Pharmacy & Therapeutics Committee Meeting
Private Dining Room
August 8, 2019 7:00 a.m.

Agenda Items	Individual Responsible
1. Call to Order	Nathan Schatzman, MD
2. Conflict of Interest Disclosure	Rachel Kile, PharmD
3. Approval of May 2019 Minutes	Nathan Schatzman, MD

Next Meeting will be October 10th, at 7:00 AM in the Private Dining Room

PHARMACY AND THERAPEUTICS COMMITTEE

DATE: May 16, 2019 CALLED TO ORDER: 7:00 A.M.
LOCATION: Private Dining Room ADJOURNED: 8:00 A.M.

Members Present:		**Members Absent**:		**Guests**:
Nathan Schatzman, M.D David Dodson, M.D. Mark Anderson, MD Richard Yap, M.D. Nathan Chamberlain, M.D Chad Paxson, MD	Patrick Ellis, PharmD Rachel Kile, PharmD Linda Johnson, PharmD Melissa Roden, RN Susan Fuchs, RD	Nan Payne, RN Shannon Harris, RN Michael Stipanov, M.D. Rodney Elliott Scott Harbaugh, Finance Jeffrey Mullins, M.D Jamie Barrie, PharmD Allen Atchley, M.D. Avni Kapadia, M.D F. Lee Hamilton, M.D.	Elvira Smith, RN Petra Green, RN Rhonda Polson, CNO	Nisha Patel, Resident Courtney Pearson, Resident Megan Nesbitt, Resident

This meeting will be convened under the protection of the Tennessee Statute 63-6-219 and the Health Care Quality Improvement Act of 1986, Public Law 99-660. All information, case reviews, meeting minutes, statistics and correspondence are confidential and protected. Included in that protection are those that are involved in the review of the information. Any discussion of this information outside the realm of Peer Review constitutes a breach and violates the protection of the persons involved in the breach.

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
Minutes	The February 2019 minutes were approved as submitted.	Approved	Complete
CHI P&T Committee	**CHI P&T Committee March Decision Brief**: The full decision brief was not included in the P&T packet as all new system formulary medications or formulary changes were either consistent with existing Memorial formulary decisions or are described in the "Therapeutic Interchanges and Formulary Changes" section of the minutes below. The miscellaneous medication review listed below is part of the ongoing system P&T review completed for the intent of national formulary standardization opportunities across the entire CHI system. *Sacubitril/valsartan (Entresto)*- Rachel reviewed the updated usage restriction criteria which also removes previous prescriber restrictions (no longer restricted to cardiology only).	Information Approved	Complete Complete
Therapeutic Interchanges and Formulary Decisions	**1. Drug Class Reviews –** The below medications and classes represent formulary variances from the current CHI Memorial formulary. Rachel reviewed the below proposed formulary modifications as noted below. **a. Ophthalmic anti-infectives class**: The following ophthalmic agents were recommended for non-formulary status per system review: bacitracin ointment, Pred G ointment or suspension, gentamicin ointment, and neomycin/polymixin B/hydrocortisone suspension. A therapeutic interchange table was presented. **b. Miscellaneous agents:** The following medications were recommended for non-formulary status per system review. Each of the medications are low use and it was recommended to designate each "non-formulary", with details as listed below. i. Chlorpheniramine 4 mg tablet ii. Hemocyte Plus capsule: Interchange to: Multivitamin 1 tablet + ferrous sulfate 300 mg tablet iii. The following will be non-formulary but use of patient's own supply, if admitted	Approved Approved	Complete Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	on this as a home regimen, will be allowed: 1. Piroxicam 10 mg capsule 2. Cabergoline 0.5 mg tablet 3. Trimethobenzamide 300 mg capsule 4. Oxandrolone 2.5 mg tablet 5. Tolnaftate 15 gm cream		
	2. Vabomere® / Avycaz® Formulary Interchange – Vabomere (meropenem/vaborbactam) is an IV anti-infective agent for the treatment of multidrug resistant (MDR) gram-negative bacteria (GNB). Published literature demonstrates improved outcomes compared to best available therapy, including Avycaz, and it is more cost-effective. It was recommended to replace Avycaz with Vabomere as the formulary agent for MDR GNB, restricted to infectious disease service and in patients who meet specific clinical criteria. Vabomere will be dose-adjusted per pharmacist renal dose adjustment protocol.	Approved	Complete
	3. Andexanet alfa (Andexxa®) Xa reversal agent – Rachel shared the March CHI System P&T committee decision to designate andexanet alfa as "non-formulary: do not stock" system-wide, along with reasoning which included the lack of availability of anti-Xa specific lab testing to confirm use of a DOAC prior to administration. Our committee discussed the available alternative, PCC at 50 units/kg, for DOAC-associated major bleeding as discussed at the February P&T meeting. The recommendation was to continue utilizing PCC in light of the system decision and data supporting PCC use for this indication.	Information	Complete
	4. N-acetylcysteine capsule Formulary Removal – Rachel presented a literature review of recently published randomized controlled studies that concluded n-acetylcysteine does not prevent contrast-induced nephropathy. CHI System P&T will also be removing this agent from formulary. Given this data, paired with low local utilization of the agent, the committee supported formulary removal of n-acetylcysteine capsules for contrast-induced nephropathy. This does not impact acetylcysteine for treatment of acetaminophen toxicity.	Approved	Complete
	5. Panhematin Restriction Criteria – Due to the high cost of Panhematin (hemin), an agent for the treatment of acute intermittent porphyria attacks, restriction criteria was proposed in order to ensure appropriate and cost-effective utilization. The committee approved the following criteria: **a.** Treatment of mild, moderate, or severe attacks of AIP in patients with established AIP i. Repeat urinary PBG test is recommended for confirmation of an acute AIP attack **b.** Treatment of suspected AIP with appropriate diagnostic lab tests collected at presentation of attack: i. Elevated urinary PBG concentration ii. Elevated total urinary porphyrin level **c.** Treatment with Panhematin (hemin) should not be delayed while awaiting laboratory results	Approved	Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
Medication Use Evaluation	1. **Alternatives to Opioids (ALTO) –** Rachel reviewed our ALTO emergency department (ED) data and our Tennessee Hospital Association reportable data through December 2018. Given the sustained success of decreased opioid prescribing in the ED, the committee followed with a lengthy discussion about expanding the use of this protocol for inpatients admitted to the hospital. Regarding the two medications that would require the most RN education, lidocaine and ketamine infusions, it was recommended to consider a slow implementation with one at a time. It was also recommended to limit the initial implementation to only a portion of nursing units. Rachel will schedule a meeting with a small group of hospitalists to discuss and outline steps for implementation.	Follow-up discussion/progress update at next meeting.	Pending
Medication Safety	1. **ADR Summary (September 2018-December 2018) –** Rachel briefly reviewed the adverse drug reaction summary and no new trends were observed. Eighteen percent of ADRs were related to opioids and the percentage is anticipated to decrease with the implementation of Epic which will bring the elimination of range orders for doses. Two category 3 ADRs will be reported to the FDA MedWatch program.	Information	Complete
	2. **ISMP 2018-2019 Best Practice - Injectable promethazine –** The ISMP Best Practice 13 "Eliminate injectable promethazine from the hospital" was reviewed with the committee. The committee discussed the difficulty in removing injectable promethazine entirely from formulary. Promethazine is currently second or last line treatment for nausea/vomiting on existing order sets and the dose is limited to 12.5 mg maximum per dose. Suggestions were made to consider further dose limitations (e.g. 6.25 mg maximum dose), but any changes would be made post Epic implementation. It was the committee recommendation to contact nursing educators and IV team leadership to discuss the potential for underreporting of tissue injury due to promethazine at our institution, as this is not a known issue currently.	Follow-up discussion at a future meeting.	Pending
Protocols & Orders	1. **IV Lidocaine (continuous infusion for pain) –** Rachel presented the updated Epic system ordering panel for lidocaine infusion for post-operative pain control, including contraindications, baseline monitoring/labs, nursing assessment/monitoring, and medication ordering options which reflected changes discussed during the last P&T meeting. The committee requested further clarification from cardiology on the "heart block" and "heart failure" contraindications, in addition to ongoing cardiac monitoring during the infusion. It was proposed to limit initial utilization to a subset of spinal patients in the ICUs, however Dr. Schatzman will speak with orthopedics to determine if 3 South should also be included. Rachel will follow up with Drs, Schatzman, Atchley, and Ramjee for clarifications to the panel in order to move forward with the Epic build on schedule.	Approved	Complete
	2. **Alcohol Withdrawal – BZD "light" Protocol Update –** Megan Nesbitt, PGY1 pharmacy resident, presented the results of our data collection from the utilization of this protocol for treatment of mild to moderate alcohol withdrawal syndrome (AWS) or in patients at risk of developing AWS (Feb-May 2019), compared to our traditional alcohol withdrawal protocol (July-Dec 2018). Use of our benzodiazepine (BZD) sparing protocol has demonstrated success compared to the traditional protocol with the following results: lower average daily doses of lorazepam, lower daily CIWA scores, significantly less documentation of lethargy/sedation, and no escalations of care to ICU. The BZD sparing alcohol withdrawal protocol will be built in Epic.	Approved	Complete
	3. **Antibiotic Dosing in Obesity –** Linda Johnson presented proposed dosing regimen changes to the existing pharmacist dose-adjustment protocol for piperacillin/tazobactam and cefepime in patients with obesity, per antimicrobial stewardship committee recommendations. The recommendations are		

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	based on recent pharmacokinetic/pharmacodynamics studies which show that our current dosing regimens may be inadequate to rapidly hit pharmacodynamic targets in this patient population. The committee approved the dosing changes as below, which will begin following the implementation of Epic: **a.** Piperacillin/tazobactam 4.5 gm IV x1 loading dose for all patients, followed by a BMI dosing strategy: i. BMI <30: 3.375 gm IV q8 hrs (4 hr infusion) ii. BMI ≥30: 4.5 gm IV q8 hrs (4 hr infusion) **b.** Cefepime 2 gm IV q8 hrs initial dose in critically ill patients with a BMI ≥30 **c.** Piperacillin/tazobactam and cefepime BMI dosing will continue to be dose-adjusted per pharmacist renal dose adjustment protocol.		
Policy	**1. Look Alike, Sound Alike Medications –** Patrick reviewed the updated list of medications on the look alike/sound alike drug list.	Approved	Complete
	2. Insulin U-500 Administration – Pharmacy will now dispense insulin U-500 pens instead of vials per ISMP recommendation. Use of the pen device requires the total dose of insulin to be rounded to the nearest 5 units. The policy was updated to reflect these changes. The committee was supportive of this requirement which allows for the safer pen device use of U-500 insulin.	Approved	Complete
	3. IV Push – Medication Administration & Monitoring – Based on ISMP survey results which suggest action is needed to improve safety with adult IV push medications, CHI requires the development of a local, institutional policy for IV push administration. The following procedures were added to the existing medication administration and monitoring policy and was approved by the committee: a. Licensed, independent providers (e.g. physicians, nurse anesthetists, and others) may reconstitute and administer IV push medications, including the modification of administration rate minimums where appropriate b. Nurses shall only reconstitute (adding sterile diluent to a lyophilized powder) IV push medications, when one of the following occur: i. There is an emergent need for reconstitution. ii. A kit is provided that includes the diluent, vial and instructions. The instructions will be provided via the eMAR, medication label, and/or Pyxis alert.	Approved Approved	Complete Complete
	4. Range Orders for Medications – Patrick reviewed the proposed revisions to the range orders for medications policy. Dose range orders are not allowed and will not be accepted in electronic provider order entry systems or as handwritten orders. Any dose range orders must be clarified with the ordering provider. The exceptions are titratable drips and insulin orders (sliding scale, etc.) based on objective clinical findings as outlined in the order. The committee approved these policy updates.	Approved	Complete
	5. Anticoagulation Management – The Joint Commission National Patient Safety Goal (NPSG) for anticoagulant therapy will include eight new required elements effective July 1, 2019. To ensure compliance with this NPSG with regards to direct oral anticoagulant (DOAC) therapy, our anticoagulation management policy will be updated to include DOACs within approved protocols for the initiation and maintenance of anticoagulation therapy appropriate to the medication used, to the condition being treated, and to the potential for medication interactions; to define required baseline and ongoing laboratory testing for DOACs; and include DOACs within educational requirements.	Approved	Complete

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	Our existing guidelines for reversal of anticoagulation for bleeding events & perioperative management were also added to the policy. The committee approved the above policy additions.		
	6. Angiotensin II (Giapreza®) – Patrick reviewed the recommended updates to the existing titration parameters for Giapreza (angiotensin II), which provide specific titration guidance for ICU nursing.	Approved	Complete
	7. Therapeutic Duplication Policy – Policy content was reviewed and approved with no changes.	Approved	Complete

There being no further business, the meeting was adjourned at 8:00 A.M. The next P&T meeting is **August 8th at 7:00 a.m.**

Respectfully submitted,

Patrick Ellis, PharmD Director of Pharmacy
Rachel Kile, Pharm.D Pharmacy Clinical Manager

Approved by,

Nathan Schatzman, MD Chairman

CHI SYSTEM PHARMACY AND THERAPEUTICS COMMITTEE DECISION BRIEF

May 2019 Decisions

NOTE: Markets may implement more restrictive formulary statuses.

Medication Name	Medication Used For	Decision			Comments/Restrictions/Therapeutic Interchange	Timeline to Implementation
		Formulary, Unrestricted	Formulary, Restricted	NonFormulary		
Aristada	*Psychiatric Disorders*	ARIPIPRAZOLE LAUROXIL INTRAMUSC SUSER SY (ARISTADA)				60 days from 5/21/2019
			ARIPIPRAZOLE LAUROXIL ER INTRAMUSC SUSER SY (ARISTADA INITIO)		Restricted to Psychiatry for new starts in adult patients with schizophrenia or bipolar disorder	
Brexaolone	*Post-partum depression*			Brexaolone (Zulresso)		60 days from 5/21/2019
Lipiodol	*Interventional radiology*		Ethiodized Oil (Lipiodol)		1. Use by interventional radiology 2. If used for transarterial chemoembolization (TACE) appropriate closed system transfer device must be used, and precautions taken to mitigate the risk of hazardous medication exposure.	60 days from 5/21/2019
Hemin	*Porphyria*		HEMIN INTRAVEN VIAL 313MG (PANHEMAT ASD)		Restrictions: • Treatment of mild, moderate, or severe attacks of Acute intermittent porphyria (AIP) in patients with established o Repeat urinary porphobilinogen (PBG) test is recommended for confirmation of an acute AIP attack • Treatment of suspected AIP with appropriate diagnostic lab tests collected at presentation of attack: 1. Elevated urinary PBG concentration 2. Elevated total urinary porphyrin level	90 days from 5/21/2019

Medication Name	Medication Used For	Decision			Comments/Restrictions/Therapeutic Interchange	Timeline to Implementation
		Formulary, Unrestricted	Formulary, Restricted	NonFormulary		
			HEMIN INTRAVEN VIAL 350 MG (PANHEMATI ASD)		Restrictions: • Treatment of mild, moderate, or severe attacks of Acute intermittent porphyria (AIP) in patients with established o Repeat urinary porphobilinogen (PBG) test is recommended for confirmation of an acute AIP attack • Treatment of suspected AIP with appropriate diagnostic lab tests collected at presentation of attack: 1. Elevated urinary PBG concentration 2. Elevated total urinary porphyrin level	
Zilretta	*Knee pain*			TRIAMCINOLONE ACETONIDE INTRAARTIC SUSER (ZILRETTA ASD)		60 days from 5/21/2019
Libtayo	*Squamous cell carcinoma*		CEMIPLIMAB-RWLC INTRAVEN VIAL 350 MG/7ML (LIBTAYO ASD)		Outpatient setting for FDA-approved indications or payer-approved off-label subsequent to insurance approval or prior authorization.	90 days from 5/21/2019
Mvasi	*Various carcinomas*		bevacizumab-awwb (Mvasi)		Outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization	90 days from 5/21/2019
Ogivri	*Breast cancer*			trastuzumab and hyaluronidase-oysk (Herceptin Hyleta)		90 days from 5/21/2019
			trastuzumab-dkst (Ogivri)		Outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization	
Angioedema Treatments	*Angioedema*	C1 ESTERASE INHIBITOR INTRAVEN KIT 500(1 (BERINERT ASD)				120 days from 5/21/2019

Medication Name	Medication Used For	Decision			Comments/Restrictions/Therapeutic Interchange	Timeline to Implementation
		Formulary, Unrestricted	Formulary, Restricted	NonFormulary		
				C1 esterase inhibitor, recombinant (Ruconest)		
				ECALLANTIDE SUBCUT VIAL 10MG/ML(1) (KALBITOR ASD)		
				ICATIBANT ACETATE SUB-Q SYRINGE 30 MG/3 (FIRAZYR DS)		
			C1 esterase inhibitor, human (Cinryze)		Outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization	
Bisphosphonates (Bone resorption inhibitors)	*Bone disorders*		ALENDRONATE SODIUM ORAL SOLUTION 70 MG/7 (ALENDRONATE)		• Long-term care patients continuing home therapy • Patients with Paget's disease • Outpatient setting for FDA-approved indications or payer-approved off-label subsequent to insurance approval or prior authorization.	90 days from 5/21/2019
			ALENDRONATE SODIUM ORAL TABLET 10 MG (ALENDRONATE)		• Long-term care patients continuing home therapy • Patients with Paget's disease • Outpatient setting for FDA-approved indications or payer-approved off-label subsequent to insurance approval or prior authorization.	
			ALENDRONATE SODIUM ORAL TABLET 35 MG (ALENDRON SOD)		• Long-term care patients continuing home therapy • Patients with Paget's disease • Outpatient setting for FDA-approved indications or payer-approved off-label subsequent to insurance approval or prior authorization.	

CHI SYSTEM PHARMACY AND THERAPEUTICS COMMITTEE DECISION BRIEF

July 2019 Decisions

NOTE: Markets may implement more restrictive formulary statuses.

Medication Name	Medication Used For	Decision			Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary		
Lokelma	*Hyperkalemia*	Sodium Polystyrene Sulfonate (SPS, Kayexelate)	Sodium zirconium cyclosilicate (Lokelma)	Patiromer (Veltassa)	**Lokelma restrictions:** 1. Management of severe hyperkalemia (K ≥ 6.0mEq/L). Not be used as monotherapy for emergency treatment of life-threatening hyperkalemia because of its delayed onset of action. 2. If patient intolerant to or failed therapy with SPS 3. Continuation of home therapy	90 days from 7/16/2019
Digifab	*Digoxin toxicity*		Digoxin Immune Fab Intraven Vial 40 mg (Digifab)		**Restrictions** 1. To patients with life-threatening or potentially life-threatening digoxin toxicity or overdose, including: Acute ingestion of fatal doses of digoxin a. Digoxin >10 mg in adults b. Digoxin level >10 ng/mL post-distribution (generally 6-8 hours post-dose) 2. Chronic ingestions causing steady-state serum digoxin concentrations > 6 ng/mL in adults 3. Manifestations of life-threatening toxicity (at supratherapeutic digoxin level > 2 ng/mL post-distribution- 6 to 8 hours post-dose) a. Ventricular arrhythmias (multifocal ventricular bigeminy, ventricular tachycardia, AV dissociation b. Bradycardia (< 50 bpm) unresponsive after atropine 1 mg IV with hyperkalemia > 5.5 mEq/L c. Second- or third-degree heart block	90 days from 7/16/2019

Medication Name	Medication Used For	Decision			Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary		
					4. Serum potassium levels > 5.5 mEq/L in patients with rapidly progressive signs/symptoms of digoxin toxicity **Dosing Guidelines:** • For acute and chronic digoxin intoxication in adults, administer 40-80 mg (1-2 vials) digoxin-Fab at a time and repeat after 60 min if patient is still symptomatic, sooner if patient is clinically unstable. In general, 40 – 120 mg (1 – 3 vials) should be sufficient. • In the event of cardiac arrest or other life-threatening signs or symptoms, a larger neutralizing dose (10-20 vials = 400-800 mg) of digoxin-Fab is indicated.	
Anavip	*Antivenom*	Crotalidae Immune F(ab')2 (Equine) (ANAVIP)				90 days from 7/16/2019
		Crotalidae Polyvalent Immune Fab (Ovine) (CroFab)				90 days from 7/16/2019
Orilissa	*Endo-metriosis*			Elagolix Sodium Oral Tablet 150 MG (Orilissa)		60 days from 7/16/2019
Constipation class review	*Constipation*		Linaclotide Oral Capsule 145 mcg (Linzess)		**Linaclotide and Lubiprostone Restriction** • Continuation from home	90 days from 7/16/2019
			Linaclotide Oral Capsule 290 mcg (Linzess)			90 days from 7/16/2019
			Linaclotide Oral Capsule 72 mcg (Linzess)			90 days from 7/16/2019

Medication Name	Medication Used For	Decision			Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary		
			Methylnaltrexone		**Methylnaltrexone Restrictions** • Pediatrics • Patient unable to take oral naloxegol See Methylnaltrexone Therapeutic Interchange	90 days from 7/16/2019
			Naloxegol		**Naloxegol Restrictions** • Taking naloxegol prior to admission for chronic opioid induced constipation (OIC) • Receiving chronic (>4 weeks) opioid therapy with failure to respond to oral and rectal laxative therapy • Candidates for methylnaltrexone (Relistor®) subcutaneously for OIC but who can tolerate oral therapy	90 days from 7/16/2019
			Alvimopan		**Alvimopan Restrictions** • Restricted to use for upper and lower gastrointestinal recovery following bowel resection surgeries with primary anastomosis and recommended with enhanced recovery after surgery (ERAS) protocols • Facilities where alvimopan is used should have automatic stop orders in place to limit to maximum of 15 doses • Facilities where alvimopan is used should have protocols in place to automatically discontinue alvimopan once bowel function returns	90 days from 7/16/2019
				Naldemedine Tosylate Tab 0.2 mg (Symproic)		
				Plecanatide Tablet 3 mg (Trulance)		

Medication Name	Medication Used For	Decision			Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary		
				Prucalopride (Motegrity)		
Pancreatic enzyme class review	*Pancreatic enzyme insufficiency*	Lipase/Protease/ Amylase Oral Capsule Dr (Creon 12000)			See Pancreatic Enzymes Therapeutic Interchange	90 days from 7/16/2019
		Lipase/Protease/ Amylase Oral Capsule Dr (Creon 24000)				90 days from 7/16/2019
		Lipase/Protease/ Amylase Oral Capsule Dr (Creon 3000)				90 days from 7/16/2019
		Lipase/Protease/ Amylase Oral Capsule Dr (Creon 36000)				90 days from 7/16/2019
		Lipase/Protease/ Amylase Oral Capsule Dr (Creon 6000)				90 days from 7/16/2019
				Lipase/Protease/ Amylase Oral Capsule Dr (Pancreaze)		90 days from 7/16/2019
				Lipase/Protease/ Amylase Oral Capsule (Pancrelipase)		90 days from 7/16/2019
				Lipase/Protease/ Amylase Oral Capsule Dr (Pertzye)		90 days from 7/16/2019
		Lipase/Protease/ Amylase Oral Capsule Dr (Zenpep Cap)				90 days from 7/16/2019
		Lipase/Protease/ Amylase Oral Capsule Dr (Zenpep)				90 days from 7/16/2019
				Lipase/Protease/ Amylase Oral		90 days from 7/16/2019

Medication Name	Medication Used For	Decision			Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary		
				Tablet 10.4 (Viokace)		
				Lipase/Protease/ Amylase Oral Tablet 20.9 (Viokace)		90 days from 7/16/2019
Benzoyl peroxide topical gel and cleanser	*Acne*	Benzoyl Peroxide Topical Cleanser 10 % (Benzoyl Perox)				60 days from 7/16/2019
		Benzoyl Peroxide Topical Cleanser 10 % (Clean/Clear)				60 days from 7/16/2019
		Benzoyl Peroxide Topical Cleanser 10 % (Panoxyl Acne)				60 days from 7/16/2019
		Benzoyl Peroxide Topical Gel (Gram) 10 % (Acne Medicat)				60 days from 7/16/2019
		Benzoyl Peroxide Topical Gel (Gram) 10 % (Benzoyl Perox)				60 days from 7/16/2019
		Benzoyl Peroxide Topical Gel (Gram) 10 % (Benzoyl)				60 days from 7/16/2019
		Benzoyl Peroxide Topical Gel (Gram) 10 % (Bp)				60 days from 7/16/2019
		Benzoyl Peroxide Topical Gel (Gram) 10 % (Jj Persagel)				60 days from 7/16/2019
		Benzoyl Peroxide Topical Gel (Gram) 5 % (Acne Medicat)				60 days from 7/16/2019
		Benzoyl Peroxide Topical Gel (Gram) 5 % (Benzoyl Perox)				60 days from 7/16/2019

Medication Name	Medication Used For	Decision			Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary		
		Benzoyl Peroxide Topical Gel (Gram) 5 % (Bp)				60 days from 7/16/2019
Trace elements	*Nutrition*	Zinc/Copper/Mangan/Chrom/Selen Iv (MultiTrace-5)				90 days from 7/16/2019
		Zinc/Copper/Mangan/Chrom/Intraven (MultiTrace-4)				90 days from 7/16/2019
Meningococcal B vaccine	*Meningitis prevention*	Meningococcal B Vaccine,4-Comp (Bexsereo)	N.Meningitidis B,Lipid Fhbp Rc Intramusc (Trumenba)		**Trumenba Restrictions** • Patients with a latex allergy • Patients who started their serogroup B meningococcal vaccine with Trumenba. All new serogroup B meningococcal vaccine series starts should use Bexsero.	90 days from 7/16/2019
Cangrelor	*Antiplatelet*		Cangrelor Tetrasodium Intraven Vial 50 M (Kengreal)		1. STEMI or high-risk PCI patients when oral or enteral (e.g. per NG tube) loading is not feasible or GI absorption of oral/enteral agents is questionable. This includes: a. Patients who can't swallow and do not have a functioning enteral tube (tube placement should be considered as soon as feasible) b. Patients with hemodynamic instability or cardiogenic shock where GI absorption might be significantly impaired c. Patients with GI dysfunction where gut absorption is likely minimal (e.g. high NG tube output, bowel obstruction) d. Glycoprotein IIb/IIIa inhibitors (tirofiban) should be considered on a case by case basis as an alternative to cangrelor e. Patients with a history of prior adverse reaction with IIb/IIIa inhibitors	90 days from 7/16/2019

Medication Name	Medication Used For	Decision			Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary		
					2. Selected cases where likelihood of urgent* CABG is high [*Urgent procedure: Defined as a procedure required within 24 hours in order to minimize chance of further clinical deterioration] 3. Use in perioperative bridging outside of urgent CABG is prohibited due to lack of indication and documented benefit 4. Patients should be transitioned to oral/enteral therapy as soon as possible after initiation; either per package insert guidance (at least 2 hours after start of infusion or for the duration of the procedure, whichever is longer) or as soon as patient can tolerate oral or enteral intake. Extended infusions of cangrelor at current FDA approved dosing have not been studied, and the risk vs. benefit is unknown. If maintenance infusions beyond the procedure are deemed necessary, lower dosing (0.75 mcg/kg/min) should be considered and necessity of such infusions should be re-evaluated regularly. 5. Use restricted to interventional cardiologists and cardiothoracic surgeons	
Pegfilgrastim-jmdb (OnPro)	*Neutropenia*		Pegfilgrastim Subcut Syr W/ Inj 6 mg/0.6 (Neulasta Onpro)		Outpatient use only. Outpatient reimbursement should be confirmed prior to use. Neulasta Onpro should only be used if patients have difficulty returning for a second visit due to a prolonged driving distance or transportation hardship to the nearest CHI infusion clinic.	90 days from 7/16/2019
System Table	*Various indications*			Morphine Sulfate ER 15mg (Arymo)		90 days from 7/16/2019

Medication Name	Medication Used For	Decision			Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary		
				Morphine Sulfate ER 30mg (Arymo)		90 days from 7/16/2019
				Morphine Sulfate ER 60mg (Arymo)		90 days from 7/16/2019
				Desmopressin Acetate Nasal Spray/Pump (Noctiva)		90 days from 7/16/2019
				Desmopressin Acetate Nasal Spray/Pump (Noctiva)		90 days from 7/16/2019
				Amantadine 68.5 mg ER (Gocovri)		90 days from 7/16/2019
				Amantadine 137 mg ER (Gocovri)		90 days from 7/16/2019

CHI SYSTEM FORMULARY REVIEW – CLASS REVIEWS & MISC MEDICATIONS

BACKGROUND:

During the March, May, and July 2019 CHI System P&T committee meetings, several classes of medications and misc. medications were reviewed for formulary standardization opportunities across the entire CHI system. The below medications and classes represent formulary variances from the current CHI Memorial formulary. As per the system formulary process, local P&T's may approve the below with no changes or approve with more restrictions. Additionally, sites may request an exception or appeal to any formulary decision with accompanying clinical documentation supporting the appeal. Implementation of EPIC will require formularies to be standardized across CHI due to the sharing of drug dictionaries within the various EHR platforms.

The medications recommended for formulary removal are detailed below:

Estrogen Class Review

- Premarin vaginal cream
    - Recommendation/Discussion: Low utilization (<30/year) primarily in surgery. Non-formulary status very unlikely to impact patient care with the following interchange:
        - *Interchange to*: estradiol cream
- Menest (esterified estrogens) tablet
    - Recommendation/Discussion: Low utilization (20/yr) and non-formulary status very unlikely to impact patient care. Change to non-formulary status and allow use of patient home meds if patients are admitted on this as a home regimen.
- Estropipate tablet
    - Recommendation/Discussion: Low utilization (20/yr) and non-formulary status very unlikely to impact patient care. Change to non-formulary status and allow use of patient home meds if patients are admitted on this as a home regimen.

Rectal Product Class Review

- Cortifoam rectal foam (hydrocortisone acetate 10% 15 gm aerosol can)
    - Recommendation/Discussion: Unavailable for purchase. Zero utilization and non-formulary status very unlikely to impact patient care. Change to non-formulary status.
- Epifoam rectal foam (hydrocortisone/pramoxine)
    - Recommendation/Discussion: Zero utilization and non-formulary status very unlikely to impact patient care. Change to non-formulary status.

Miscellaneous Medications

- Co-enzyme Q-10 (ubiquinone) capsule
    - Recommendation/Discussion: Coenzyme Q10 is no longer recommended for statin-associated muscle symptoms (SAMS). The ACC/AHA 2018 Guideline on the Management of Blood Cholesterol assigned a Class of Recommend of III (no benefit). Utilization is high (175 capsules/month), but primarily home medication continuation.
        - Change to non-formulary status and classify as an herbal medication: do not continue during hospitalization if a home medication and new orders for coenzyme Q10 will not be verified.
- Stadol (butorphanol) injection
    - Recommendation/Discussion: Very low utilization (<5/year) and non-formulary status unlikely to impact patient care. Change to non-formulary status.
- Diclofenac potassium tablet
    - Recommendation/Discussion: Moderate utilization (~12/month) and non-formulary status unlikely to impact patient care. Change to non-formulary status and do not allow continuation of home medication. Recommend interchange to alternative oral NSAID if needed.

To be implemented with Epic go-live (formulary restriction):

Constipation Class Review

- Amitiza (lubiprostone) and Linzess (linaclotide)
    - Recommendation/Discussion: Restrict usage to continuation of home medications only; no new starts during hospitalization. This will be accomplished by limiting these two medications to the "pharmacy" medication preference list only and removing from the "facility" preference list.

FORMULARY REVIEW

GENERIC NAME: Sodium zirconium cyclosilicate (AstraZeneca)

PROPRIETARY NAME: *Lokelma®*

INDICATIONS:

FDA Approved
• Treatment of hyperkalemia in adults

THERAPEUTIC CATEGORY: Potassium binder

PHARMACOKINETICS:

Absorption	Not systemically absorbed
Distribution	Not systemically absorbed
Metabolism	Not systemically absorbed (none)
Elimination	Not systemically absorbed (feces)

SPECIAL POPULATIONS:

Pregnancy	Not systemically absorbed, unlikely to result in fetal exposure to the drug
Lactation	Not systemically absorbed, unlikely to result in exposure of child to drug
Pediatrics	Safety and efficacy not established
Geriatrics	No overall difference in safety or effectiveness noted in clinical studies
Hepatic Impairment	No dosage adjustments in manufacturer's labeling
Renal Impairment	No dosage adjustments in manufacturer's labeling

CLINICAL STUDIES:

Sodium Zirconium Cyclosilicate in Hyperkalemia (ZS-003 Protocol)	
METHODS	
Study Design	Double-blind, randomized, placebo-controlled
Patient Enrollment Inclusion	• At least 18 years of age • Serum potassium level of 5.0 to 6.5 mmol per liter • Able to undergo repeated blood draws
Patient Enrollment Exclusion	• Patients receiving dialysis • Presence of diabetic ketoacidosis • Potassium level greater than 6.5 mmol per liter • Cardiac arrhythmia requiring immediate treatment • Received organic polymer resins or phosphate binders within 1 week of enrollment

Treatment Plan	• Initial phase:
	  • Patients with potassium level of 5.0 to 6.5 mmol per liter randomly assigned to receive 1.25 g, 2.5g, 5 g, or 10 g of study drug or placebo three times daily with meals for initial 48 hours
	• Maintenance phase:
	  • Patients in study drug group who reached a potassium level of 3.5 to 4.9 mmol per liter were randomly assigned in a 1:1 ratio to receive their original dose or placebo once daily before breakfast from days 3 to 14
	  • Patients in placebo group were randomly assigned to receive either 1.25 g or 2.5 g of study drug once daily before breakfast from days 3 to 14

RESULTS	

Outcomes Summary	ZS-9 was associated with a significant decrease in serum potassium levels from baseline to 48 hours among patients receiving 2.5, 5, and 10 g doses. Patients who received 1.25 g of ZS-9 did not show a significant difference in serum potassium reduction within the first 48 hours. ZS-9 maintenance using 5 or 10 g once daily dosing was significantly superior to placebo in maintaining normokalemia. Maintenance with 1.25 or 2.5 g of ZS-9 were not significantly different in maintaining normokalemia when compared to placebo.
Effect of Sodium Zirconium Cyclosilicate on Potassium Lowering for 28 Days Among Outpatients With Hyperkalemia The HARMONIZE Randomized Clinical Trial	
METHODS	
Study Design	Phase III, multicenter, randomized, double-blind, placebo-controlled trial
Patient Enrollment Inclusion	• Over 18 years of age • Two consecutive i-STAT potassium values, measured 60-minutes apart, both ≥5.1 mmol/l and measured within 1 day of the first ZS dose on AP Study Day 1. • Ability to have repeated blood draws or effective venous catheterization • Women of childbearing potential must be using two forms of medically acceptable contraception (at least one barrier method) and have a negative pregnancy test at AP Study Day 1. Women who are surgically sterile or those who are post-menopausal for at least 2 years are not considered to be of childbearing potential.
Patient Enrollment Exclusion	• Pseudo hyperkalemia signs and symptoms, such as excessive fist clenching hemolyzed blood specimen, history of severe leukocytosis or thrombocytosis. • Subjects treated with lactulose, Xifaxan or other non-absorbed antibiotics for hyperammonemia within 7 days prior to the first dose of study drug. • Subjects treated with resins (such as sevelamer acetate or sodium polystyrene sulfonate [SPS; e.g. Kayexalate®]), calcium acetate, calcium carbonate, or lanthanum carbonate, within 7 days prior to the first dose of study drug. • Subjects with a life expectancy of less than 3 months. • Subjects who are severely physically or mentally incapacitated and who in the opinion of investigator are unable to perform the subjects' tasks associated with the protocol. • Women who are pregnant, lactating, or planning to become pregnant. • Subjects with diabetic ketoacidosis. • Presence of any condition which, in the opinion of the investigator, places the subject at undue risk or potentially jeopardizes the quality of the data to be generated. • Known hypersensitivity or previous anaphylaxis to ZS or to components thereof • Randomization into the previous ZS-002 or ZS-003 studies. 11. Treatment with a drug or device within the last 30 days that has not received regulatory approval at the time of study entry. • Subjects with cardiac arrhythmias that require immediate treatment. • Subjects on dialysis.

Treatment Plan	• Open-label phase
	  • Received 10 g of zirconium cyclosilicate 3 times daily with meals for 48 hours
	• Randomized phase
	  • Patients included if they achieved normokalemia at the end of open-label phase
	  • Received once-daily zirconium cyclosilicate (5, 10, or 15 g) or placebo, respectively, for 28 days
	  • If a patient's potassium value was between 3.0 and 3.4 mEq/L at any time during the randomized phase, the dose was reduced from once daily to every other day
	  • Study drug was discontinued if a patient developed significant hypokalemia (potassium 6.2 mEq/L) or significant arrhythmias during the randomized phase

RESULTS	
Outcomes Summary	• ZS-9 significantly reduced serum potassium during the initial 48 hours vs baseline • Significant changes in potassium were noted at 1 hour after the first 10 g dose compared with baseline (-0.2 mEq/L; 95% CI, -0.3 to -.02) • Mean potassium change at 2 and 4 hours after the first dose was −0.4 mEq/L (95% CI,

	−0.5 to −0.4) and −0.5 mEq/L (95% CI, −0.6 to −0.5), respectively (P < .001 for both time points). • Serum potassium was within the normal range in 84% of patients (95% CI, 79% to 88%) by 24 hours and in 98% (95% CI, 96% to 99%) by 48 hours • Median time to potassium normalization was 2.2 hours (interquartile range, 1.0 to 22.3) • A greater degree of potassium lowering with zirconium cyclosilicate compared with placebo was consistent across all prespecified subgroups in the randomized portion of the study

COMPARATIVE EFFICACY:

- Potassium binders are used to decrease potassium levels in non-emergent, non-life threatening settings.
- Head to head studies comparing safety and efficacy of sodium zirconium cyclosilicate to other potassium binders are not available
- In vitro studies have shown a 9 times greater potassium binding capacity with sodium zirconium cyclosilicate when compared to sodium polystyrene sulfonate
- Novel potassium binders including patiromer and Sodium Zirconium Cyclosilicate have been developed in an effort to avoid current issues experienced with SPS therapy. Similar to SPS, Sodium Zirconium Cyclosilicate works by trapping potassium within the gastrointestinal tract leading to fecal excretion of potassium. In vitro studies have shown Sodium Zirconium Cyclosilicate to possess 9-times greater potassium binding capacity when compared to SPS. Furthermore, Sodium Zirconium Cyclosilicate is more selective for potassium over calcium by a factor of 125.
- Clinical trials with Sodium Zirconium Cyclosilicate in the ambulatory setting indicate a faster onset of action when compared to other potassium binding alternatives (approximately 1-6 hours with Sodium Zirconium Cyclosilicate, 7-48 hours with patiromer, and inconsistent onset of action with SPS).

WARNING AND PRECAUTIONS:

- Gastrointestinal adverse events in patients with motility disorders: avoid use in severe constipation, bowel obstruction or impaction, including post-operative disorders
- Edema
- Sodium content: Each 5 gm dose contains approximately 400 mg sodium

CONTRAINDICATIONS: None

ADVERSE REACTIONS: Dose-dependent edema, generalized (4 to 16%) and peripheral (8 to 11%); Hypokalemia (4%)

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:

Interacting Drug	Effect
Clopidogrel	Sodium Zirconium Cyclosilicate may decrease serum concentrations of the active metabolite of clopidogrel
Dabigatran	Sodium Zirconium Cyclosilicate may decrease serum concentrations of the active metabolite of dabigatran
Warfarin	Sodium Zirconium Cyclosilicate may increase serum concentrations of the active metabolite of warfarin

DOSING AND ADMINISTRATION:

- Initial dosing: 10 gm orally as a suspension in water three times a day for up to 48 hours
- Adjust dose by 5 gm daily at 1 week intervals as needed based on serum potassium
- For continued use, administer 10 gm once daily (range 5 gm every other day to 15 gm once daily).
- Maximum maintenance dose: 15 gm daily
- Empty entire contents of the packet(s) into a glass with ≥ 3 tablespoons (45 mL) of water. Stir well and drink immediately; if powder remains in the glass, add water, stir and drink immediately; repeat until no powder remains.
- Administer other oral medications ≥ 2 hours before or 2 hours after dose

RECOMMENDED MONITORING:

- Baseline and weekly serum potassium levels; signs and symptoms of edema

PHARMACOECONOMICS/COST:

Product (Drug, Strength, Form)	Cost/Day	Cost/single dose
VELTASSA 8.4 GM PWD 30	$25.43-76.29	8.4 gm - $25.43
SPS 15 GM-60 ML SUS 10X60 ML UD	$7.27-29.08	15 gm - $7.27
LOKELMA 10 GM	$16.03-48.09	10 gm - $16.03

CONCLUSION & RECOMMENDATION:

Lokelma (sodium zirconium cyclosilicate) was approved to the CHI System formulary at the July 2019 P&T committee meeting. In 2016, Veltassa (patiromer) was reviewed and classified system-wide and locally as non-formulary, and it remains as a non-formulary agent system-wide. It is recommended for its designation to remain non-formulary locally. The addition of sodium zirconium cyclosilicate to formulary is recommended for acute management of hyperkalemia with the following restrictions, as approved by the CHI system P&T committee:

1) Management of severe hyperkalemia ($K \geq 6.0$mEq/L). Not be used as monotherapy for emergent treatment of life-threatening hyperkalemia because of its delayed onset of action.
2) If patient intolerant to or failed therapy with SPS (Kayexalate)
3) Continuation of home therapy

Patients using Veltassa as a home medication may use their own supply during hospitalization. If home supply is unobtainable, the physician will be contacted to discuss an appropriate substitution to Lokelma, if indicated.

FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)

Medication Management Step	Identified Risk	Steps for Prevention
Selection & Procurement		
Therapeutic interchange?	N/A	
Special Ordering Requirements?	N/A	
Storage		
LASA* separation of stock?	N/A	
Special storage (e.g. refrigeration, protect from light, controlled substance)?	N/A	
Pharmacist/Technician Education?	N/A	
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	Yes	Approve through local P&T committee. Restriction criteria posted for pharmacist review.
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	None	
Drug Interactions?	Yes	Separate dosing of ZS-9 by at least 2 hours (before or after) from other oral medications. May decrease concentration of clopidogrel, dabigatran, and warfarin.
Pregnancy?	No known risk	
Absolute Contraindications?	None	
Requires Order Set, Protocol, concomitant therapy with another drug?	None	
LASA* nomenclature issues?	None	
Prescriber education?	Yes	Not be used as monotherapy for emergent treatment of life-threatening hyperkalemia because of its delayed onset of action.
Processing, Preparing, & Dispensing		
High-risk drug double check?	No	
Drug Interaction check in place?	Yes	Separate dosing of ZS-9 by at least 2 hours (before or after) from other oral medications
LASA* computer warnings?	None	
Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)?	Yes	Separate dosing of ZS-9 by at least 2 hours (before or after) from other oral medications
Packaging/Labeling (e.g. prepacking)?	None	
Dispensing (e.g. auxiliary labeling, light protection, refrigeration)?	None	
Documentation required (e.g. double check, worksheet)?	None	
Pharmacist/Technician Education?	Yes	Pharmacist education of restriction criteria and appropriate use.

Medication Management Step	Identified Risk	Steps for Prevention
Administration		
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	None	
Special delivery system (e.g. pump)?	None	
Documentation required? (e. g. double check)	None	
Nurse education?	None	
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?	Yes	Serum potassium levels, worsening edema, gastrointestinal side effects
Follow-up laboratory tests?	Yes	Serum potassium levels
Education?	None	

FORMULARY UPDATE & DOSE OPTIMIZATION

GENERIC NAME: Digoxin Immune Fab

PROPRIETARY NAME: Digifab®

BACKGROUND/RATIONALE:
The July 2019 CHI System P&T committee reviewed and approved the below dosing restrictions and guidelines for Digifab. As per the system formulary process, local P&T's may approve the below with no changes or approve with more restrictions. Additionally, sites may request an exception or appeal to any formulary decision with accompanying clinical documentation supporting the appeal.

For acute and chronic digoxin intoxication in adults, starting with lower doses of digoxin-Fab (1-2 vials = 40-80 mg) followed by repeat dosing based on clinical indicators and symptoms is a reasonable treatment approach due to:

- Complete neutralization with digoxin immune fab is often unnecessary to treat acute toxic effects.
- A single, large bolus of digoxin-Fab will completely neutralize digoxin in the circulation but the excess antibodies will likely be excreted before more digoxin is redistributed into the serum from tissue stores.
- Digoxin serum concentrations following acute poisonings often overestimate total body burden due incomplete tissue distribution (higher serum concentration) if drawn within 6 hours of ingestion.

Of note, serum digoxin concentration will artificially increase after the antidote is given and therefore not provide a reasonable guideline for additional dosing.

PHARMACOECONOMICS/COST:

Dose	Cost	Cost/Standard (high) Dose	Cost/Low Dose
Digifab 40 mg vial	$3,382.09 per vial	Standard (high) dose: 6 vials initial dose **$20,292.54**	Low dose: 1-2 vials initial dose **$3,382.09 - $6,764.18**

PROPOSED FORMULARY RESTRICTIONS:
Restrict Digifab use to patients with life-threatening or potentially life-threatening digoxin toxicity or overdose, including:

1. Acute ingestion of fatal doses of digoxin
    a. Digoxin >10 mg in adults
    b. Digoxin level >10 ng/mL post-distribution (generally 6-8 hours post-dose)
2. Chronic ingestions causing steady-state serum digoxin concentrations > 6 ng/mL in adults
3. Manifestations of life-threatening toxicity (*at supratherapeutic digoxin level >2 ng/mL post-distribution- 6 to 8 hours post-dose*)
    a. Ventricular arrhythmias (multifocal ventricular bigeminy, ventricular tachycardia**,** AV dissociation)
    b. Bradycardia (<50 bpm) unresponsive after atropine 1 mg IV with hyperkalemia > 5.5 mEq/L
    c. Second- or third-degree heart block
4. Serum potassium levels > 5.5 mEq/L in patients with rapidly progressive signs/symptoms of digoxin toxicity

PROPOSED DOSING GUIDELINES:

1. For acute and chronic digoxin intoxication in adults, administer 40-80 mg (1-2 vials) digoxin-Fab
    a. If patient is still symptomatic after 60 min, repeat the 40-80 mg (1-2 vials) dose, and sooner if patient is clinically unstable.
2. For cardiac arrest or other life-threatening signs or symptoms, a larger neutralizing dose (10-20 vials = 400-800 mg) of digoxin-Fab is indicated.

RECOMMENDATION/DISCUSSION:
The above formulary restrictions and dosing guidelines were reviewed and approved by the CHI System Cardiovascular Service Line and P&T Committee. It is recommended to adopt the above restrictions and dosing guidelines.

FORMULARY REVIEW

GENERIC NAME: Bevacizumab-awwb

PROPRIETARY NAME: *Mvasi®*

INDICATIONS:

FDA Approved
• Metastatic colorectal cancer (mCRC) with intravenous 5-fluorouracil-based chemotherapy for first or second line treatment • Metastatic colorectal cancer (mCRC) with fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin-based chemotherapy for second line treatment in patient who have progressed on a first line bevacizumab product-containing regimen   o Limitation of use: Mvasi® is not indicated for adjuvant treatment of colon cancer. • Non-squamous non-small cell lung cancer (NSCLC) with carboplatin and paclitaxel for first line treatment of unresectable, locally advanced, recurrent, or metastatic disease • Glioblastoma as a single agent for adult patients with progressive disease following prior therapy • Metastatic renal cell carcinoma (mRCC) with interferon alfa • Persistent, recurrent, or metastatic carcinoma of the cervix in combination with paclitaxel and cisplatin or paclitaxel and topotecan
Non-FDA Approved
• Age-related macular degeneration • Breast cancer, metastatic • Diabetic macular edema • Endometrial cancer, recurrent or persistent • Hereditary hemorrhagic telangiectasia • Malignant pleural mesothelioma (unresectable) • Soft tissue sarcoma, angiosarcoma • Soft tissue sarcoma, hemangiopericytoma

THERAPEUTIC CATEGORY:
Antineoplastic agent, monoclonal antibody; antineoplastic agent, vascular endothelial growth factor (VEGF) inhibitor

PHARMACOKINETICS:

Absorption	-
Distribution	CV% central volume: 2.9 (22%) L
Metabolism	None known
Excretion	-
t ½ (hr)	20 days (range 11-50)
Elimination	Clearance varies by weight, gender, and tumor burden; Males and higher tumor burden correlate with a higher clearance with no evidence that this results in reduced efficacy

SPECIAL POPULATIONS:

Pregnancy	Based on findings in animal reproduction studies and on the mechanism of action, bevacizumab may cause fetal harm if administered to a pregnant woman. Information from post-marketing reports following exposure in pregnancy is limited. Women of reproductive potential should use effective contraception during therapy and for 6 months following the last bevacizumab dose. Bevacizumab treatment may also increase the risk of ovarian failure and impair fertility; long term effects on fertility are not known.
Lactation	It is not known if bevacizumab is present in breast milk. Immunoglobulins are excreted in breast milk, and it is assumed that bevacizumab may appear in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, breastfeeding is not recommended during treatment and for 6 months following the last dose of bevacizumab products
Geriatrics	Patients ≥ 65 years of age have increased incidence of arterial thrombotic events, increased risk for proteinuria; other serious adverse events occurring often include weakness, sepsis, hyper-/hypotension, CHF, constipation, anorexia, anemia, hyper-/hypokalemia, and diarrhea
Hepatic Impairment	No dose adjustments necessary
Renal Impairment	No dose adjustments required

	Renal toxicity during treatment - Nephrotic syndrome: discontinue bevacizumab-awwb - Proteinuria ≥2g/24hr in the absence of nephrotic syndrome: withhold bevacizumab-awwb until proteinuria <2g/24hr

CLINICAL STUDIES:

MAPLE study comparing ABP 215 (bevacizumab-awwb) to bevacizumab for the treatment of NSCLC			
METHODS			
Study Design	Randomized 1:1, double blind, active controlled phase III trial		
Study Funding	Amgen, Inc.		
Patient Enrollment Inclusion	o Age ≥ 18 and < 80 yo with histologically or cytologically confirmed, stage IV or recurrent metastatic nonsquamous NSCLC with measurable disease according to the modified RECIST v1.1 o Baseline CT or MRI scan of the chest and abdomen to assess disease burden before enrollment and receiving 1st line chemotherapy for NSCLC o At least 12 months elapsed since completing adjuvant chemotherapy o 1st line carboplatin/paclitaxel chemotherapy had to be initiated within 8 days after randomization o Expected to receive at least 4 cycles of chemotherapy		
Patient Enrollment Exclusion	o Small cell lung cancer or mixed small cell lung cancer and NSCLC o Mixed adenosquamous carcinomas with predominantly squamous component o History or known presence of CNS metastases o Malignancy other than NSCLC within 5 years (except adequately treated *in situ* cervical cancer or squamous or basal cell carcinoma of the skin) o Planned major surgical procedure during the treatment phase		
Baseline Characteristics	o Male: 59.8% vs 59.9% o Race, white: 96% vs 95.5% o Mean age: 61.6 vs 61.6 o Disease stage at baseline, IV: 94.2% vs 92.4%		

Outcome Measures	o Primary efficacy endpoint was the risk ratio of objective response rate (ORR) defined as the rate of the best overall response of either complete response (CR) or partial response (PR) according to RECIST v1.1 during study
	  o Primary analysis was based on the central, independent, blinded radiologists' review of radiologic images in the ITT population
	  o All patients who didn't meet criteria for CR or PR by the end of the study were considered non-responders
	o Secondary efficacy endpoints included risk difference of ORR, duration of response (DOR), and progression-free survival (PFS)
	  o DOR was calculated as time from the first objective response to disease progression according to RECIST v1.1
	  o PFS defined as the time from randomization until the first occurrence of disease progression per RECIST v1.1 or death
	o Safety endpoints included incidence of adverse events, adverse events of interest (including anti-VEGF related adverse events), overall survival (OS), changes in clinical laboratory tests and vital signs, and incidence of ADAs		

Treatment Plan	o Randomized 1:1 to receive IV ABP 215 or bevacizumab 15 mg/kg administered TIW for 6 cycles o All patients received carboplatin and paclitaxel chemotherapy TIW for ≥4 and ≤6 cycles		
RESULTS			
Primary Endpoint		ABP 215 (n = 328)	Bevacizumab (n = 314)
	Best overall response, n (%)		
	Complete response	2 (0.6)	2 (0.6)
	Partial response	126 (38.4)	129 (41.1)
	Stable disease	144 (43.9)	137 (43.6)
	Progressive response	21 (6.4)	18 (5.7)
	Not evaluable	35 (10.7)	28 (8.9)
	ORR, n (%)	35 (10.7)	28 (8.9)

Secondary Endpoint	The risk ratio for ORR (bevacizumab-awwb to bevacizumab) was 0.93 (90% CI 0.80 – 1.09). The 90% CI for OOR was within the pre-specified equivalence margin of 0.67 to 1.5. The estimate DOR mediates were 5.8 months (95% CI, 4.9 – 7.7) and 5.6 months (95% CI, 5.1 – 6.3) PFS was similar with bevacizumab-awwb and bevacizumab at 197 patient (60.1%) and 189 (60.2%) respectively.		
Adverse Events		ABP 215 (n = 328)	Bevacizumab (n = 314)
	Any AE	308 (95.1)	289 (93.5)
	Any grade ≥3 AE	139 (42.9)	137 (44.3)
	Any fatal AE	13 (4.0)	11 (3.6)
	Any serious AE	85 (26.2)	71 (23.0)
	Any AE leading to discontinuation of study drug	61 (18.8)	53 (17.2)
	Any AE leading to discontinuation of any component of chemotherapy	74 (22.8)	59 (19.1)
	Any AE leading to dose delay of study drug	73 (22.5)	69 (22.3)
	Any AE leading to dose delay of any component of chemotherapy	86 (26.5)	83 (26.9)
	Any AE leading to dose reduction of any component of chemotherapy	48 (14.8)	49 (15.9)
	OS, n (%)	281 (86.7)	273 (88.3)
Limitations	○ The choice of response rate as a primary endpoint ○ The lack of a maintenance phase to determine DOR and long-term safety		
Author's Conclusion	This phase III equivalence study, along with results of previous studies, shows that ABP 215 is similar to bevacizumab.		

COMPARATIVE EFFICACY:

A single biological product that is already FDA approved based on a full evaluation of safety and efficacy data is called a reference product. A proposed biosimilar product is compared to and evaluated against a reference product to ensure the product is both highly similar and has no clinically meaningful differences. Bevacizumab-awwb (Mvasi®) is a newly approved monoclonal antibody biosimilar agent to the reference product, bevacizumab (Avastin®) that works by binding and neutralizing vascular endothelial growth factor preventing its association with endothelial receptors, Flt-1 and KDR. Mvasi® has been shown to have the same primary and higher-order structure. In the MAPLE trial, bevacizumab-awwb (Mvasi®) demonstrated similar clinical efficacy to bevacizumab (Avastin®) for the treatment of advanced nonsquamous non-small cell lung cancer. Unlike Avastin, Mvasi is does not carry indications for ovarian (epithelial), fallopian tube, or primary peritoneal cancers.

WARNING AND PRECAUTIONS:

• Perforation or fistula • Heart failure • Surgery and wound healing complications • Hemorrhage • Hypertension	• Arterial thromboembolic events • Venous thromboembolic events • Posterior reversible encephalopathy syndrome (PRES) • Infusion reactions

CONTRAINDICATIONS: None

ADVERSE REACTIONS:

Adverse Reactions	ABP 215 (N= 324)	Bevacizumab (N=309)
Cardiovascular		
Hypertension	22 (6.8)	17 (5.5)
Pulmonary embolism	5 (1.6)	6 (1.9)
Central Nervous System	-	-
Gastrointestinal		
GI perforation	3 (0.9)	4 (1.3)
Hematologic and Oncologic		
Febrile neutropenia	11 (3.4)	8 (2.6)
Neutropenia	6 (1.9)	3 (1.0)

Anemia Pulmonary hemorrhage Rectal hemorrhage	3 (0.9) 2 (0.6) 2 (0.6)	6 (1.9) 5 (1.6) 0 (0)
Hepatic	-	-
Infection	-	-
Metabolic	-	-
Neuromuscular & Skeletal	-	-
Adverse Reactions	**ABP 215 (N= 324)**	**Bevacizumab (N=309)**
Renal Proteinuria	 1 (0.3)	 1 (0.3)
Respiratory Pneumonia Dyspnea Hemoptysis	 6 (1.9) 3 (0.9) 2 (0.6)	 5 (1.6) 4 (1.3) 2 (0.6)
Skin	-	-
Systemic	-	-
Miscellaneous Wound healing complications	 1 (0.3)	 2 (0.6)

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:

Interacting Drug	**Effect**
Anthracyclines	Bevacizumab-awwb may enhance the cardiotoxic effect of anthracyclines
BCG (intravesical)	Myelosuppressive agents may diminish the therapeutic effect of BCG (intravesical)
Belimumab	Monoclonal antibodies may enhance the adverse/toxic effect of belimumab
Deferiprone	Myelosuppressive agents may enhance the neutropenic effect of deferiprone
Dipyrone	Dipyrone may enhance the adverse/toxic effect of myelosuppressive agents. Specifically, the risk for agranulocytosis and pancytopenia may be increased
Sunitinib	Sunitinib may enhance the adverse/toxic effect of Bevacizumab-awwb. Specifically, the risk for a specific form of anemia, microangiopathic hemolytic anemia (MAHA), may be increased. Bevacizumab-awwb may enhance the hypertensive effect of sunitinib.

DOSING AND ADMINISTRATION:

Adult Dosing/Indication and Administration
Metastatic Colorectal Cancer (mCRC)
5 mg/kg or 10 mg/kg every 2 weeks when used in combination with IV 5-FU-based chemotherapy • Administer 5 mg/kg every 2 weeks when used in combination with bolus-IFL • Administer 10 mg/kg every 2 weeks when used in combination with FOLFOX4 • Administer 5 mg/kg every 2 weeks or 7.5 mg/kg every 3 weeks when used in combination with a fluoropyrimidine-irinotecan or fluoropyrimidine-oxaliplatin based chemotherapy regimen in patients who have progressed on a 1st line bevacizumab product-containing regimen
Non-squamous non-small cell lung cancer (NSCLC)
15 mg/kg every 3 weeks in combination with carboplatin and paclitaxel
Glioblastoma
10 mg/kg every 2 weeks
Metastatic renal cell carcinoma (mRCC)
10 mg/kg every 2 weeks in combination with interferon alfa
Persistent, recurrent, or metastatic carcinoma of the cervix
15 mg/kg every 3 weeks in combination with one of the following chemotherapy regimens: paclitaxel and cisplatin, or paclitaxel and topotecan

RECOMMENDED MONITORING:

- Monitor for proteinuria/nephrotic syndrome with urine dipstick; collect 24-hour urine in patients with ≥2+ reading.
- Monitor blood pressure every 2 to 3 weeks; more frequently if hypertension develops during therapy; continue to monitor blood pressure after discontinuing due to bevacizumab-induced hypertension.
- Monitor closely during the infusion for signs/symptoms of an infusion reaction.
- Monitor for signs/symptoms of GI perforation or fistula (including abdominal pain, constipation, vomiting, and fever), bleeding (including epistaxis, hemoptysis, GI, and/or CNS bleeding), thromboembolism (arterial and venous), wound healing complications, and heart failure.

PHARMACOECONOMICS/COST:

Product (Drug, Strength, Form)	Cost
bevacizumab-awwb (Mvasi) 100 mg in 4 mL	$616.99 (23% savings)
bevacizumab-awwb (Mvasi) 400 mg in 16 mL	$2467.94
Avastin 100 MG VL 4 ml	$796.94 (23% savings)
Avastin 400 MG VL 16 ml	$3187.75

CONCLUSION & RECOMMENDATION:

The following restrictions were approved by the CHI System P&T committee and it is recommended to adopt the following ordering restrictions for all bevacizumab biosimilars and Avastin:

1. Bevacizumab-awwb (Mvasi®) and other bevacizumab biosimilars:
    a. Restricted to outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization.
2. Bevacizumab (Avastin)
    a. If a bevacizumab biosimilar is not available or payer-approved, may be used outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization.

The Epic treatment regimen for Avastin will have the following order instructions added: "Pharmacy may substitute biosimilar product per P&T committee approved restriction criteria."

FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)

Medication Management Step	Identified Risk	Steps for Prevention
Selection & Procurement		
Therapeutic interchange?	None	
Special Ordering Requirements?	No	
Storage		
LASA* separation of stock?	Yes	Separate from look-alike/sound-alike medications: Bevacizumab, bezlotoxumab, brentuximab, cetuximab, ranibizumab, rituximab
Special storage (e.g. refrigeration, protect from light, controlled substance)?	Yes	Store intact vials at 2ºC to 8ºC (36ºF to 46ºF) in the original carton until time of use; protect from light; Do not freeze or shake. Store diluted solution for 8 hours at 2ºC – 8ºC (36ºF to 46ºF).
Pharmacist/Technician Education?	Yes	Requires refrigeration and protection from light
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	Yes	Restrict to ordering outpatient use by oncology or hematology services
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	Yes	Renal toxicity during treatment • Nephrotic syndrome: discontinue bevacizumab-awwb • Proteinuria ≥2g/24hr in the absence of nephrotic syndrome: withhold bevacizumab-awwb until proteinuria <2g/24hr
Drug Interactions?	Yes	Anthracyclines, belimumab, deferiprone, sunitinib, and BCG (intravesical)
Pregnancy?	No	Check pregnancy status and educate patients of childbearing age on the importance of not becoming pregnant and using reliable birth control while on this medication
Absolute Contraindications?	None	
Requires Order Set, Protocol, concomitant therapy with another drug?	No	
LASA* nomenclature issues?	Yes	Separate from Bevacizumab, bezlotoxumab, brentuximab, cetuximab, ranibizumab, rituximab
Prescriber education?	Yes	Requires monitoring of CBC, proteinuria, blood pressure, infusion reactions, signs and symptoms

Medication Management Step	Identified Risk	Steps for Prevention
		of GI perforation, abscess, or fistula, signs and symptoms of bleeding, and signs and symptoms of thromboembolism
Processing, Preparing, & Dispensing		
High-risk drug double check?	No	
Drug Interaction check in place?	Yes	Anthracyclines, belimumab, deferiprone, sunitinib, and BCG (intravesical).
LASA* computer warnings?	No	
Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)?	Yes	Hazardous drug; use appropriate precautions for receiving, handling, administration, and disposal
Packaging/Labeling (e.g. prepacking)?	No	
Dispensing (e.g. auxiliary labeling, light protection, refrigeration)?	Yes	Store in refrigerator; protect from light
Documentation required (e.g. double check, worksheet)?	None	
Pharmacist/Technician Education?	Yes	Requires monitoring of CBC, proteinuria, blood pressure, infusion reactions, signs and symptoms of GI perforation, abscess, or fistula, signs and symptoms of bleeding, and signs and symptoms of thromboembolism
Administration		
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	Yes	Hazardous drug; use appropriate precautions for receiving, handling, administration, and disposal
Special delivery system (e.g. pump)?	None	
Documentation required? (e. g. double check)	None	
Nurse education?	Yes	Hazardous drug; use appropriate precautions for receiving, handling, administration, and disposal
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?	Yes	Requires monitoring of CBC, proteinuria, blood pressure, infusion reactions, signs and symptoms of GI perforation, abscess, or fistula, signs and symptoms of bleeding, and signs and symptoms of thromboembolism
Follow-up laboratory tests?	Yes	CBC with differential before each cycle, obtain urine dipstick and collect 24 hour urine in patients with ≥2+ reading or proteinuria, asses blood pressure every 2-3 weeks
Education?	Yes	Adverse effects - bleeding, blood clots, abdominal pain, constipation, vomiting, or fever; females of reproductive potential should be educated on the importance of not becoming pregnant and using reliable birth control while on this medication

FORMULARY REVIEW

GENERIC NAME: Trastuzumab-anns (Amgen), trastuzumab-dkst (Mylan)

PROPRIETARY NAME: *Kanjinti*® (Amgen), *Ogivri*® (Mylan)

INDICATIONS:

FDA Approved
• Adjuvant treatment of HER2 overexpressing breast cancer • Treatment of metastatic HER2 overexpressing breast cancer • Treatment of metastatic HER2 overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma
Non-FDA Approved
• Breast cancer (early stage, locally advanced, or inflammatory), neoadjuvant treatment, HER2+ • Endometrial cancer (uterine serous), advanced or recurrent, HER2-positive

THERAPEUTIC CATEGORY: Antineoplastic Agent/HER2 antagonist

PHARMACOKINETICS:

Metabolism	None known
Excretion	Will decrease to ~3% by 7 months following 7 months
Cmax (mg/L)	• 3-weekly dosing at steady state: o 179 mcg/mL in breast cancer patients o 131 mcg/mL in gastric cancer patients • Weekly dosing at study state: o 109 mcg/mL
Bioavailability (%)	N/A
t ½ (hr)	Time to steady state is 9 weeks in patients with metastatic cancer and 12 weeks in breast cancer
AUC (mg*day/mL)	• 3-weekly dosing at steady state: o 1794 mcg*day/mL in breast cancer patients o 1338 mcg*day/mL in gastric cancer patients • Weekly dosing at steady state: o 1765 mcg*day/mL
Clearance	• 0.173-0.283 L/day in patients with breast cancer who received trastuzumab loading dose of 8 mg/kg IV followed by 6 mg/kg IV every 3 weeks • 0.201-0.244 L/day in patients with breast cancer who received 4 mg/kg IV followed by 2 mg/kg IV weekly • 0.189-0.337 L/day in patients with metastatic gastric cancer and at steady state

SPECIAL POPULATIONS:

Pregnancy	Exposure during pregnancy may result in oligohydramnios and oligohydramnios sequence (pulmonary hypoplasia, skeletal malformations and neonatal death). Women of reproductive potential should use effective contraception during treatment and for at least 7 months after the last trastuzumab dose.
Lactation	It is not known if trastuzumab is present in human milk. Because many immunoglobulins are secreted in milk, and the potential for serious adverse reactions in the breastfed infant exists, the decision to discontinue trastuzumab or discontinue breastfeeding during treatment should take in account the benefits of treatment to the mother. The 7-month wash out period for trastuzumab should be considered for decisions regarding breastfeeding after treatment is completed.
Pediatrics	The safety and effectiveness of trastuzumab products in pediatric patients have not been established.
Geriatrics	No overall differences in safety or efficacy were observed between subjects 65 years of age or older and younger subjects.
Hepatic Impairment	The pharmacokinetics of trastuzumab in hepatic impairment is unknown.
Renal Impairment	No clinically significant differences were observed in the pharmacokinetics of trastuzumab in patients with mild renal impairment (CLcr 60 to 90 mL/min) or moderate renal impairment (CLcr 30 to 60 mL/min). The

	pharmacokinetics of trastuzumab in patients with severe renal impairment, end-stage renal disease with or without hemodialysis is unknown.

CLINICAL STUDIES:

2018 LILAC Study: Kanjinti (ABP 980)	
METHODS	
Study Design	Randomized, multi-center, double-blind, active-controlled, phase III equivalence trial
Patient Enrollment Inclusion	• Female >=18 yo • Histologically confirmed invasive breast cancer with Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1 • Planned surgical resection of tumor with lymph node dissection and adjuvant chemotherapy • HER2-positive • Known estrogen-receptor and progesterone-receptor status at study entry • Measurable disease in the breast after diagnostic biopsy • Left ventricular ejection fraction (LVEF) of at least 55%
Patient Enrollment Exclusion	• Presence of bilateral breast cancer or known distant metastases • Previous treatment for primary breast cancer, including chemotherapy, a biological agent, radiotherapy, or surgery; concomitant active malignancy • Malignant disease in the previous 5 years, except treated basal-cell carcinoma of the skin or carcinoma in situ of the cervix
Outcome Measures	Co-primary efficacy endpoints: risk difference and risk ratio (RR) of pathological complete response, defined as the absence of invasive tumor cells in the breast tissue and in axillary lymph nodes regardless of ductal carcinoma in situ. Safety assessments: Incidence of treatment-emergent adverse events, changes in LVEF, exposure to investigational product and paclitaxel, and formation of antibodies against an investigational product (immunogenicity).
Treatment Plan	• After screening, patients entered the 24-week neoadjuvant treatment phase. o Initial 12-week run-in chemotherapy period (clinical response was not assessed) o Intravenous epirubicin 90 mg/m² and cyclophosphamide 600 mg/m² every 3 weeks for 4 cycles • Random assignments to one of three treatment groups: ABP 980, trastuzumab, or neoadjuvant trastuzumab followed by adjuvant ABP 980. o Neoadjuvant treatment: 1 cycle of 8 mg/kg investigational product (i.e., either ABP 890 or trastuzumab) o If the loading dose was tolerated, patients received 3 cycles of trastuzumab or ABP 980 6 mg/kg every 3 weeks. o Patients also received intravenous paclitaxel 175 mg/m² with all doses of investigational product (or 80 mg/m² every week for 12 cycles if that was the local standard of care). • Patients underwent lumpectomy or mastectomy with sentinel or axillary lymph node dissection within 3–7 weeks of receiving the last dose of neoadjuvant investigational product, then entered the adjuvant phase. o Patients either continued with ABP 980 or trastuzumab (dose 6 mg/kg) or switched from trastuzumab to ABP 980 6 mg/kg every 3 weeks for up to 1 year after the first dose of neoadjuvant treatment.
RESULTS	
Outcomes Summary	172 (48%) of 358 patients who received neoadjuvant ABP 980 and 137 (41%) of 338 patients who received neoadjuvant trastuzumab achieved a pathological complete response in breast tissue and axillary nodes based on local laboratory assessments. The risk difference (ABP 980 minus trastuzumab) of pathological complete response was 7.3%. The RR (ABP 980 vs trastuzumab) of pathological complete response was 1.188. The primary endpoint of pathological complete response was not met because the upper boundaries of the 90% CIs for risk difference and RR exceeded the predefined equivalence margins. In the sensitivity analyses based on central pathology review of tumor samples, 162 (48%) of 339 patients in the ABP 980 group and 138 (42%) of 330 in the trastuzumab group showed pathological complete response in breast tissue and axillary nodes. The overall incidence of adverse events in the two treatment groups during both the neoadjuvant and adjuvant phases was similar. No differences in the incidence of events of interest

	between treatment groups in the neoadjuvant or adjuvant phases.
Author's Conclusion	Safety, efficacy, and clinical outcomes did not differ for the biosimilar ABP 980 and trastuzumab reference product in women with HER2-positive early breast cancer. This is the first study of a trastuzumab biosimilar encompassing a single-switch design from the reference product to a biosimilar, which allowed assessment of the clinical safety and immunogenicity of this approach to treatment.
2017 Phase III HERiTAge trial: Ogivri	
METHODS	
Study Design	Multi-center, double-blind, randomized, parallel-group, phase III
Patient Enrollment Inclusion	• Male or female • HER2-positive breast cancer without prior exposure to chemotherapy or trastuzumab in the metastatic setting • ECOG performance status of 0 to 2 • LVEF within institutional range • At least 1 year since adjuvant therapy with trastuzumab • Patients with newly detected central nervous system metastases had to have stable disease following treatment (e.g., radiotherapy, stereostatic surgery) • Hormonal agents had to be discontinued before the beginning of study therapy
Patient Enrollment Exclusion	• History of unstable angina • Heart failure • Myocardial infarction less than 1 year from randomization • Other clinically significant cardiac disease • Grade 2 or higher peripheral neuropathy according to the national Cancer Institute Common Terminology Criteria for Adverse Events version 4.03 • History of any other cancer within 5 years prior to screening with the exception of in situ cancers or non-melanomatous skin cancers • Any significant illness that would increase the risk of treatment or impede evaluation of response in the judgment of treating physician
Outcome Measures	To compare the overall response rate (ORR) and assess the safety of proposed trastuzumab biosimilar plus a taxane or trastuzumab plus a taxane in patients without prior treatment for HER 2 positive metastatic breast cancer.

Treatment Plan	• Trastuzumab (Herceptin; Roche Pharma AG) or the proposed biosimilar (MYL-1401O; Mylan) was administered as an intravenous infusion every 3 weeks
	• Initial 8-mg/kg loading dose was administered over 90 minutes, followed by dosing every 3 weeks of 6 mg/kg over 30 minutes.
	• Choice of taxane (docetaxel or paclitaxel) was by investigator decision:
	  o Docetaxel was administered at 75 mg/m2 every 3 weeks and paclitaxel at 80 mg/m2 weekly
	  o Paclitaxel could be omitted by investigator choice for 1 week every 4 weeks
	• The proposed biosimilar plus a taxane or trastuzumab plus a taxane was administered for a minimum of 8 treatment cycles (1 treatment cycle = 3 weeks based on trastuzumab administration)
	• In patients with responding or stable disease, chemotherapy could be discontinued after 8 treatment cycles; trastuzumab was continued every 3 weeks until disease progression occurred
	• Tumor assessments were conducted every 6 weeks and responses were confirmed with a second tumor assessment at least 4 weeks after the first response.

RESULTS	
Outcomes Summary	The primary outcome was week 24 overall response rate defined as complete or partial response. Equivalence boundaries were 0.81 to 1.24 with a 90% CI for ORR ratio (proposed biosimilar/trastuzumab) and −15% to 15% with a 95% CI for ORR difference. Secondary outcome measures included time to tumor progression, progression-free and overall survival at week 48, and adverse events.
Author's Conclusion	Among women with HER2-positive metastatic breast cancer receiving taxanes, the use of a proposed trastuzumab biosimilar compared with trastuzumab resulted in an equivalent overall response rate at 24 weeks. Further study is needed to assess safety and long-term clinical outcome.

COMPARATIVE EFFICACY:
A single biological product that is already FDA approved based on a full evaluation of safety and efficacy data is called a reference product. A proposed biosimilar product is compared to and evaluated against a reference product to ensure the product is both highly similar and has no clinically meaningful differences. Kanjinti and Ogivri are among the first several biosimilars to be approved as therapy for HER2-positive metastatic breast cancer. Kanjinti is available for purchase, but Ogivri is not yet available. The phase III LILAC study showed safety, efficacy, and clinical outcomes did not differ for Kanjinti and trastuzumab reference product in women with HER2-positive early breast cancer. The phase III HERiTAge trial showed that Ogivri had similar overall response rates at 24 weeks when compared to trastuzumab in patients with HER2-positive metastatic cancer.

WARNING AND PRECAUTIONS:
- Cardiomyopathy
- Infusion reactions
- Embryo-fetal toxicity: Verify the pregnancy status of females of reproductive potential prior to the initiation of Ogivri.
- Pulmonary toxicity
- Exacerbation of chemotherapy-induced neutropenia

BLACK BOX WARNINGS:
- Cardiomyopathy, especially when administered with anthracycline-containing chemotherapy.
    - Evaluate left ventricular function in all patients prior to and during treatment with trastuzumab. Discontinue trastuzumab treatment in patients receiving adjuvant therapy and withhold trastuzumab in patients with metastatic disease for clinically significant decrease in left ventricular function.
- Infusion reactions and pulmonary toxicity
    - Symptoms usually occur during or within 24 hours of administration. Interrupt trastuzumab infusion for dyspnea or clinically significant hypotension. Monitor patients until symptoms completely resolve. Discontinue trastuzumab for anaphylaxis, angioedema, interstitial pneumonitis, or acute respiratory distress syndrome.
- Embryo-fetal toxicity
    - Exposure to trastuzumab products during pregnancy can result in oligohydramnios and oligohydramnios sequence manifesting as pulmonary hypoplasia, skeletal abnormalities, and neonatal death. Advise patients of these risks and the need for effective contraception.

CONTRAINDICATIONS: None

ADVERSE REACTIONS:

Phase III LILAC Study in breast cancer: Kanjinti (ABP 980)												
	ABP 980 (n=349)				**Trastuzumab (n=171)**				**Switched from adjuvant trastuzumab to ABP 980 (n=171)**			
	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5	Grade 1-2	Grade 3	Grade 4	Grade 5
Infusion Reactions	26 (8%)	2 (1%)	0	0	12 (7%)	2 (1%)	0	0	17 (10%)	2 (1%)	1 (1%)	0
Neutropenia	35 (10%)	2 (1%)	1 (<1%)	0	14 (8%)	2 (1%)	0	0	12 (7%)	1 (1%)	00	
Infections	50 (14%)	4 (1%)	0	0	15 (9%)	2 (1%)	0	0	21 (12%)	1 (1%)	0	1 (1%)
Hypersensitivity	11 (3%)	0	0	0	7 (4%)	0	0	0	8 (5%)	0	0	0
Heart failure	2 (1%)	0	0	0	1 (1%)	0	0	0	0	1 (1%)	0	0
Pulmonary toxicity	4 (1%)	0	0	0	1 (1%)	1 (1%)	0	0	0	1 (1%)	0	0

Phase III Heritage study in breast cancer: Ogivri		
	traztuzumab-dkst+taxane	**traztuzumab+ Taxane**
Cardiovascular		
Central Nervous System		
Asthenia	22%[a]	16%[a]
Headache	6%	6% [a]
Gastrointestinal		

Diarrhea	21%[a]		21%[a]	
Nausea	20%[a]		14%[a]	
Vomiting	11%[a]		8%[a]	
Decreased appetite	9%[a]		10%[a]	
Cough	6%[a]		7%[a]	
Hematologic and Oncologic				
Alopecia	58%[a]		55%[a]	
Neutropenia	58%[a]	28%[b]	53%[a]	25%[b]
Leukopenia	17%[a]	2%[b]	21%[a]	5%[b]
Anemia	16%[a]		16%[a]	
Neutropenia with fever	5%[b]		4%[ba]	
Hepatic				
ALT elevation	7%[a]		9%[a]	
AST elevation	5%[a]		9%[a]	
Infection				
Urinary tract infection	9%[a]		7%[a]	
Metabolic				
Hyperglycemia	5% [a]		7%[a]	
Neuromuscular & Skeletal				
Peripheral neuropathy	23% [a]		25%[a]	
Fatigue	9% [a]		13%[a]	
Myalgia	9% [a]		9%[a]	
Arthralgia	12% [a]		9%[a]	
Renal				
Respiratory				
Dyspnea	5% [a]		7%[a]	
Pneumonia	2%[b]		2%[b]	
Skin				
Alopecia	58% [a]		55%[a]	
Pyrexia	9% [a]		12%[a]	
Rash	9% [a]		9%[a]	
Nail disorder	7% [a]		8%[a]	
Systemic				
Bone pain	7% [a]		5%[a]	
Infusion related reaction	7% [a]		5%[a]	

[a]Treatment emergent adverse events by week 24 in more than 5% of patients in either treatment group.
[b]Serious adverse events as defined by the investigator as grade 4 requiring hospitalization by week 24 in at least 2% in either treatment group.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:

Interacting Drug	Effect
Anthracyclines	May enhance the cardiotoxic effect of Ogivri, when possible avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab.
Immunosuppressants	May enhance the neutropenic effect
Paclitaxel (conventional)	May decrease the serum concentration of paclitaxel. Paclitaxel may increase the serum concentration of trastuzumab.

DOSING AND ADMINISTRATION:
Adult Dosing/Indication and Administration
Adjuvant Treatment, breast cancer

- Administer according to one of the following doses and schedules for a total of 52 weeks of trastuzumab therapy:
  - During and following paclitaxel, docetaxel, or docetaxel/carboplatin
    - Initial dose of 4 mg/kg as IV infusion over 90 minutes then at 2 mg/kg as an IV infusion over 30 minutes weekly during chemotherapy for the first 12 weeks (paclitaxel or docetaxel) or 18 weeks (docetaxel/carboplatin)
    - One week following the last weekly dose of trastuzumab, administer trastuzumab at 6 mg/kg as an IV infusion over 30 to 90 minutes every 3 weeks
  - As a single agent within 3 weeks following completion of multi-modality, anthracycline-based chemotherapy regimens:

- Initial dose at 8 mg/kg as an IV infusion over 90 minutes
- Subsequent doses at 6 mg/kg as an IV infusion over 30 to 90 minutes every 3 weeks
- Extending adjuvant treatment beyond one year is not recommended

Metastatic Treatment, breast cancer

- Administer trastuzumab, alone or in combination with paclitaxel, at initial dose of 4 mg/kg as a 90 minute IV infusion followed by subsequent once weekly doses of 2 mg/kg as a 30 minute IV infusion until disease progression

Metastatic Treatment, gastric cancer

- Administer trastuzumab at an initial dose of 8 mg/kg as a 90 minute IV infusion followed by subsequent doses of 6 mg/kg as an IV infusion over 30 to 90 minutes every 3 weeks until disease progression

Toxicity

- Infusion reactions:
  - Decrease the rate of infusion for mild or moderate infusion reactions
  - Interrupt the infusion in patients with dyspnea or clinically significant hypotension
- Cardiomyopathy:
  - Assess LVEF prior to initiation of trastuzumab and at regular intervals during treatment. Withhold trastuzumab dosing for at least 4 week for either of the following:
    - Greater than or equal to 16% absolute decrease in LVEF from pre-treatment values
    - LVEF below institutional limits of normal and greater than or equal to 10% absolute decrease in LVEF from pretreatment values

RECOMMENDED MONITORING:

- Cardiac monitoring: conduct thorough cardiac assessment, including history, physical examination, and determination of LVEF by echocardiogram or MUGA scan. The following schedule is recommended:
  - Baseline LVEF measurement immediately prior to initiation of trastuzumab
  - LVEF measurements every 3 months during and upon completion of trastuzumab
  - Repeat LVEF measurement at 4 week intervals if trastuzumab is withheld for significant left ventricular cardiac dysfunction
  - LVEF every 6 months for at least 2 years following completion of trastuzumab as a component of adjuvant therapy
- Pregnancy: Test for pregnancy prior to treatment in women of reproductive potential
- Vital signs during infusion, signs and symptoms of infusion reactions
- Signs and symptoms of pulmonary toxicity

PHARMACOECONOMICS/COST:

Product (Drug, Strength, Form)	Cost/vial	Cost per milligram
Kanjinti 420 mg vial	$3367.51	$8.02 (23% savings)
Herceptin 150 mg vial	$1558.42	$10.39

CONCLUSION & RECOMMENDATION:

The following restrictions were approved by the CHI System P&T committee and it is recommended to adopt the following ordering restrictions for all trastuzumab biosimilars and Herceptin:

3. Trastuzumab-anns (Kanjinti®) and other trastuzumab biosimilars:
   a. Restricted to outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization.
4. Trastuzumab (Herceptin)
   a. If a trastuzumab biosimilar is not available or payer-approved, may be used in the outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization

The Epic treatment regimen for Herceptin will have the following order instructions added: "Pharmacy may substitute biosimilar product per P&T committee approved restriction criteria."

FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)

Medication Management Step	Identified Risk	Steps for Prevention
Selection & Procurement		
Therapeutic interchange?	No	N/A
Special Ordering Requirements?	No	N/A
Storage		
LASA* separation of stock?	No. None deemed significant	N/A

Medication Management Step	Identified Risk	Steps for Prevention
Special storage (e.g. refrigeration, protect from light, controlled substance)?	Vials must be stored in the refrigerator and protected from light	Standard procedure for other refrigerated medications
Pharmacist/Technician Education?	Lack of education on appropriate use	Provide education
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	No	N/A
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	No adjustments for renal/hepatic. Dose adjustments for cardiac toxicity and infusion related-reactions	Follow package insert recommendations
Drug Interactions?	Anthracyclines: May enhance the cardiotoxic effect of trastuzumab, when possible avoid anthracycline-based therapy for up to 7 months after stopping trastuzumab; Immunosuppressants: May enhance the neutropenic effect	Monitor cardiac function (LVEF), monitor CBC + differential, platelets and ANC
Pregnancy?	Exposure during pregnancy may result in oligohydramnios and oligohydramnios sequence (pulmonary hypoplasia, skeletal malformations and neonatal death). Women of reproductive potential should use effective contraception during treatment and for at least 7 months after the last trastuzumab dose.	Avoid use in pregnancy. Recommend contraception during treatment and for at least 7 months after the last dose.
Absolute Contraindications?	None	N/A
Requires Order Set, Protocol, concomitant therapy with another drug?	No	N/A
LASA* nomenclature issues?	No major issues	N/A
Prescriber education?	No	N/A
Processing, Preparing, & Dispensing		
High-risk drug double check?	Yes	Two pharmacist chemotherapy check
Drug Interaction check in place?	Interaction between anthracyclines and immunosuppressants	Provide staff education and ensure it is built in the interaction-checking function of EPIC
LASA* computer warnings?	No	N/A
Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)?	No	N/A
Packaging/Labeling (e.g. prepacking)?	No	No
Dispensing (e.g. auxiliary labeling, light protection, refrigeration)?	Yes	Provide auxiliary labels to indicate the need for refrigeration and yellow chemotherapy bag to encase the medication while out for delivery
Documentation required (e.g. double check, worksheet)?	Yes	Pharmacist double check
Pharmacist/Technician Education?	No	N/A
Administration		
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	Trastuzumab should be handled using appropriate precautions for receiving, handling, administration, and disposal. Gloves (single) should be worn during receiving, unpacking, and placing in storage. High risk double check should be performed to ensure appropriate product is being administered. Not be administered with D5W. Not to be administered as IV push or by rapid bolus. Should not be mixed with any other medications.	Educate pharmacist, technicians and nursing staff. Insert administration instruction in EPIC within order instructions in the MAR.
Special delivery system (e.g. pump)?	No	N/A
Documentation required? (e. g. double check)	No	N/A
Nurse education?	Administration, storage and handling instructions	Provide education and auxiliary labels when possible
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?	See risks identified above in regards to interactions. Monitor for safety while administering trastuzumab to the patient.	Follow established guidelines, practices for monitoring for safety, including package insert instructions for toxicity (infusion-related reactions)
Follow-up laboratory tests?	Yes	Monitor cardiac function (LVEF), monitor CBC + differential, platelets and ANC
Education?	Pharmacists and providers should be educated on appropriate clinical utilization.	Provide education

FORMULARY UPDATE

GENERIC NAME: Pentamidine isethionate (parenteral)

PROPRIETARY NAME: Pentam®

BACKGROUND:
Pentamidine is an antifungal agent FDA approved for treatment of Pneumocystis jirovecii (formerly Pneumocystis carinii, PJP) pneumonia. Off-label use includes prevention of PJP in non-HIV infected patients and for trypanosomiasis infection. For patients with cancer or HIV/AIDS and at high risk of Pneumocystis pneumonia caused by infection, pentamidine is an alternative agent for prevention or treatment of infection of PJP. Significant adverse reactions include nephrotoxicity, electrolyte disorders, severe and potentially fatal hypotension (5%) following a single dose, hypoglycemia, hematologic abnormalities (-penias), and elevated hepatic enzymes.

The 2019 Guidelines for Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults and Adolescents recommend clinicians to consider using intermittently administered parenteral pentamidine for prophylaxis only in situations in which TMP-SMX or the recommended alternative prophylactic regimens cannot be administered or are not tolerated (CIII recommendation).

The 2019 National Comprehensive Cancer Network (NCCN) guidelines for Prevention and Treatment of Cancer-Related Infections recommends TMP-SMX desensitization or atovaquone, dapsone, or pentamidine (aerosolized or IV) when PJP prophylaxis is required in patients who are TMP-SMX intolerant (2A recommendation).

It is recommended to develop an ordering "panel" for Epic EHR as listed below:

IV Pentamidine (Pentam)

Ordering Restrictions:

1) Infectious disease physicians
   -OR-
2) For use as an alternative agent to PO TMP-SMX for PJP prophylaxis in hematology/oncology patients

1) Nursing Interventions:
   a. Vitals: Blood pressure monitoring every 15 minutes during infusion
   b. Patient should remain in the supine position during infusion
   c. If a drop in blood pressure ≥ 20 mmHg from baseline occurs or BP <80/50 mmHg, stop pentamidine infusion, notify MD & begin lactated ringers IV fluid bolus
   d. If allergic reaction occurs, initiate anaphylaxis & acute drug hypersensitivity protocol & call MD.

2) Labs:
   a. Baseline CMP
   b. Baseline CBC

3) Medications:
   a. Pentamidine 4 mg/kg IV x 1 dose (max dose: 300 mg), infuse over 2 hours
      i. If available, infuse via central line
      ii. If peripheral IV site, observe for infiltration/phlebitis
   b. Lactated Ringers 500 mL IV bolus x1 PRN drop in SBP ≥ 20 mmHg from baseline or BP <80/50 mmHg. Notify MD.
   c. Ondansetron 4 mg IV/PO q4 prn for nausea/vomiting

RECOMMENDATION/DISCUSSION:
It is recommend to implement the above restriction criteria for IV pentamidine orders. The above panel will be tabled for build in Epic EHR during the optimization phase since the timeframe for new panel build for go-live has passed. The above restriction criteria will be implemented immediately.

FORMULARY INTERCHANGE

Synthetic Glucocorticoids

Ordered	**Substitution**
Prednisolone tablet or liquid	Methylprednisolone tablet at 20% dose reduction

Medication	**Usage (monthly)**	**Cost**	**Cost/Dose**
Millipred (prednisolone) 5 mg tab	< 5 doses	$13.06/tablet	$13.06 per 5 mg dose
Methylprednisolone 4 mg tab	~ 20 doses	$0.30 per tab	$0.30 per 4 mg dose

Recommendation/Discussion:

Prednisolone and methylprednisolone are intermediate-acting glucocorticoids and therefore have similar durations of action (12 to 36 hours). Methylprednisolone has slightly higher anti-inflammatory activity relative to hydrocortisone than prednisolone (5 to 4, respectively). Prednisolone and methylprednisolone are currently designated as formulary agents.

Due to low usage and higher cost compared to methylprednisolone, it is recommend to remove prednisolone oral products from formulary and interchange all orders for prednisolone to methylprednisolone tablets at a twenty percent dose reduction, as stated in the table above. For example, an order for prednisolone 5 mg would be substituted to methylprednisolone 4 mg.

FORMULARY INTERCHANGE

Ophthalmic Prostaglandin Analogs

Ordered	**Substitution**
Bimatoprost (Lumigan®) 0.03%	Latanoprost (Xalatan®) 0.005% at same dose
Travoprost (Travatan®) 0.004%	Latanoprost (Xalatan®) 0.005% at same dose
Tafluprost (Zioptan®) 0.0015%	Latanoprost (Xalatan®) 0.005% at same dose
Latanoprostene bunod (Vyzulta®) 0.024%	**Latanoprost (Xalatan®) 0.005% at same dose**

Medication	**Cost/bottle (2.5 mL)**
Latanoprost (Xalatan®) 0.005%	$5.00
Latanoprostene bunod (Vyzulta®) 0.024%	$177.33

Recommendation/Discussion:

Vyzulta (latanoprostene bunod) ophthalmic solution is a prostaglandin analog indicated for the reduction of intraocular pressure in patients with open angle glaucoma or ocular hypertension. The dosage is 1 drop applied to each affected eye once daily in the evening, the same dosage as latanoprost ophthalmic solution.
It is recommended to add Vyzulta ophthalmic solution to the existing formulary interchange table for prostaglandin analogs and therefore substitute all orders for Vyzulta to latanoprost ophthalmic solution at the same dosage**.**

Antibiotic Dosing Guidelines: CRRT

The antimicrobial stewardship committee recommends the below changes to the renal dose adjustment protocol for the dosing of patients receiving CRRT. Patients on CRRT frequently have an increased volume of distribution; a loading dose will be utilized if not initiating therapy at full dose for rapid target attainment. Additionally, flow rates of >2 L/hr and residual renal function are rarely addressed in the literature. For patients receiving high flow rates, dosing intervals should be decreased to maintain concentrations above MIC for time-dependent antibiotics, specifically for agents with limited protein binding and low volumes of distribution. When a dosing range is indicated in the table below, a more aggressive dose is recommended for severe infections.

Drug	**Loading Dose**	**Maintenance Dosage for CRRT**			**High Dose***
		CVVH	CVVHD	CVVHDF	
Ampicillin	2 g	1-2 g q8-12h	1-2 g q8h	1-2 g q6-8h	2 g q4-6h
Ampicillin/sulbactam	3 g	1.5-3 g q8-12h	1.5-3 g q8h	1.5-3 g q6-8h	3 g q6h
Aztreonam	2 g	1-2 g q12h	1 g q8h or 2 g q12h	1 g q8h or 2 g q12h	2 g q8h
Cefazolin	2 g	1-2 g q12h	1 g q8h or 2 g q12h	1 g q8h or 2g q12h	2 g q8h
Cefepime	2 g	1-2 g q12h	1 g q8h or 2 g q12h	1 g q8h or 2 g q12h	1 g q6h or 2 g q8h
Ceftaroline	600 mg	400-600 mg q12h			600mg q8h
Ceftazidime/avibactam	2.5 g	1.25 g IVq8h			2.5 g q8h (based on ceftazidime data)
Ceftolozane/tazobactam	3 g	750 mg q8h	1.5 g q8h	1.5 g q8h	1.5 g q8h (data lacking for higher dose)
Ciprofloxacin	N/A	400 mg q12-24h	400 mg q12-24h	400 mg q12h	400 mg q8-12h
Levofloxacin	N/A	750 mg q48h	750 mg q48h	750 mg q24h	750 mg q24h
Meropenem	1 g	500 mg-1g q12h	500 mg-1g q8-12h	500 mg-1g q8-12h	500 mg q6h/ 1 g q8h
Meropenem/vaborbactam	4 g	1-2 g q8h (extended)			2 g q8h (extended); based on meropenem data
Piperacillin/tazobactam	4.5 g	3.375-4.5 g IV q8h (extended)			

**High Dose Parameters:*

- Ultrafiltration/dialysate flow rate of >2 L/hr
- Residual renal function

Recommendation/Discussion:

To ensure adequate antibiotic concentrations in patients on CRRT, it is recommended to adopt the above CRRT antibiotic dosing guidelines for inclusion into the existing pharmacist renal dose adjustment protocol. All pharmacists will be educated on the appropriate use of these guidelines and will write orders for dose adjustments per protocol.

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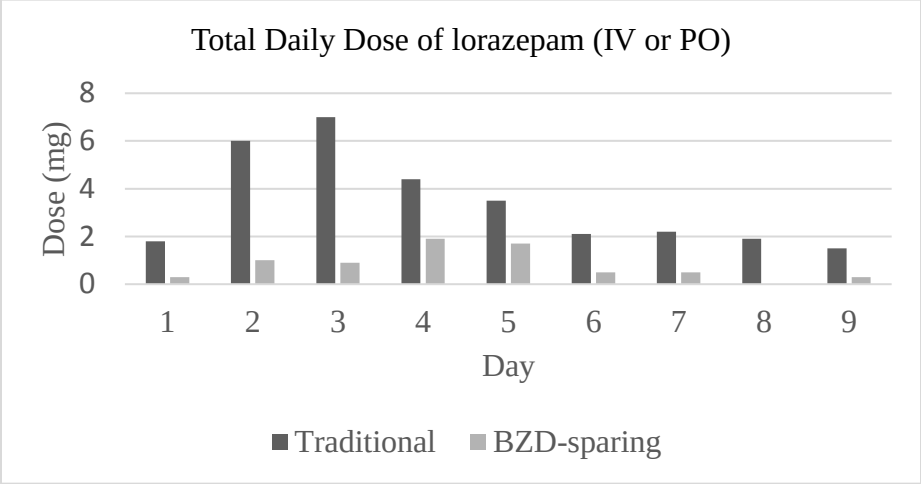
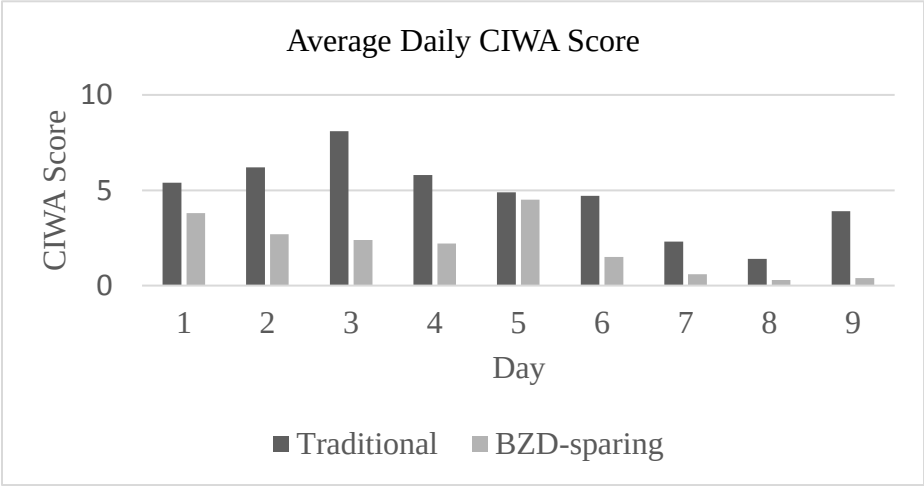
8. Hanson E, Bucher M, Jakob W, et al. Pharmacokinetics of levofloxacin during continuous veno-venous hemofiltration. Intensive Care Med. 2001;27:371-375.

Evaluation of a Benzodiazepine-Sparing Alcohol Withdrawal Management Protocol

	Traditional *(n=20)*	**BZD-Sparing** *(n=20)*
Baseline Demographics		
Average Age (years)	54	59.3
Gender (male)	75% (15)	80% (16)
Primary Diagnosis EtOH-related	45% (9)	30%(6)
Length of Stay (days)	9.4	7.7
Outcomes		
Primary Outcomes		
		
		
Secondary Outcomes		
Transfer to ICU	20% (4)	10% (2)
Intubation	10% (2)	5% (1)
Seizure	5% (1)	0
Adjunctive valproic acid	-	0
Adverse Effects (lethargy/sedation)	65% (13)	10% (2)

POLICY

Title: PRN ORDERS		
	Page 1 of 2	
Policy Number: MM-05422	Date Last Reviewed/Revised: 8/19	Valid Until: 8/22
Department(s) Affected: All Clinical Areas	Review Period: every 3 years	

OUTCOME: The use of PRN for medication orders will be qualified.

POLICY:
"PRN" orders require a reason or indication for use. The following meds only require an indication if different than what is listed.

Medication or Class of Medication	PRN Indication
Acetaminophen	Fever/pain
Albuterol	SOB/wheezing
Atropine/Diphenoxylate	Loose stools
Benzodiazepine (one time or more frequently)	Anxiety
Benzodiazepine at bedtime	Sleep
Bisacodyl	Constipation
Buprenorphine-Buprenex®	Pain
Codeine	Pain
Codeine/Acetaminophen	Pain
Cyclobenzaprine (Flexeril®)	Spasm
Diphenhydramine (other than bedtime)	Itching/allergic reaction
Docusate Sodium	Constipation
Fentanyl	Pain
Fleet enema	Constipation
Granisetron (Kytril®)	Nausea/vomiting
Guaifenesin	Cough
Guaifenesin/Dextromethorphan	Cough
Haloperidol	Agitation
Hydrocodone/Acetaminophen	Pain
Hydrocortisone rectal cream	Hemorrhoid
Hydromorphone	Pain
Ipratropium (Atrovent®)	SOB/wheezing
Ketorolac	Pain
Loperamide (Imodium®)	Loose stools
Maalox®	Indigestion
Meclizine	Dizziness
Metoclopramide	Nausea/vomiting
Milk of Magnesia®	Constipation
Morphine	Pain
Mylanta®	Indigestion
Nalbuphine	Pain
Nitroglycerin SL	Chest pain
Non-Steroidal Anti-Inflammatory	Pain
Ondansetron (Zofran®)	Nausea/vomiting
Oxycodone	Pain
Oxycodone/ Acetaminophen	Pain
Phenazopyridine (Pyridium®)	Dysuria
Prochlorperazine	Nausea/vomiting

Medication or Class of Medication	PRN Indication
Promethazine	Nausea/vomiting
Pseudoephedrine	Allergic rhinitis/nasal congestion
Senokot	Constipation
Simethicone	Gas
Temazepam (Restoril®)	Sleep
Tizanidine (Zanaflex®)	Spasm
Tramadol	Pain
Tums®	Indigestion
Zolpidem (Ambien®)	Sleep

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