	250 units 500 units 1000 units 2000 units	$1.82 $1.82 $1.82 $1.82	$455 $910 $1,820 $3,640
Von Willebrand					
Vonvendi		Initial: 40 to 80 units/kg Subsequent: 40 to 60 units/kg every 8-24 hours	650 units 1300 units	$2.38	$1547 $3094

DEFINITIONS — Hemophilia typically refers to an inherited bleeding disorder caused by deficiency of coagulation factor VIII (hemophilia A), factor IX (hemophilia B or Christmas disease), or factor XI (hemophilia C or Rosenthal syndrome).

●**Acquired factor deficiencies** – Acquired coagulation factor deficiencies caused by an autoantibody (often to factor VIII) are sometimes referred to as acquired hemophilia. The terms "acquired factor inhibitor" or "acquired factor deficiency" are

preferable to avoid potential mislabeling the patient as having hemophilia A or B. Management of these conditions is discussed separately. (See "Acquired inhibitors of coagulation".)

●**Inhibitors** – In hemophilia, inhibitor refers to an autoantibody that typically forms in response to infused factor. Inhibitors are most common in individuals with very low baseline factor levels. (See "Factor VIII and factor IX inhibitors in patients with hemophilia".)

●**Severity** – Hemophilia is characterized as mild, moderate, or severe, based on the residual or baseline factor activity level (also referred to as "factor level"); this is expressed as a percent of normal or in international units (IU)/mL [1]. Factor levels typically correlate with the degree of bleeding symptoms [2,3].

•**Severe hemophilia** – Severe hemophilia is defined as <1 percent factor activity, which corresponds to <0.01 IU/mL.

•**Moderate hemophilia** – Moderate hemophilia is defined as a factor activity level ≥1 percent of normal and <5 percent of normal, corresponding to ≥0.01 and <0.05 IU/mL.

•**Mild hemophilia** – Mild hemophilia is defined as a factor activity level ≥5 percent of normal and <40 percent of normal (≥0.05 and <0.40 IU/mL).

Urea Cream 37.5% (Rynoderm)

Geoffrey Fenich
Date 07/25/2016

Labeled Use: Debridement and promotion of normal healing of hyperkeratotic surface lesions, particularly where healing is retarded by local infection, necrotic tissue, fibrinous or purulent debris, or eschar; treatment of hyperkeratotic conditions, such as dry, rough skin; skin cracks and fissures; dermatitis; psoriasis; xerosis; ichthyosis; eczema; keratosis; keratoderma; corns and calluses; damaged, ingrown, and devitalized nails (lexicomp)

Comparator Drugs:

Drug
Urea Cream: 10, 12, 20, 30% creams: OTC 10% (85 g): $9.00
Urea Cream: 39, 40, 41, 45, 50% creams: Rx Only **Cream** (Urea External) 39% (226.8 g): $350.39 40% (85 g): $20.70 45% (255 g): $171.13 47% (142 g): $490.60 50% (142 g): $113.87

Mechanism of Action: Dissolves the intracellular matrix, resulting in loosening the horny layer of the skin.

Contraindications: Clinically significant hypersensitivity to urea or any component of the formulation

Adverse Reactions: Transient stinging, local irritation

Drug Interactions: None presently identified
Evidence:

Recommendation: Do not cover. Code 13.

EBRx Outcome: Exclude Rynoderm, exclude rx products including 39%, 45%, 47% new users only. Could grandfather 2 users at EBD using the 50% product. POS messaging will read "use 40%"

Obeticholic Acid
5, 10mg tablets
Jill Johnson, Pharm.D., BCPS
7/26/16

FDA indication: Primary biliary cholangitis (formerly "cirrhosis") in combination with ursodiol in adults with an inadequate response to ursodiol, or as monotherapy in adults unable to tolerate ursodiol.
Off-label: non-alcoholic steatohepatitis or non-alcoholic fatty liver disease (NASH)

Cost: (AWP) $228/unit, each strength, 30 days supply $6840
Mechanism of Action: FXR, a nuclear receptor expressed in the liver and intestine. FXR is a key regulator of bile acid, inflammatory, fibrotic, and metabolic pathways. FXR activation decreases the intracellular hepatocyte concentrations of bile acids by suppressing de novo synthesis from cholesterol as well as by increased transport of bile acids out of the hepatocytes. These mechanisms limit the overall size of the circulating bile acid pool while promoting choleresis, thus reducing hepatic exposure to bile acids.

Evidence:
PBC

- Hirschfield, et al.[1] assigned PBC patients with an inadequate response to ursodiol to obeticholic acid 10mg, 25mg, or 50mg or placebo, daily for 3 months. Pts remained on their existing dose of urso throughout the study. 1` outcome was change in alkaline phosphatase from baseline to end of study (day 85 or early termination). Results: Alk Phos levels decreased 21-25% on average from baseline in the OCA group and 3% with placebo.
- POISE: The primary endpoint was a composite of:
  1. ALP less than 1.67-times the ULN*
  2. Total bilirubin less than or equal to ULN*
  3. ALP decrease of at least 15%.

RCT	Study 201	Study 202 Hirschfield et al.	Study 301 (POISE)
Patient Characteristics	N=59 (ITT) Mean age: 55 years Female: 85% Mean ALP: 432.6 U/L	N=161 (ITT, N=165) Mean age: 55 years Female: 95% Mean ALP: 286.9 U/L Mean UDCA dose: 15.9 mg/day	N=216 (ITT, N=217) Mean age: 56 years Female: 91% Mean ALP: 323.2 U/L Mean UDCA dose: 15.4 mg/day
Interventions/Comparators	OCA 10 mg OCA 50 mg Placebo	OCA 10 mg OCA 25 mg OCA 50 mg Placebo	OCA 5-10 mg OCA 10 mg Placebo
Duration	DB: 3 months LTSE: Up to 4.5 years	DB: 3 months LTSE: 1 year	DB: 1 year LTSE: 5 years (ongoing)
Inclusion criteria	OCA as monotherapy for patients not on UDCA for ≥3 months ALP 1.5-10xULN	OCA+UDCA for patients with inadequate response to UDCA (stable dose ≥6 months) ALP 1.5-10xULN	OCA±UDCA for patients with inadequate response to UDCA (on UDCA for ≥12 months and stable dose ≥3 months), or intolerant to UDCA (7%) ALP ≥1.67xULN **or** bilirubin >1xULN but <2xULN
% Change in ALP	OCA 10 mg: -44.5 OCA 50 mg: -37.6 Placebo: +11.7 All OCA groups from baseline, p<0.0001	OCA 10 mg: -23.7 OCA 25 mg: -24.7 OCA 50 mg: -21.0 Placebo: -3.1 All OCA groups from baseline, p<0.0001	OCA 5-10 mg: -33.0 OCA 10 mg: -39.1 Placebo: -4.8 All OCA groups vs. placebo, p<0.0001

ITT = intent-to-treat; DB = double-blind; LTSE = long-term safety extension; ULN = upper limit of normal; UDCA = ursodeoxycholic acid; OCA = obeticholic acid; ALP = alkaline phosphatase

Table ES2. Proportion of Trial Patients Achieving the POISE Primary Endpoint[16]

% of Patients	Study 201, n=43	Study 202, n=76	Study 301, n=146	Pooled, n=306
Placebo	4	8	10	8
OCA 10 mg	40	42	47	45 (all OCA groups)
p-value	p=0.0026	p=0.0002	p<0.0001	p<0.0001

The average life years per patient treated with UDCA versus OCA plus UDCA were 19.97 and 22.23, respectively (increment = 2.26 years). The corresponding average discounted QALYs gained were 10.74 and 11.78, respectively (increment = 1.04 years). The average lifetime discounted cost per patient treated with UDCA was $142,300. Assuming that the price of OCA is $69,350/year, the average lifetime cost of a patient treated with OCA plus UDCA was $633,900 (an increment of $491,400). The incremental cost-effectiveness of OCA plus UDCA was approximately $473,400 per QALY gained (Table ES4).

Table ES4. Cost-effectiveness of OCA when the Annual Cost of OCA is $69,350 per Year

	UDCA*	OCA + UDCA
Undiscounted Life Years	19.97	22.23
Discounted QALYs	10.74	11.78
Discounted Total Cost ($)	142,300	633,900
ICER ($/QALY)		473,400

*Results correspond to inadequate response to UDCA, as observed in POISE study

Next we conducted a price threshold analysis to determine the price of OCA that would meet commonly cited thresholds for cost-effectiveness (Table ES5). We found that OCA would meet thresholds of $50,000, $100,000, and $150,000 per QALY gained if priced below $11,629, $18,445, and $25,261 per year, respectively.

Table ES5. OCA Price Threshold Analysis

Willingness to Pay ($/QALY)	Annual Price of OCA
$50,000	$11,629
$100,000	$18,445
$150,000	$25,261

NASH

FLINT.[2] MC, DB, PC, parallel group, RCT in the USA in non-cirrhotic, NASH randomized to obeticholic acid 25mg daily or placebo X72w, stratified by diabetes status. +concealed allocation. 1` outcome was improvement in centrally scored liver histology defined as a decrease in NAFLD activity score by ≥2 points w/o worsening in fibrosis from baseline to EOT.

Key Trials	Patient Characteristics	Treatment	Comparator	Harms
FLINT[14] **Phase II** **Double-blind RCT** **Multicenter** **ITT analysis**	Mean age: 52 Percent male: 34% Mean weight: ~98kg Hyperlipidemic: 62% Diabetic: 53% Vitamin E last 6 mos: 22% Antilipidemic last 6 mos: 48% Definite steatohepatitis: 80% Mean NAFLD score: 5.2	OCA 25 mg daily (n=141; ITT* n=110)	Placebo (n=142; ITT* n=109)	Pruritus: 23% vs. 6% (p<0.0001)
		Administered for 72 wks w/ 24 wks follow-up Primary outcome: ≥2 point decrease in centrally scored NAS w/o worsening fibrosis 72 wks (OCA 45% vs. PBO 21%) RR 1.9 (95% CI 1.3-2.8); p=0.0002 Secondary outcomes: -Mean change in NAS (-1.7 vs. -0.7) RR -0.9 (95% CI -1.3 to -0.5); p<0.0001 -Patients w/ improved fibrosis (35% vs. 19%) RR 1.8 (95% CI 1.1-2.7); p=0.004 -Resolution of NASH (22% vs. 13%) RR 1.5 (95% CI 0.9-2.6); p=0.08		
		-Mean change (baseline to 72 wks): ALT -38 AST -27 ALP -12 GGT -37 Total cholesterol 0.16 HDL -0.02 HOMA-IR 15 Weight (kg) -2.3	-Mean change (baseline to 72 wks): ALT -18 (p<0.001) AST -10 (p=0.0001) ALP -6 (p<0.0001) GGT -6 (p<0.0001) Total cholesterol -0.19 (p=0.0009) HDL 0.03 (p=0.01) HOMA-IR 4 (p=0.01) Weight (kg) 0.0 (p=0.008)	
NCT00501592 by Mudaliar et al.[15] **Phase II** **Double-blind RCT** **Multicenter**	Mean age: 52 Percent male: 53% Mean weight: ~106kg Diabetic: 100%	OCA 25 mg daily (n=20) or OCA 50 mg daily (n=21)	Placebo (n=23)	Any AEs (OCA 25 mg vs. 50 mg vs. PBO): 45% vs. 76% vs. 61% Treatment-related AEs: 5% vs. 38% vs. 26% Pruritus: 0 vs. 5% vs. 9%
		Administered for 6 wks Primary outcomes: -Percent change in low-dose glucose infusion rate (OCA 24.5 vs. PBO -5.5); p=0.011 -Percent change in high-dose glucose infusion rate (OCA 15.0 vs. PBO -5.4); p=0.025		
		Secondary outcomes: change in mean values 25 mg/50 mg AST -2/5 ALT -10/10 ALP 14/27 GGT -37/-22 Total cholesterol 18/13 HDL -2/-6 Weight 1/1.9	Secondary outcomes: change in mean values (p-value 25 mg/p-value 50 mg) AST 5 (0.12/0.73) ALT 11 (0.003/0.84) ALP 0 (0.003/<0.001) GGT 5 (<0.001/<0.001) Total cholesterol 8 (0.08/0.15) HDL 0 (0.42/0.01) Weight (0.096/0.008)	

ITT = intent-to-treat; DB = double-blind; LTSE = long-term safety extension; ULN = upper limit of normal; UDCA = ursodeoxycholic acid; OCA = obeticholic acid; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; GGT = gamma-glutamyl transferase; HDL = high-density lipoprotein; AEs = adverse events; HOMA-IR = Homeostasis model assessment of insulin resistance

*ITT population was defined in FLINT trial as those 219 patients who received both baseline and 72-week follow-up biopsies

Incremental Costs per Outcomes Achieved: Results

In comparison with placebo (i.e., usual care), treatment with OCA would decrease the 15-year cumulative incidence of decompensated cirrhosis from 10% to 8.8%, hepatocellular carcinoma from 4.7% to 4.2%, liver transplant from 0.9% to 0.8%, and liver-related deaths from 12.9% to 11.3%, respectively. In addition, treatment with OCA increased 15-year transplant-free survival from 68.6% to 69.9%. Compared with placebo, treating 10,000 patients using OCA could prevent 120 cases of decompensated cirrhosis, 50 cases of hepatocellular carcinoma, 10 liver transplants and 160 liver-related deaths.

The average (undiscounted) life years per patient in placebo versus OCA were 16.45 and 17.36 (increment = 0.91 years), respectively. The corresponding discounted QALYs were 10.91 and 11.02 (increment = 0.11 years), respectively. The average lifetime discounted cost per patient treated with placebo was $70,300. Using the wholesale acquisition cost of OCA of $69,350/year, average lifetime cost of patients in the OCA arm was $371,000 (increment of $300,700). The incremental cost-effectiveness ratio (ICER) of OCA was approximately $2.75 million per QALY gained (Table ES2).

Table ES2. Cost-Effectiveness of OCA When the Annual Cost of OCA is $69,350 per Year

	Placebo	OCA
Undiscounted Life Years	16.45	17.36
Discounted QALYs	10.91	11.02
Discounted Total Cost	$70,300	$371,000
ICER ($/QALY)		2,748,300

Next we conducted a price threshold analysis to determine the price of OCA that would meet commonly cited thresholds for cost-effectiveness (Table ES5). Using willingness-to-pay thresholds of $50,000, $100,000 and $150,000 per QALY gained, the maximum annual price of OCA was $2,654, $3,889, and $5,124, respectively (Table ES3).

Table ES3. OCA Price Threshold Analysis for NASH Patients

Willingness to Pay ($/QALY)	Annual Price of OCA
$50,000	$2,654
$100,000	$3,889
$150,000	$5,124

References:

1. Hirschfield, Gideon M., et al. "Efficacy of obeticholic acid in patients with primary biliary cirrhosis and inadequate response to ursodeoxycholic acid." *Gastroenterology* 148.4 (2015): 751-761.
2. Neuschwander-Tetri, Brent A., et al. "Farnesoid X nuclear receptor ligand obeticholic acid for non-cirrhotic, non-alcoholic steatohepatitis (FLINT): a multicentre, randomised, placebo-controlled trial."*The Lancet* 385.9972 (2015): 956-965.

Buprenorphine Subdermal Implant (Probuphine)
Jill Johnson, Pharm.D., BCPS
10/25/16

FDA approved for maintenance treatment of opioid dependence in patients who have achieved and sustained prolonged clinical stability on low-to-moderate doses of transmucosal (TM) buprenorphine-containing product (i.e., doses of ≤8mg/d of Subutex or Suboxone sublingual (SL) tablet or generic equivalent); should be part of a complete treatment program to include counseling and psychosocial support. Not appropriate for new entrants to treatment and patients who have not achieved and sustained prolonged clinical stability while being maintained on buprenorphine 8mg/d or less of Subutex or Suboxone SL or generic equivalent.

REMS program: all healthcare providers who intend to prescribe Probuphine must successfully complete a live training program.

Acceptable patients for Probuphine must meet ALL of:

1. achieved and sustained prolonged clinical stability of TM buprenorphine
2. are currently on a maintenance dose of 8mg/d or less of Subutex or Suboxone SL or equivalent; patients should not be tapered to a lower dose for the sole purpose of transitioning to Probuphine
3. Stable TM buprenorphine dose for ≥3 months w/o any need for supplemental dosing or adjustments

Examples of acceptable doses of TM buprenorphine include:

- Subutex (buprenorphine) SL tablet (generic equivalent) 8 mg or less
- Suboxone (buprenorphine and naloxone) SL tablet (generic equivalent) ≤8 mg/2 mg
- Bunavail (buprenorphine and naloxone) buccal film ≤4.2 mg/0.7 mg
- Zubsolv (buprenorphine and naloxone) SL tablets ≤5.7 mg/1.4 mg

Consider these factors in determining clinical stability and suitability for PROBUPHINE treatment:

- period free from illicit opioid drug use
- stability of living environment
- participation in a structured activity/job
- consistency in participation in recommended behavioral therapy/peer support program
- consistency in compliance with clinic visit requirements
- minimal to no desire or need to use illicit opioids
- period without episodes of hospitalizations (addiction or mental health issues), emergency room visits, or crisis interventions
- social support system

Prescription use is limited under the Drug Addiction Treatment Act:
4 implants are inserted subdermally in the upper arm for 6m of treatment and are removed by the end of the 6th month.

Each implant is a 26mm X 2.5mm implant containing 74.2mg of buprenorphine (equivalent to 80mg buprenorphine HCl).

Evidence:
From PI: One study compared Probuphine vs treatment as usual with SL buprenorphine. Those showing negative opiate usage at 6 months was 63% Probuphine vs 64% SL buprenorphine. 11 patients in the Probuphine arm required supplemental SL buprenorphine but had no evidence of other opioid use.

2 studies in patients who were new entrants to buprenorphine treatment suggested that Probuphine should NOT be used for new entrants who have not achieved and sustained prolonged clinical stability on low-mod doses of transmucosal buprenorphine-containing product because the dose appears to be too low to be effective in these populations.

Cost:

	Drug cost (AWP)	EBD Current coverage	Current # utilizers 2016Q2	Plan paid 2016Q2	Avg cost/day (AWP or MAC)	Proposed coverage
Probuphine*	$1485 **£$1000**				$8.16 **£$13.65**	
Buprenorphine SL		T1	16	$5389	$5(MAC)	
Buprenorphine-naloxone CL		T1	19	$12720	$13(MAC)	
Suboxone film		T2PA	58	$56102	$17	

*Office procedure to have implants placed and removed at 6 months will add to this cost.

£Assume $1000q6months.

References:

1. Probuphine website. http://probuphine.com/prescribing-info/ Accessed 10/25/16.

Nitisinone (Orfadin®) Suspension 4mg/mL (also available 2mg, 5mg 10mg capsules)
Geoffrey Fenich 07-25-2016, J Johnson10-26-2016

Background: Tyrosine metabolism disorders encompass 4 autosomal recessive disorders. Hereditary tyrosinemia type 1, aka hepatorenal tyrosinemia, is the most severe disorder of tyrosine metabolism; occurs in 1/12000 to 1/100,000 individuals of northern European descent. Hypertyrosinemia with the presence of liver disease leads to additional and urgent testing to detect HT type 1, a potentially lethal disorder characterized by severe progressive liver disease and renal tubular dysfunction. The latter typically is manifest as the Fanconi syncrome with renal tubular acidosis, aminoaciduria, and hypophosphatemia due to phosphate wasting. Rickets is often present.
Product Summary / Labeled Use: Adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of hereditary tyrosinemia type 1 (HT-1).

Comparator Drugs: No Comparators. Orphan drug.

Drug	**Cost**	**Monthly dose 25kg person**	**Monthly cost**
Orfadin sus 4mg/mL	217.97/mL, 90mL (WAC)	12.5mL/day; 375mL/30d	$81738.75
Orfadin 2mg cap	2mg #60, $5999.33	???	
Orfadin 5mg cap	5mg #60, $14998.22	???	
Orfadin 10mg cap	10mg #60, $29996.48	???	

1mg/kg/day divided into 2 daily doses.
Initial Dosing: 0.5 mg/kg BID. Increase to 0.75 mg/kg BID if succinylacetone is detectable 1 month after initiation. Further increase to 1 mg/kg BID may be needed based on the evaluation of all biochemical parameters (max dose: 2 mg/kg/day).
Mechanism of Action: Inhibits normal catabolism of tyrosine in patients with HT-1, thus, nitisinone prevents the accumulation of the catabolic intermediates maleylacetoacetate and fumarylacetoacetate. In patients with HT-1, these catabolic intermediates are converted to the toxic metabolites succinylacetone and succinylacetoacetate, which are responsible for the observed liver and kidney toxicity. Succinylacetone can also inhibit the porphyrin synthesis pathway leading to the accumulation of 5-aminolevulinate, a neurotoxin responsible for the porphyric crises characteristic of HT-1
Contraindications: NONE
Adverse Reactions: Most common adverse reactions (incidence >2%) are hepatic neoplasm, liver failure, thrombocytopenia, leucopenia, visual system complaints including conjunctivitis, corneal opacity, keratitis, and photophobia
Drug Interactions: Concurrent use with cyclophosamide may reduce cyclophosamide activity

Evidence:
Orfadin was studied in one open-label, uncontrolled study of 207 patients with HT-1, ages 0 to 21.7 years at enrollment (median age 9 months), who were diagnosed with HT-1 by the presence of succinylacetone in the urine or plasma. The starting dose of Orfadin was 0.6 to 1 mg/kg/day, and the dose was increased in some patients to 2 mg/kg/day based on weight, biochemical, and enzyme markers. Median duration of treatment was 22.2 months (range 0.1 to 80 months).

EVIDENCE:
In this clinical study, for patients presenting with HT-1 younger than 2 years of age who were treated with dietary restriction and nitisinone, the results are below:. (see table)

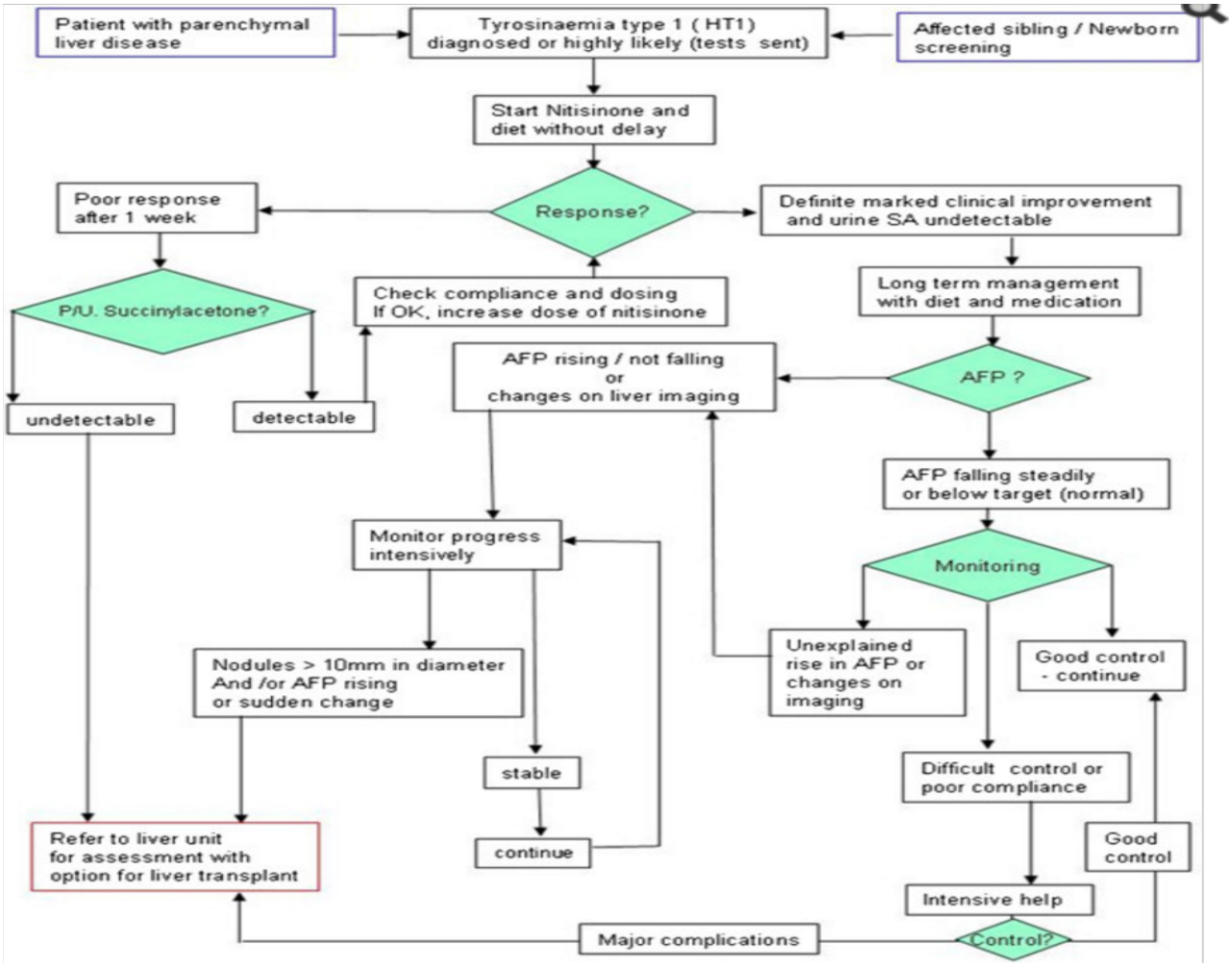
	2 & 4 year surv prob
Diet res & nitisinone, HT1, <2years old	88%, 88%
Diet res, historical controls	29%, 29%
Diet res, nitisinone, 2-6 months of age	94%, 94%

Diet res alone, historical controls	74%, 60%

The effects on urine and plasma succinylacetone, porphyrin metabolism, and urinary alpha-1-microglobulin were also assessed in this clinical study. Urine succinylacetone was measured in 186 patients. In all 186 patients, urinary succinylacetone level decreased to less than 1 mmol/mol creatinine. The median time to normalization was 0.3 months. The probability of recurrence of abnormal values of urine succinylacetone was 1% at a nitisinone concentration of 37 µmol/L (95% confidence interval: 23-51 µmol/L). Plasma succinylacetone was measured in 172 patients. In 150 patients (87%), plasma succinylacetone decreased to less than 0.1 µmol/L. The median time to normalization was 3.9 months. Porphyria-like crisis were reported in 3 patients (0.3% of cases per year) during the clinical study. This compares to an incidence of 5 to 20% of cases per year expected as part of the natural history of the disorder. An assessment of porphyria-like crises was performed because these events are commonly reported in patients with HT-1 who are not treated with nitisinone.

References:

1. Package Insert
2. Journal of Rare Disease 7/2016.
3.



Recommendation: Specialty tier, PA. Criteria: 1. Dx of hereditary tyrosinemia type 1 including the detection of succinylacetone in blood or urine above normal limits (healthy individuals have undetectable levels).

EBRx Outcome: Cover at specialty tier with a PA.

Hydroxyprogesterone Caproate IM in Oil 1.25g/5mL, generic; also brand Makena
Jill Johnson, Pharm.D., BCPS
10/26/16

FDA indication:
1. Preterm birth; to reduce the risk of preterm birth in women with a singleton pregnancy and who have a history of singleton spontaneous preterm birth. Use is not intended for women with multiple gestations or other risk factors for preterm birth.
2. in non-pregnant women: for the treatment of advanced adenocarcinoma of the uterine corpus (Stage III or IV);
3. in the management of amenorrhea (primary and secondary) and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as submucous fibroids or uterine cancer;
4. as a test for endogenous estrogen production and for the production of secretory endometrium and desquamation.

Products		AWP cost/unit (10/26/16)	Dose:	Cost	Current coverage	Proposed
Cost for Preterm birth; cost for maximum dosing of 22 doses						
Makena 250mg/mL	1mL 5mL	$873.54	IM 250mg QW; may begin between 16 weeks) days and 20 weeks 6 days; continue weekly until 37 weeks gestation or until delivery, whichever comes first	$19,217.88	Excluded; EBD policy called for having this product compounded	Exclude
Hydroxyprogesterone Caproate IM in oil 1.25g/5mL (250mg/mL)	5mL	$2310.69		$10167.04	New drug for consideration today	T3 PA
Hydroxyprogesterone caproate compounded product					Covered w/ $200 max under compounds	Exclude
Cost for Amenorrhea and/or abnormal uterine bleeding (Cyclic regimen); cost for maximum dosing for 4 cycles						
Makena 250mg/mL	1mL 5mL	$873.54	IM 375mg Qmonth X 4 cycles	$1310.31/dose X 4 doses=$5241.24	Excluded; EBD policy called for having this product compounded	Exclude
Hydroxyprogesterone Caproate IM in oil 1.25g/5mL	5mL	$2310.69		$693/dose X 4 doses=$2772	New drug for consideration today	T3 PA

(250mg/mL)						
Hydroxyprogesterone caproate compounded product					Covered w/ $200 max under compounds	Exclude
Cost for Adenocarcinoma or uterine corpus in advanced stage III or IV (Non-Cyclic regimen), dosed 1000mg or more, 1-7g per week, stopped when relapse occurs or after 12 weeks with no objective response						
Makena 250mg/mL	1mL 5mL	$873.54	7g/week or 28g/month	$24,459.12/month	Excluded; EBD policy called for having this product compounded	Exclude
Hydroxyprogesterone Caproate IM in oil 1.25g/5mL (250mg/mL)	5mL	$2310.69	7g/week or 28g/month	$13,864.14/month	New drug for consideration today	T3 PA
Hydroxyprogesterone caproate compounded product					Covered w/ $200 max under compounds	Exclude

Previously, EBD's policy called for having hydroxyprogesterone compounded for use. At the time, the FDA relaxed their enforcement of prohibiting compounding of a drug for which there is a commercially available product. On 7/11/16, the FDA revised their position on compounded drugs:

SUMMARY:

The Food and Drug Administration (FDA or the Agency) is announcing the availability of a draft guidance for industry entitled "Compounded Drug Products That Are Essentially Copies of a Commercially Available Drug Product Under Section 503A of the Federal Food, Drug, and Cosmetic Act." To qualify for exemptions under section 503A of the Federal Food, Drug, and Cosmetic Act (the FD&C Act), a drug product must be compounded by a licensed pharmacist or physician who does not compound regularly or in inordinate amounts any drug products that are essentially copies of a commercially available drug product. This guidance sets forth FDA policies regarding this provision of section 503A, including the terms "commercially available," "essentially a copy of a commercially available drug," and "regularly or in inordinate amounts."

References:

1. http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/PharmacyCompounding/ucm166743.htm
2. Lexicomp. Hydroxyprogesterone. Accessed 10/26/16.

EBRx Hepatitis C Coverage Policy
AASLD HCV Treatment Guidelines SUMMARY (accessed 9/13/16)
Jill Johnson, Pharm.D.
10/20/16

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

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

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

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

C. Likelihood of progressing without treatment

The premise for the policies below is multifactorial.

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

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

Drugs for HCV and current AWP costs before any rebates (10/20/16)

Brand	Components	Common dose	**FDA Approval**	**AWP Pricing (on 9/14/16)**	**12w AWP**	**16w**	**24w**
Zepatier	Elbasvir 50mg/grazoprevir 100mg	1 tablet daily	**Treatment with or w/o Riba for GT 1 or 4 in adults**	**$10,920 (#14) 50-100mg**	**$65,520**	**$87360**	
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	1 tablet daily	**Treatment with or w/o Riba for chronic HCV GT 1, 4, 5, or 6 infection**	**$37,800 (#28) 90-400mg**	**$113,400**		**$226,800**
Viekira Pak (company's website has only XR info)	Paritaprevir 150/ritonavir 100mg/ombitasvir 25mg, PLUS BID dasabuvir 250mg and wt-based Riba	**2 tabs daily plus dasabuvir 1 twice daily (comes in a pack)**	**Treatment of chronic HCV in adults,** • **GT 1b w/o cirrhosis or with compensated cirrhosis, or** • **GT 1a without cirrhosis or with compensated cirrhosis for use in combination with Riba**	**$33,327.60 (#112) 12.5-75-50 & 250mg**	**$99,982.80**		
Viekira XR 24hour	Ombitasvir 8.33mg/paritaprevir 50mg/ ritonavir 33.33 mg/ dasabuvir 200mg	3 tablets daily X 12w		**$33,327.60 (#84) 200-8.233-50-33.33**	**$99,982.80**		
Olysio+Sovaldi	Simeprevir 150mg/sofosbuvir 400mg	Olysio 1 tab once daily Sovaldi 1 tab once daily	**Treatment of chronic HCV in adults,** • **In combo w/ sofosbuvir in GT1 w/o cirrhosis or w/ compensated cirrhosis** • **In combo w/ PEG-IFN alfa and RBV in GT1 or 4 without cirrhosis or with compensated cirrhosis**	**Olysio $26,544.00 (#28)** **Sovaldi $33,600.00 (#28)**	**$180,432**		**$360,864**
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	1 tablet once daily	**Treatment of chronic HCV in adults, GT 1,2,3,4,5, or 6 without cirrhosis or with compensated cirrhosis or in combo w/ RBV in patients with decompensated cirrhosis**	**$29,904.00 (#28)**	**$89,712**		**$179,424**
Daklinza+Sovaldi	Daclatasvir 60mg/ sofosuvir 400mg	**Dak: 1 tablet daily** **Sov: 1 tablet daily**	**Treatment of chronic HCV in adults GT 1 or 3 for use with sofosbuvir; GT1a w/ cirrhosis should be tested for NS5A resistance-associated polymorphisms.**	**$25,200 (#28) Dak $33,600.00 (#28) Sov**	**$176,400**	**$264,600**	**$352,800**
Technivie	Paritaprevir 150/ritonavir 100mg/ombitasvir 25mg PLUS wt-based Riba	**2 tablets daily**	**Treatment of chronic HCV, GT4 without cirrhosis**	**$1,095.04 (#2)**	**$91983,36**		

INITIAL THERAPY

PM=polymorphism, TN=treatment naïve, SVR=sustained viral response, RAV=resistant-associated variant,

	Daily Drug Combination	Duration (w)	%SVR	Notes
	GT1a, TN, NO Cirrhosis			
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12		Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12		Class I, A
Viekira Pak	Paritaprevir 150/ritonavir 100mg/ombitasvir 25mg, PLUS BID dasabuvir 250mg and wt-based Riba	12		Class I, A
Olysio+Sovaldi	Simeprevir 150mg/sofosbuvir 400mg	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg/ sofosbuvir 400mg	12		Class I, B
	ALTERNATIVE			
Zepatier	Elbasvir 50mg/grazoprevir 100mg plus wt-based ribavirin	16		Class IIa, B, RAV+
	GT1a, TN, COMPENSATED Cirrhosis			
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12		Class I, A; RAV-
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
	ALTERNATIVE			
Viekira Pak	Paritaprevir 150mg/ ritonavir 100mg/ombitasvir 25mg + BID dasabuvir 250mg + wt-based Riba	24		Class I, A
Olysio+Sovaldi	Simeprevir 150mg PLUS sofosbuvir 400mg w/ or w/o Riba	24		Class II, Level B; no Q80K PM
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg w/ or w/o wt-based Riba	24		Class IIa, B
Zepatier	Elbasvir 50mg/grazoprevir 100mg PLUS wt-based ribavirin	16		Class IIa, B; RAV+
	GT1b, TN, NO Cirrhosis			
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12		Class I, A; RAV-
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12		Class I, A
Viekira Pak	Paritaprevir 150/ritonavir 100mg/ ombitasvir 25mg, PLUS BID dasabuvir 250mg	12		Class I, A
Olysio+Sovaldi	Simeprevir 150mg PLUS sofosbuvir 400mg	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg	12		Class I, A
	GT1b, TN, COMPENSATED Cirrhosis			
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12		Class I, A;
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12		Class I, A
Viekira Pak	Paritaprevir 150/ritonavir 100mg/ ombitasvir 25mg, PLUS BID dasabuvir 250mg	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
	ALTERNATIVE			
Daklinza+Sovaldi	Daclatasvir 60mg + sofosbuvir 400mg w/ or w/o wt-based Riba	24		Class IIa, B
Olysio+Sovaldi	Simeprevir 150mg + sofosbuvir 400mg w/ or w/o wt-based Riba	24		Class IIa, B

	Daily Drug Combination	Duration (w)	%SVR	Notes
	GT2, TN, NO Cirrhosis			
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
	ALTERNATIVE			
Daklinza+Sovaldi	Daclatasvir 60mg/sofosuvir 400mg	12		Class IIa, B
	GT2, TN, COMPENSATED Cirrhosis			
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
	ALTERNATIVE			
	Daclatasvir 60mg + sofosbuvir 400mg	16-24		Class IIa, B

	GT3, TN, NO Cirrhosis			
Daklinza+Sovaldi	Daclatasvir 60mg + sofosbuvir 400mg	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
	GT3, TN, COMPENSATED Cirrhosis			
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg w/ or w/o wt-based riba	24		Class IIa, B

	Daily Drug Combination	Duration (w)	%SVR	Notes
	GT4 TN, NO Cirrhosis			
Technivie	Paritaprevir 150/ritonavir 100mg/ombitasvir 25mg, PLUS wt-based Riba	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12		Class IIa, B
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12		Class IIa, B
	GT4, TN, COMPENSATED Cirrhosis			
Technivie	Paritaprevir 150/ritonavir 100mg/ombitasvir 25mg, PLUS wt-based Riba	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class IIa, B
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12		Class IIa, B
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12		Class I, A

	GT 5 or 6 with and without Cirrhosis			
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12		Class IIa, B

TREATMENT-EXPERIENCED

	Daily Drug Combination	Duration (w)	%SVR	Notes
	GT1a, PEG-IFN/Ribavirin TE, NO Cirrhosis			
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12		Class I, A, RAV-
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12		Class I, A
Viekira Pak	Paritaprevir 150/ritonavir 100mg/ombitasvir 25mg, PLUS BID dasabuvir 250mg and wt-based Riba	12		Class I, A
Olysio+Sovaldi	Simeprevir 150mg/sofosbuvir 400mg	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg/ sofosbuvir 400mg	12		Class I, B
	ALTERNATIVE			
Zepatier	Elbasvir 50mg/grazoprevir 100mg w/ Wt-based Ribav	16		Class IIa, B; NS5A RAV+
	GT1a, PEG-IFN/Ribavirin TE, COMPENSATED Cirrhosis			
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12		Class I, A; NS5A RAV-
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg PLUS wt-based Riba	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
	ALTERNATIVE			
Viekira Pak	Paritaprevir 150mg/ ritonavir 100mg/ombitasvir 25mg + BID dasabuvir 250mg +wt-based Riba	24		Class I, A
Harvoni	Ledipasvir 90mg/sofosbuvir 400mg	24		Class I, A
Zepatier	Elbasvir 50mg/grazoprevir 100mg PLUS wt-based ribavirin	16		Class IIa, B; RAV+
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg w/ or w/o wt-based Riba	24		Class IIa, B
Olysio+Sovaldi	Simeprevir 150mg PLUS sofosbuvir 400mg w/ or w/o Riba	24		Class II, Level B; no Q80K PM
	GT1b, PEG-IFN/Ribavirin TE, NO Cirrhosis			
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12		Class I, A; RAV-
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12		Class I, A
Viekira Pak	Paritaprevir 150/ritonavir 100mg/ ombitasvir 25mg, + BID dasabuvir 250mg	12		Class I, A
Olysio+Sovaldi	Simeprevir 150mg PLUS sofosbuvir 400mg	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg	12		Class I, A
	GT1b, PEG-IFN/Ribavirin TE, COMPENSATED Cirrhosis			
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12		Class I, A;
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12		Class I, A
Viekira Pak	Paritaprevir 150/ritonavir 100mg/ ombitasvir 25mg, +BID dasabuvir 250mg	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
	ALTERNATIVE			
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	24		Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg w/ or w/o wt-based Riba	24		Class IIa, B
Olysio+Sovaldi	Simeprevir 150mg PLUS sofosbuvir 400mg w/ or w/o wt-based Riba	24		Class IIa, B

	Daily Drug Combination	Duration (w)	%SVR	Notes
	GT1, Sofosbuvir/Ribavirin w/ or W/O PEG-IFN Treatment experienced; NO Cirrhosis			
Harvoni	Ledipasvir 90mg/sofosbuvir 400mg w/ Wt-based Ribavirin	12		Class IIa, B
	GT1, Sofosbuvir/Ribavirin w/ or W/O PEG-IFN Treatment experienced; COMPENSATED Cirrhosis			
Harvoni	Ledipasvir 90mg/sofosbuvir 400mg w/ Wt-based Ribavirin	24		Class IIa, B
	GT1 Nonstructural Protein 3 (NS3) Protease Inhibitor (teleprevir, boceprevir, or simeprevir) plus PEG-IFN/Ribavirin TE; NO Cirrhosis			
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg	12		Class I, A
Epclusa	Sofosbuvir 400mg /velpatasvir 100mg	12		Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg PLUS Sofosbuvir 400mg	12		Class IIa, B
Zepatier	Elbasvir 50mg/ grazoprevir 100mg w/ Wt-based Riba	12-16		Class IIa, B; GT1a w/ NS5A RAV+ for elbasvir should have 16w

	GT1 NS3 Protease Inhibitor (telaprevir, boceprevir, or simeprevir) Plus PEG-IFN/Ribavirin TE; COMPENSATED Cirrhosis			
Harvoni	Ledipasvir 90mg/ sofosbuvir 400mg + wt-based Riba	12		Class I, A
Harvoni	Ledipasvir 90mg/sofosbuvir 400mg	24		Class I, A
Epclusa	Sofosbuvir 400mg/ velpatasvir 100mg	12		Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg PLUS Sofosbuvir 400mg w/ or w/o Wt-based Ribavirin	24		Class IIa, B
Zepatier	Elbasvir 50mg/grazoprevir 100mg + wt-based Ribavirin	12		Class IIa, B; GT1a with NS5A RAV+ for elbasvir should have 16w
	GT1 Simeprevir PLUS Sofosbuvir TE			
	Deferral of treatment is recommended			Class IIb, C
	Testing for resistance-associated variants			Class II, C
	(SEE Guidelines); if drug therapy is used, AASLD recommends 24 w and use of ribavirin, unless contraindicated.			
	GT1 NS5A Inhibitor TE			
	Deferral of treatment in recommended			Class IIb, C
	Testing for resistance-associated variants			Class II, C
	(SEE Guidelines); if drug therapy is used, AASLD recommends 24 w and use of ribavirin, unless contraindicated.			

	Daily Drug Combination	Duration (w)	%SVR	Notes
	GT2 PEG-IFN/Ribavirin TE without Cirrhosis			
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
	ALTERNATIVE			
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg	12		Class IIa, B
	GT2 PEG-IFN/Ribavirin TE; COMPENSATED Cirrhosis			
Epclusa	Sofosbuvir 400mg/velpatasvir 10mg	12		Class I, A
	ALTERNATIVE			
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg	16-24		Class IIa, B
	GT2 Sofosbuvir PLUS Riba TE (regardless of cirrhosis status)			
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg w/ or w/o wt-based ribavirin	24		Class IIa, C
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg w/ wt-based riba	12		Class IIa, C

	Daily Drug Combination	Duration (w)	%SVR	Notes
	GT3 PEG-IFN/Ribavirin TE without Cirrhosis			
Daklinza+Sovaldi	Daclatasvir 60mg PLUS sofosbuvir 400mg	12		Class I ,A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
	GT3 PEG-IFN/Ribavirin TE; COMPENSATED Cirrhosis			
Epclusa	Sofosbuvir 400mg/velpatasvir 10mg	12		Class I, B
Daklinza+Sovaldi	Daclatasvir 60mg + sofosbuvir 400mg	16-24		Class IIa, B
	GT3 Sofosbuvir PLUS Riba TE (regardless of cirrhosis status)			
Daklinza+Sovaldi	Daclatasvir 60mg + sofosbuvir 400mg + wt-based ribavirin	24		Class IIa, C
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg + wt-based riba	12		Class IIa, C

	Daily Drug Combination	Duration (w)	%SVR	Notes
	GT4 PEG-IFN/Ribavirin TE without Cirrhosis			
Technivie	Paritaprevir 150/ritonavir 100mg/ ombitasvir 25mg + wt-based riba	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12		Class IIa, B
Harvoni	Ledipasvir 90mg/sofosbuvir 400mg	12		Class IIa, B

	GT4 PEG-IFN/Ribavirin TE; COMPENSATED Cirrhosis			
Technivie	Paritaprevir 150mg/ritonavir 100mg/ombitasvir 25mg + wt-based Ribavirin	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 10mg	12		Class I, A
Zepatier	Elbasvir 50mg/grazoprevir 100mg	12		Class IIa, B; for GT4 who experienced virologic relapse after prior PEG-IFN/riba. GT4 with prior on-treatment virologic failure while on PegIFN/Riba should have 16w and have ribavirin added.
Harvoni	Ledipasvir 90mg/sofosbuvir 400mg + wt-based ribavirin	12		Class IIa, B
	ALTERNATIVE			
Harvoni	Ledipasivr 90mg/sofosbuvir 400mg	24		Class IIa, B

	Daily Drug Combination	Duration (w)	%SVR	Notes
	GT5 or 6 PEG-IFN/Ribavirin TE without or without Cirrhosis			
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg	12		Class I, A
Harvoni	Ledipasvir 90mg/sofosbuvir 400mg	12		Class IIa, C

NOT RECOMMENDED:

In pregnancy, or in women unable or unwilling to use adequate contraception including those who are receiving ribavirin themselves or are sexual partners of males receiving ribavirin. **Female patients who have received ribavirin and sexual partners of male patients who have received ribavirin should NOT become pregnant for at least 6 months after stopping ribavirin.**	**Ribavirin.**
Decompensated Cirrhosis (moderate or severe hepatic impairment; Child Pugh Class B or c)	**SImeprevir-based regimens, paritaprevir-based regimens, elbasvir/grazoprevir-based regimens**
Allograft, including compensated cirrhosis	**Elbasvir/grazoprevir-based regimens**
Allograft, decompensated cirrhosis	**Simeprevir-based regimens, paritaprevir/ritonavir/ombitasvir w/ or w/o dasabuvir or ribavirin, elbasvir/grazoprevir-based regimens.**

DECOMPENSATED CIRRHOSIS: (NOT COVERED UNLESS ON THE LIVER TRANSPLANT LIST)

Because many decompensated cirrhosis patients experienced improvement in clinical and biochemical indicators of liver disease between baseline and post-treatmetn week 12 including CP class C cirrhosis, using the drugs may help. **AASLD states that death and need for liver transplant were observed in the trials highlighting that not everyone benefits from therapy.** The predictors of improvement or decline have not been clearly identified.

	Daily Drug Combination	Duration (w)	%SVR	Notes
	GT 1 or 4, DECOMPENSATED Cirrhosis			
Harvoni	Ledipasvir 90/sofosbuvir 400mg + low-dose riba 600mg	12		Class I, A
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg + wt-based riba	12		Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg + sofosbuvir 400mg+ low dose riba 600mg	12		Class I, B
	GT 1 or 4, DECOMPENSATED Cirrhosis, Ribavirin ineligible:			
Epclusa	Sofosbuvir 400mg/velpatasvir 400mg	24		Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg plus sofosvubir 400mg	24		Class Ii, C
Harvoni	Ledipasvir 90mg/sofosbuvir 400mg	24		Class II, C
	GT 1 or 4, DECOMPENSATED Cirrhosis, failed prior sofosbuvir-based therapy			
Harvoni	Ledipasvir 90mg/sofosbuvir 400 and ribavirin 600mg	24		Class II, C
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg + wt-based ribavirin	24		Class II, C; also for other NS5A-based failures
	GT 2 or 3, DECOMPENSATED Cirrhosis (CP class B or C and who may or may NOT be liver transplant candidates, including those with HCC			
Epclusa	Sofosbuvir 400mg/velpatasvir 100mg + wt-based riba	12		Class I, A
Daklinza+Sovaldi	Daclatasvir 60mg + sofosbuvir 400mg + low dose riba 600mg	12		Class II, B

Alex Lomax 08/09/2016, JJ 9/21/16

Daclizumab (Zinbryta) 150mg/mL (1mL prefilled syringe for SC inj.)

Indication: Relapsing Multiple Sclerosis

Black Box Warnings: 1) Hepatotoxicity including autoimmune hepatitis. 2) Immune-mediated disorders such as skin reactions, lymphadenopathy, and noninfectious colitis 3) Some patients required systemic corticosteroids or other immunosuppressant treatment for autoimmune hepatitis or other immune-mediated disorders and continued this treatment after the last dose of daclizumab. 4) REMS Program: available only through a restricted program under REMS called the ZINBRYTA REMS Program (risks of hepatic injury, including autoimmune hepatitis, and other immune-mediated disorders)

Drug	Strength	Dosing	AWP Cost (per Month) 8/18/2016	Monitoring
Zinbryta (daclizumab)	150 mg SQ	150 mg QMo	$8200 ($8200)	**Monthly AST/ALT**
Avonex (Interferon beta-1a)	30 mcg/0.5 ml IM inj	30 mcg QW	Pen IM -30 mcg/0.5 mL (1): $6985.20 ($27940.80) IM -30 mcg (1): $1746.30 ($6985.20) Prefilled IM - 30 mcg/0.5 mL (1): $6985.20 ($27940.80)	6 month intervals

Evidence: Clinical Trial Information: The efficacy of ZINBRYTA was demonstrated in two R, DB, controlled studies (Study 1 and Study 2). Both studies evaluated 150 mg of SC daclizumab taken qM in patients w/relapsing MS (RMS).

Kappos, Ludwig, et al. "Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis." New England Journal of Medicine 373.15 (2015): 1418-1428.

Kappos, et al, compared daclizumab to 30 mcg QW IM AVONEX in 1841 patients up to 144 weeks until the last enrolled patient completed 96 weeks of treatment. Clinical assessments were to occur q12w and after relapse events. 1` endpt was the annualized relapse rate (ARR). In Study 1, randomization assigned 919 patients to Daclizumab and 922 patients to AVONEX; 71% of Daclizumab - and 70% of AVONEX-treated patients completed at least 96 weeks of treatment with the assigned drug. Daclizumab had a significant effect on the ARR and on the number of new or newly enlarging T2 hyperintense lesions on MRI scans at Week 24 and Week 96. There was no significant effect on 12-week confirmed disability progression.

Clinical and MRI Results of Study 1	**Daclizumab** 150 mg SQ Every 4 Weeks N=919	**AVONEX** 30 mcg IM Once Weekly N=922	**p-value**
Clinical Results Values refer to results up to144 weeks			
Annualized relapse rate	0.216	0.393	<0.0001
Relative reduction	45%		
Proportion Relapse Free	67%	51%	
MRI Results MRI analysis used evaluable dataset and values reflect results at 96 weeks			
Mean number of new or newly enlarging T2 hyperintense lesions	4.31	9.44	<0.0001
Relative reduction	54%		

Table 2: Adverse Events

Adverse Event	Avonex	Daclizumab
Any event	842 (91)	838 (91)
Any event, excluding multiple sclerosis relapse	816 (89)	823 (90)
Serious adverse event		
Any event	194 (21)	221 (24)
Any event, excluding multiple sclerosis relapse	**88 (10)**	**142 (15)**
Treatment discontinuation		
Due to adverse event	112 (12)	142 (15)
Due to adverse event, excluding MS relapse	**84 (9)**	**131 (14)**
Adverse events of special interest		
Infection	523 (57)	595 (65)
Cutaneous event	176 (19)	344 (37)

Hepatic laboratory abnormality		
ALT or AST ≥3× ULN	80 (9)	96 (10)
ALT or AST >5× ULN	31 (3)	59 (6)
ALT or AST ≥3× ULN and total bilirubin >2× ULN	1(<1)	7(1)

Results: Among patients with RMS, daclizumab showed efficacy superior to that of Avonex with regard to the ARR and lesions, as assessed by means of MRI, but was not with disability progression at 12 weeks. The rates of infection, rash, and abnormalities on liver-function testing were higher with daclizumab.

Study 2 compared Daclizumab to placebo in 412 patients. Treatment duration was 52 weeks. Clinical assessments occurred every 12 weeks and after relapse events. MRI scans at weeks 24, 36, and 52 in all patients and every 4 weeks in a subset of patients. The primary outcome measure was the ARR at Week 52. In Study 2, randomization assigned 208 patients to receive Daclizumab and 204 patients to receive placebo; 91% of Daclizumab patients and 91% of placebo patients completed treatment. Daclizumab had a significant effect on the ARR, the proportion of patients relapse free, the number of new T1 Gd-enhancing lesions, and new or newly enlarging T2 hyperintense lesions.

Clinical and MRI Results of Study 2	**Daclizumab 150 mg SQ Every 4 Weeks N=208**	**Placebo N=204**	**p-value**
Clinical Results Values refer to results at 52 weeks			
Annualized relapse rate	0.211	0.458	<0.0001
Relative reduction	54%		
Proportion Relapse Free	81%	64%	
Proportion with 12-week confirmed disability progression[3]	6%	13%	
Relative risk reduction	57%		
MRI Results MRI analyses used evaluable dataset for each endpoint; T1 Gd-enhancing: MRI intensive population, between 8-24 weeks			
Mean number of new or newly enlarging T2 hyperintense lesions	2.4	8.1	<0.0001
Relative reduction	70%		
Mean number of new T1 Gd-enhancing lesions	1.46	4.79	<0.0001
Relative reduction	69%		

3 The proportion of patients with 12-week confirmed disability progression was an exploratory measure in Study 2. As the proportion of patients with 12-week confirmed disability was used as a key secondary outcome in Study 1, and is one of the main outcome measures in MS studies, the disability progression results are presented for Study 2. The nominal p value for that comparison, p=0.02, is not adjusted for multiple comparisons.

Results: SQ daclizumab administered every 4 weeks led to clinically important effects on RMS disease activity during 1 year of treatment. Findings support the potential for daclizumab to offer an additional treatment option for RMS.

The findings of these trials are promising, suggesting that daclizumab reduces disability progression compared with placebo or Avonex in patients with RMS. However, the risk of serious adverse events, makes it a second- or third-line agent for patients who have had an inadequate response to 2 or more disease-modifying agents for RMS.

Recommendation: Cover with PA, allowing patients Daclizumab after failing 2 previous relapsing therapies, and enrollment in REMS program.

References: Zinbryta Prescription Guide

1. Kappos, Ludwig, et al. "Daclizumab HYP versus interferon beta-1a in relapsing multiple sclerosis." New England Journal of Medicine 373.15 (2015): 1418-1428.

2. Gold, Ralf, et al. "Daclizumab high-yield process in relapsing-remitting multiple sclerosis (SELECT): a randomized, double-blind, placebo-controlled trial." The Lancet 381.9884 (2013): 2167-2175.

Outcome from EBRx meeting: Tabled; **Re-addressed on 9/27/16 and excluded the drug. It was compared to Avonex which was shown in a Cochrane Systematic Review and in the MS DERP report to be inferior to Rebif, Betaseron, Copaxone, and Glatiramer. It is unknown how daclizumab compares to any of these. The FDA considers it 3rd line, has placed a REMS program on it, and has 3 other boxed warnings including hepatotoxicity including autoimmune hepatitis, other immune-mediated disorders (skin, colitis), and corticosteroid requirements.**