Pharmacy & Therapeutics Committee Meeting

Private Dining Room

August 11, 2022 7:00 a.m.

Next Meeting Date: October 6, 2022 at 7:00 a.m.

PHARMACY AND THERAPEUTICS COMMITTEE

DATE: May 12, 2022 CALLED TO ORDER: 7:00 a.m.
LOCATION: Private Dining Room ADJOURNED: 8:00 a.m.

Voting Member Attendance:				Non-Voting Member Attendance:		Guests:
X	**Nathan Chamberlain, MD- Chairman**	X	**Matthew Kodsi, MD- Quality**	X	**Karen Babb, PharmD- Manager**	**Tina Mathew, Pharmacy Resident**
	Mark Anderson, MD- Infectious Disease	X	**Aditya Mandawat, MD- Cardiology**		Jamie Barrie, PharmD- Manager, HX	**Doug Dertien, Pharmacy Resident**
X	**Justin Blinn, MD- Anesthesiology**	X	**Daniel Marsh, PharmD- Director of Pharmacy**	X	**Chris Chastain- Admin Coordinator**	**Jessica Duke, Pharmacy Resident**
X	**David Dodson, MD- Hospitalist**	X	**Chad Paxson, MD- Intensivist**		Kenneth Dyer, PharmD- Operations Manager	**Gabby Hall, Pharmacy Student**
	Karen Frank, RN- Quality		Vimal Ramjee, MD- Cardiology	X	**Rodney Elliott- Purchasing**	**Drew Smith, Pharmacy Student**
	Sherry Fusco, RN- CNO		James Wahl, MD- Hospitalist, GA	X	**Lori Hammon, RN- Quality**	
	F. Lee Hamilton, MD- Hospitalist	X	**Richard Yap, MD- Hospitalist**	X	**Shannon Harris, RN- Infection Prevention**	
	William Haren, MD- Psychiatry				Kevin Hopkins, RT- Director of Resp Therapy	
				X	**Rachel Kile, PharmD- Clinical Manager**	
				X	**Farrah Reidt- Clinical Nutrition**	
				X	**Carey Smith, RPh- Manager, GA**	

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 2022 minutes were approved as submitted.	Approved	Complete
CommonSpirit Health System P&T Committee	**March 2022 Decision Brief:** The medication decisions that were approved at the CommonSpirit Health System P&T committee meeting were reviewed. All new system formulary medications or changes were either consistent with existing CHI Memorial formulary decisions or are described in the "Formulary Decisions & Therapeutic Interchanges" section of the minutes below, or will be reviewed at an upcoming P&T committee meeting.	Approved	Complete
Old Business	**A. Sedatives-Hypnotics for Sleep Policy:** At the February meeting, Rhonda recommended a best practice review for sleep in hospitalized patients. Doug Dertien provided a summary of the available literature, which is unfortunately lacking, however there is support for limiting the use of zolpidem in patients 65 years and greater. Dr. Paxson recommended revisiting the use of other medications ordered for sleep/sedation, such as benzodiazepines. Dr. Kodsi asked if a stepwise algorithm for sleep medications would be helpful. A workgroup will meet to review with Dr. Paxson, and will be sure to include a member of Memorial's Fall Prevention Team. No policy changes will be made at this time.	Informational	Complete
Formulary Decisions & Therapeutic Interchanges	**A. Pneumococcal vaccines:** The ACIP and CDC released new pneumococcal vaccine recommendations in January in light of the two new pneumococcal immunizations (Prevnar 20 and Vaxneuvance) entering the market. Rachel reviewed the monograph for newly developed pneumococcal 20-valent conjugate (Prevnar 20) vaccine and it was recommended to be added to formulary with the following restrictions for use: a. Post-splenectomy with no pneumococcal vaccination history b. Patients 65 years and older or with underlying medical conditions or other risk factors who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown AND where continuation of care is not likely (e.g. homeless) The committee also reviewed and approved the following formulary statuses for additional pneumococcal vaccines:	Approved	Complete

	a. Pneumococcal conjugate vaccine 15 valent (Vaxneuvance): Non-formulary b. Pneumococcal conjugate vaccine 13 valent (Prevnar 13): Non-formulary c. Pneumococcal polysaccharide vaccine 23 valent (Pneumovax 23): Formulary, with restrictions to post-splenectomy patients who have already received Prevnar 13		
	B. Post-splenectomy vaccines: Rachel presented the updated Post-Splenectomy Vaccine Schedule and Post-Splenectomy Vaccine Guidelines for patients which reflect utilization of the pneumococcal 20-valent conjugate (Prevnar 20) vaccine as the initial pneumococcal vaccine (replacing Prevnar 13). The schedule was also updated to reflect the ACIP and CDC recommendations if the patient has already received prior pneumococcal vaccination.	Approved	Complete
	C. Bezlotoxumab (Zinplava): Bezlotoxumab is a human monoclonal antibody approved for the reduction of the recurrence of Clostridioides difficile infection (CDI). The 2021 Infectious Diseases Society of America (IDSA) update on the management of CDI suggests bezlotoxumab as an adjunctive treatment with standard of care antibiotics for patients with a recurrent CDI episode within the last 6 months. It is a single IV infusion and the safety and efficacy of repeat administrations have not been studied. Heart failure occurred more frequently with bezlotoxumab in clinical trials. Infusion-related reactions are also likely. It was recommended to adopt the recommendation of the ASP Subcommittee and approve bezlotoxumab to formulary with restrictions as follows: a. Restricted to outpatient infusion only (subsequent to insurance approval or prior authorization) for patients with any of the following risk factors: i. ≥ 65 years old ii. History of one or more CDI episode in the past 6 months iii. Immunocompromised status iv. ≥2 points on the Zar score for severity ▪ 1 point each is given for age >60 years; temperature >38.3°C; albumin level <2.5 mg/dL; WBC count >15,000 cells/mm3 ▪ 2 points are given for endoscopic evidence of pseudomembranous colitis; treatment in ICU v. Dose: 10mg/kg (max: 1,000 mg) x 1 dose during administration of active CDI treatment. vi. Adjunctive therapy to prevent recurrent CDI. Use caution in patients with underlying congestive heart failure (CHF).	Approved	Complete
	D. C. diff treatment guidelines: Linda Johnson reviewed the updates to the CDI Clinical Pathway/Treatment Guidelines. Updates include the addition of fidaxomicin for first or subsequent recurrences, non-fulminant; bezlotoxumab as adjunctive therapy for outpatient use; and considerations for fecal microbiota transplantation and secondary prophylaxis with oral vancomycin. Routine use of probiotics is discouraged.	Approved	Complete
	E. Cobicistat (Tybost): Linda presented the drug monograph for cobicistat. Cobicistat is a pharmacokinetic (PK) enhancer for certain protease inhibitors and non-nucleoside reverse transcriptase inhibitors. Ritonavir is also utilized as a PK enhancer and is on formulary, but there are important PK distinctions between the two agents. Significant issues can arise when switching from cobicistat to ritonavir in certain patients with multiple comorbidities and concomitant medications. It was recommended to approve cobicistat (Tybost) to formulary with restrictions as follows: a. Ordering or approval by Infectious Disease for new therapy initiation	Approved	Complete

	b. Any provider may order to continue a patient's established home medication **F. Rifaximin (Xifaxan):** Rachel presented the anticipated cost savings (~$68,000 annually based on historical utilization) by converting all doses of 550 mg to 600 mg utilizing three 200 mg tablets instead of one 550 mg tablet. It was recommended to designate the rifaximin (Xifaxan®) 550 mg tablet as non-formulary and approve an automatic therapeutic interchange to convert all doses of 550 mg to 600 mg.		
	G. Anifrolumab-fnia (Saphnelo): Jessica Duke presented this new drug monograph. Anifrolumab-fnia is the first type 1 interferon (IFN) antagonist monoclonal antibody approved for adults with moderate to severe systemic lupus erythematosus (SLE) already receiving standard therapy. There is an increased risk of respiratory infections, infusion-related reactions, and herpes zoster with this medication compared to placebo. Memorial Rheumatologists have requested access to this medication for a few patients already and will be informed of the formulary decision. It was recommended to approve to formulary with the following restriction(s): Outpatient setting subsequent to insurance approval or prior authorization for FDA approved indications or payer approved off-label indications.	Approved	Complete
	H. Pafolacianine (Cytalux): Pafolacianine is a folate analog conjugated to a near-infrared (NIR) fluorescent dye. It is a novel imaging agent that targets folate receptors, which may be overexpressed in ovarian cancer. Pafolacianine is an adjunct for intraoperative identification of malignant lesions in adult women with a diagnosis, or high clinical suspicion, of ovarian cancer. Pafolacianine assists optical imaging during surgery by absorbing light in the NIR region and emitting fluorescence. It is not included in the NCCN ovarian cancer guidelines. In a phase 3 trial, 26.9% of patients in the study had a confirmed ovarian cancer lesion detected, but the patient-level false-positive rate was 20.2%. Based on unknown and limited drug supply, need for a capital purchase of equipment, and limitations in current evidence, it was recommended that pafolacianine should not be added to the formulary at this time and the formulary status may be revisited once the supply chain issues are addressed.	Approved	Complete
	I. Olanzapine/samidorphan (Lybalvi) to olanzapine-Therapeutic interchange: Olanzapine/samidorphan is the only second generation (atypical) antipsychotic and opioid antagonist combination medication, and was formulated specifically to decrease weight gain associated with olanzapine monotherapy. It is approved for the treatment of adults with schizophrenia and bipolar I disorder. Olanzapine/samidorphan is contraindicated in patients taking opioids or those who are undergoing acute opioid withdrawal. A seven day course of Lybalvi is $267.12, and a 7 day course of the highest dose of olanzapine (20 mg) is $5.36. Based on the specialized place in therapy, lower cost treatment options with similar efficacy, and contraindications with opioids, it was recommended to classify olanzapine/samidorphan as non-formulary. An automatic therapeutic interchange from olanzapine/samidorphan to the corresponding olanzapine monotherapy dose was also recommended.	Approved	Complete
	J. Erythropoietin stimulating agents: Recently, the manufacturer of Retacrit communicated an expected supply disruption of Retacrit. It was recommended to temporarily add Epogen and Procrit to formulary for use only when Retacrit is unavailable or the required dose cannot be made with the on-hand vial size(s) of Retacrit. An automatic pharmacist therapeutic interchange from Retacrit to Epogen or Procrit, based on product availability, was recommended while Retacrit is in short supply.	Approved	Complete
	K. Azelastine hydrochloride nasal spray: Azelastine nasal spray is currently a non-formulary medication, but the patient may use their own home supply, if available. Due to the workflow	Approved	Complete

	burden on staff and unlikely clinical significance of holding this medication for the duration of a hospitalization, It is recommended to designate azelastine nasal spray as non-formulary and will not be continued during hospitalization. New medication orders will be rejected at pharmacist order verification. **L. Medications for COVID-19:** Rachel reviewed the updates to the Medications for COVID-19 guidelines approved by the COVID medications subcommittee. It was recommended to add nirmatrelvir and ritonavir (Paxlovid) to formulary with restrictions for use; update the 3 day remdesivir course use criteria (for Incidental COVID+ (symptomatic) while admitted for non-COVID diagnosis); and updated the sotrovimab use criteria (note Sotrovimab is no longer authorized to treat COVID-19 in any U.S. region due to increases in the proportion of COVID-19 cases caused by the Omicron BA.2 sub-variant). Bebtelovimab was also added to formulary with restriction criteria.	Approved	Complete
Medication Use	**A. Collagenase ointment (Santyl):** Tina Mathew, pharmacy resident, presented the results of her medication use evaluation. She concluded that implementation of restriction criteria for prescribing and dispensing unit doses of Santyl was a cost-effective choice for our institution and the practices will be continued. **B. Angiotensin II (Giapreza):** Jessica Duke, pharmacy resident, presented the results of her medication use evaluation. The results demonstrated that out of 12 included patients over 19 months, there was high prescriber adherence to restriction criteria for use, however in-hospital mortality was 100% and there was suboptimal nursing titration of the medication. Medication administration instructions in the EHR have been revised to further limit titration errors, and additional EHR enhancements are planned to ensure optimal administration and monitoring is achieved. Angiotensin II will remain on formulary and a subsequent MUE will be performed following the implemented changes.	Approved Approved	Complete Complete
Policies	**A. Hypertonic Saline (Sodium Chloride) for Adults:** Policy changes to reflect updates in alignment with development of the Hyperosmolar Therapy Order set were reviewed.	Approved	Complete

There being no further business, the meeting was adjourned at 8:00 a.m. The next P&T meeting is **August 11, 2022 @ 7:00 a.m.**

Respectfully submitted,
Daniel Marsh, Director of Pharmacy; Rachel Kile, PharmD, Pharmacy Clinical Manager

Approved by,
Nathan Chamberlain, MD, Chairman

CSH SYSTEM PHARMACY AND THERAPEUTICS COMMITTEE DECISION BRIEF

May 2022 Decisions

NOTE: Local/divisional P&T committees may implement more restrictive statuses

Medication name	Medication used for	Formulary Decision				Restrictions (if applicable)/Comments	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	NonFormulary		
Tisotumab edotin-tftv (Tivdak)	Cervical cancer		Tivdak			Outpatient setting for FDA-approved indications or payor-approved off-label indications subsequent to insurance approval or prior authorization	Within 90 days of System P&T Committee approval
Loncastuximab tesirine-lpyl (Zynlonta)	Diffuse large B-cell lymphona		Zynlonta			Outpatient setting for FDA-approved indications or payor-approved off-label indications subsequent to insurance approval or prior authorization	Within 90 days of System P&T Committee approval
Pafolacianine (Cytalux)	Imaging agent that targets folate receptors, which may be over expressed in ovarian cancer				Cytalux		Within 60 days of System P&T Committee approval
Tacrolimus (Astragraf XL, Envarsus XR)	Immunosuppressant to prevent transplant rejection		Astagraf XL, Envarsus XR			• Inpatient use is restricted to established patients, patients whose levels are unstable on IR formulations or who experience toxicities on IR formulations. • Restricted to nephrology and transplant providers for initial transition to Envarsus XR or Astragraf XL • Use the patient's own supply if available	Within 90 days of System P&T Committee approval
Anifrolumab-fnia (Saphnelo)	Systemic lupus erythematosus		Saphnelo			Outpatient setting for FDA-approved indications or payor-approved off-label indications subsequent to insurance approval or prior authorization	Within 90 days of System P&T Committee approval
Inclisiran sodium (Leqvio)	Heterozygous familial hypercholesterolemia (HeFH) or clinical atherosclerotic				Leqvio		Within 60 days of System P&T Committee approval

Medication name	Medication used for	Formulary Decision				Restrictions (if applicable)/Comments	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	NonFormulary		
	cardiovascular disease (ASCVD)						
Insulin glargine	Blood glucose management				Lantus	Link to insulin glargine therapeutic interchange	Within 90 days of System P&T Committee approval
				Insulin glargine-yfgn			
Rifaximin	*C. Difficile* infection and hepatic encephalopathy				Rifaxamin 550mg tablets	Link to rifaximin therapeutic interchange	Within 90 days of System P&T Committee approval
				Rifaxamin 200mg tablets			
Epoetin alfa	Anemia			Epogen, Procrit, Retacrit			Within 90 days of System P&T Committee approval
Aducanumab-avwa	Alzheimer's disease	Aduhelm				Non-formulary criteria for use: 1. Medicare Patients - The Centers for Medicare & Medicaid Services (CMS) proposes to cover FDA approved monoclonal antibodies directed against amyloid for the treatment of Alzheimer's disease (AD) under Coverage with Evidence Development (CED) in CMS approved randomized controlled trials that satisfy the coverage criteria specified in Section C of the CMS National Coverage Analysis Decision Memo, and in trials supported by the National Institutes of Health (NIH). All trials must be conducted in a hospital-based outpatient setting. https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=Y&NCAId=305 2. For commercially insured patients - In OP setting, restricted for FDA-approved	Within 60 days of System P&T Committee approval

Medication name	Medication used for	Formulary Decision				Restrictions (if applicable)/Comments	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	NonFormulary		
						indications subsequent to insurance approval or prior authorization. 3. Facility Requirements - Facilities requesting access to order and administer must complete and submit for approval, the CSH "Aducanumab application". If approved, permission to order will be granted by CSH Pharmacy Procurement. Tertiary Neurology Center Application to Procure & Administer Non-Formulary Aduhelm	
Mafenide powder	Topical antibiotic		Mafenide acetate powder			Mafenide topical powder is restricted to topical application of open burn wounds when a skin substitute/graft is required (BTM, Integra)	Within 90 days of System P&T Committee approval
				Mafenide cream (Sulfamylon)			
Pentobarbital sodium	Status epilepticus or intracerebral pressure (ICP) crisis		Pentobarbital sodium (Nembutal)			Use only for status epilepticus or intracerebral pressure (ICP) crisis Restricted to cases refractory to all other therapies	Within 90 days of System P&T Committee approval
Liposomal bupivacaine (Exparel)	Pain				Exparel	Exparel pilot has ended	Facilities who participated in the pilot should implement within 60 days of System P&T Committee

THERAPEUTIC INTERCHANGES

Insulin glargine

Order	Interchange to
Insulin glargine (Lantus)	Insulin glargine-yfgn 1 unit: 1 unit at same interval as ordered

Rifaximin

Order	Interchange to
Rifaximin 550mg tablet any dose interval	Rifaximin total daily dose using the 200mg tablets

CSH SYSTEM PHARMACY AND THERAPEUTICS COMMITTEE DECISION BRIEF

July 2022 Decisions

NOTE: Local/divisional P&T committees may implement more restrictive statuses

Medication Name	Medication Used For	Formulary Decision				Restrictions and Therapeutic Interchanges	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	NonFormulary		
azelastine HCl	Treatment of allergic rhinitis				AZELASTINE 0.15% Nasal	Link to therapeutic interchange	Within 90 days of System P&T Committee approval
				AZELASTINE 0.1% Nasal			Within 90 days of System P&T Committee approval
olopatadine HCl	Treatment of allergic rhinitis				OLOPATADINE 0.6% Nasal	Link to therapeutic interchange	Within 90 days of System P&T Committee approval
iron sucrose complex	Iron replacement		VENOFER			• Patients with known hypersensitivity to sodium ferric gluconate • Pregnant and hospitalized postpartum women (ACOG supports use of sodium ferric gluconate as well) • Patients 6 years of age and younger	Within 90 days of System P&T Committee approval
primaquine phosphate	Antimalarial that may be used for opportunistic infections in HIV patients		PRIMAQUINE			Restricted to ordering or approval by ID, or HIV specialist for initiation of therapy, or for continuation of home medication.	Within 90 days of System P&T Committee approval

Medication Name	Medication Used For	Formulary Decision				Restrictions and Therapeutic Interchanges	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	NonFormulary		
cabotegravir (extended release injectable suspension)	HIV pre-exposure prophylaxis		APRETUDE			Restriction Criteria: Outpatient setting subsequent to insurance approval or prior authorization for FDA approved indications or payer approved off-label indications	Within 90 days of System P&T Committee approval
efgartigimod alfa-fcab	Generalized myasthenia gravis		VYVGART			Outpatient setting subsequent to insurance approval or prior authorization for FDA approved indications or payer approved off-label indication Rapid immunotherapies (plasma exchange and IVIG) are recommended for the inpatient setting	Within 90 days of System P&T Committee approval
finerenone	To reduce the risk of sustained estimated glomerular filtration rate (eGFR) decline, end stage kidney disease, cardiovascular death, non-fatal myocardial infarction, and hospitalization for heart failure in adult patients with chronic kidney disease (CKD) associated with type 2 diabetes (T2D)				KERENDIA		Within 60 days of System P&T Committee approval
maribavir	Cytomegalovirus treatment				LIVTENCITY		Within 60 days of System P&T Committee approval

Medication Name	Medication Used For	Formulary Decision				Restrictions and Therapeutic Interchanges	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	NonFormulary		
tezepelumab-ekko	Add-on treatment of severe asthma		TEZSPIRE			Outpatient setting subsequent to insurance approval or prior authorization for FDA approved indications or payer approved off-label indications	Within 90 days of System P&T Committee approval
pneumococcal 23-valent polysaccharide vaccine	Prevention of pneumococcal pneumonia		PNEUMOVAX 23			Restricted to pediatrics	Within 90 days of System P&T Committee approval
pneumococcal 13-valent conjugate vaccine	Prevention of pneumococcal pneumonia		PREVNAR 13			Restricted to pediatrics	Within 90 days of System P&T Committee approval
hepatitis B virus vaccine recombinant/PF	Prevention of hepatitis B		RECOMBIVAX HB (adult)			Outpatient use • no restrictions Inpatient use • 1 time dose for patients with a recent and known exposure to hepatitis B • Vaccination of an admitted patient about to undergo solid organ transplantation who is unlikely to be discharged to the outpatient prior to transplantation • To be given as part of normal pediatric vaccination series if patient is currently an inpatient, i.e., at 1 month of age if still inpatient • Vaccination should be deferred until outpatient for other inpatient populations, including	Within 90 days of System P&T Committee approval

Medication Name	Medication Used For	Formulary Decision				Restrictions and Therapeutic Interchanges	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	NonFormulary		
						patients with hepatitis C	
hepatitis B virus vaccine recombinant/PF	Prevention of hepatitis B		ENGERIX-B (pediatric)			Outpatient use • no restrictions Inpatient use • 1 time dose for patients with a recent and known exposure to hepatitis B • Vaccination of an admitted patient about to undergo solid organ transplantation who is unlikely to be discharged to the outpatient prior to transplantation • To be given as part of normal pediatric vaccination series if patient is currently an inpatient, i.e., at 1 month of age if still inpatient • Vaccination should be deferred until outpatient for other inpatient populations, including patients with hepatitis C	Within 90 days of System P&T Committee approval
hepatitis B virus vaccine recombinant/PF	Prevention of hepatitis B				ENGERIX-B (adult)		Within 90 days of System P&T Committee approval
hepatitis B virus vaccine recombinant/PF	Prevention of hepatitis B				RECOMBIVAX HB (pediatric)		Within 90 days of System P&T Committee approval

Medication Name	Medication Used For	Formulary Decision				Restrictions and Therapeutic Interchanges	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	NonFormulary		
atazanavir sulfate	HIV treatment		ATAZANAVIR			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
atazanavir sulfate/ cobicistat	HIV treatment				EVOTAZ	HIV medication restrictions and formulary status details	Within 60 days of System P&T Committee approval
doravirine/lamivudine/ tenofovir disoproxil fumarate	HIV treatment				DELSTRIGO	HIV medication restrictions and formulary status details	Within 60 days of System P&T Committee approval
ritonavir	HIV treatment		RITONAVIR			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
efavirenz	HIV treatment		EFAVIRENZ			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
lopinavir/ritonavir	HIV treatment		KALETRA			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
efavirenz/emtricitabine /tenofovir disoproxil fumarate	HIV treatment		ATRIPLA			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval

Medication Name	Medication Used For	Formulary Decision				Restrictions and Therapeutic Interchanges	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	NonFormulary		
abacavir sulfate/lamivudine	HIV treatment		EPZICOM			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
emtricitabine/tenofovir disoproxil fumarate	HIV treatment		TRUVADA			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
abacavir sulfate	HIV treatment		ABACAVIR			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
lamivudine	HIV treatment		LAMIVUDINE			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
fosamprenavir calcium	HIV treatment		FOS-AMPRENAVIR			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
nevirapine	HIV treatment		NEVIRAPINE			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
tenofovir disoproxil fumarate	HIV treatment		TENOFOVIR			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
lamivudine/zidovudine	HIV treatment		COMBIVIR			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval

Medication Name	Medication Used For	Formulary Decision				Restrictions and Therapeutic Interchanges	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	NonFormulary		
zidovudine	HIV treatment		ZIDOVUDINE			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
maraviroc	HIV treatment		MARAVIROC			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
efavirenz/lamivudine/ tenofovir disoproxil fumarate	HIV treatment				SYMFI	HIV medication restrictions and formulary status details	Within 60 days of System P&T Committee approval
lamivudine/tenofovir disoproxil fumarate	HIV treatment				CIMDUO, TEMIXYS	HIV medication restrictions and formulary status details	Within 60 days of System P&T Committee approval
Abacavir sulfate/ dolutegravir sodium/ lamivudine	HIV treatment		TRIUMEQ			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval

Medication Name	Medication Used For	Formulary Decision				Restrictions and Therapeutic Interchanges	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	NonFormulary		
cabotegravir/rilpivirine	HIV treatment		CABENUVA			Ambulatory Clinic setting Initiation of therapy is restricted to ID/HIV specialist or other provider with experience in HIV management Administer at an appropriate injection setting by medical professional (local site to determine site based on community HIV resources) Not to be initiated in the inpatient setting. In the occasion that a patient is hospitalized, therapy they will be bridged with daily oral cabotegravir/rilpivirine within 14 days of their anticipated next injection (obtain patient specific supply from specialty pharmacy if necessary)	Within 90 days of System P&T Committee approval
dolutegravir sodium/ rilpivirine HCl	HIV treatment				JULUCA	HIV medication restrictions and formulary status details	Within 60 days of System P&T Committee approval
rilpivirine	HIV treatment		RILPIVIRINE			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
dolutegravir sodium/ lamivudine	HIV treatment				DOVATO	HIV medication restrictions and formulary status details	Within 60 days of System P&T Committee approval

Medication Name	Medication Used For	Formulary Decision				Restrictions and Therapeutic Interchanges	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	NonFormulary		
elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide	HIV treatment		GENVOYA			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
etravirine	HIV treatment		ETRAVIRINE			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
darunavir/ cobicistat/ emtricitabine/tenofovir alafenamide	HIV treatment				SYMTUZA	HIV medication restrictions and formulary status details	Within 60 days of System P&T Committee approval
emtricitabine	HIV treatment		EMTRICITABINE			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
emtricitabine/ rilpivirine / tenofovir disoproxil fumarate	HIV treatment				COMPLERA	HIV medication restrictions and formulary status details	Within 60 days of System P&T Committee approval
elvitegravir/cobicistat/ emtricitabine/ tenofovir disoproxil fumarate	HIV treatment		STRIBILD			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
emtricitabine/tenofovir alafenamide fumarate	HIV treatment		DESCOVY			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval

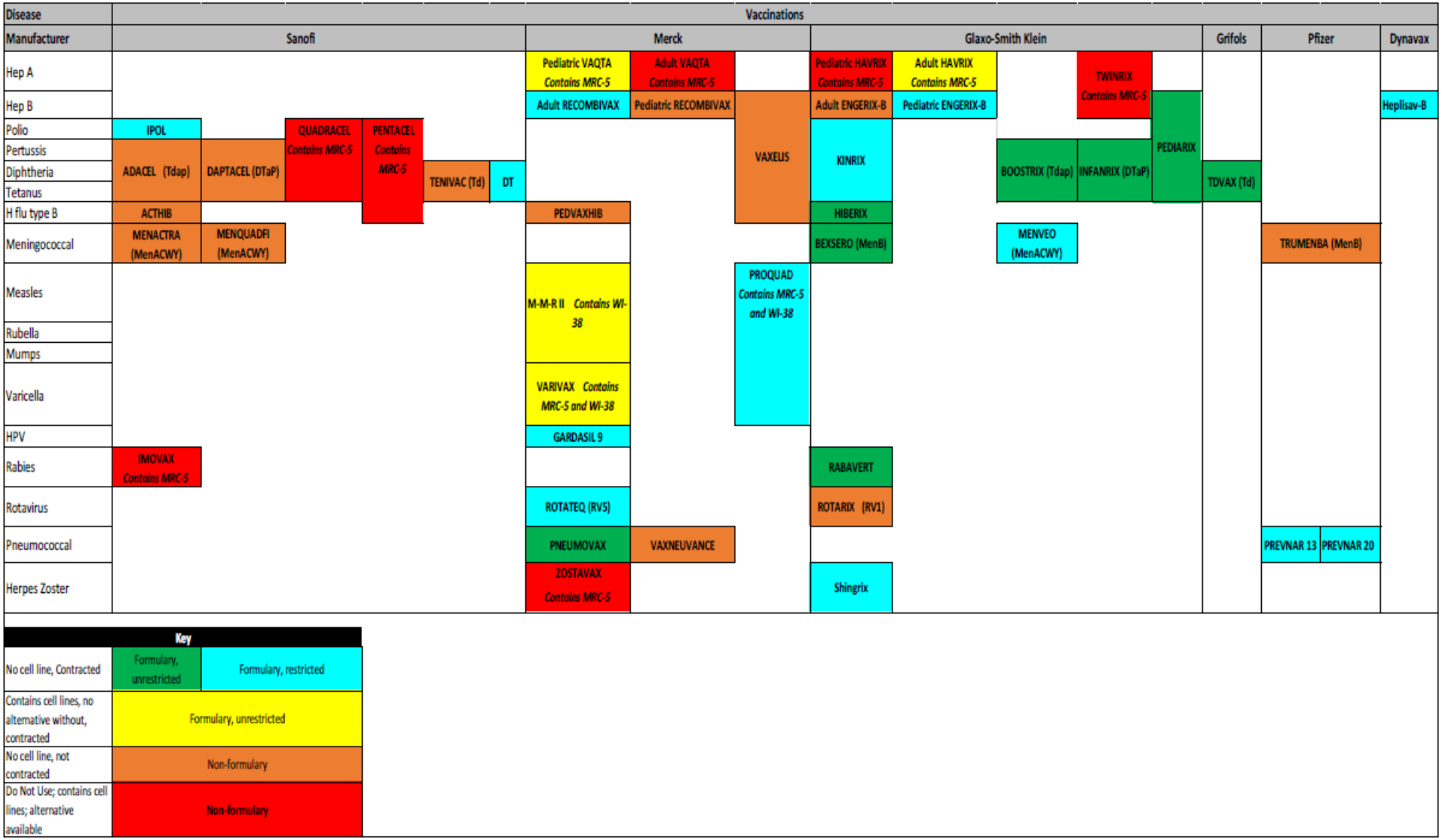
Medication Name	Medication Used For	Formulary Decision				Restrictions and Therapeutic Interchanges	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	NonFormulary		
emtricitabine/ rilpivirine/ tenofovir alafenamide fumarate	HIV treatment		ODEFSEY			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval
bictegravir sodium/ emtricitabine/ tenofovir alafenamide fumarate	HIV treatment		BIKTARVY			HIV medication restrictions and formulary status details	Within 90 days of System P&T Committee approval

THERAPEUTIC INTERCHANGES

Nasal antihistamines

Order	Interchange to
Azelastine 0.15% nasal	Azelastine 0.1% nasal
Olopatadine 0.6% nasal	

VACCINE FORMULARY COMPLIANCE WITH COMMONSPIRIT HEALTH ETHICAL AND RELIGIOUS DIRECTIVES



FORMULARY REVIEW

GENERIC NAME: Pentobarbital

PROPRIETARY NAME: *Nembutal®*

INDICATIONS:

FDA Approved
FDA Approved ● Sedative ● Hypnotic – for the short-term treatment of insomnia ● Pre-anesthetic ● Anticonvulsant – emergency control of certain acute convulsive episodes (status epilepticus, cholera, eclampsia, meningitis, tetanus, and toxic reactions to strychnine or local anesthetics) **Non-FDA Approved** ● Severe brain injury/elevated intracranial pressure – high-dose barbiturate therapy for control of ICP when all other medical and surgical treatments have failed

THERAPEUTIC CATEGORY: Anticonvulsant, barbiturate, hypnotic

PHARMACOKINETICS:

	PENTobarbital	**PHENobarbital**
Absorption	IV administration	IV administration
Metabolism	Hepatic via hydroxylation and glucuronidation	Hepatic by oxidation via CYP2C9 (CYP2C19 and CYP2E1 and N-glucosidation to a lesser extent)
t ½ (hr)	15-50 hours (dose dependent) Children: 26 ± 16 hours Adults: 22 hours (average)	Based on age: ≤ 10 days: 114.2 ± 43 hours 11-30 days: 73.19 ± 24.17 hours 2-3 months: 62.9 ± 5.2 hours 4-12 months: 63.2 ± 4.2 hours 1-5 years: 68.5 ± 3.2 hours Adults: 53-118 hours (79 hours on average)
Vd (L/kg)	Children: 0.8 Adults: 1.0	Neonates: 0.85 ± 0.059 L/kg 2-3 months: 0.857 ± 0.089 L/kg 4-12 months: 057 ± 0.046 L/kg 1-5 years: 0.666 ± 0.073 L/kg Adults: 0.61 L/kg
Protein binding (%)	45-70%	Neonates/infants: 36-43% Adults: 48%
Fraction excreted unchanged in urine (%)	< 1%	25-50%

SPECIAL POPULATIONS:

	PENTobarbital	**PHENobarbital**
Pregnancy	Barbiturates can be detected in the placenta, fetal liver, and fetal brain. Fetal and maternal blood concentrations may be similar following parenteral administration. An increased incidence of fetal abnormalities may occur following maternal use.	
Lactation	Barbiturates are present in breast milk. Infantile spasms and other withdrawal symptoms have been reported following abrupt discontinuation of breast feeding. Caution when administering to breastfeeding women.	
Pediatrics	● Dose based on the patient's age, weight, and medical condition. Potential for delayed metabolism/elimination in infants < 6 months of age. ● Pediatric neurotoxicity: patients < 3 years of age and patients in the third trimester of pregnancy, repeated/lengthy exposure to sedatives/anesthetics may have detrimental effects on child/fetal brain development and may	● Associated with cognitive deficits in children receiving therapy for complicated febrile seizures. ● Some dosage forms contain benzyl alcohol. Large doses (≥ 99 mg/kg/day) have been associated with potentially fatal toxicity (gasping syndrome) in neonates. Avoid use (or use with caution) of dosage forms containing benzyl alcohol in neonates. ● Repeated exposure associated with significant decrease in BSID cognitive and motor scores and an

	contribute to cognitive and behavioral problems (neurodevelopmental delay, learning disabilities, ADHD). No specific anesthetic/sedative has been found to be safer.	increased probability for development of cerebral palsy (2.3 fold for every 100 mg/kg exposure) ● Increased risk for vitamin D deficiency with chronic therapy. Monitor vitamin D levels periodically with prolonged treatment ● Phenobarbital elixir and oral solutions contain 15% alcohol ● Some dosage forms contain propylene glycol, associated with potentially fatal toxicities
Geriatrics	Avoid use	Avoid use
Hepatic Impairment	No dose adjustments in the manufacturer's labeling. Reduced dose is recommended.	No dose adjustments in the manufacturer's labeling. Reduced dose is recommended. PHENobarbital exposure is increased with hepatic impairment, use with caution.
Renal Impairment	No dose adjustments in the manufacturer's labeling. Reduced dose is recommended. Risk of propylene glycol toxicity is increased in patients with renal impairment.	No dose adjustments in the manufacturer's labeling. Reduced dose is recommended.

WARNING AND PRECAUTIONS:

- CNS depression
- Respiratory depression - Increased risk with IV administration, intubation is required prior to treatment for seizures and traumatic brain injury
- Substance abuse – use with caution in patients with a history of drug abuse, potential for drug dependency exists
- Hepatic/renal impairment – use with caution in patients with hepatic or renal impairment, reduce dose as appropriate
- Propylene glycol – some formulations contain propylene glycol, large amounts are potentially toxic
- Withdrawal – anti-seizure medications should not be discontinued abruptly due to the possibility of increasing seizure frequency
- Pediatric neurotoxicity – in pediatric patients < 3 years of age and patients in the third trimester of pregnancy prolonged exposure may have detrimental effects on child/fetal brain development

CONTRAINDICATIONS:

- Hypersensitivity to barbiturates or any component of the formulation
- Porphyria

ADVERSE REACTIONS:

Adverse Reaction(s)	PENTobarbital
Cardiovascular	Bradycardia, hypotension, syncope, thrombophlebitis
Central Nervous System	Agitation, anxiety, ataxia, CNS stimulation, CNS depression, confusion, dizziness, drowsiness, hallucination, hangover effect, headache, impaired judgment, insomnia, lethargy, nervousness, nightmares, psychiatric disturbances, abnormalities in thinking, depression
Dermatologic	Exfoliative dermatitis, skin rash, Stevens-Johnson syndrome
Gastrointestinal	Constipation, nausea, vomiting
Genitourinary	Oliguria
Hematologic and Oncologic	Agranulocytosis, thrombocytopenia, megaloblastic anemia
Local	Pain at injection site
Neuromuscular & Skeletal	Hyperkinesia, laryngospasm
Respiratory	Apnea, hypoventilation, respiratory depression

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:

Interacting Drug	Effect
Alcohol, alizapride, azelastine (nasal), blonanserin, brexanolon, brimonidine (topical), bromopride, bromperidol, buprenorphine, cannabinoid products, chlormethiazole, chlorphenesin, CNS depressants, difelikefalin, dimethindene (topical), doxylamine, droperidol, esketamine, flunitrazepam, hydroxyzine, kava kava, kratom, lemborexant, lisuride, lofexidine, magnesium sulfate, methotrimeprazine, metoclopramide, metyrosine, minocycline, olopatadine (nasal), opioids, orphenadrine, oxomemazine, oxbate salt products, paraldehyde, perampanel, piribedil, pramipexole,	Enhanced CNS depressant effects

ropeginterferon alfa-2b, ropinirole, rotigotine, rufinamide, thalidomide, theophylline, trimeprazine, valerian, zolpidem	
Blood pressure lowering agents	Enhanced hypotensive effects
Desmopressin	Enhanced hyponatremia effects
Doxycycline	Decreased serum concentrations of doxycycline
Griseofulvin	Decreased serum concentration of griseofulvin
Hemin	Diminished therapeutic effect of hemin
Mefloquine	Mefloquine may diminish therapeutic effects of anti-seizure agents by decreasing the serum concentration
Methoxyflurane	Enhanced nephrotoxic effects of methoxyflurane. Increased metabolism of methoxyflurane
Metoprolol	Enhanced hypotensive effects. Decreased serum concentration of metoprolol
Metronidazole	Enhanced adverse/toxic effects (due to propylene glycol). Disulfiram-like reaction may occur
Mianserin	Enhanced CNS depressant effects. Diminished therapeutic effect of barbiturates. Decreased serum concentration of mianserin
Multivitamins/minerals	Decreased serum concentration of barbiturates
Primidone	Primidone is converted to phenobarbital creating an additive effect with barbiturates
Secnidazole	Products containing propylene glycol may enhance the adverse/toxic effects of secnidazole
TCAs	Increased metabolism of TCAs
Valproate	Increased serum concentration of barbiturates. Decreased serum concentrations of valproate
Warfarin	Increased metabolism of warfarin

DOSING AND ADMINISTRATION:

Adult Dosing/Indication and Administration

- Seizures
    - Loading dose: 5-15 mg/kg IV administered at a rate of ≤ 50 mg/min, follow with continuous infusion
        - May give an additional 5-10 mg/kg
    - Continuous infusion: 0.5-5 mg/kg/hr IV
    - Breakthrough status epilepticus while on continuous infusion: additional 5 mg/kg bolus and increase infusion rate by 0.5-1 mg/kg/hr IV every 12 hours
    - Note: mechanical ventilation and cardiovascular monitoring are required. Titrate to cessation of electrographic seizures or burst suppression. A period of at least 24-48 hours of electrographic control is recommended prior to withdrawing continuous infusion. Withdraw gradually to prevent recurrent status epilepticus
- Severe brain injury/elevated intracranial pressure (off label)
    - Loading dose: 10 mg/kg IV over 30 minutes (or ≤ 25 mg/min) then 5 mg/kg every hour for 3 doses
    - Maintenance infusion: 1 mg/kg/hr, may increase to 2-4 mg/kg/hour. Maintain burst suppression on EEG

DOSING ADJUSTMENTS

Hepatic Impairment: No dose adjustments provided, but a reduced dose recommended

Renal Impairment

- No dose adjustments provided, but a reduced dose is recommended
- Risk of propylene glycol toxicity increases in patients with renal impairment. Monitor osmolal gap closely if using for prolonged periods or high doses

Geriatrics: Avoid use (per Beers Criteria)

Preparation for Administration

- May dilute in D5W or NS to a concentration of 4 or 8 mg/mL
- Precipitation can occur when diluted to concentrations > 8 mg/mL, use caution when diluting

RECOMMENDED MONITORING:

- Respiratory status - for conscious sedation
- Cardiovascular status
- CNS status
- Cardiac monitor and blood pressure monitor required
- Clinical signs of propylene glycol toxicity (for continuous high dose and/or long duration of IV use): serum creatinine, BUN, serum lactate, and osmolal gap
- Barbiturate coma: monitor oxygenation, arterial and central venous pressures, temperature
- Elevated ICP: monitor ICP, CPP, EEG

PHARMACOECONOMICS/COST:

Product (Drug, Strength, Form)	NDC	Cost per vial
PENTobarbital Sodium 1000 mg/20 mL MDV (1)	25021-0676-20	$535.28
PENTobarbital Sodium 2500 mg/50 mL MDV (1)	25021-0676-50	$958.01
PHENobarbital Sodium 65 mg/mL (25)	42494-0415-25	$14.60
PHENobarbital Sodium 130 mg/mL (25)	0641-0477-25	$46.93

CONCLUSION & RECOMMENDATION:

Pentobarbital is a barbiturate FDA approved for emergency control of seizures and for use as a sedative/hypnotic. Off label, pentobarbital is used to control elevated intracranial pressure (ICP) as a third line agent after midazolam and propofol. Pentobarbital acts with both sedative and hypnotic properties. At high doses pentobarbital exhibits antiseizure properties and reduces brain metabolism and cerebral blood flow in order to decrease intracranial pressure.

With the expansion of Neuroscience service lines at CHI Memorial, pentobarbital was requested by Dr. Shah to be added to formulary with the following restrictions (all must apply):

- Status epilepticus restricted to cases refractory to or with contraindications to all other therapies (third line agent)
- Must be ordered by a Neurologist or Neurosurgeon
- Patient is undergoing invasive mechanical ventilation

It is recommended to add pentobarbital to formulary and adopt the above restriction criteria for use. Pentobarbital will be stocked in the pharmacy and added to the EHR for ordering. Patient monitoring requirements will be built into the EHR/MAR entry.

FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)

Medication Management Step	Identified Risk	Steps for Prevention
Selection		
Therapeutic interchange?	None	NA
Special Ordering Requirements?	None	NA
Storage		
LASA* Separation of stock?	Yes, PENTobarbital and PHENobarbital	If both PENTobarbital and PHENobarbital are stocked, separate storage locations and use LASA auxiliary labels
Special storage (e.g. refrigeration, protect from light, controlled substance)?	Yes	Controlled substance
Pharmacist/Technician Education?	No	NA
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	Yes	Restricted to status epilepticus or intracerebral pressure crisis as a third line agent or if there are contraindications to both midazolam and propofol, allergies to both midazolam and propofol, or greater than 48 hours of propofol use. Restricted to inpatients in a critical care setting.

Medication Management Step	Identified Risk	Steps for Prevention
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	No	NA
Drug Interactions?	Yes	DDI warning
Pregnancy?	Yes	Risk vs benefit discussion with ordering provider
Absolute Contraindications?	No	NA
Requires Order Set, Protocol, concomitant therapy with another drug?	Yes	Use requires mechanical ventilation, blood pressure monitoring, and ICP/EEG monitoring (depending on indication)
LASA* nomenclature issues?	Yes, PENTobarbital and PHENobarbital	Use tall man lettering and LASA warnings on orders
Prescriber education?	No	NA
Processing, Preparing, & Dispensing		
High-risk drug double check?	Yes	
Drug Interaction check in place?	Yes	
LASA* computer warnings?	Yes	PENTobarbital and PHENobarbital
Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)?	No	
Packaging/Labeling (e.g. prepacking)?	No	
Dispensing (e.g. auxiliary labeling, light protection, refrigeration)?	Yes	High Alert, LASA
Documentation required (e.g. double check, worksheet)?	No	
Pharmacist/Technician Education?	No	
Administration		
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	High-risk double check	Do not exceed 50 mg/min, avoid extravasation
Special delivery system (e.g. pump)?	No	
Documentation required? (e. g. double check)	Yes	High alert medication
Nurse education?	No	
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?	Yes	Barbiturate coma: monitor oxygenation, arterial and central venous pressures, temperature. Elevated ICP: monitor ICP, CPP, EEG. All IV use: monitor for propylene glycol toxicity
Follow-up laboratory tests?	No	
Education?	No	
Operational Impact		
Unique procurement process? (e.g. orphan medication)	No	
Unique equipment required?	No	
Complex preparation process required	No	

FORMULARY UPDATE

THERAPEUTIC CLASS: Hepatitis B vaccines

BACKGROUND/RATIONALE:

In 2020, CommonSpirit Health shifted to a GSK/Merck vaccine portfolio to allow the system to optimize vaccine contracting and improve our resource stewardship. The recent changes to the pneumococcal vaccine market (new products & guidelines) have resulted in contract adjustments and bundling discounts that prompted the review of additional preferred formulary vaccine categories. The hepatitis B vaccine portfolio was reevaluated based on new contracting updates to further optimize and provide maximum value for CommonSpirit Health contracted entities.

Engerix-B (GSK) and Heplisav (Dynavax) are the formulary hepatitis B vaccines at CHI Memorial, with Engerix B being preferred.

Current restrictions for use of Engerix-B:

- One-time dose for patients with a recent and known exposure to hepatitis B
    - Vaccination should be deferred until outpatient for other inpatient populations, including patients with hepatitis C
- Outpatient use, including employee health

Current restrictions for Heplisav:

- Outpatient use only, including employee health, under only the following conditions:
    - For use in patients with HIV, chronic kidney disease expected to begin dialysis within 6 months or currently on dialysis, solid organ transplantation or expected transplantation, chronic systemic corticosteroid use, or other significant immunomodulating disease, OR
    - Patient who failed seroconversion after 3 shot series of Engerix-B plus 1 booster.

Recombivax HB (Merck) was voted as the formulary preferred hepatitis B vaccine and Engerix B was voted as non-formulary at the July 2022 system P&T committee meeting. Engerix-B and Recombivax-B vaccines are interchangeable for patients that may be partially vaccinated for hepatitis B as both are 3 dose regimens (0, 1, and 6 months) for non-immunocompromised adult patients. The estimated system cost savings to convert to Recombivax HB is $89,664.

PHARMACOECONOMICS/COST:

Product	Current formulary status	Cost per dose	Utilization (6 months)	Estimated annual cost savings
Recombivax HB® (adult) - 10 mcg	Non-formulary	$32.03	n/a	~$600
Engerix B® (adult) - 20 mcg	Formulary preferred	$40.57	35 doses	n/a

DISCUSSION:
The vast majority of use of hepatitis B vaccines at CHI Memorial is for employee health. Contracting opportunities have provided us the opportunity to achieve cost savings without impacting quality of care.

RECOMMENDATION:

- It is recommended to adopt the decision of the CSH system P&T committee in order to align with the contracting opportunity across the system. The current CHI Memorial restriction criteria for Engerix B will apply to Recombivax HB.
- Employee health will be provided Recombivax HB once any remaining Engerix B supply is exhausted.
- There are no changes to the formulary status or restriction criteria for Heplisav.

FORMULARY REVIEW

GENERIC NAME: Tezepelumab

PROPRIETARY NAME: *Tezspire®*

INDICATIONS:

FDA Approved
Add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma

THERAPEUTIC CATEGORY: Monoclonal Antibody, Anti-Asthmatic; subcutaneous thymic stromal lymphopoietin blocker

PHARMACOKINETICS:

Absorption	The bioavailability of subcutaneous tezepelumab is approximately 77%.
Distribution	Tezepelumab central and peripheral volume of distribution is 3.9 L and 2.2 L respectively.
Metabolism	Tezepelumab is degraded by proteolytic enzymes widely distributed in the body, not by hepatic enzymes.
Elimination	The half-life of tezepelumab is approximately 26 days. The available data does not show evidence of target-mediated clearance within the studied dose range.

SPECIAL POPULATIONS:

Pregnancy	There is no data regarding tezepelumab use in pregnant women. Placental transfer of monoclonal antibodies is greater during the third trimester; therefore, potential effects on the fetus are likely greater during the third trimester.
Lactation	There is no information regarding the presence of tezepelumab- in human milk, the effects on breastfed children or the effects on milk production.
Pediatrics	The safety and effectiveness of tezepelumab has been established in pediatric patients aged 12 years and older.
Geriatrics	Clinical studies of tezepelumab showed no overall differences in safety and efficacy between patients 65 years of age or older and younger patients.
Hepatic Impairment	No formal studies with tezepelumab have been conducted in patients with hepatic impairment. Due to tezepelumab- being metabolized by proteolytic enzymes and not hepatic enzymes, change in hepatic function is not expected to influence clearance.
Renal Impairment	No formal studies with tezepelumab have been conducted in patients with renal impairment.

CLINICAL STUDIES:

PATHWAY Trial -- Tezepelumab in Adults with Uncontrolled Asthma	
METHODS	
Study Design	Phase 2, multi-center, randomized, double-blind, placebo controlled
Study Funding	Medimmune [a member of AstraZeneca] and Amgen
Patient Enrollment Inclusion	● Age 18 through 75 ● Body mass index (BMI) between 18-40 kg/m2 and weight greater than or equal 40 kg ● Documented physician-diagnosed asthma
Patient Enrollment Exclusion	● Diagnosis of vocal cord dysfunction, reactive airways dysfunction syndrome, hyperventilation and panic attacks, or other mimics of asthma. ● Current smokers or subjects with a smoking history of ≥ 10 pack years ● Former smokers with < 10 pack years must have stopped for at least 1 year to be eligible. ● Any concomitant respiratory disease that in the opinion of the investigator and/or medical monitor will interfere with the evaluation of the investigational product or interpretation of subject safety or study results ● Evidence of active liver disease. ● History of cancer ● Known history of active tuberculosis (TB) ● History of anaphylaxis to any biologic therapy ● History of hepatitis B, hepatitis C or HIV
Treatment Plan	Treatment group 1.) 70 mg – injection every 4 weeks with placebo injection at intermediate visits

	2.) 210 mg –injection every 4 weeks with placebo injection at intermediate visits 3.) 280 mg – injection every 2 weeks Placebo group: Placebo injection every 2 weeks Randomization was stratified according to location, blood eosinophil count, and dose level of inhaled glucocorticoids.
RESULTS	
Outcomes Summary	Primary ● Annualization rates of asthma exacerbations at week 52 was overall lower in low-dose, medium-dose and high dose tezepelumab groups when compared to placebo Secondary ● FEV_1 before bronchodilation was significantly improved in all tezepelumab groups ● ACQ_6 scores improved in all tezepelumab groups ● AQLQ scores improved in the high dose tezepelumab group only when compared to placebo ● All tezepelumab groups showed improvements in all secondary outcomes when compared to placebo; except for the annualized asthma exacerbation rate in patients with a history of smoking.
Adverse Events	● Adverse events were similar across trial groups ● 3 serious adverse events were reported in the tezepelumab groups; two (pneumonia and stroke) occurred in the same patient and the other was Guillain-Barre syndrome ● 1 death occurred in the low dose tezepelumab group
Limitations	● AQLQ contains subjective components which could change based on the participant; it includes an emotional/mood component ● Open label for background asthma-control medications
Author's Conclusion	When compared to placebo, tezepelumab resulted in lower rates of asthma exacerbations among patients who remained uncontrolled despite the use of LABAs and glucocorticoids
NAVIGATOR Trial – Tezepelumab in Adults and Adolescents with Severe, Uncontrolled Asthma	
METHODS	
Study Design	Phase 3, multicenter, double-blind, randomized, placebo-controlled trial
Study Funding	AstraZeneca and Amgen
Patient Enrollment Inclusion	● Age 12-80 ● Documented physician-diagnosed asthma for at least 12 months ● Subjects who have received a physician-prescribed asthma controller medication with medium or high dose ICS for at least 12 months. ● Documented treatment with a total daily dose of either medium or high dose ICS ● At least one additional maintenance asthma controller medication is required according to standard practice of care and must be documented for at least 3 months. ● Morning pre-BD FEV1 <80% predicted normal (<90% for subjects 12-17 yrs) ● Documented history of at least 2 asthma exacerbation events within 12 months. ● ACQ-6 score ≥1.5 at screening and on day of randomization
Patient Enrollment Exclusion	● Pulmonary disease other than asthma ● History of cancer ● History of a clinically significant infection ● Current smokers or subjects with smoking history ≥10 pack-years and subjects using vaping products, including electronic cigarettes ● History of chronic alcohol or drug abuse within 12 months ● Hepatitis B, C, or HIV ● Pregnant or breastfeeding ● History of anaphylaxis following any biologic therapy ● Subject randomized in the current study or previous tezepelumab studies
Treatment Plan	Treatment group: Tezepelumab 210 mg injection every 4 weeks Placebo: Placebo injection every 4 weeks

RESULTS	
Outcomes Summary	Primary: Annualized rates were significantly lower in tezepelumab groups, among all stratified groups, when compared to placebo Secondary ● Among key secondary endpoints, tezepelumab improved prebronchodilator FEV_1, ACQ-6 scores, AQLD[S]+12 score and ASD scores when compared to placebo ● Improvements were observed from the first postbaseline assessment and were sustained throughout the treatment period.
Adverse Events	● 9.8% of patients in the tezepelumab group and 13.7% in the placebo group reported a serious adverse event ● Most common adverse events were: nasopharyngitis, upper respiratory tract infection, headache and asthma ● There were 2 deaths reported: both in the placebo group
Limitations	● AQLQ contains objective components which could change based on the participant; it includes an emotional/mood component ● Open label for background asthma-control medications
Author's Conclusion	When compared to placebo, tezepelumab 210 mg injections every 4 weeks significantly reduced annualized rates of asthma exacerbations and improved FEV_1, ACQ-6 scores, AQLQ[S]+12 scores, and ASD scores. There were also substantial reductions in exacerbations that lead to hospitalizations in the tezepelumab group.

COMPARATIVE EFFICACY:
Tezepelumab is currently the first and only FDA-approved thymic stromal lymphopoietin (TSLP) monoclonal antibody for add-on maintenance treatment of severe asthma in adults and children aged 12 and above whose asthma cannot be controlled by their existing asthma medication. Tezepelumab's indication is not phenotype specific (eosinophilic or allergic) like benralizumab and mepolizumab. Additionally, the mechanisms of action are different so they cannot be directly compared for asthma maintenance treatment.

WARNING AND PRECAUTIONS:
- Hypersensitivity reactions
- Should not be used to treat acute asthma symptoms or acute exacerbations
- Risk associated with abrupt reduction of corticosteroid dosage
- Parasitic infection
- Live attenuated vaccines

CONTRAINDICATIONS:
Tezepelumab is contraindicated in patients with a previous severe hypersensitivity reaction to tezepelumab or to any of the excipients.

ADVERSE REACTIONS:
There were no clinically or statistically significant differences compared to placebo for pharyngitis, arthralgia, or back pain.

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:
There have been no formal interaction studies that have been conducted using tezepelumab.

DOSING AND ADMINISTRATION:
- 210 mg subcutaneous injection given every 4 weeks
- Must be administered by a health care provider

RECOMMENDED MONITORING: Potential hypersensitivity reactions; Injection site reactions

PHARMACOECONOMICS/COST:

Product (Drug, Strength, Form)	NDC	Contract/GPO Price
Tezspire 210 mg single-dose pre-filled syringe	55513-112-01	$3,633.00 per syringe

Product (Drug, Strength, Form)	Cost/Defined Course of Therapy	Cost/Year
Tezspire 210 mg single-dose pre-filled syringe	$3,633.00 every 4 weeks	$47,229 per year

CONCLUSION & RECOMMENDATION:
The standard of care for asthma per the Global Initiative for Asthma (GINA) guidelines includes inhaled glucocorticoids, long-acting beta agonists (LABAs) and long-acting muscarinic antagonists (LAMAs). Monoclonal antibodies have been recently introduced for add-on therapy in patients with uncontrolled severe asthma. Tezepelumab is the first and only thymic TSLP monoclonal antibody for the add-on treatment of severe asthma in patients 12 years or older. TLSP is an epithelial cytokine that has a known role in the asthma inflammatory mechanism. Tezepelumab may also be used regardless of certain types of severe asthma, phenotype and eosinophil count.

In the PATHWAY and NAVIGATOR trials, there were significant improvements in annualized rates of asthma exacerbations in patients regardless of phenotype or eosinophil count when tezepelumab was added to routine maintenance therapy such as LABAs and inhaled glucocorticoids. Tezepelumab also showed significant improvement in exacerbations irrespective of baseline levels of inflammatory biomarkers and allergic status.

Addition of tezepelumab to the current standard of care could improve the care of those who have severe uncontrolled asthma who are not currently managed by standard treatments regimens, regardless of phenotype or eosinophil count.

It is recommended to add tezepelumab (Tezspire®) to formulary with restrictions to the outpatient setting subsequent to insurance approval or prior authorization for FDA approved indications or payer approved off-label indications.

FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)

Medication Management Step	Identified Risk	Steps for Prevention
Selection & Procurement		
Therapeutic interchange?	NA	NA
Special Ordering Requirements?	NA	NA
Storage		
LASA* separation of stock?	NA	NA
Special storage (e.g. refrigeration, protect from light, controlled substance)?	Yes	Store refrigerated in original carton at 2°C to 8°C (36°F to 46°F). Do not freeze, shake or expose to heat. Store at room temperature in original carton between 68°F to 77°F for a maximum of 30 days. Do not put back in the refrigerator once it has reached room temperature.
Pharmacist/Technician Education?	No	NA
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	Yes	Restrict to outpatient use
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	None known	NA
Drug Interactions?	No	NA
Pregnancy?	None known	NA
Absolute Contraindications?	Yes	Do not use in patients with a previous severe hypersensitivity reaction to tezepelumab or to any of the excipients.
Requires Order Set, Protocol, concomitant therapy with another drug?	Yes	Pair with anaphylaxis and hypersensitivity protocol
LASA* nomenclature issues?	No	NA
Prescriber education?	Prescribers should be educated on appropriate clinical utilization.	Provide provider education from pharmacy and medication manufacturer.
Processing, Preparing, & Dispensing		
High-risk drug double check?	NA	NA
Drug Interaction check in place?	No	NA
LASA* computer warnings?	No	NA
Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)?	Air bubbles in single-dose pre-filled syringe	Do not expel air bubbles prior to administration
Packaging/Labeling (e.g. prepacking)?	NA	NA

Medication Management Step	Identified Risk	Steps for Prevention
Dispensing (e.g. auxiliary labeling, light protection, refrigeration)?	Yes	Dispense in original carton to protect from light. Add do not shake auxiliary labeling to carton.
Documentation required (e.g. double check, worksheet)?	No	NA
Pharmacist/Technician Education?	No	NA
Administration		
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	No	NA
Special delivery system (e.g. pump)?	No	NA
Documentation required? (e. g. double check)	No	NA

FORMULARY REVIEW

GENERIC NAME: Inclisiran

PROPRIETARY NAME: *Leqvio®*

INDICATIONS:

FDA Approved
Heterozygous familial hypercholesterolemia ● Adjunct to diet and maximally tolerated statin therapy in patients who require additional lowering of low-density lipoprotein cholesterol (LDL-C) Clinical atherosclerotic cardiovascular disease (atherosclerosis) ● Adjunct to diet and maximally tolerated statin therapy in patients who require additional lowering of low-density lipoprotein cholesterol (LDL-C)

THERAPEUTIC CATEGORY: Antilipemic - Small interfering ribonucleic acid (siRNA) agent that prevents proprotein convertase subtilisin/kexin type 9 (PCSK9) production in the liver

SIMILAR DRUGS:
- PCSK9 Inhibitors – Alirocumab (Praluent) and evolocumab (Repatha)
    - Human monoclonal IgG1 antibody that binds to and inhibits PCSK9 binding to low-density lipoprotein receptors (LDLR)

PHARMACOKINETICS:

	Inclisiran
Absorption	● Cmax: 509 ng/mL ● Time to peak: ~4 hours ● Mean AUC: 7980 ng*h/mL
Distribution	● Volume of distribution: ~500 L ● Protein binding: 87%
Metabolism	● Metabolized primarily by nucleases to shorter nucleotides of varying length
Elimination	● Half-life elimination ~9 hours ● Renal elimination: ~16%

SPECIAL POPULATIONS:

	Inclisiran
Pregnancy	Discontinue inclisiran when pregnancy is recognized. There are no available data on the use of inclisiran in pregnant patients to evaluate for a drug-associated risk of major birth defects, miscarriage or adverse maternal or fetal outcomes. Treatment of hyperlipidemia is not generally necessary during pregnancy and the lipid lowering effects of inclisiran may cause fetal harm.
Lactation	There is no information on the presence of inclisiran in human milk, the effects on the breastfed infant, or the effects on milk production. In animal studies, inclisiran was present in the milk of lactating rats in all dose groups, however, there was no evidence of systemic absorption in the suckling rat neonates. Oligonucleotide-based products typically have poor oral bioavailability; therefore, it is considered unlikely that low levels of inclisiran present in milk will adversely impact an infant's development during lactation.
Pediatrics	Not studied
Geriatrics	No overall differences in safety or effectiveness were observed between age ranges in the 1833 patients treated with inclisiran in clinical studies.
Hepatic Impairment	Approximately 1.1 to 2.1-fold increase in inclisiran Cmax and 1.3 to 2.0-fold increase in AUC reported in patients with mild and moderate hepatic impairment. Reductions in LDL-C were similar with normal hepatic function and mild hepatic impairment, but were less in those with moderate hepatic impairment. Inclisiran has not been studied in severe hepatic impairment.
Renal Impairment	Approximately 2.3 to 3.3-fold increase in inclisiran Cmax and 1.6 to 2.3-fold increase in AUC reported in patients with mild, moderate or severe renal impairment. Reductions in LDL-C were similar across all groups based on renal function.

CLINICAL STUDIES:

ORION-10 (NCT03399370) - LDL-C Reduction in Patients with Clinical Atherosclerotic Cardiovascular Disease	
METHODS	
Study Design	● Multicenter, double-blind, randomized, placebo-controlled conducted in the United States
Study Funding	● Funded by the Medicines Company – Designed trial protocol along with authors and the steering committee (with subsequent review and approval by regulators) and selected participating sites
Patient Enrollment Inclusion	● Ages ≥18 years ● LDL cholesterol levels at screening ≥70 mg per deciliter ● History of ASCVD ● Maximum tolerated or intolerance to statin therapy ● On a stable dose of lipid-lowering therapy for ≥30 days before screening with no planned medication or dose changes ● eGFR >30 mL/min/1.73 m2
Patient Enrollment Exclusion	● Treatment with monoclonal antibodies directed towards PCSK9 within the past 90 days ● Major adverse cardiovascular event within the past 3 months ● Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study ● Cardiac arrhythmia within past 3 months that is not controlled by medication/ablation ● New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction <25% ● Uncontrolled severe hypertension ● Active liver disease ● Life expectancy less than 2 years
Baseline Characteristics	● Mean age: Inclisiran – 66.4 years, Placebo – 65.7 years ● Male sex: Inclisiran – 68.5%, Placebo – 70.3% ● White race: Inclisiran – 83.6%, Placebo – 87.8% ● Percentage with diabetes: 42% ● Percentage of patients on stable doses of statin treatment: 89.2% ● Percentage of patients using ezetimibe: 9.9% ● **Mean (±SD) LDL cholesterol level at baseline: 104.7±38.3 mg/dL**
Treatment Plan	● Screened 2329 patients with 1561 undergoing randomization ● Randomized 1:1 to inclisiran 284 mg or placebo administered as a 1.5 ml subcutaneous injection under blinded conditions for four injections (day 1, 90, 270, and 450) ● Patients attended clinic on days 30, 150, 330, and 510 for follow-up and laboratory assessments. The end-of-trial visit was conducted on day 540.
RESULTS	
Primary Endpoint	● **Percentage change in LDL cholesterol level** at day 510 o Inclisiran: -52.3%, Placebo: 1.0% o Between-group difference of −52.3% (95% CI, −55.7 to −48.8; P<0.001) ● **Time-adjusted change in LDL cholesterol** level after day 90 and up to day 540 as compared with baseline o Inclisiran: -51.3%, Placebo: 2.5% o Between-group difference of −53.8% (95% CI, −56.2 to −51.3; P<0.001)
Secondary Endpoint	● Absolute change in LDL cholesterol level at day 510 o Inclisiran: -56.2 mg/dL, Placebo: -2.1 mg/dL o Between-group difference of −54.1 mg/dL (95% CI, −57.4 to −50.9 mg/dL; P<0.001) ● Time-adjusted absolute change in LDL cholesterol level from day 90 to day 540 o Inclisiran: -53.7 mg/dL, Placebo: -0.4 mg/dL o Difference of −53.3 mg per deciliter (95% CI, −55.8 to −50.8 mg/dL; P<0.001) ● Percentage change in PCSK9 levels from baseline at day 510 o Inclisiran: -69.8%, Placebo: 13.5% o Between-group difference of −83.3% (95% CI, −89.3 to −77.3; P<0.001) ● Inclisiran resulted in improvement in other key secondary end points at day 510 as compared with placebo, including lower levels of total cholesterol, non-HDL cholesterol, and apolipoprotein B (P<0.001 for all three comparisons)
Adverse Events	● Total adverse events o Inclisiran: 574/781 patients (73.5%), Placebo: 582/778 (74.8%) ● Serious adverse events o Inclisiran: 175/781 patients (22.4%), Placebo: 205/778 (26.3%)

	○ All cause death - Inclisiran: 12/781 (1.5%), Placebo: 11/778 (1.4%) ● Injection-site adverse events ○ Inclisiran 20/781 (2.7%), Placebo 7/778 (0.9%) ● AEs reported in ≥ 5% of patients that occurred more frequently in the inclisiran group than the placebo group ○ Diabetes Mellitus- Inclisiran (15%), Placebo (14%) ○ Bronchitis- Inclisiran (6%), Placebo (4%) ○ Dyspnea- Inclisiran (5%), Placebo (4%)
Limitations	● High degree of involvement from the sponsor ● Study was not designed or powered to analyze patient-centered outcomes ● Low proportion of non-white patients enrolled
ORION-11 (NCT03400800) - LDL-C Reduction in Patients with Clinical Atherosclerotic Cardiovascular Disease	
METHODS	
Study Design	● Multicenter, double-blind, randomized, placebo-controlled conducted in Europe and South Africa (trial protocol nearly identical to ORION-10)
Study Funding	● Funded by the Medicines Company – Designed trial protocol along with authors and the steering committee (with subsequent review and approval by regulators) and selected participating countries and sites
Patient Enrollment Inclusion	● Ages ≥18 years ● LDL cholesterol levels at screening ≥70 mg per deciliter ● History of ASCVD *or an ASCVD risk equivalent (type 2 diabetes, familial hypercholesterolemia, or a 10-year risk of a cardiovascular event of ≥20%)* ○ **Only difference in trial protocol between ORION-10 and ORION-11** ● Maximum tolerated or intolerance to statin therapy ● On a stable dose of lipid-lowering therapy for ≥30 days before screening with no planned medication or dose changes ● eGFR >30 mL/min/1.73 m2
Patient Enrollment Exclusion	● Treatment with monoclonal antibodies directed towards PCSK9 within the past 90 days ● Major adverse cardiovascular event within the past 3 months ● Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study ● Cardiac arrhythmia within past 3 months that is not controlled by medication/ablation ● New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction <25% ● Uncontrolled severe hypertension ● Active liver disease ● Life expectancy less than 2 years
Baseline Characteristics	● Mean age: 64.8 years ● Male sex: Inclisiran – 71.5%, Placebo – 72.0% ● White race: Inclisiran – 97.7%, Placebo – 98.6% ● Patients with a history of ASCVD: 87.6% ● Patients with ASCVD risk-equivalents: 12.4% ● **Mean baseline LDL-C: 112 mg/dl** ● Percentage of patients on statin treatment: 96.2% ● Percentage of patients on ezetimibe: 7.1%
Treatment Plan	● Screened 2381 patients with 1617 undergoing randomization ● Randomized 1:1 to inclisiran 284 mg or placebo administered as a 1.5 ml subcutaneous injection under blinded conditions for four injections (day 1, 90, 270, and 450) ● Patients attended clinic on days 30, 150, 330, and 510 for follow-up and laboratory assessments. The end-of-trial visit was conducted on day 540.
RESULTS	
Primary Endpoint	● **Percentage change in LDL cholesterol level** at day 510 was ○ Inclisiran: -45.8%, Placebo: 4.0% ○ Between-group difference of −49.9% (95% CI, −53.1 to −46.6; P<0.001) ● **Time-adjusted change in LDL cholesterol** level after day 90 and up to day 540 as compared with baseline ○ Inclisiran: -45.8%, Placebo: 3.4% ○ Between-group difference of −49.2% (95% CI, −51.6 to −46.8; P<0.001)
Secondary Endpoint	● Absolute change in LDL cholesterol level at day 510 ○ Inclisiran: -50.9 mg/dL, Placebo: 1.0 mg/dL

	○ Between-group difference of −51.9 mg/dL (95% CI, −55.0 to −48.7 mg/dL; P<0.001) ● Time-adjusted absolute change in LDL cholesterol level from day 90 to day 540 ○ Inclisiran: -48.6 mg/dL, Placebo: 0.3 mg/dL ○ Difference of −48.9 mg/dL (95% CI, −51.4 to −46.5 mg/dL; P<0.001) ● Percentage change in PCSK9 levels from baseline at day 510 ○ Inclisiran: −63.6%, Placebo: 15.6% ○ Between-group difference of −79.3% (95% CI, −82.0 to −76.6; P<0.001) ● Inclisiran resulted in improvement in other key secondary end points at day 510 as compared with placebo, including lower levels of total cholesterol, non-HDL cholesterol, and apolipoprotein B (P<0.001 for all three comparisons)
Adverse Events	● Total adverse events ○ Inclisiran: 671/811 patients (82.7%), Placebo: 655 of 804 (81.5%) ● Serious adverse events ○ Inclisiran: 181/811 patients (22.3%), Placebo: 181/804 (22.5%) ○ All cause death - Inclisiran: 14/811 (1.7%), Placebo: 15/804 (1.9%) ● Injection-site adverse events ○ Inclisiran 38/811 (4.7%), Placebo 4/804 (0.5%) ● AEs reported in ≥ 5% of patients that occurred more frequently in the inclisiran group than the placebo group ○ Upper respiratory tract infection- Inclisiran: 6.4%, Placebo: 6.1% ○ Arthralgia- Inclisiran: 5.8%, Placebo: 4.0%
Limitations	● High degree of involvement from the sponsor ● Study was not designed or powered to analyze patient-centered outcomes ● Low proportion of non-white patients enrolled
Inclisiran for the Treatment of Heterozygous Familial Hypercholesterolemia (HeFH) (ORION-9, NCT03397121)	
METHODS	
Study Design	● Multicenter, double-blind, randomized, placebo-controlled
Study Funding	● Funded by the Medicines Company - Designed trial protocol along the steering committee
Patient Enrollment Inclusion	● Age ≥18 years ● History of HeFH ● Maximum tolerated or intolerance to statin therapy ● On a stable dose of lipid-lowering therapy for ≥30 days before screening with no planned medication or dose changes ● Stable low-fat diet ● Serum LDL-C ≥2.6 mmol/L (≥100 mg/dL) at screening ● Fasting triglyceride <4.52 mmol/L (<400 mg/dL) at screening ● eGFR >30 mL/min
Patient Enrollment Exclusion	● Major adverse cardiovascular event within the past 3 months ● Any uncontrolled or serious disease, or any medical or surgical condition, that may either interfere with participation in the clinical study ● Cardiac arrhythmia within past 3 months that is not controlled by medication/ablation ● New York Heart Association (NYHA) class IV heart failure or last known left ventricular ejection fraction <25% ● Uncontrolled severe hypertension ● Active liver disease or known history of alcohol and/or drug abuse in the past 5 years ● Life expectancy less than 2 years
Baseline Characteristics	● Mean age: 56 years ● Male sex: 47% ● White race: 94% ● Preexisting coronary heart disease: 25% ● History of diabetes: 10%. ● **Mean baseline LDL: 153.1±54.0 mg/dL** ● Statin use: 90% (75% receiving high-intensity statins) ● Ezetimibe use: 52.9%
Treatment Plan	● Screened 617 patients with 482 undergoing randomization ● Randomized in a 1:1 ratio to receive inclisiran 284 mg or placebo, administered as a 1.5 ml subcutaneous injection on days 1, 90, 270, and 450. ● Patients attended clinic on days 30, 150, 330, and 510 for follow-up and laboratory assessments. The end-of-trial visit was conducted on day 540.

RESULTS	
Primary Endpoint	● **Percent change from baseline in LDL cholesterol** at day 510 o Inclisiran: -39.7%, Placebo: 8.2% o Between-group difference of −47.9% (95% CI, −53.5 to −42.3; P<0.001) ● **Time-adjusted percent change from baseline in the LDL cholesterol level** between day 90 and day 540 o Inclisiran: -38.1%, Placebo: 6.2% o Between-group difference of −44.3% (95% CI, −48.5 to −40.1; P<0.001)
Secondary Endpoint	● Mean absolute change in LDL-C at Day 510 o Inclisiran: -59.0 mg/dL, Placebo: 9.9 mg/dL o Between-group difference −68.9 mg/dL (95% CI, −77.1 to −60.7; P<0.001) ● Time-adjusted absolute reduction in LDL-C from baseline between Day 90 and day 540 o Inclisiran: −56.9 mg/dL, Placebo: 5.8 mg/dL o Between-group difference of −62.6 mg/dL (P<0.001)
Adverse Events	● Total adverse events o Inclisiran: 185/241 (76.8%), Placebo: 172/240 (71.7%) ● Serious adverse events o Inclisiran: 18/241 patients (7.5%), Placebo: 33/240 (13.8%) o All cause death - Inclisiran: 1/241 (0.4%), Placebo: 1/240 (0.4%) ● Injection-site adverse events o Inclisiran 41/241 (17.0%), Placebo 4/240 (1.7%) ● AEs reported in ≥ 5% of patients that occurred more frequently in the inclisiran group than the placebo group o Nasopharyngitis- Inclisiran: 11.6%, Placebo: 8.3% o Back pain- Inclisiran: 7.1%, Placebo: 4.2%
Limitations	● High degree of involvement from the sponsor ● Study was not designed or powered to analyze patient-centered outcomes ● Low proportion of non-white patients enrolled

COMPARATIVE EFFICACY:
The most current 2018 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines on the management of cholesterol, high-intensity or maximally tolerated statin therapy is recommended as first line treatment for the reduction of ASCVD risk. If LDL-C is still >70 mg/dL in patients on maximally tolerated statins, the addition of ezetimibe is recommended. If LDL-C is still elevated, PCSK9 inhibitors, such as alirocumab or evolocumab, are then recommended in addition to maximally tolerated statin and ezetimibe. Inclisiran (Leqvio) is a newly approved medication targeting PCSK9 that can be added to maximally tolerated statin therapy to help decrease LDL-C for treatment of HeFH or ASCVD risk.

Inclisiran works similarly to alirocumab (Praluent) and evolocumab (Repatha) to reduce cholesterol by targeting PCSK9. However, Inclisiran does so in a novel manner, by degrading the mRNA molecules used to translate genetic instructions into proteins during PCSK9 production, while Repatha and Praluent are monoclonal antibodies that inhibit PCSK9 activity. In all of inclisiran's phase three trials, inclisiran added to statin therapy significantly reduced LDL cholesterol compared to placebo by approximately 50% over an 18 month study period. This is similar to the efficacy shown by other PCSK9 targeting therapies. In their phase three studies, alirocumab and evolocumab reduced serum LDL concentrations from baseline by 44-61% and 50-60% respectively compared with placebo after 18 months of therapy. All three medications were shown to have similar rates of adverse reactions, although mild to moderate injection site reactions were more common with inclisiran use (8.2%), and nasopharyngitis was more common with alirocumab (11.3%) and evolocumab (4.0%) use.
The benefit that inclisiran provides over these similar medications is its twice-yearly injection schedule, while alirocumab and evolocumab are injected every two weeks or monthly. However, unlike alirocumab and evolocumab that can be dispensed by outpatient pharmacies for patients to self inject, inclisiran must be administered by a healthcare professional which may be less convenient and provide additional billing considerations.

Inclisiran's phase three trials were not powered or designed to evaluate patient-centered cardiovascular outcomes. Alirocumab and evolocumab have both been proven to significantly reduce the risk of major adverse cardiovascular events and are associated with decreased mortality. The ongoing ORION-4 study is currently investigating this knowledge gap, and is examining the association between lower cholesterol levels with improved cardiovascular outcomes in patients on inclisiran.

WARNING AND PRECAUTIONS:
-Pregnancy - Discontinue inclisiran when pregnancy is recognized. Treatment of hyperlipidemia is not generally necessary during pregnancy and the lipid lowering effects of inclisiran may cause fetal harm.
-Breastfeeding - The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for inclisiran and any potential adverse effects on the breastfed infant from inclisiran or from the underlying maternal condition.

CONTRAINDICATIONS: None

ADVERSE REACTIONS:

Occurring in Greater Than or Equal to 3% of inclisiran-treated Patients and More Frequently than with Placebo

Adverse Reactions	Intervention Group (N=1833)	Placebo (N=1822)
Injection site reaction	8.2%	1.8%
Arthralgia	5.0%	4.0%
Urinary tract infection	4.4%	3.6%
Diarrhea	3.9%	3.5%
Bronchitis	4.3%	2.7%
Pain in extremity	3.3%	2.6%
Dyspnea	3.2%	2.6%

CLINICALLY SIGNIFICANT DRUG INTERACTIONS: None known

DOSING AND ADMINISTRATION:

Adult Dosing/Indication and Administration

- Heterozygous familial hypercholesterolemia and Clinical atherosclerotic cardiovascular disease
  - **o** 284 mg administered as a single subcutaneous injection initially, again at 3 months, and then every 6 months thereafter
- Missed dose
  - o If a planned dose is missed by less than 3 months, administer inclisiran and maintain dosing according to the patient's original schedule.
  - o If a planned dose is missed by more than 3 months, restart with a new dosing schedule - administer inclisiran initially, again at 3 months, and then every 6 months.
- Administration
  - o Inclisiran should be administered by a healthcare professional. Inject inclisiran subcutaneously into the abdomen, upper arm, or thigh. Do not inject in areas of active skin disease or injury, such as sunburns, skin rashes, inflammation, or skin infections.

RECOMMENDED MONITORING:

- Serum lipid panel
  - o Assess LDL-C when clinically indicated. These LDL-lowering effect of inclisiran may be measured as early as 30 days after initiation and anytime thereafter without regard to timing of the dose.

PHARMACOECONOMICS/COST:

Product (Drug, Strength, Form)	Contract/GPO Price
Leqvio (inclisiran) 284 mg/1.5 mL prefilled syringe	**$3,217.50 per syringe**
Repatha (evolocumab) 140 mg/mL prefilled Sureclick syringe (every 2 weeks) 420 mg/3.5 mL Pushtronex system (on-body infuser- once monthly)	 $237.82 per syringe $515.26 per system
Praluent (alirocumab) 75 mg/syringe pens, 2-count 150 mg/syringe pens, 2-count	 $436.83 per package ($218.42 per syringe pen) $436.83 per package ($218.42 per syringe pen)

Product (Drug, Strength, Form)	Cost/Dose	Cost/Year
Leqvio (Inclisiran) 284 mg/1.5 mL prefilled syringe- *administered by HCP*	$3,217.50	**$9,652.50 (Y1)** **$6,435 (Y2 and beyond)**
Repatha (evolocumab)- *self-administered* 140 mg/mL prefilled Sureclick syringe (every 2 weeks) 420 mg/3.5 mL Pushtronex system (on-body infuser- once monthly)	 $237.82 $515.26	 $6183.32 $6183.32
Praluent (alirocumab)- *self-administered* 75 mg/syringe pens, 2-count 150 mg/syringe pens, 2-count	$218.42	$5,679.70

Medication specific billing codes: J-code: J1306 (effective 7/1/22)

CONCLUSION & RECOMMENDATION:
Inclisiran (Leqvio) is a newly approved medication indicated as an adjunct to diet and maximally tolerated statin therapy for the treatment of adults with HeFH or clinical ASCVD, who require additional lowering of LDL-C. Inclisiran works similarly to alirocumab (Praluent) and evolocumab (Repatha) to reduce cholesterol by targeting PCSK9. However, inclisiran does so in a novel manner, by degrading the mRNA molecules used to translate genetic instructions into proteins during PCSK9 production, while Repatha and Praluent are monoclonal antibodies that inhibit PCSK9 activity.

In all phase three trials, inclisiran added to statin therapy significantly reduced LDL cholesterol compared to placebo by approximately 50% over an 18 month study period. This is similar to the efficacy shown by other PCSK9 targeting therapies (alirocumab and evolocumab). However, inclisiran's phase three trials were not designed to evaluate patient-centered cardiovascular risk outcomes. The benefit that inclisiran provides over similar PCSK9 medications is its twice-yearly injection schedule, while alirocumab and evolocumab are injected every two weeks or monthly. Although, unlike alirocumab and evolocumab that are self-administered, inclisiran must be administered by a HCP.

Inclisiran is being marketed as an outpatient product to be administered in clinic offices or outpatient infusion centers, with its place in therapy for patients already on statins needing additional LDL-C lowering therapy. CommonSpirit Health system P&T committee evaluated inclisiran at the May 2022 meeting and voted it as non-formulary at this time until a permanent billing code (J-code) and clinical outcomes data are available. A permanent billing code was assigned on July 1st.

Due to inclisiran's lack of published data on cardiovascular outcomes in addition to the high cost of the medication, it is recommended that inclisiran be non-formulary.
Inclisiran may be re-reviewed by the P&T committee once clinical outcomes data are published.
This recommendation is supported by cardiology physician leadership.

FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)

Medication Management Step	Identified Risk	Steps for Prevention
Selection		
Therapeutic interchange?	No	NA
Special Ordering Requirements?	No	NA
Storage		
LASA* separation of stock?	No	NA
Special storage (e.g. refrigeration, protect from light, controlled substance)?	No	NA
Pharmacist/Technician Education?	No	NA
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	No	NA
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	No	NA
Drug Interactions?	No	NA
Pregnancy?	Yes	Inclisiran should not be used in pregnant females
Absolute Contraindications?	No	NA
Requires Order Set, Protocol, concomitant therapy with another drug?	No	NA
LASA* nomenclature issues?	No	NA
Prescriber education?	No	NA
Processing, Preparing, & Dispensing		
High-risk drug double check?	No	NA
Drug Interaction check in place?	No	NA
LASA* computer warnings?	No	NA
Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)?	No	NA
Packaging/Labeling (e.g. prepacking)?	No	NA
Dispensing (e.g. auxiliary labeling, light protection, refrigeration)?	No	NA
Documentation required (e.g. double check, worksheet)?	No	NA
Pharmacist/Technician Education?	No	NA

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?	No	NA
Special delivery system (e.g. pump)?	No	NA
Documentation required? (e. g. double check)	Yes	Medication injection documentation
Nurse education?	Yes	Inclisiran should only be administered by a healthcare professional
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?	No	NA
Follow-up laboratory tests?	Yes	Lipid panel
Education?	No	NA

FORMULARY UPDATE

THERAPEUTIC CLASS: Vitamin D analog

GENERIC NAME: Paricalcitol

PROPRIETARY NAME: Zemplar®

BACKGROUND/RATIONALE:

Paricalcitol is a synthetic vitamin D analog which binds to and activates the VDR in kidney, parathyroid gland, intestine and bone, thus reducing PTH levels and improving calcium and phosphate homeostasis. Oral paricalcitol is FDA approved for prevention and treatment in adults and pediatric patients 10 years and older with secondary hyperparathyroidism associated with stage 3 and 4 CKD and stage 5 CKD patients on hemodialysis or peritoneal dialysis.

Oral paricalcitol (1 mcg capsule) is on formulary, while IV paricalcitol has been non-formulary for years. In the past 12 months, oral paricalcitol has only been ordered for one dose for one patient (in the emergency dept).

The cost for thirty 1 mcg capsules is $27.

RECOMMENDATION/DISCUSSION:

It is recommended to remove oral paricalcitol from formulary. All paricalcitol formulations will be non-formulary. Patients will be allowed to continue their own home supply.

Anavip Antivenom Treatment Guidelines

Step 1: Mark skin to delineate local area affected by envenomation.
Confirm that CBC, PT/PTT, fibrinogen, CPK, metabolic panel, and HCG (if female) are done.

Step 2: Administer initial Anavip infusion. Time administered _____
(Rattlesnake, Water moccasin, Cottonmouth)/or Moderate envenomation (Copperhead, general crotalid or unknown) – 10 vials in NS 250 mL IV – Start at 25 mL/hr x 10 minutes, then increase to 250 mL/hr if no allergic reaction occurs

Step 3: One hour after infusion is finished, complete the following:
1. Reassess and mark local skin changes and check vital signs (including temp)
2. Monitor patient for signs of allergic or hypersensitivity reaction.

Step 4: Determine if **initial control** has been achieved. If initial control is **NOT** achieved:
****The majority of patients (>95%) achieve initial control with one dose. Most patients will not need a repeat dose (Anavip has a 133 hour half-life).**
1. Give an additional dose of anti-venom 10 vials in NS 250 mL over 60 minutes and return to Step 3.

*Note: Severe envenomation may require more aggressive dosing of anti-venom to achieve initial control.

Initial Control of envenomation will be judged to have been achieved IF the following are true:
1. Resolution of systemic symptoms, **AND**
2. Leading edge of local injury is not progressing more than 1 inch per hour **AND**
3. Platelet count, serum fibrinogen level, PT and PTT are either in the normal range, or if abnormal are returning toward the normal range as compared with baseline values.

IF initial control has **NOT** been achieved **1 hour AFTER** the **END** of the first infusion, a second dose of anti-venom should be infused.

Step 5: Maintenance Phase: **Maintenance doses of Anavip are not recommended unless symptoms progress (progression of swelling, new or enlarging blisters, new necrotic areas, coagulation abnormalities, and systemic signs/symptoms)**
1. If symptoms progress after initial control is achieved, give 4 vials in NS 250 mL over 60 minutes every 6 hours PRN symptom progression

Step 6: Monitoring Phase:
1. Patient should be monitored for rebound effects after anti-venom therapy has been discontinued, including return of local symptoms and coagulopathy.
2. Re-administration of anti-venom therapy is at physician discretion based on severity of symptoms and significance of coagulopathy.
3. Patient should have at least one repeat CBC, PT/PTT, Fibrinogen 6-12 hours after the last anti-venom infusion and prior to discharge.

Minor, moderate or severe envenomation by a North American crotaline snake:

Early use of Crotalidae polyvalent antivenin is recommended within **6 hours** of envenomation to prevent clinical deterioration and to prevent signs of systemic coagulation abnormalities.

Pediatric or adult patients: The anti-venom dose reflects venom size rather than patient size, the FDA recommends the same initial dose and subsequent doses for pediatric patients.

Snakebite Treatment Guidelines		
Severity	**General Crotalid (or unknown)**	**Known rattlesnake or moccasin (cottonmouth)**
Dry Bite	No anti-venom. Local wound care. Observation and d/c home.	No anti-venom. Local wound care, observation, d/c home if no clinical signs develop.
Minor	No anti-venom. Analgesia. Local wound care. Observe for 8-12 hours.	**Begin anti-venom therapy. Admit to hospital.**
Moderate	**Begin anti-venom therapy. Admit to hospital.**	**Begin anti-venom therapy. Admit to hospital.**
Severe	**Begin anti-venom therapy. Admit to ICU**	**Begin anti-venom therapy. Admit to ICU.**

__Anavip Inventory__ (CHI Memorial): GW & GA campuses each stock 10 vials. HX stocks 20 vials. Once an initial dose is ordered at GW or GA, the Pharmacy will call a super-stat courier to obtain additional vials from HX to prepare for potential subsequent doses.

Type of Signs or Symptoms	Dry Bite	Minor	Moderate	Severe
Local	**Puncture mark(s) with NO associated swelling, erythema, or ecchymosis**	**Swelling, erythema or ecchymosis confirmed to area around site of the bite**	**Progression of swelling, erythema, or ecchymosis beyond site of the bite**	**Rapid swelling, erythema or ecchymosis involving the entire body part**
Systemic	No systemic signs or symptoms	No systemic signs or symptoms	**Non-life threatening signs and symptoms (N/V, mild hypotension, perioral paresthesias, myokymia)**	**Markedly severe signs and symptoms (hypotension SBP<80mmHg, altered sensorium, tachycardia, and respiratory distress)**
Coagulation	No coagulation or lab abnormalities	No coagulation or lab abnormalities	**Mild abnormal coag profile w/o significant bleeding**	**Abnormal coag profile w/bleeding (↓INR, PTT, fibrinogen, platelet count<20,000)**

Anavip (snake antivenom) EHR Ordering Panel

MD Help Text:
Antivenom should only be administered for minor to severe rattlesnake, water moccasin, or cottonmouth bites OR moderate to severe copperhead, general crotalid or unknown bites.

Follow the Anavip Antivenom Treatment Guidelines
The majority of patients (>95%) achieve initial control with one dose (10 vials) of Anavip.
Maintenance doses of Anavip are NOT recommended unless symptoms progress.

Medication Orders:

- ☐ Anavip antivenom per treatment guidelines
- ☐ Td 0.5 mL IM once (if not done in ED)
- ☐ HOLD ERX: Discontinue all anticoagulants, antiplatelet agents, and NSAID medications.

Anavip mixture in panel
Order Instructions:
Follow the Anavip Antivenom Treatment Guidelines to guide dosing. ***The majority of patients (>95%) achieve initial control with one dose (10 vials) of Anavip. Maintenance doses of Anavip are not recommended unless symptoms progress.*** Assess for treatment response ONE HOUR after completion.

Admin Instructions:
-Infuse at a rate of 25 ml/hour for the first 10 minutes, carefully monitoring for any allergic reactions. If no reactions occur, increase the infusion rate incrementally to 250 mL/hour until completion. Discontinue the infusion if any allergic reaction occurs and initiate the Anaphylaxis & Acute Drug Hypersensitivity Protocol. Upon completion, monitor the patient for at least 60 minutes for any allergic reaction.
-Discontinue all anticoagulants, antiplatelet agents, and NSAID medications.
-Notify physician immediately if symptom progression indicates more severe envenomation than initial evaluation.
-Re-administration of anti-venom therapy is at physician discretion based on severity of symptoms and significance of coagulopathy.

ANAVIP (snake anti-venom) Information Sheet

The recent expansion of FDA approval for Anavip to all North American Pit Vipers has shifted CHI Memorial to using Anavip instead of CroFab as the snake anti-venom on formulary.

	Anavip	CroFab
Indications	North American rattlesnakes and Pit Vipers snake groups (including Cottonmouth and Copperhead)	Polyvalent: rattlesnake, copperhead, cottonmouth
Source	Venom from eastern diamondback rattlesnakes, western diamondback rattlesnakes, Mojave rattlesnakes, and cottonmouth snakes, manufactured in sheep	Venom from South American rattlesnakes and fer-de-lance snakes, manufactured from horse serum
Kinetics	Prolonged action; reduced late coagulopathy from venom (7.8% overall; 5.3% in Anavip+ placebo group)	Shorter acting; higher prevalence of late coagulopathy from venom (29.7%)

Anavip Dosing

Initial Control: **10 vials in NS 250 mL IV** (pharmacy compounds)

- Start 25 mL/hr x 10 min, then if no adverse reactions increase to 250 mL/hr
- **The majority of patients (>95%) achieve control with one dose of Anavip. Most patients will not need a repeat dose.**
- If initial symptoms are not controlled within 1 hour after completion of the first dose, repeat 10 vials again

Initial Control of envenomation will be judged to have been achieved **IF** the following are true:

1. Resolution of systemic symptoms, **AND**
2. Leading edge of local injury is not progressing more than 1 inch per hour **AND**
3. Platelet count, serum fibrinogen level, PT and PTT are either in normal range, or if abnormal are returning toward the normal range as compared with baseline values

Maintenance dose: **Not ordered unless symptoms progress (progression of swelling, new or enlarging blisters, new necrotic areas)**

- Dose: 4 vials in NS 250 mL over 60 min Q6hr PRN symptom progression
- Anavip has a **133 hour half-life**, thus a maintenance dose is not recommended. Crofab has a 15 hour half-life thus it requires multiple doses during the initial control phase.

Severity	General Crotalid (or unknown) Including copperheads	Known Rattlesnake or moccasin (including cottonmouth)
Dry Bite	No anti-venom. Local wound care. Observation and d/c home	No anti-venom. Local wound care, observation, d/c home if no clinical signs develop.
Minor	No anti-venom. Analgesia. Local wound care. Observe for 8-12 hours.	Begin anti-venom therapy. Admit to hospital.
Moderate	Begin antivenom therapy. Admit to hospital.	Begin anti-venom. Admit to hospital.
Severe	Begin anti-venom therapy. Admit to ICU.	Begin anti-venom therapy. Admit to ICU.

Notes:

- Use of Crotalid polyvalent anti-venom is recommended within 6 hours of envenomation to prevent clinical deterioration and to prevent signs of systemic coagulation abnormalities.
- As the anti-venom dose reflects venom size rather than patient size, the FDA recommends the same initial dose and subsequent doses for pediatric patients.

Anavip Inventory (CHI Memorial)

10 vials of Anavip are stocked on site at the Glenwood and Georgia campuses, respectively, and 20 vials at the Hixson campus (due to higher incidence of snake bite presentations). Once the initial dose is ordered, pharmacy will call a super-stat courier to obtain additional vials in the event a second dose or maintenance dose is needed.

Injectable promethazine (Phenergan®)

BACKGROUND/RATIONALE:

Removal of injectable promethazine from hospital formularies has remained an ISMP Best Practice Recommendation since 2018. Our local P&T committee reviewed this recommendation in 2019 (*see minutes from May 2019*). Our local Med Safety Committee reviewed this topic again in June 2022.

May 2019 P&T Committee Meeting Minutes:

> **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.

ISMP Best Practice 2022-2023:

BEST PRACTICE 13:

Eliminate injectable promethazine from the formulary.

- Remove injectable promethazine from all areas of the organization including the pharmacy.
- Classify injectable promethazine as a non-stocked, non-formulary medication.
- Implement a medical staff-approved automatic therapeutic substitution policy to convert all injectable promethazine orders to another antiemetic.
- Remove injectable promethazine from all medication order screens, and from all order sets and protocols.

This *Best Practice* includes not using intramuscular administration of promethazine because this can also cause tissue damage if accidentally injected intraarterially.

Rationale:

The goal of this *Best Practice* is to eliminate the risk of serious tissue injuries and amputations from the inadvertent arterial injection or intravenous (IV) extravasation of injectable promethazine. ISMP brought attention to this serious issue in August 2006 and conducted a survey to determine the prevalence of the issue. Of the nearly 1,000 responses to the survey, 1 in 5 reported awareness of such an occurrence in their facility during the prior 5 years. The US Food and Drug Administration (FDA) requires the manufacturer to include strong warnings about the risk of inadvertent intraarterial injection or perivascular extravasation of this drug in the package insert. Injectable promethazine has been included on the ***ISMP List of High-Alert Medications in Acute Care Settings*** (www.ismp.org/node/103) since 2007.

In 2009, ISMP recommended removal of injectable promethazine from an organization's formulary, if possible, and use of safer alternatives such as 5-HT 3 antagonists (e.g., ondansetron). However, these products were significantly higher in cost at the time. Since then, these alternative injectable antiemetics have become available as generic products and are significantly less costly. Thus, injectable promethazine has been used less frequently, and for safety, should now be removed from all formularies.

Best Practice 13 First Introduced:

2018-2019

Related *ISMP Medication Safety Alerts!*:

June 27, 2013; October 8, 2009; September 24, 2009; October 9, 2008; November 2, 2006; **August 10, 2006**.

June 2022 CHI Memorial Medication Safety Committee Meeting:

In alignment with the Institute for Safe Medication Practices (ISMP) 2018-2019 Targeted Medication Safety Best Practices for Hospitals and the Safety First Alert issued from CHI in 2016, many CHI hospitals and many large hospitals across the nation outside of the CHI system have eliminated injectable promethazine from their hospital formulary.

We have not had an IRIS related to IV push promethazine until last month.

Details of IRIS: Midline placed 5/24, order for IV promethazine placed 5/30 and 6/1. Pharmacy will usually get notification upon insertion of a midline to change promethazine to Compazine, however if promethazine is ordered after placement there is not a mechanism for the pharmacist to know the line type. The midline had to be pulled, however it was not clear from the documentation that the reason for pulling the line was due to an ADE from promethazine but based on the notes it is likely.

Historic examples (*not in our facilities*) of IV promethazine ADEs:

- 19 year old patient receives IV promethazine in the ER. During and after administration, the patient complained of pain in her arm and stated that she felt something was wrong. The patient's concerns were dismissed. Soon, the patient's arm and fingers became purple and blotchy. She was kept inpatient for 30 days while her previously healthy fingers turned black and shriveled up. Her thumb, index finger, and top of middle finger had to be amputated.
- Patient received 12.5 mg of IV promethazine. Patient complains of extreme burning during injection. The patient's hand became necrotic and required a skin graft and extensive physical therapy.
- Supreme Court Case: Wyeth v. Levine. The court ruled in favor of Diana Levine who received IV promethazine in an outpatient clinic for migraine. Due to progressive gangrene associated with IV promethazine administration, the patient's right arm was amputated. She was awarded $2.4 million for medical expenses and $5 million for pain and suffering.

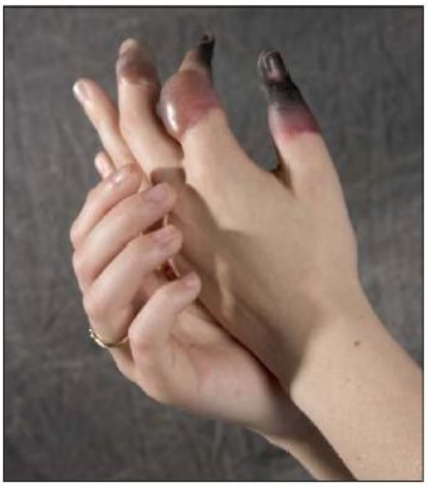


Figure 1. Woman Develops Gangrene after Receiving Phenergan IV. Image provided courtesy of ISMP.

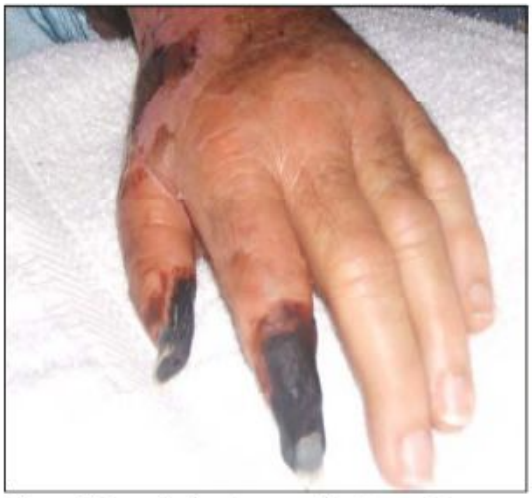


Figure 2. Promethazine Extravasation Causes Gangrene in Man's Fingers. Image provided courtesy of ISMP.

Med Safety Committee Recommendation:

Promethazine IV push

- Long time recommendation to remove promethazine IV push due to ADEs
- IRIS from May reviewed, first IV promethazine IRIS according to reporting history available
- Discussed major ADEs and outcomes - including supreme court case Wyeth v Levine
- **Committee recommends bringing the recommendation to stop the use of promethazine IV push to Pharmacy & Therapeutics committee for discussion.**

Example of Anti-Emetic Alternatives (CHI St. Vincent):

Promethazine oral, topical, and rectal formulations do not pose the same risks.

Alternatives available for nausea include:

Selection of Antiemetics by Clinical Situation		
Situation	**Associated Neurotransmitters**	**Available Antiemetics**
Migraine Headache	Dopamine (probably a primary mediator)	Metoclopramide 5-10 mg PO/IM/IV q 6 hrs Prochlorperazine 2.5-10 mg IM/IV q 6 hrs Prochlorperazine 5-10 mg PO q 6 hrs Prochlorperazine 25 mg PR q 12 hrs Ondansetron 4 mg PO/IV/IM q 6 hrs
Vestibular Nausea	Histamine, acetylcholine	Diphenhydramine 25-50 mg PO/IV/IM q 4-6 hrs Meclizine 12.5-25 mg PO q 6 hrs Scopolamine 1.5 mg patch q 72 hrs Promethazine 25 mg PO/PR q 6 hrs
Pregnancy Induced Nausea	Unknown	*For Nausea:* Pyridoxine 100 mg PO q 12 hrs *For Hyperemesis:* **First Line:** Promethazine 25 mg PR q 6 hrs Second Line: Ondansetron 4 mg PO/IV/IM q 6 hrs
Gastroenteritis	Dopamine, serotonin	**First Line:** Metoclopramide 5-10 mg PO/IM/IV q 6 hrs Second Line: Ondansetron 4 mg PO/IV/IM q 6 hrs
Post-Op Nausea/Vomiting	Dopamine, serotonin	*Prevention:* Ondansetron 4 mg PO/IV/IM q 6 hrs *Treatment:* Metoclopramide 5-10 mg PO/IM/IV q 6 hrs Ondansetron 4 mg PO/IV/IM q 6 hrs

Please refer to Prescribing Information for contraindications in specific patient populations

MEDICATION USE:

Feb-July 2022	
Row Labels	Count of MEDICATION NAME
promethazine (PHENERGAN) 12.5 mg in sodium chloride 0.9% (NS) 50 mL IVPB	1
(blank)	1
promethazine (PHENERGAN) 25 mg in sodium chloride 0.9% (NS) 50 mL IVPB	72
25	72
promethazine (PHENERGAN) 25 mg/mL injection	61
12.5	6
2.5	1
25	1
3	1
3.5	1
5	1
6.25	50
promethazine (PHENERGAN) 50 mg in sodium chloride 0.9% (NS) 50 mL IVPB	1
50	1
promethazine (PHENERGAN) injection	80
10	3
12.5	13
2.5	1
20	1
25	2
5	5
6.25	48
6.5	1
7.5	6
promethazine (PHENERGAN) injection 12.5 mg	147
12.5	147
promethazine (PHENERGAN) injection 2.5 mg	3
2.5	3
promethazine (PHENERGAN) injection 25 mg	29
25	29
promethazine (PHENERGAN) injection 3.75 mg	1
3.75	1
promethazine (PHENERGAN) injection 6.25 mg	86
25	1
6.25	85
promethazine (PHENERGAN) IV Push	4665
12.5	1638
2.5	3
3	1
3.25	2
6.25	3019
(blank)	2
Grand Total	5146

Feb-July 2022				
Count of MEDICATION NAME	Column Labels			
Row Labels	Intramuscular	Intravenous	(blank)	Grand Total
Allied Health Professional		3		3
Anesthesiology	1	128	1	130
Bariatrics		9		9
Cardiology		25		25
Cardiothoracic Surgery		3		3
Certified Registered Nurse Anesthetist		47		47
Colon and Rectal Surgery		27		27
Emergency Medicine	31	541		572
Family Medicine	4	87		91
Gastroenterology	1	488		489
General Surgery		280		280
Gynecology		17		17
Hospitalist		7		7
Internal Medicine	45	1384		1429
Nephrology		4		4
Neurological Surgery		1		1
Neurology		3		3
Nurse Practitioner	24	797		821
Obstetrics and Gynecology		47		47
Oral Surgery		4		4
Orthopedic Surgery	4	174		178
Otolaryngology		4		4
Physician Assistant	6	131		137
Podiatry		3		3
Psychiatry	1	3		4
Pulmonary Medicine		116		116
Radiology		2		2
Rheumatology		2		2
Student/Resident		1		1
Surgery		100		100
Thoracic Surgery		28		28
Urology	1	40		41
Vascular Surgery		175		175
(blank)		285	61	346
Grand Total	**118**	**4966**	**62**	**5146**

DISCUSSION/RECOMMENDATION:

ISMP continues to annually emphasize the importance of removing all injectable promethazine (not just IV push) from hospital formularies to prevent patient harm including serious tissue injury and amputations.

In alignment with the ISMP best practice recommendation, it is recommended to adopt the Med Safety Committee's recommendation and additionally approve the following actions:

- Implement an automatic therapeutic interchange (i.e. LMA pop-up alert) that provides a list of alternative antiemetic(s) and routes of administration on formulary, provides easy-click ordering options for a few alternatives, and does not allow the ordering provider to continue with the current order for injectable promethazine
- Remove injectable promethazine from all order sets (the LMA can function within order sets)
- ~~Designate injectable promethazine (IV and IM) as non-formulary and do not stock (including outpatient infusion center)~~
- ~~Do not allow continuation of orders from home~~

Medication Use Evaluation on Continuous Intravenous Infusions of Lorazepam

BACKGROUND:

Ativan (lorazepam) works post-synaptically by binding receptors on the gamma-aminobutyric acid (GABA) neuron, which increases the inhibitory effect on excitability in the central nervous system.[1] Indications for its use are in Table 1.[1]

Table 1. Lorazepam Indications[1]	
Labeled Indications	Anxiety, premedication for procedural anxiety, status epilepticus
Off-Label Indications	Akathisia from antipsychotics, alcohol withdrawal syndrome, catatonia, chemotherapy-induced nausea and vomiting, intoxication from cocaine, methamphetamine, or other sympathomimetics, sedation for mechanically ventilated patients in the intensive care unit, neuroleptic malignant syndrome, opioid withdrawal, serotonin syndrome, vertigo

As of June 2022, there is an ongoing shortage of lorazepam vials for injection (2 mg/mL) with manufacturers citing increased demand as the reason for the shortage.[2] Continuous intravenous infusions of lorazepam, or lorazepam drips, use a significant amount of lorazepam and drip rates range from 0.5 mg/hour to 10 mg/hour depending on patient response. Due to this shortage and an increase in the use of lorazepam drips, a medication use evaluation was conducted to determine the appropriateness of its use. Patients who received a lorazepam drip from December 2021 – May 2022 at our institution were retrospectively evaluated.

The current order set for mild to moderate alcohol withdrawal syndrome (AWS) at our institution follows a benzodiazepine-sparing, symptom-triggered approach. It includes as needed (PRN) lorazepam based on the Clinical Institute Withdrawal Assessment (CIWA) score plus a scheduled gabapentin taper (Table 2). Patients should be monitored for improvement after each dose of lorazepam. This order set is not intended for use in patients with severe AWS, which is characterized by seizures, hallucinations, or delirium tremens. Severe AWS can be hard to define and is often left to the discretion of the provider. A lorazepam drip may be necessary in the treatment of these patients.

Table 2. Order Set- Mild/Moderate Alcohol Withdrawal Syndrome

Lorazepam	
CIWA < 10	Assess CIWA Q4H
CIWA 10-14	1 mg IV or PO Q4H PRN, CIWA Q2H
CIWA 15-19	2 mg IV or PO Q2H PRN, CIWA Q2H
CIWA > 20	2 mg IV Q30 minutes PRN *reassess CIWA 30 minutes after each dose **if CIWA > 20 for 2 assessments, notify provider

Gabapentin		
	If normal renal function, CrCl ≥ 60 mL/min	If moderate renal impairment, CrCl 30-59 mL/min
Days 1-4	900 mg PO Q8H	600 mg PO Q8H
Days 5-7	600 mg PO Q8H	300 mg PO Q8H
Days 8-9	300 mg PO Q8H	100 mg PO Q8H
Other	vitamins, clonidine, hydroxyzine, valproic acid	

LITERATURE REVIEW:

Benzodiazepines are the standard therapeutic class of medications used to prevent and treat AWS. Several treatment strategies exist, including symptom-triggered, front-loading, and fixed-dose regimens of benzodiazepines.[3] Specific benzodiazepines are not preferred over the others. However, the route of administration depends on patient status, and a physician may choose a specific benzodiazepine based on the duration of effect. Chlordiazepoxide and diazepam are considered long-acting benzodiazepines, but oxazepam and lorazepam may be preferred in patients with metabolic dysfunction in the liver due to a lack of active metabolites requiring phase II metabolism, which reduces the risk over-sedation and respiratory depression.[3]

Recent literature suggests adjunctive or alternative agents to benzodiazepines for the treatment of AWS.[4] Although benzodiazepines are the standard, there are problems associated with their use, including development of benzodiazepine-induced delirium and an increased risk of respiratory depression in combination with alcohol.[4] The use of phenobarbital alone or in addition to lorazepam appears to be effective, decrease the length of hospital stay, and lower the need for other adjunctive therapies.[5,6] However, more robust studies are needed to confirm these observations.[5,6]

METHODS/RESULTS:

Eleven patients received lorazepam drips from December 2021 – May 2022 for a combined total of ninety-five drips dispensed to patients from the inpatient pharmacies. Indications for lorazepam drip usage are illustrated in Figure 1. Approximately 20 percent of patients received a drip for indications that were non-alcohol related, including acute encephalopathy due to amphetamine withdrawal and comfort care. Of the approximately 80 percent of patients who received a lorazepam infusion for alcohol-related indications, six patients were treated with lorazepam drips for AWS, and two of these patients either presented with or quickly developed severe AWS. Three patients presented intoxicated with alcohol, were quickly intubated, and were started on a lorazepam drip. The average duration of infusion use by indication is illustrated in Table 3.The average duration of infusion for all patients was 4.2 days, with the shortest duration being one day and the longest seven days.

Figure 1. Lorazepam infusion indications

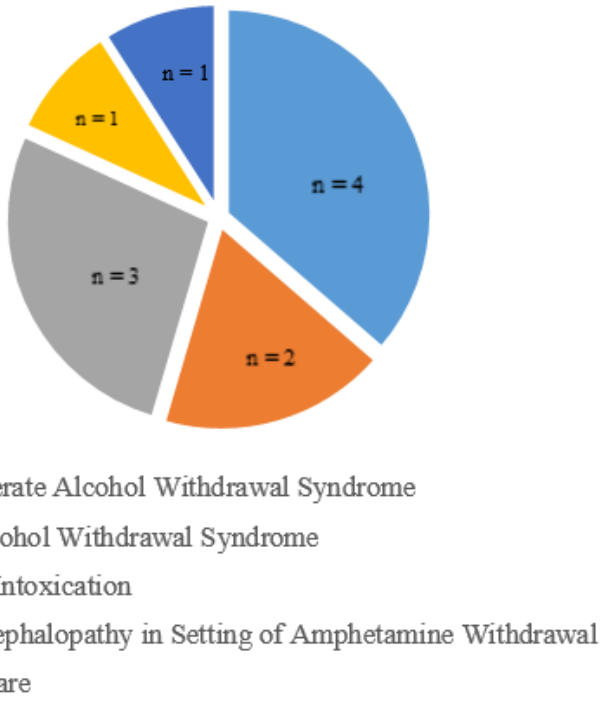


Table 3. Infusion Duration by Indication	
Indication	**Average Duration of Infusion Use (days)**
Mild/Moderate AWS	4.8
Severe AWS	5.5
Alcoholic Intoxication	2.3
Acute Encephalopathy in Setting of Amphetamine Withdrawal	1
Comfort Care	1

The nine patients who received a lorazepam infusion for an indication related to alcohol use were evaluated for the appropriate use of PRN lorazepam, the scheduled gabapentin taper, and valproic acid *prior to the start of the infusion even though the order set is intended to be used for mild/moderate alcohol withdrawal only*. Valproic acid is indicated if the patient has a history of severe AWS, prior brain injury, an existing seizure disorder, or a history of withdrawal

seizure. Of the nine patients in which the order set was placed, valproic acid was indicated in four patients due to a history of seizure. It was only ordered and administered in one of those four patients as intravenous valproate. Criteria determining appropriate and inappropriate use of lorazepam and gabapentin prior to drip initiation are described in Figure 2. Appropriate use of lorazepam and gabapentin for mild/moderate AWS is outlined in Figure 3. Figures 4 and 5 detail lorazepam and gabapentin usage by indication but do not state appropriateness.

	Appropriate	Inappropriate
Lorazepam	Timely assessment of CIWA at designated intervals Timely administration of lorazepam based on CIWA Correct lorazepam dose based on CIWA Use of mild/moderate alcohol withdrawal order set for at least 24 hours	CIWA not assessed as frequently as indicated Lorazepam not given when indicated based on CIWA > 10 Incorrect lorazepam dose based on CIWA Use of mild/moderate alcohol withdrawal order set for less than 24 hours
Gabapentin	Taper ordered and doses administered Missed doses due to patient being NPO	Taper not ordered and no contraindication documented Taper ordered but not administered prior to drip Scheduled doses not administered (excluding NPO)

Figure 2. Criteria to determine appropriate and inappropriate use of as needed lorazepam and gabapentin

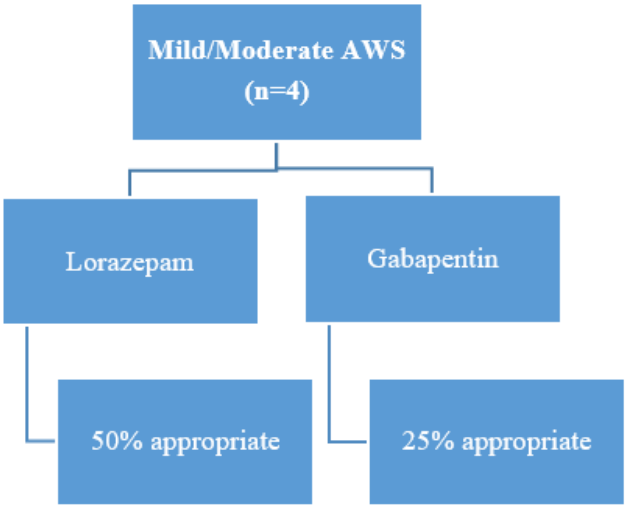


Figure 3. Adherence to order set parameters for mild/moderate AWS for lorazepam and gabapentin

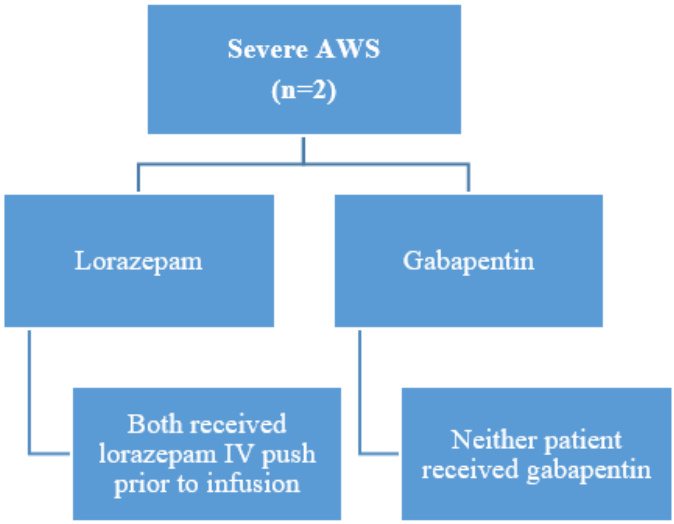


Figure 4. Assessment of medication management of severe AWS prior to lorazepam infusion

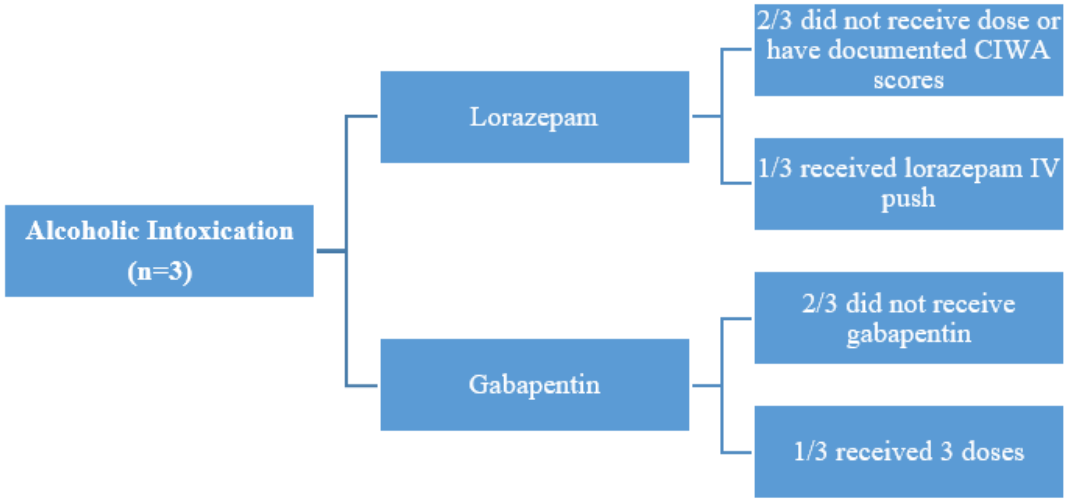


Figure 5. Assessment of medication management of alcoholic intoxication prior to lorazepam infusion

Table 4. Appropriate Use of Lorazepam Infusion by Indication	
Indication	**% Appropriate**
Mild/Moderate AWS	50% (2/4)
Severe AWS	100% (2/2)
Alcoholic Intoxication	0% (0/3)
Acute Encephalopathy in Setting of Amphetamine Withdrawal	100% (1/1)
Comfort Care	100% (1/1)

DISCUSSION:

The majority of patients receiving lorazepam infusions were experiencing AWS or acutely intoxicated with alcohol. While a small number of patients (n=11) received an infusion during the specified time frame, the volume of drips per patient was high (8.6 dispensed per patient). For each patient who received a lorazepam infusion due to an alcohol-related indication, the symptom-triggered order set for mild/moderate AWS was ordered. However, this is the only available order set available to guide treatment of AWS.

Of the patients experiencing mild/moderate AWS, only 25 percent of patients appropriately received both the PRN lorazepam and scheduled gabapentin taper before transitioning to the infusion for better control of AWS symptoms. The remaining patients either did not receive gabapentin or went a prolonged period of time without it being administered, or the administration of lorazepam with respect to documented CIWA score was not timely. In many instances, the CIWA score was not assessed at the recommended interval(s) and therefore the administration of lorazepam was delayed.

The initiation of a lorazepam infusion in the case of severe AWS is appropriate (documentation of delirium tremens present). However, the quick initiation of a lorazepam infusion in patients presenting with alcoholic intoxication requiring intubation is more controversial. The majority of those patients did not receive any PRN lorazepam doses or scheduled gabapentin prior to initiation of the infusion. Unfortunately, current literature is not explicit on the appropriate course of treatment for these patients, especially those requiring intubation.[7] A positive blood alcohol level upon admission does not rule out the possibility of AWS, as patients who consume large amounts of alcohol can still experience withdrawal symptoms when alcohol ingestion is decreased. Patients intoxicated upon admission and showing concurrent withdrawal symptoms may be at an increased risk of severe AWS and should be initiated on pharmacotherapy with benzodiazepines, phenobarbital, or phenobarbital adjunct to benzodiazepines for prophylaxis. Notably, the early use of a lorazepam infusion is not specified in this case, and the symptoms of active AWS while intoxicated was not documented for these patients.[7]

CONCLUSION:

The prescribing of lorazepam infusions for the prophylaxis and treatment of AWS utilizes a significant amount of intravenous lorazepam at our institution (approximately 40 percent of all parenteral lorazepam use). For the patients in which the mild/moderate alcohol withdrawal protocol was indicated, it was rarely optimized to prevent breakthrough symptoms, which may have led to the prescribing of a lorazepam infusion. The protocol was incorrectly initiated for patients experiencing severe AWS, and intoxicated patients at risk for AWS were initiated on the order set and started on lorazepam infusions as well. While the frequent monitoring required by a symptom-triggered approach can be cumbersome and its failure may be contributing to the overuse of lorazepam infusions, this approach is recommended for the treatment of AWS. However, recent literature prompts the reevaluation of benzodiazepines for this indication and introduces benzodiazepine-sparing alternatives, such as phenobarbital. In the setting of an intravenous lorazepam shortage, reconsidering the use of benzodiazepines for alcohol withdrawal may be beneficial.

FORMULARY UPDATE (DRUG SHORTAGE)

THERAPEUTIC CLASS: Benzodiazepines

GENERIC NAME: Lorazepam

PROPRIETARY NAME: Ativan®

BACKGROUND/RATIONALE:

In June, injectable lorazepam was added to the list of medications in short supply. Our inventory remained stable until July, when backorders and allocated supply options were exhausted.

MEDICATION USE:

Three months (Apr-Jun 2022) of injectable lorazepam utilization was evaluated. The following methods were employed:

- All campuses included
- Narrowed to doses documented as "Given"
- Excluded lorazepam infusions (separate MUE)
- Excluded orders originating from order sets (excluded AWS/CIWA; otherwise order set use was negligible)

Results (n=2122)

- 38 different frequencies ordered (e.g. once, scheduled, PRN)
    - 18 (47%) were PRN frequencies (i.e. q12 prn, q20 min prn, q8 prn, etc). PRN frequencies accounted for ~55% of given doses (1172/2122) doses
        - Of the 18 prn frequencies ordered, there were 47 different prn indications
            - Of the 47 prn indications, 32 (68%) have two or more ordered indications (i.e. anxiety, hallucinations; insomnia, anxiety; seizures, anxiety, hallucinations, insomnia).
        - Over 70% of indications include "anxiety" as at least one of the indications for PRN use
    - The majority of the indications were appropriate for oral route of administration

INVENTORY:

Current supply as of 8/10/22:

	Glenwood
# of 2 ml vials in stock	~120
# of 10 ml vials in stock	~210

A panel of physician, nursing, and pharmacy leaders met to emergently on July 28th to develop mitigation strategies. The decisions of that group are summarized below.

- Pharmacists may automatically substitute orders for injectable lorazepam to oral lorazepam in a 1:1 ratio if the patient can take oral/NG/FT medications, unless indicated for seizure or alcohol withdrawal (approved emergently on 7/22/22)
- Benzodiazepine equivalents: Lorazepam 1 mg = Midazolam 1 mg = Diazepam 5 mg
- IV lorazepam is permanently formulary restricted for the treatment of only acute seizures or alcohol withdrawal
    - Chemotherapy-induced nausea and/or vomiting will be added as an approved indication per guideline recommendations
    - Build this as a hard stop on the medication in the EHR
- Lorazepam infusions are permanently non-formulary (due to availability of safer alternatives for agitation such as propofol, dexmedetomidine, ketamine and risk of propylene glycol toxicity).

- Build a new EHR alert to drive ordering to alternatives (lorazepam PO or midazolam). Alert is suppressed for the alcohol withdrawal order set. (done- see image below)
- Update the Midazolam Usage policy to allow administration of midazolam outside of ICU and procedural areas (done)
- The following order set modifications have been completed:

Order Set Name	Lorazepam Indication	OSQ that contains lorazepam	Action Item
MCT IP CAR CORONARY CTA PRE MEDICATION ORDERS	anxiety	MCT RX *LORAZEPAM FOR PROCEDURE 0.5 MG IV X1 PRN ANXIETY	replace with lorazepam PO
MCT IP CC COMFORT CARE MEASURES FOR PATIENTS ON ASSISTED VENTILATION	Agitation, Anxiety, Seizures, dyspnea, restlessness	MCT RX LORAZEPAM EVERY 2 HOURS FOR ASSISTED VENTILATION	replace with midazolam IV
MCT IP GYN GYNECOLOGY SURGERY OUTPATIENT POST-OP	anxiety	MCT RX LORAZEPAM (ATIVAN) 1MG IV OR PO Q 6 HOURS PRN ANXIETY PANEL	remove IV lorazepam
MCT IP RAD ARTERIOGRAM / VENOGRAM POST-OP	agitation, anxiety	MCT RX ANXIETY SLEEP LORAZEPAM 1 MG IV EVERY 2 HOURS PRN ZOLPIDEM 5MG PO HS PRN	remove lorazepam
MCT IP RAD KYPHOPLASTY POST-OP	agitation, anxiety	MCT RX ANXIETY SLEEP LORAZEPAM 1 MG IV EVERY 2 HOURS PRN ZOLPIDEM 5MG PO HS PRN	remove lorazepam
MCT IP RAD PLEURAL DRAINAGE CATHETER INSERTION POST-OP	agitation, anxiety	MCT RX ANXIETY SLEEP LORAZEPAM 1 MG IV EVERY 2 HOURS PRN ZOLPIDEM 5MG PO HS PRN	remove lorazepam

RECOMMENDATION/DISCUSSION:
It is recommended to adopt and approve the emergent decisions of the panel as listed above.
The P&T committee may evaluate the decisions in the future as needed.

Alternative Selection

Alternative Recommended

You selected:

LORazepam (ATIVAN) injection 1 mg: 1 mg Once, Intravenous, today at 1430, For 1 dose

Details

CRITICAL SHORTAGE: Supply of lorazepam injection is critically low. Use should be limited to indications of **acute seizures** or **alcohol withdrawal** only.

For other indications, use lorazepam tablets if the oral or enteral route is feasible, including selected patients with alcohol withdrawal.

The IV to oral route can be substituted in a 1:1 ratio (i.e. lorazepam 1 mg IV = lorazepam 1 mg PO/NG/FT).

For situations where the IV route is necessary, below are alternative injectable benzodiazepines:

Lorazepam 1 mg = Midazolam 1 mg = Diazepam 5 mg

Alternatives to Lorazepam			
Alternative Injectable Agents	**Onset**	**Half-Life (hours)**	**Metabolism**
Midazolam (Versed®)*	2-5 min	3-12	Hepatic via CYP3A4

Alternatives

Alternative	Details	Cost
○ LORazepam (ATIVAN) tablet	0.5 mg, Every 4 hours PRN	
○ LORazepam (ATIVAN) tablet	1 mg, Every 6 hours PRN	
○ midazolam (VERSED) injection	0.5 mg, Every 4 hours PRN	$$
○ midazolam (VERSED) injection	1 mg, Every 6 hours PRN	$$

Continue with:

○ LORazepam (ATIVAN) injection 1 mg: 1 mg Once, Intravenous, today at 1430, For 1 dose

✓ Accept Alternative ✗ Remove Order

Phenobarbital for Alcohol Withdrawal Order Set

Alcohol Withdrawal Management for PAWSS Score > or = 4: PHENobarbital for moderate-severe risk of Alcohol Withdrawal Syndrome.

Provider to determine risk of complicated alcohol withdrawal prior to initiating treatment. Utilize the Prediction of Alcohol Withdrawal Severity Scale (PAWSS).

Potential contraindications to PHENobarbital: 1) Allergy to PHENobarbital; 2) diagnosis of alcohol withdrawal unclear; 3) significant drug interaction (i.e. HIV medications); 4) advanced cirrhosis with hepatic encephalopathy; 5) acute intermittent porphyria; 6) chronic use of PHENobarbital*
Do NOT administer weight-based PHENobarbital loading dose to patients who have already received significant doses of benzodiazepines or other sedating medications (i.e. opioids).

ADT/Consents

☑ MD must reassess patient every 24 hours and when there is any change in patient status.

☑ MD rule out other etiologies of autonomic hyperactivity and altered mental status: (e.g. sepsis, cerebral hypoperfusion, hepatic encephalopathy, meningoencephalitis, CVA)

☑ Telemetry monitoring (for moderate or higher alcohol withdrawal)

Vital Signs

☑ Vital Signs
q1hr, While actively treating for Alcohol Withdrawal. May change to Q4 once RASS goal achieved x 3 consecutive assessments

☑ Pulse Oximetry (Continuous)
If RASS -1 or lower

☑ End Tidal CO2 Measurement
If RASS -1 or lower

Patient Care

☑ Nursing Communication
Do not administer benzodiazepines in conjunction with phenobarbital or gabapentin

☑ Notify MD if
RASS score is -2, or lower at any time. HOLD medication and notify MD to reassess and modify orders as appropriate.

☑ Notify MD if
Dangerous agitation or RASS score that remains greater than +2 for 2 hours. If patient not already in ICU or EDtransfer to higher level of care

☑ Notify MD if
patient remains acutely intoxicated when treatment plan initiated. Provider to determine when and if initial loading dose should be administered, then continue treatment as previously ordered

☑ Notify MD if
HR LESS than 50, SBP LESS than 90, RR LESS than 10, O2 Sat LESS than 90, Notify also for signs of over sedation - VS below parameters, not arousable, ataxia, or slurred speech and HOLD treatment (phenobarbital or gabapentin)

☑ Notify MD if
phenobarbital will exceed maximum cumulative dose of 20mg/kg (IBW) and symptoms still not adequately controlled

☑ Precautions
Seizure precautions, elevate HOB >30 degrees if RASS -1 or lower

☑ Monitoring of Richmond Agitation-Sedation Scale (RASS) Every 1 hour. May change to Q4 once RASS goal achieved x 3 consecutive assessments

Medications

Provider to determine risk of complicated alcohol withdrawal prior to initiating treatment using the Prediction of Alcohol Withdrawal Severity Scale (PAWSS). If Patient is actively intoxicated, do not administer loading dose and determine when loading dose should be administered

Alcohol Withdrawal Management for PAWSS Score > or = 4: PHENobarbital
PHENobarbital for moderate-severe risk of Alcohol Withdrawal Syndrome
Potential contraindications to PHENobarbital: 1) allergy to PHENobarbital; 2) diagnosis of alcohol withdrawal unclear; 3) significant drug interaction (i.e. HIV medications); 4) advanced cirrhosis with hepatic encephalopathy; 5) acute intermittent porphyria; 6) chronic use of PHENobarbital
Do NOT administer weight-based PHENobarbital loading dose to patients who have already received significant doses of benzodiazepines or other sedating medications (i.e. opioids).
Choose a Loading Dose and all Supplemental Doses

☐ PHENobarbital
10 mg/kg, IV, once Priority: STAT
Comments: Loading dose for alcohol withdrawal. Use Ideal Body Weight (IBW) to calculate dose. Do not give weight-based dose if pt has received significant doses of benzodiazepines or other sedating medications. Omit if previously received in ED.

OR
Non-weight based loading dose to be given if patient has already received significant doses of benzodiazepines or other sedating medications (i.e. opioids).

☐ PHENobarbital
260 mg, IV Push, INJ, once Priority: STAT
Comments: Loading dose for alcohol withdrawal for pts previously administered benzodiazepines or other sedating medications. Omit if previously received in ED. Administer over 5 min.

Supplemental PHENobarbital doses

☐ PHENobarbital
129.6 mg, PO, Tab, q1hr PRN Withdrawal, alcohol
Comments: To treat alcohol withdrawal. 1st choice if taking PO for RASS = +1 or +2Treatment goal = RASS 0 to -1, Repeat RASS q1 hour. May change to Q4 hour once RASS goal achieved x 3 consecutive assessmentsContact provider if dose will exceed maximum cumulative dose of 20mg/kg (IBW) and symptoms still not adequately controlled.

☐ PHENobarbital
259.2 mg, PO, Tab, q1hr PRN Withdrawal, alcohol
Comments: To treat alcohol withdrawal. 1st choice if taking PO for RASS = +3 or +4Treatment goal = RASS 0 to -1, Repeat RASS q1 hour. May change to Q4 hour once RASS goal achieved x 3 consecutive assessmentsContact provider if dose will exceed maximum cumulative dose of 20mg/kg (IBW) and symptoms still not adequately controlled.

☐ PHENobarbital
130 mg, IV Push, q1hr PRN Withdrawal, alcohol, Administer over 3 min
Comments: To treat alcohol withdrawal. Use only if patient is NPO, for RASS = +1 or +2 Treatment goal = RASS 0 to -1, Repeat RASS q1 hour. May change to Q4 hour once RASS goal achieved x 3 consecutive assessmentsContact provider if dose will exceed maximum cumulative dose of 20mg/kg (IBW) and symptoms still not adequately controlled.

☐ PHENobarbital
260 mg, IV Push, q1hr PRN Withdrawal, alcohol, Administer over 5 min
Comments: To treat alcohol withdrawal. Use only if patient is NPO, for RASS = +3 or +4 Treatment goal = RASS 0 to -1, Repeat RASS q1 hour. May change to Q4 hour once RASS goal achieved x 3 consecutive assessmentsContact provider if dose will exceed maximum cumulative dose of 20mg/kg (IBW) and symptoms still not adequately controlled.

Vitamins

☑ folic acid
1 mg, PO, Tab, qDay

☑ multivitamin, therapeutic
1 Tab, PO, qDay

☑ thiamine
100 mg, PO, Daily

Concern for Wernicke's Encephalopathy: If 2 or more of the following present: ophthalmoplegia, malnourishment, ataxia, confusion, then give treatment doses of thiamine intravenously for 3 days

☐ thiamine
200 mg, IV, Bag, q8hr, Infuse over: 30 min, for 3 Day

☐ **+3 Days** thiamine
100 mg, PO, Daily, To start after 3 days of IV treatment for Wernicke's encephalopathy

Electrolyte Replacement

☐ Initiate electrolyte replacement guidelines

Ancillary Medications

☐ cloNIDine
0.1 mg, PO, Tab, BID, for 3 Day
Comments: Hold for SBP less than 90mmHg

Laboratory

☑ Ethanol Level
Blood, Stat, if not already ordered

☑ Urine Drug of Abuse Screen w/ETOH
Urine, Stat

☑ Comprehensive Metabolic Panel
Blood, Routine-Next Collection

☑ CBC w/Diff* (man diff if indicated)
Blood, Routine-Next Collection

☑ Magnesium (Mg) Level
Blood, Routine-Next Collection

☑ Phosphorus (PO4) Level
Blood, Routine-Next Collection

☐ Ammonia Level
Blood, Routine-Next Collection

☐ PT (includes INR)
Blood, Routine-Next Collection

☐ PTT
Blood, Routine-Next Collection

Consults

☑ Pharmacy consult
Pharmacy to monitor alcohol withdrawal medication orders; phenobarbital cumulative dose

Title: **THERAPEUTIC DUPLICATION OF PRN MEDICATION ORDERS**			
Page **1** of **2**			
Policy Number: MM-05475		Date Last reviewed/Revised: 9/~~19~~8/22	Valid Until: 9/~~22~~8/25
Campus: ☒ CHI Memorial Glenwood ☒ CHI Memorial Hixson ☒ CHI Memorial Georgia *Check all that apply*			
Department(s) Affected: All Clinical Areas		Review Period: Every 3 years	

OUTCOME:
To provide direction for prioritizing nursing choices between multiple PRN medications for the same indication, when not indicated by the prescriber.

- A single PRN medication order for any given indication is preferable.
- If multiple PRN agents are ordered for the same indication, they should contain a clarification as to the criteria or clinical priority of medication administration.

POLICY:
When multiple PRN medications are ordered for the same indication, the prescriber is to provide clear and specific instructions on the desired use of medication choices. ~~Pre-printed p~~**Physician order** sets~~s~~ **will instruct that one choice only be ordered for a specific PRN indication.** In situations where the prescriber ~~hand writes~~enters orders for the same PRN indication or fails to select one medication for a PRN indication in the ~~preprinted~~ order set format, the following guidelines will be used:

1. If the prescriber's orders already provide direction for prioritizing the order of use, they will be implemented as ~~written~~ordered.
2. Of the medications ordered for a specific given indication (example: moderate pain), one medication will be considered to be the provider's choice for the patient based on pharmacy defined medication hierarchy based on therapeutic potency (least potent agent will be used)~~the first agent written in the list of orders for that indication will be considered to be the provider's choice~~. If the patient is intolerant/allergic to the medication ordered and another medication is listed for the same indication, that medication will be considered the provider's choice.
    - Multiple PRN medications for the same indication will not be allowed to exceed one option (e.g. one opiate for moderate pain) unless specific instructions for use are included (e.g. IV opioid for severe pain uncontrolled by or unable to take oral meds). If an intravenous and oral option are both ordered for the same PRN pain indication and a treatment prioritization is not designated, the IV option will automatically be designated to be utilized only if the oral medication is ineffective or if the patient is unable to tolerate oral medications. This will be notated on the electronic MAR so the treatment prioritization for each medication is clear.
    - Additional medication is allowable for breakthrough pain if patients are on a PCA and the PCA is ineffective at the maximum dose ordered.
3. If a new medication is ordered for the same specific indication as a currently ordered medication, the newly ordered medication will be considered the new choice for that indication and the previous medication will be automatically discontinued.
4. Home PRN medications ordered ~~from a medication reconciliation form~~ will be implemented if continued by the prescriber only if other prescriber orders are not ordered for the same PRN indication.
    - Whenever possible, patients will be assessed for preference of PRN home medication when multiple home medications are taken for the same PRN indication, and this information noted on the ~~medication reconciliation form~~prior to admission (PTA) medication history.
    - If no patient preference is specified and multiple home medications are ordered for a PRN indication, one medication will be selected for the patient based on pharmacy defined medication hierarchy based on therapeutic potency (~~most~~ least potent agent will be used).
    - Over-the-counter PRN pain home medications, if ordered without a specific indication will be assigned a PRN mild pain indication.

Title:
MANDATORY ID CONSULTATIONS: *STAPHYLOCOCCUS AUREUS*, *CANDIDA* SPP., AND MULTIDRUG-RESISTANT GRAM NEGATIVE BACTEREMIA

Policy Number:		Date ~~Last~~ reviewed/Revised:	Valid Until:
IC-06041		~~9/19~~8/22	~~9/22~~8/25

Campus: ☒ CHI Memorial Glenwood ☒ CHI Memorial Hixson ☒ CHI Memorial Georgia
Check all that apply

Department(s) Affected:	Review Period:
All Clinical Areas	Every 3 years

PURPOSE:
The management of certain infectious disease states in collaboration with an Infectious Diseases (ID) Consultant has been proven to improve clinical outcomes.

Staphylococcus aureus bacteremia is a serious infection that has a high mortality and complication rate. Some of the complications associated with *S. aureus* bacteremia include endocarditis, septic emboli, recurrence etc. (1,2). Obtaining an ID consultation has been proven to improve antibiotic selection, treatment duration, and overall treatment outcomes. Several hospitals have shown significant improvements in patient outcomes after mandating an automatic consult for *S. aureus* bacteremia. One study with about 100 *S. aureus* bacteremia cases in each arm showed that patients with an ID consult were more likely to have complications identified and treated (46% vs 33%, p=0.04) and be treated for durations consistent with the guidelines (74% vs 40%, p<0.001) (3). Another retrospective cohort study at an academic teaching center over a 7 year period showed significant compliance with guidelines (47.4% vs 82.2%, p<0.001) and a decrease in 30-day mortality rate (25.8% to 16.4%, p<0.001) when an ID consultant was involved in the case (4). Additional studies show similar benefits of an ID consultation (5-8).

Similarly, candidemia has a high attributable mortality rate (9). There are several management recommendations in patients with candidemia that not only includes appropriate antifungal therapy: device or catheter removal, consideration for surgical intervention etc. Similar to *S. aureus* bacteremia, there have been studies that demonstrate that an ID consultation leads to lower mortality rate. An observational study at an academic medical center which included 119 patients with candidemia found that having an ID consultation was independently associated with lower mortality (18% vs. 39%, p=0.0083) (10). Another study demonstrated that patients with a candidemia care bundle was more likely to get treatment in accordance with the guidelines (11).

In addition, bloodstream infections caused by multidrug-resistant (MDR) gram negative rod (GNR) bacteria are a significant cause of morbidity and mortality. Not unlike in the case of *S. aureus* and *Candida* spp. bacteremia, ID consultation has been shown to be a protective factor for infection related mortality in patients with MDR GNR bacteremia.

POLICY:
The policy is intended to improve the management of patients with *S. aureus*, *Candida* spp., and MDR GNR bacteremia who are admitted to CHI Memorial.

PROCEDURE:
A. Indications
   i. *Staphylococcus aureus* bacteremia
   ii. Candidemia
   iii. Carbapenem Resistant Enterobacteriaceae (CRE) and MDR *Pseudomonas aeruginosa* bacteremia
B. Exceptions
   i. None
C. Protocol

~~i. Microbiology department will automatically print all positive blood cultures to pharmacy~~
~~ii.~~i. The Antimicrobial Stewardship Program (ASP) pharmacist will identify patients with *S. aureus*, Candida, CRE, or MDR P. *aeruginosa* bacteremia via ~~Theradoc~~ review of clinical surveillance tool
~~iii.~~ii. The ASP pharmacist will contact the primary physician and inform them that an automatic ID consult is required and enter~~write~~ the order for the ID consult in ~~the patient's chart~~EPIC~~the electronic health record~~.
~~iv.~~iii. This pharmacist will also notify the ID physician on call of the pending consult

Look Alike/Sound Alike Drug List

Drug Name	Drug Name	Potential Errors	Prevention Strategies
CeleBREX®	CeleXA® and CereBYX®	Similar names	1. Tall man lettering in Pyxis, Epic & Talyst. 2. Pyxis pop-up warning. 3. Do NOT store next to each other. 4. Name alert on MAR
cloniDINE	KlonoPIN®	Similar names	1. Tall man lettering in Pyxis, Epic & Talyst. 2. Pyxis pop-up warning. 3. Do NOT store next to each other. 4. Name alert on MAR
Diamox®	Diuril®	Similar names	1. Pyxis pop-up warning. 2. Do NOT store next to each other. 3. Name alert on MAR
DOBUTamine	DOPamine	Similar names	1. Tall man letting in Pyxis, Epic & Talyst. 2. Pyxis pop-up warning. 3. Do NOT store next to each other. 4. Name alert on MAR
DOXOrubicin *Liposomal*	DOXOrubicin *Conventional* and DAUNOrubicin	Similar names	1. Tall man lettering in Pyxis, Epic & Talyst. 2. Do NOT store next to each other. 3. Name alert on MAR
Humalog®	Kenalog®	Similar names	1. Pyxis pop-up warning. 2. Do NOT store next to each other.
hydrOXYzine	hydrALAzine	Similar names	1. Tall man lettering in Pyxis, Epic & Talyst. 2. Pyxis pop-up warning. 3. Do NOT store next to each other. 4. Name alert on MAR
Keppra®	Ketamine	Similar names	1. Pyxis pop-up warning. 2. Do NOT store next to each other. 3. Name alert on MAR 4. Witness required for ketamine
metroNIDAZOLE	metFORMIN	Similar names and strengths	1. Tall man lettering in Pyxis, Epic & Talyst. 2. Pyxis pop-up warning. 3. Do NOT store next to each other. 4. Name alert on MAR
MuciNEX®	MucoMYST®	Similar names	1. Tall man lettering in Pyxis, Epic & Talyst. 2. Pyxis pop-up warning. 3. Do NOT store next to each other. 4. Name alert on MAR
oxyCODONE controlled-release	oxyCODONE immediate-release	Similar names	1. Tall man lettering in Pyxis, Epic & Talyst. 2. Pyxis pop-up warning. 3. Do NOT store next to each other. 4. Name alert on MAR
Plavix®	Pradaxa®	Similar names and strengths	1. Pyxis pop-up warning. 2. Do NOT store next to each other. 3. Name alert on MAR
predniSONE	prednisoLONE	Similar names	1. Tall man lettering in Pyxis, Epic & Talyst. 2. Pyxis pop-up warning. 3. Do NOT store next to each other. 4. Name alert on MAR
Remicade®	Rituxan®	Similar names	1. Tall man lettering in Epic. 2. Do NOT store next to each other. 3. Name alert on MAR
Versed®	Vecuronium®	Similar names	1. Tall man lettering in Pyxis 2. Pyxis pop-up warning. 3. Do NOT store next to each other. 4. Name alert on MAR

Title: RENAL DOSING ADJUSTMENTS			
		Page **1** of **4**	
Policy Number: PHRM-0579		Date Last reviewed/Revised: ~~10/19~~8/22	Valid Until: ~~10/22~~8/25
Campus: ☒ CHI Memorial Glenwood ☒ CHI Memorial Hixson ☒ CHI Memorial Georgia *Check all that apply*			
Department(s) Affected: Pharmacy		Review Period: Every 3 years	

OUTCOME:

To ensure appropriate medication dosing based on patient's renal function and optimize pharmacodynamics and pharmacokinetic properties of renally eliminated medications while decreasing toxicities associated with inappropriate dosing.

POLICY:

Pharmacists may automatically adjust the dose of renally eliminated antimicrobials, anticoagulants, and other medications as approved per the Pharmacy and Therapeutics committee after evaluation of a patient's renal function. In instances where a renal dosage change is warranted, but the medication is not included for automatic dosage adjustment, the pharmacist may contact the prescriber with the recommended dosage change.

PROCEDURE:

1. A pharmacist may evaluate a patient's medication profile for renally eliminated medications. If relevant renal labs have not been ordered within 24 hours of the medication order, the pharmacist may order a basic metabolic profile (BMP) in order to complete this evaluation.
2. During the evaluation, the pharmacist may assess the doses of renally eliminated medications. Based on the patient's calculated creatinine clearance and clinical status, the pharmacist may make necessary adjustments. In instances where a renal dosage adjustment is warranted, but the medication is not approved for automatic adjustment, the pharmacist may contact the prescriber recommending a dosage change.
3. When an automatic dosage adjustment is made, the pharmacist will enter the new order as "Rx Drug Therapy Management-no cosign required."
4. The pharmacist will follow up on dosage adjustments as appropriate, evaluating subsequent changes in patient's renal function and clinical status. If relevant renal labs have not been ordered within 48 hours after a dosage adjustment, the pharmacist may order a basic metabolic profile (BMP).
5. If any dosage adjustment made by a pharmacist is subsequently changed by a prescriber, the pharmacist will make not further automatic adjustments on that medication during the current admission, unless otherwise directed.
6. The following medications have been approved for automatic dose adjustment per pharmacist by the Pharmacy and Therapeutic committee:

Baricitinib (Olumiant®) for COVID-19	
Estimated glomerular filtration rate (eGFR)	**Renal Adjustment**
≥60 mL/min/1.73 m2	4 mg once daily
30 to 60 mL/min/1.73 m2	2 mg once daily
15 to 30 mL/min/1.73 m2	1 mg once daily
< 15 mL/min/1.73 m2	Not recommended

Nirmatrelvir and ritonavir (Paxlovid®)	
Estimated glomerular filtration rate (eGFR)	**Renal Adjustment**
≥60 mL/min/1.73 m2	300 mg/100 mg BID
>30 to <60 mL/min/1.73 m2	150 mg/100 mg BID
< 30 mL/min/1.73 m2	Not recommended

Title: **MIDAZOLAM USAGE**			
		Page **1** of **1**	
Policy Number: MM-05437		Date ~~Last~~ reviewed/Revised: ~~12/24~~8/22	Valid Until: ~~12/24~~8/25
Campus: ☒ CHI Memorial Glenwood ☒ CHI Memorial Hixson ☒ CHI Memorial Georgia ***Check all that apply***			
Department(s) Affected: Pharmacy / Nursing		Review Period: Every 3 years	

OUTCOME: Midazolam will be used for approved indications.

POLICY:
The Pharmacy and Therapeutics Committee has authorized the use of Midazolam only for approved indications as stated in the product package insert unless the patient is located in one of the intensive care units and approved criteria for use on nursing units as outlined below.

Midazolam should not be dispensed to locations other than the intensive care units for usage other than the approved indications and the following criteria:

CRITERIA

1. DNR order on chart
2. Admitted for terminal care
3. Consultation with palliative care specialist
4. Approved indications: Terminal restlessness or myoclonus
5. During critical shortages of alternative injectable benzodiazepines, midazolam may be administered in doses < 2 mg by an RN WITHOUT procedural sedation training.