Pharmacy & Therapeutics Committee Meeting

Private Dining Room

May 12, 2022 7:00 a.m.

Agenda Items	Individual Responsible
1. Call to Order	Nathan Chamberlain, MD
2. Conflict of Interest Disclosure	Rachel Kile, PharmD
3. Approval of February 2022 Minutes	Nathan Chamberlain, MD

Next Meeting Date: August 11, 2022 at 7:00 a.m.

PHARMACY AND THERAPEUTICS COMMITTEE

DATE: February 10, 2022 CALLED TO ORDER: 7:00 a.m.
LOCATION: Zoom Only 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**
X	**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**	**Sabrina Curtis, Pharmacy Resident**
X	**David Dodson, MD- Hospitalist**	X	**Chad Paxson, MD- Intensivist**	X	**Kenneth Dyer, PharmD- Ops Manager**	**Jessica Duke, Pharmacy Resident**
X	**Karen Frank, RN- Quality**		Vimal Ramjee, MD- Cardiology	X	**Rodney Elliott- Purchasing**	
	F. Lee Hamilton, MD- Hospitalist		James Wahl, MD- Hospitalist, GA	X	**Lori Hammon, RN- Quality**	
X	**William Haren, MD- Psychiatry**		Richard Yap, MD- Hospitalist	X	**Shannon Harris, RN- Infection Prevention**	
X	**Rhonda Hatfield, RN-CNO**			X	**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 December 2021 minutes were approved as submitted.	Approved	Complete
CommonSpirit Health System P&T Committee	**January 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. Bezlotoxumab (Zinplava®) for the treatment of C. difficile infection is being reviewed by the Antimicrobial Stewardship Subcommittee before being brought to our P&T Committee.	Approved	Complete
Formulary Decisions & Therapeutic Interchanges	**A. Remifentanil (Ultiva®):** Expansion of utilization criteria was requested to include all neurosurgical cases of the head in order to ensure fast wake up and quicker neurological assessment regardless if the patient is awake or asleep for the surgery. The committee approved revision of the current restriction criteria for remifentanil to the following: Ordering restricted to Anesthesia providers; craniotomies associated with very low associated post-op pain plus the need for rapid emergence and full neurological assessment; or awake fiberoptic intubations. **B. Insulin glargine (Semglee®):** Semglee (insulin glargine-yfgn) is a fully interchangeable biosimilar for the reference product, Lantus. Semglee will replace Lantus as the long-acting insulin product at CHI Memorial hospitals. The existing automatic therapeutic interchange for long acting insulins will be updated to reflect this approval. **C. PCC (Kcentra®) Dosing for DOAC Reversal:** Rachel shared with the committee recent data supporting conversion to a fixed dose of 4-factor prothrombin complex concentrate (PCC) for oral factor Xa inhibitors/direct oral anticoagulation reversal, which is a decrease from the current dose of 50 units/kg (max dose 5000 units). The update aligns with CommonSpirit Health system P&T committee recommendations. The following lower, fixed dose strategy was recommended for DOAC reversal: a. 2000 units for urgent reversal for surgery or major (life threatening) bleeding	Approved Approved Approved	Complete Complete Complete

	b. If ICH (spontaneous or traumatic) use 2500 units c. May repeat the same dose once within 6 hours of the initial dose if hemostasis is not achieved and/or maintained The Antithrombotic Reversal & Surgical Management Guidelines for reversal of oral Factor Xa inhibitors or DOACs and the Anticoagulation Management policy will be updated. A future pharmacy resident project will evaluate outcomes following this implementation. CSH will also be performing a medication use evaluation. **D. Medications for COVID 19:** The committee reviewed and approved an automatic pharmacist therapeutic interchange to either bamlanivimab/etesevimab, casirivimab/imdevimab, or sotrovimab based on product availability and anticipated efficacy against variant(s) of concern (per CDC/FDA guidance).The oral antivirals, Paxlovid and molnupiravir, were recommended to be non-formulary but to allow continuation of patient's own supply. The Pfizer adult formulation COVID-19 vaccine will remain the only available COVID-19 vaccination on formulary. The appropriate use/restriction criteria for remdesivir were updated and reviewed.	Approved	Complete
Medication Use	**A. Pharmacist-Driven PPI & H2RA Deescalation Protocol:** Jessica Duke, pharmacy resident, presented a proposal for a pharmacist-driven automatic discontinuation of stress ulcer prophylaxis agents (IV or PO pantoprazole or famotidine) ordered for patients in the ICU based on specific patient criteria. The committee approved this as an automatic, pharmacist-driven process. She will collect pre and post-implementation data and the results will be reported back to this committee upon completion. Dr. Dodson suggested expansion hospital-wide (not limited to ICU), and this will be considered following the results of the initial data evaluation.	Approved	Complete
Medication Safety	**A. ADR Summary**: Karen Babb presented the adverse drug reaction summary results for Oct-Dec 2021. There were no trends to report. The ADR review now includes patient chart reviews by Karen for all inpatients on opiates who received naloxone to determine if naloxone was administered within 12 hours of a patient receiving anesthesia. Of the 12 patients who received naloxone, 3 were within 12 hours of receiving anesthesia. Dr. Blinn and Rhonda will begin routinely reviewing this patient list as part of the ongoing audit process.	Informational	Complete
Policies	**A. Anticoagulation Management:** The committee reviewed updates to this policy which included: removal of argatroban (non-formulary); pharmacist ordering of INR every other day if the INR is stable; clarification of baseline labs to align with current orders; instructions for provider notification if labs cannot be drawn for heparin infusions; updated PCC dosing for DOAC reversal. **B. Bradycardia Management Protocol:** A policy to support the previously approved protocol was adopted. The atropine dose was updated to 1 mg in alignment with 2020 ACLS guideline updates. **C. Contrast Media Administration:** This policy was updated to remove Omnipaque from the product column of the diagnostic radiology protocol table since Omnipaque was previously removed from formulary. **D. Drug and Food Interaction/Education:** The committee reviewed this policy per periodic review requirements. No updates were needed. **E. Sedatives-Hypnotics for Sleep:** This policy was updated to include suvorexant (Belsomra®) to the automatic therapeutic interchange to Ambien 5 mg. Dr. Paxson suggested that the policy stating that no sedative/hypnotics for sleep be administered to any patient greater than 65 may be overly restrictive and recommended that it be re-reviewed separately. Per Lori, the current policy was based on a >10 year old internal study on falls. Rhonda recommended a best practice review for sleep in hospitalized patients. Rachel will coordinate a small group to review the prior study and	Approved Approved Approved Approved	Complete Complete Complete Complete

	determine next steps. **F. Respiratory Distress Protocol:** The committee reviewed this policy per annual protocol review requirements. No updates were needed.	Approved	Complete
Nutrition	**A. Nutrition Care Manual:** Farrah shared updates to the nutrition care manual which were reviewed by the committee.	Approved	Complete

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

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

Approved by,
Nathan Chamberlain, MD, Chairman

CSH SYSTEM PHARMACY AND THERAPEUTICS COMMITTEE DECISION BRIEF

March 2022 Decisions

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

Medication Name	Medication Used For	Formulary Decision				Restrictions (if applicable)	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	Nonformulary		
Olanzapine/samid orphan	Treatment of adults with schizophrenia and bipolar I disorder				Lybalvi	Lybalvi Therapeutic interchange	Within 60 days of System P&T Committee approval
Avalglucosidase alfa-ngpt	Treatment of Late-Onset Pompe Disease		Nexviazyme			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
Ribociclib	Indicated for hormone receptor positive, human epidermal growth factor receptor 2 negative metastatic breast cancer				Kisqali		Within 60 days of System P&T Committee approval
Sarilumab	Treatment of moderately to severely active rheumatoid arthritis and off-label use for COVID-19.		Kevzara			**Inpatient** for COVID-19: Per most recent CommonSpirit Health COVID-19 Treatment guidelines **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
Guselkumab	Treatment of moderate-to-severe plaque psoriasis and active psoriatic arthritis in adult patients		Tremfya			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

Medication Name	Medication Used For	Formulary Decision				Restrictions (if applicable)	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	Nonformulary		
Idursulfase	Treatment of Hunter syndrome.		Elaprase			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
Piflufolastat F 18	Used for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer.		Pylarify			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
Gallium 68 psma-11	Used for positron emission tomography (PET) of prostate-specific membrane antigen (PSMA) positive lesions in men with prostate cancer		Gallium 68 PSMA-11			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
Mifepristone	A progesterone antagonist used in combination with misoprostol for the medical management of early pregnancy loss (< 13 weeks gestation)		Mifepristone			• For use in outpatient setting for early pregnancy loss in those without infection, hemorrhage, severe anemia, bleeding disorders, or contraindications to mifepristone or misoprostol and elect medical management. • Must not be used for abortifacient purposes other than following early pregnancy loss. Early pregnancy loss is defined as a nonviable, intrauterine pregnancy with either an empty gestational sac or a gestational sac containing an embryo or fetus without	Within 90 days of System P&T Committee approval

Medication Name	Medication Used For	Formulary Decision				Restrictions (if applicable)	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	Nonformulary		
						fetal heart activity within the first 12 6/7 weeks of gestation. • Must only be prescribed by certified prescribers who follow the REMS requirements (e.g., completing the Prescriber Agreement Form and having the ability to assess the duration of pregnancy, diagnose ectopic pregnancies, provide surgical intervention in cases of incomplete abortion or severe bleeding, and assure patient access to medical facilities equipped to provide blood transfusions and resuscitation, if needed). • Policy and procedures in place to ensure adherence to REMS criteria.	
Pneumococcal 20-valent conjugate vaccine	Prevention of pneumococcal pneumonia		Prevnar 20			**Inpatient:** • Patients who are 65 years or older or with underlying medical conditions or other risk factors* and cannot wait until after discharge to be vaccinated who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown • Patients where continuation of care is not likely (e.g. homeless) or where routine pneumococcal screening is required per state law	Within 90 days of System P&T Committee approval

Medication Name	Medication Used For	Formulary Decision				Restrictions (if applicable)	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	Nonformulary		
						Outpatient use, unrestricted *Risk factors include: alcoholism; chronic heart, liver, or lung disease; chronic renal failure; cigarette smoking; cochlear implant; congenital or acquired asplenia; cerebrospinal fluid leak; diabetes mellitus; generalized malignancy; HIV; Hodgkin disease; immunodeficiency; iatrogenic immunosuppression; leukemia, lymphoma, or multiple myeloma; nephrotic syndrome; solid organ transplant; sickle cell disease; or other hemoglobinopathies	
Pneumococcal 15-valent conjugate vaccine	Prevention of pneumococcal pneumonia	Vaxneuvance					Within 60 days of System P&T Committee approval
Bebtelovimab	COVID-19		Bebtelovimab			Inpatient and outpatient • Per the CommonSpirit Health COVID-19 treatment guidelines	Within 90 days of System P&T Committee approval
Acyclovir, topical	Topical antiviral			Acyclovir ointment			Within 90 days of System P&T Committee approval
					Acyclovir cream	Acyclovir cream therapeutic interchange	Within 60 days of System P&T Committee approval
Benzocaine 20%, topical	Topical anesthesia			Hurricaine one unit dosed products			Within 90 days of System P&T Committee

Medication Name	Medication Used For	Formulary Decision				Restrictions (if applicable)	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	Nonformulary		
							approval
Injectable chromium	Parenteral nutrition			Injectable chromium			Within 90 days of System P&T Committee approval
Injectable copper	Parenteral nutrition			Injectable copper			Within 90 days of System P&T Committee approval
Injectable manganese	Parenteral nutrition			Injectable manganese			Within 90 days of System P&T Committee approval
Baricitinib	Rheumatoid arthritis and off-label use for COVID-19		Olumiant			• COVID-19 Indications per the CommonSpirit Health COVID-19 treatment guidelines • Non-Formulary for non-COVID-19 related indications	Within 90 days of System P&T Committee approval
Human prothrombin complex concentrate (PCC), 4-factor	Hemostasis		Kcentra			Modified restriction for DOAC reversal as follows: DOAC reversal • Initial dose 25 units/kg (maximum of 2500 units) or a fixed dose of 2000 units • May repeat a single dose of up to 25 units/kg (max dose of 2500 units for a total maximum dose of 5000 units) or a fixed dose of 2000 units (maximum of 4000 units total dose) within 6 hours of the initial dose if hemostasis is not achieved and/or maintained • Round all doses to the nearest vial size	Within 90 days of System P&T Committee approval

Medication Name	Medication Used For	Formulary Decision				Restrictions (if applicable)	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	Nonformulary		
						* For patients with a large subdural hematoma (SDH, > 5 mm shift or GCS < 9) or intracerebral hemorrhage, 50 units/kg may be used if deemed clinically necessary.	
Asciminib hydrochloride	To treat Philadelphia chromosome-positive chronic myeloid leukemia with disease that meets certain criteria				Scemblix		Within 60 days of System P&T Committee approval
Atogepant	To prevent episodic migraines				Qulipta		Within 60 days of System P&T Committee approval
Avacopan	To treat severe active anti-neutrophil cytoplasmic autoantibody-associated vasculitis (granulomatosis with polyangiitis and microscopic polyangiitis) in combination with standard therapy, including glucocorticoids				Tavneos		Within 60 days of System P&T Committee approval
Lonapegsomatropin-tcg	To treat short stature due to inadequate secretion of endogenous growth hormone				Skytrofa		Within 60 days of System P&T Committee approval
Maralixibat chloride	To treat cholestatic pruritus associated with Alagille syndrome				Livmarli		Within 60 days of System P&T Committee approval

Medication Name	Medication Used For	Formulary Decision				Restrictions (if applicable)	Timeline to implementation
		Do Not Stock	Formulary Restricted	Formulary Unrestricted	Nonformulary		
Ropeginterferon alfa-2b-njft	To treat polycythemia vera, a blood disease that causes the overproduction of red blood cells				Besremi		Within 60 days of System P&T Committee approval
Tralokinumab-ldrm	To treat moderate-to-severe atopic dermatitis				Adbry		Within 60 days of System P&T Committee approval
Vosoritide	To improve growth in children five years of age and older with achondroplasia and open epiphyses				Voxzogo		Within 60 days of System P&T Committee approval
Mobocertinib	To treat locally advanced or metastatic non-small cell lung cancer with epidermal growth factor receptor exon 20 insertion mutations				Exkivity		Within 60 days of System P&T Committee approval

THERAPEUTIC INTERCHANGES

Lybalvi

Order	Interchange to
Lybalvi (olanzapine/samidorphan) 5mg/10mg	Olanzapine 5mg
Lybalvi (olanzapine/samidorphan) 10mg/10mg	Olanzapine 10mg
Lybalvi (olanzapine/samidorphan) 15mg/10mg	Olanzapine 15mg
Lybalvi (olanzapine/samidorphan) 20mg/10mg	Olanzapine 20mg

Acyclovir cream

Order	Interchange to
Acyclovir 5% topical cream	Acyclovir 5% topical ointment at same dose and interval

FORMULARY REVIEW

GENERIC NAME: Pneumococcal conjugate vaccine (20 valent)

PROPRIETARY NAME: *Prevnar 20®*

INDICATIONS:

FDA Approved
Indicated for active immunization for the prevention of pneumonia and invasive disease caused by Streptococcus pneumoniae serotypes 1,3,4,5,6A,6B,7F,8,9V,10A,11A,12F,14,15B, 18C, 19A, 19F, 22F, 23F, and 33F in adults 18 years of age and older

THERAPEUTIC CATEGORY: Vaccine

SPECIAL POPULATIONS:

Pregnancy	There are no adequate and well-controlled studies of Prevnar 20 in pregnant women. Available data on Prevnar 20 administered to pregnant women are insufficient to inform vaccine-associated risks in pregnancy. A developmental toxicity study was performed in female rabbits administered Prevnar 20 prior to mating and during gestation. The dose was 0.5 mL at each occasion (a single human dose is 0.5 mL). This study revealed no evidence of harm to the fetus due to Prevnar 20
Lactation	No data are available to assess the impact of Prevnar 20 on milk production, its presence in breast milk, or its effects on the breastfed infant.
Pediatrics	The safety and effectiveness of Prevnar 20 in individuals younger than 18 years of age have not been established. However, a randomized controlled trial evaluated the safety of Prevnar 20 in healthy infants where each received a 4-dose series of either Prevnar 20 or Prevnar 13 (control) at 2, 4, 6, and 12 months of age and found that Prevnar 20 was well tolerated with a safety profile similar to Prevnar 13.
Geriatrics	In the clinical trials for Prevnar 20, only 26.7% of the recipients were 65 years of age and older and only 1.7% of patients were 80 years and older. Studies showed that recipients 70 years of age and older had a lower immune response to all serotypes compared to patients younger than 65 years of age.
Hepatic Impairment	No dose adjustments required.
Renal Impairment	No dose adjustments required.

CLINICAL STUDIES:

Study Name 1: A Phase 3, Randomized, Double-Blind Trial to Evaluate the Safety and Immunogenicity of a 20-Valent Pneumococca Conjugate Vaccine in Pneumococcal Vaccine-Naive Adults 18 Years of Age Through 49 Years of Age. [3]	
METHODS	
Study Design	This was a phase 3 randomized, double blind trial among men and women 18-49 years of age trialing three lots of Prevnar 20 compared to Prevnar 13 (control) to evaluate immunogenicity as well as safety. The study was conducted at 21 US sites from February 2019 to October 2019.
Study Funding	Pfizer
Patient Enrollment Inclusion	Inclusion criteria included both male and female adults ≥ 18 years of age and <50 years of age who were pneumococcal vaccine naive .
Patient Enrollment Exclusion	Exclusion criteria included those who had a planned pneumococcal vaccination, a history of microbiologically proven invasive disease caused by *S pneumoniae,* a serious chronic disorder, and/or pregnant or breastfeeding females.
Baseline Characteristics	The study population included representation from women (65.3%), Black or African American race (18.5%), and Hispanic/Latino ethnicity (11.2%). Demographic characteristics were similar across vaccine groups and the mean age at vaccination was 35.3 years
Treatment Plan	Participants were randomly assigned to 1 of 4 groups in a 2:2:2:1 ratio to receive a single dose of 1 of 3 Prevnar 20 lots or Prevnar 13, which was used as a control.Blood was drawn for immunogenicity assessments before vaccination and approximately 1 month (28–42 days) after vaccination.
RESULTS	

Primary Endpoint	Non-inferiority was achieved in both safety profile and immunogenicity in regards to the all three lots of Prevnar 20 in comparison with Prevnar 20.
Secondary Endpoint	At 1 month after vaccination, iImmunogenicity was found to be similar between each of the Prevnar 20 lots and they were all found to be non-inferior to Prevnar13.
Adverse Events	Local reactions categorized as mild-moderate were similar between the pooled Prevnar 20 lots and Prevnar 13 in which pain at the injection site (most common), redness and swelling were seen. Systemic events were also similar between both vaccines in which muscle pain (most common), joint pain, fatigue, and headache were most commonly noted within 7 days after vaccination. The percentage of patients reporting systemic adverse events and newly diagnosed chronic medical conditions (NDCMS) were not only rare but similar between vaccinations and considered by investigators to be unrelated to the vaccinations.
Study 2: Safety, Tolerability, and Immunogenicity of a 20-Valent Pneumococcal Conjugate Vaccine (PCV20) in Adults 60 to 64 Years of Age[4]	
METHODS	
Study Design	This was a phase 2, randomized, active-controlled, double-blind study to evaluate the safety and immunogenicity of Prevnar 20 in healthy pneumococcal vaccine-naive adults 60–64 years of age This study was conducted at 14 US sites from October, 2017 to December, 2017. .
Study Funding	Pfizer
Patient Enrollment Inclusion	Inclusion criteria included generally healthy adults (including those with stable preexisting diseases) ages 60 to ≥64 who were not of childbearing potential.
Patient Enrollment Exclusion	Exclusion criteria included previous vaccination with any pneumococcal vaccine, a history of microbiologically proven invasive disease caused by *S pneumoniae* and/or a serious chronic disorder
Baseline Characteristics	Subject demographics were similar between study groups. The majority of subjects were women, non-hispanic, white individuals with a mean age of 62 years.
Treatment Plan	Subjects were randomly assigned in a 1:1 ratio to receive either Prevnar 20 or Prevnar 13 (control) . After 1 month, Prevnar 20 recipients were given saline placebo vaccination and Prevnar 13 recipients were given Pneumovax 23.
RESULTS	
Primary Endpoint	Local reactions, systemic events, and adverse events were found to be similar between Prevnar 20 and Prevnar 13 in which most reactions were considered to be mild to moderate. Most commonly reported side effects were muscle and injection site pain
Secondary Endpoint	Immune responses were found to be noninferior to both Prevnar 13 and Pneomovax 23
Adverse Events	Safety of Prevnar 20 was noninferior to Prevnar 13. Local reactions were categorized as mild-moderate and injection site pain was most commonly reported. Muscle pain was the most commonly reported systemic event

COMPARATIVE EFFICACY:

Newly approved Prevnar 20 is a vaccine indicated for the prevention of pneumonia, similar to Prevnar 13 and Pneumovax23 which are also pneumococcal vaccines currently on the market. Efficacy data comparing Prevnar 20 to Prevnar 13, Pneumovax23, and placebo does not exist at this time as this is a newly developed vaccine; however studies have looked at both safety and immunogenicity data and found that Prevnar 20 showed a robust immune response while displaying a safety profile comparable to the other pneumococcal vaccines on the market, which led researchers to believe that Prevnar 20 is non-inferior to both Pneumovax23 and Prevnar 13 in both safety and immunogenicity.

ACIP Pneumococcal Vaccine Recommendations and Schedule

Recommendation

- Adults aged ≥65 years who have not previously received PCV or whose previous vaccination history is unknown should receive 1 dose of PCV (either PCV20 or PCV15). When PCV15 is used, it should be followed by a dose of PPSV23

- Adults aged 19–64 years with certain underlying medical conditions or other risk factors including alcoholism; chronic heart, liver, or lung disease; chronic renal failure; cigarette smoking; cochlear implant; congenital or acquired asplenia; cerebrospinal fluid leak; diabetes mellitus; generalized malignancy; HIV; Hodgkin disease; immunodeficiency; iatrogenic immunosuppression; leukemia, lymphoma, or multiple myeloma; nephrotic syndrome; solid organ transplant; sickle cell disease; or other hemoglobinopathies who have not previously received PCV or whose previous vaccination history is unknown should receive 1 dose of PCV (either PCV20 or PCV15). When PCV15 is used, it should be followed by a dose of PPSV23.

Schedule

- Adults who have only received PPSV23 may receive a PCV (either PCV20 or PCV15) ≥1 year after their last PPSV23 dose. When PCV15 is used in those with a history of PPSV23 receipt, it need not be followed by another dose of PPSV23.

WARNING AND PRECAUTIONS:

- Due to the risk of acute allergic reactions, appropriate medical treatment and supervision should be used to manage immediate allergic reactions and must be immediately available should an acute anaphylactic reaction occur following administration of Prevnar 20.
- Based on experience with pneumococcal vaccines, individuals with altered immunocompetence may have reduced immune responses to Prevnar 20.

CONTRAINDICATIONS: Severe allergic reaction (e.g., anaphylaxis) to any component of Prevnar 20 or to diphtheria toxoid

ADVERSE REACTIONS:

Percentage of Participants With Solicited Local Adverse Reactions Within 10 Days After Vaccination in Pneumococcal Vaccine-Naive Adults						
	18-49 Years of Age		**50-59 years of Age**		**≥ 60 Years of Age**	
	Prevnar 20 (N= 335)	**Prevnar 13** (N= 112)	**Prevnar 20** (N= 331)	**Prevnar 13** (N= 111)	**Prevnar 20/ Saline** (N= 1505)	**Prevnar 13/ PPSV23** (N= 1483)
Local Reactions						
Pain at Injection Site	81.1%	82.2%	72.5%	69.4%	55.4%	54.1%
Swelling	11.6%	12.5%	8.8%	10.8%	7.5%	8%
Redness	9%	9.8%	8.2%	5.4%	7.3%	6.2%
Any local reaction	81.2%	82.1%	72.8%	70.3%	57.4%	56%

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:

Interacting Drug	**Effect**
Prior vaccination with Pneumovax 23	Receipt of PPSV23 1 to 5 years prior to Prevnar 20 resulted in reduced immune responsiveness to Prevnar 20 compared to the immune response seen in those who received Prevnar 13 at least 6 months previously, and those who received Prevnar 13 followed by PPSV23, with the last dose of PPSV23 given at least 1 year prior to Prevnar 20 .
Immunosuppressive Therapies	Individuals with impaired immune responsiveness due to the use of immunosuppressive therapy may not respond optimally to Prevnar 20.

DOSING AND ADMINISTRATION:
Pneumococcal disease prevention: IM: 0.5 mL as a single dose

RECOMMENDED MONITORING:
Monitor for anaphylaxis and syncope for 15 minutes following administration. If seizure-like activity associated with syncope occurs, maintain the patient in supine or Trendelenburg position to reestablish adequate cerebral perfusion.

PHARMACOECONOMICS/COST:

Product (Drug, Strength, Form)	**Cost per dose**
Prevnar 20	$216
Vaxneuvance	$192
Pneumovax 23	$104
Prevnar 13	$203

CONCLUSION & RECOMMENDATION:
The ACIP and CDC officially released new pneumococcal vaccine recommendations on January 28, 2022 in light of the two new pneumococcal immunizations (Prevnar 20 and Vaxneuvance) entering the market. The ACIP now recommends that for adults 65 years and older and for adults 19-64 years of age with certain underlying medical conditions or other risk factors who have not previously received a pneumococcal conjugate vaccine or whose previous vaccination history is unknown should receive a pneumococcal conjugate vaccine (either Prevnar 20 or Vaxneuvance). If Vanxneuvance is used, this should be followed by a dose of Pneumovax 23. The cost of Prevnar 20 is comparable to other pneumococcal conjugate vaccines such as Prevnar 13.

It is recommended to approve Prevnar 20 to formulary with the following restrictions:

- Post-splenectomy with no pneumococcal vaccination history
- 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)

It is also recommended that the following formulary statuses be approved for pneumococcal vaccines at CHI Memorial hospitals:

Pneumococcal vaccine	**Formulary status**
Pneumococcal conjugate vaccine 20 valent (Prevnar 20)	Formulary, with restrictions (see above)
Pneumococcal conjugate vaccine 15 valent (Vaxneuvance)	Non-formulary
Pneumococcal conjugate vaccine 13 valent (Prevnar 13)	Non-formulary
Pneumococcal polysaccharide vaccine 23 valent (Pneumovax 23)	Formulary, with restrictions to post-splenectomy patients who have already received Prevnar 13

Education will be provided to hospitalists, ID physicians, and pharmacists.

FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)

Medication Management Step	**Identified Risk**	**Steps for Prevention**
Selection & Procurement		
Therapeutic interchange?	No	
Special Ordering Requirements?	No	
Storage		
LASA* separation of stock?	Yes	Separate from closely-related vaccines (Prevnar 13, Pneumovax 23) and use tall-man lettering.
Special storage (e.g. refrigeration, protect from light, controlled substance)?	Yes	Refrigeration required
Pharmacist/Technician Education?	Yes	Educate regarding sound alike look alike. Vaccine schedule.
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	Yes, to be used only in adults ≥ 18 years of age	Built into EHR
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	No	
Drug Interactions?	Yes, potentially other pneumococcal vaccines depending on ACIP recommendations for Prevnar 20.	Build into EHR and provider education
Pregnancy?	N/A	
Absolute Contraindications?	Yes	Build into EHR

Requires Order Set, Protocol, concomitant therapy with another drug?	No	
LASA* nomenclature issues?	Yes	Educate purchasers on LASA and related vaccines prior to placing orders
Prescriber education?	Yes	Educate providers regarding vaccine's place in therapy and schedule
Processing, Preparing, & Dispensing		
High-risk drug double check?	No	
Drug Interaction check in place?	Yes	Build into EHR
LASA* computer warnings?	Yes	Tall man lettering and label comments as appropriate
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	Refrigeration required
Documentation required (e.g. double check, worksheet)?	No	
Pharmacist/Technician Education?	Yes	Educate providers regarding vaccine's place in therapy and schedule
Administration		
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	Yes	Keep epinephrine hydrochloride solution (1:1,000) available in case of anaphylaxis or acute hypersensitivity reaction.
Special delivery system (e.g. pump)?	No	
Documentation required? (e. g. double check)	No	
Nurse education?	Yes	Educate nursing staff on appropriate injection sites and monitoring parameters for vaccine product.
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?	Yes	Build into EHR and educate on monitoring for acute hypersensitivity reactions.
Follow-up laboratory tests?	No	
Education?	Yes	Educate providers on monitoring for acute hypersensitivity reactions.

Post-Splenectomy Vaccine Schedule

If no vaccines previously received:

	Initial vaccination	2 month follow-up	Long-term follow-up
Pneumococcal 20-valent conjugate (Prevnar 20®)	√		
Haemophilus B conjugate vaccine (actHIB®)	√		
Meningococcal polysaccharide vaccine (Menveo®)	√	√	√ (Every 5 yrs.)
Meningococcal serogroup B vaccine (Bexsero®)	√	√	
Seasonal influenza vaccine	√ (If not received this yr.)		√ (Every yr.)

If some vaccines received, follow the below schedule:

Pneumococcal vaccines

- Patients who have received Prevnar 13® should wait at least 8 weeks before receiving Pneumovax 23® and revaccinated 5 years after first dose

- Patients who have received Pneumovax 23® in the past year should wait at least 1 year to receive Prevnar 20® vaccine

Meningococcal vaccines

- Menveo® doses should be scheduled at least 1 month apart

- Bexsero® doses should be scheduled at least 1 month apart

- If patient has received Menactra® or Trumenba® as an outpatient, it is best to write follow-up scripts for these brands of meningococcal vaccines for their respective due date
    - Menactra® requires 2 doses - at least 1 month apart
        - If patient has received Menactra® but not Prevnar 13®, wait at least **4 weeks** prior to administering Prevnar 13®. Menactra® is thought to interfere with the antibody response to pneumococcal conjugate vaccine if given too close together.
    - Trumenba® requires 3 doses – doses given at 0, 2, and 6 months

Haemophilus B conjugate vaccine

- Only a single dose is required. If already vaccinated, do not re-vaccinate

**** When educating a patient who has received some vaccines, provide them with an individualized copy of the "Post-splenectomy Vaccine Guidelines," by modifying the table to match their specific schedule**

Post-Splenectomy Vaccine Guidelines

Summary: Asplenic patients are at high risk for acquiring infections cause by certain encapsulated bacteria (ex: *Streptococcus pneumoniae*, *Haemophilus influenza* and *Neisseria meningitidis*). This risk can be decreased via appropriate vaccination and patient education. The following guidelines outline the current vaccine recommendations for initial immunization and re-vaccinations.

Vaccine Schedule:

	Initial vaccination	2 month follow-up	Long-term follow-up
Pneumococcal 20-valent conjugate (Prevnar 20®)	√		
Haemophilus B conjugate vaccine (actHIB®)	√		
Meningococcal polysaccharide vaccine (Menveo®)	√	√	√ (Every 5 yrs.)
Meningococcal serogroup B vaccine (Bexsero®)	√	√	
Seasonal influenza vaccine	√ (If not received this yr.)		√ (Every yr.)

Patient Education:

- Inform all healthcare providers of splenectomy status.
- In order to prevent serious infections, you will need an initial set of vaccines and be re-vaccinated in 2 months and approximately every 5 years for the rest of your life.
- If you experience signs and symptoms of an infection, it is important to immediately inform your doctor.
- You should consult with your doctor before traveling abroad. Additional vaccinations may be recommended in some cases.

FORMULARY UPDATE

THERAPEUTIC CLASS: Monoclonal antibody

GENERIC NAME: Bezlotoxumab

PROPRIETARY NAME: Zinplava®

BACKGROUND/RATIONALE:

Bezlotoxumab is a human monoclonal antibody approved for the reduction of the recurrence of *Clostridioides difficile* infection (CDI) in patients 18 years or older who are receiving antibacterial drug treatment for CDI, and are at high risk for CDI recurrence. Bezlotoxumab is administered as a single 10 mg/kg dose by intravenous infusion over 60 minutes. The safety and efficacy of repeat administrations have not been studied. Bezlotoxumab should be administered during antibacterial treatment for CDI.

In 2017, the CHI Memorial P&T Committee voted bezlotoxumab as non-formulary, at the recommendations of the Antimicrobial Stewardship (ASP) Subcommittee and the CHI System P&T committee.

The Infectious Diseases Society of America (IDSA) released a focused update on the management of CDI in June 2021, and suggested bezlotoxumab be administered as adjunctive treatment with standard of care antibiotics for patients with a recurrent CDI episode within the last 6 months.

In March of 2022, the CommonSpirit Health P&T Committee voted to approve bezlotoxumab to formulary with restrictions as follows:

1. **Outpatient setting is preferred.** Restricted to FDA-approved indications or payor-approved off-label indications subsequent to insurance approval or prior authorization
2. Inpatient setting:
    a. Outpatient administration is not possible during active C. difficile treatment
    b. To ID physicians where available

    Inpatient- must meet ALL of the following:
    - Have a positive stool test for C. difficile toxin.
    - Receiving active treatment for C. difficile infection with oral vancomycin, metronidazole, or fidaxomicin.
    - Have a history of one or more CDI episodes in the past 6 months
    - Age 65 years or above* (*May consider for patients with a primary or recurrent CDI episode who are immunocompromised or who have severe disease on a case-by-case basis regardless of age.)

    In addition, the patient must either:
    - Meet ONE of the following:
        - Required ICU admission as a result of the current CDI episode
        - Presence of pseudomembranous colitis on endoscopy
        - Immunocompromised status

    OR
    - Meet TWO of the following:
        - Body temperature greater than 38.3°C (100°F)
        - Serum albumin < 2.5g/dL
        - WBC > 15,000 cells/uL

3. Bezlotoxumab should be used with caution in patients with underlying congestive heart failure (CHF). The benefits of using bezlotoxumab in this patient population should be weighed against the risk of CHF.
4. Bezlotoxumab should not be given to patients who meet ONE of the following exclusion criteria:
    a. Patients who are not expected to survive for 72 hours
    b. Pregnant and lactating women
5. For patients greater than 100 kg actual body weight the maximum dose is 1,000 mg (1 vial).

ADVERSE REACTIONS

Serious Adverse Reactions and Adverse Reactions Leading to Discontinuation

Among the participants from the clinical trials, 29% of those treated with bezlotoxumab had a serious adverse reaction compared with 33% of those treated with placebo. Heart failure occurred in 2.3% and 1% of the total patients treated with bezlotoxumab and placebo, respectively.

Treatment in one patient was discontinued due to ventricular tachyarrhythmia occurring 30 minutes after the start of the infusion.

Mortality rates within 12 weeks following infusion were reported in 7.1% of subjects treated with bezlotoxumab and 7.6% of subjects treated with placebo.

Infusion Related Reactions

Infusion specific adverse reactions occurring on the day of, or the day after, the infusion was experienced in 10% of bezlotoxumab-treated patients compared to 8% of placebo-treated patients. The reactions reported in ≥0.5% of patients receiving bezlotoxumab and at a frequency greater than placebo were nausea (3%), fatigue (1%), pyrexia (1%), dizziness (1%), headache (2%), dyspnea (1%) and hypertension (1%). These reactions resolved within 24 hours following onset.

PHARMACOECONOMICS/COST:

Product	Cost per 1000 mg vial (max dose = 1 vial regardless of weight)
Bezlotoxumab (Zinplava) 1000 mg/40 ml vial	$3,799.95

DISCUSSION/RECOMMENDATION:

The CHI Memorial ASP Subcommittee recommends a more restrictive (than CommonSpirit) formulary status for bezlotoxumab at CHI Memorial, as follows:

- Restricted to outpatient infusion use (subsequent to insurance approval or prior authorization) for patients with any of the following risk factors:
  - ≥ 65 years old
  - History of one or more CDI episode in the past 6 months
  - Immunocompromised status
  - ≥2 points on the Zar score for severity
    - 1 point each is given for age >60 years; temperature >38.3ºC; 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
  - Dose: 10mg/kg (max: 1,000 mg) x 1 dose during administration of active CDI treatment.
  - Adjunctive therapy to prevent recurrent CDI. Use caution in patients with underlying congestive heart failure (CHF).

It is recommended to adopt the recommendation of the CHI Memorial ASP Subcommittee and approve bezlotoxumab (Zinplava) to formulary with the restrictions as listed above. The CHI Memorial *Clostridioides difficile* Clinical Pathway/Treatment Guidelines will be updated to reflect this formulary decision.

CHI Memorial
Clostridioides difficile Infection (CDI) Clinical Pathway

Principles of CDI Management

- Stop all unnecessary antibiotics, shorten antibiotic courses, and narrow the spectrum of antibiotic activity when possible
  - Consider discussion with ID Physician or ASP Pharmacist (x7536)
- Stop acid suppressive medication when possible, especially proton-pump inhibitors
- Discontinue all anti-motility agents

Treatment Recommendations

Clinical definition	Criteria	Management
Initial episode, non-fulminant, no risk factors		• Vancomycin 125mg PO q6 hours x 10 days
Initial episode, non-fulminant & ≥1 risk factors for recurrent infection	• Age ≥ 65 • Severe immunosuppression • Concomitant systemic antibiotic(s) that cannot be stopped • NAP1/BI/027 strain (+)	• Vancomycin taper
First recurrence, non-fulminant	New onset of CDI symptoms within 3 months of previous episode	• Vancomycin taper **OR** • Fidaxomicin(ID restricted) 200mg PO BID x 10 days or pulsed, especially for patients who used a PO vancomycin taper for first episode or ≥1 risk factors for recurrent infection
Second or subsequent recurrence, non-fulminant		Consider ID Consult • Vancomycin taper **OR** • Fidaxomicin(ID restricted) 200mg PO BID x 10 days or pulsed
Fulminant episode, any occurrence	Hypotension, shock, ileus, or megacolon	Consult ID & Surgery Consults **AND** • Vancomycin 500 mg given PO q6 hours x10 days **AND** • Metronidazole 500 mg IV q8 hours until resolution of ileus (if present) and hemodynamically stable (up to 10 days) **AND/OR** • If ileus present: Vancomycin 500 mg/100 mL NS retention enemas PR Q 6 hours x 10 days

- Vancomycin taper: Vancomycin 125 mg PO Q 6 hours x 14 days, then 125 mg Q 8 hours x 7 days, 125 mg Q 12 hours x 7 days, 125 mg Daily x 7 days, 125 mg Q2D x 7 days

- Fidaxomicin: requires approval by ID/ASP and drug affordability check with case management prior to inpatient administration. Alternative dosing of fidaxomicin can be considered and may further reduce recurrent CDI (200mg PO BID x 5 days, then once every other day for 20 days)

Adjunctive Therapies

- **Bezlotoxumab** (10mg/kg (max: 1,000mg) x 1 dose during administration of active CDI treatment): Adjunctive therapy to prevent recurrent CDI. Use caution in patients with underlying congestive heart failure (CHF). Restricted to outpatient infusion use (if approved) for patients with any of the following risk factors:
  - ≥ 65 years old
  - History of one or more CDI episode in the past 6 months
  - Immunocompromised status
  - ≥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
- **Fecal Microbiota Transplantation (FMT):** consider in patients with ≥2 recurrences of CDI. Discuss with GI &/or ID physicians
- **Secondary prophylaxis:** Oral vancomycin prophylaxis (OVP) may be considered for patients with a history of CDI (within last 3 months) who require systemic antibiotic therapy. Consider dosing vancomycin at 125mg PO daily until 5 days post completion of systemic antibiotics. OVP may be most beneficial in patients who are at high risk for recurrence: ≥ 65 years old, significant immunocompromise, or those with a history of severe CDI
- **Probiotics:** Mixed data exist regarding use of probiotics for primary prevention of CDI. There is insufficient data to support use for secondary prophylaxis. Routine use is discouraged.

Comments

- There is no evidence to support dual therapy with ORAL Flagyl & ORAL Vancomycin (only IV Flagyl + PO Vanco)
- No need to repeat *Clostridioides difficile* testing for test of cure

FORMULARY REVIEW

GENERIC NAME: Cobicistat (Gilead Sciences)

PROPRIETARY NAME: *Tybost®*

INDICATIONS:

FDA Approved
CYP3A inhibitor, indicated to increase systemic exposure of atazanavir or darunavir in combination with other antiretroviral agents in the treatment of HIV-1 infection.

THERAPEUTIC CATEGORY:
Pharmacokinetic enhancer

PHARMACOKINETICS:

Absorption	In a trial where subjects were instructed to take coadministered cobicistat and darunavir with food, median cobicistat peak plasma concentrations were observed approximately 3.5 hours post dose. Steady-state cobicistat Cmax, AUCtau, and Ctau (mean ± SD) values were 0.99 ± 0.3 mcg/mL (n=60), 7.6 ± 3.7 mcg*hr/mL (n=59), and 0.03 ± 0.1 mcg/mL (n=59), respectively.
Distribution	Cobicistat is 97–98% bound to human plasma proteins and the mean blood-to-plasma ratio was approximately 0.5.
Metabolism	Cobicistat is metabolized by CYP3A and to a minor extent by CYP2D6 enzymes and does not undergo glucuronidation.
Elimination	The terminal plasma half-life of cobicistat following administration is approximately 3 to 4 hours. With single dose administration of cobicistat after multiple dosing of cobicistat for 6 days, the mean percent of the administered dose excreted in feces and urine was 86.2% and 8.2%, respectively.

SPECIAL POPULATIONS:

Pregnancy	There are no data with cobicistat in pregnant women to inform a drug-associated risk. In animal reproduction studies in rats and rabbits, no evidence of fetal harm was observed with oral administration of cobicistat during organogenesis at doses that produced exposures up to 1.4 and 3.3 times, respectively, the maximal recommended human dose of 150 mg. Consider the benefits and risks when prescribing cobicistat to a pregnant woman.
Lactation	There is no information regarding the presence of cobicistat in human milk, the effects on the breastfed infant, or the effects on milk production. The Centers for Disease Control and Prevention recommend that HIV-infected mothers not breastfeed their infants to avoid risking postnatal transmission of HIV.
Pediatrics	Safety and effectiveness of cobicistat in pediatric patients younger than 18 years of age have not been established.
Geriatrics	Clinical trials of cobicistat did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects.
Hepatic Impairment	No additional considerations provided.
Renal Impairment	No additional considerations provided.

WARNING AND PRECAUTIONS:

- Assess creatinine clearance (CLcr) before initiating treatment.
- When cobicistat is used in combination with a tenofovir disoproxil fumarate (tenofovir DF) containing regimen, cases of acute renal failure and Fanconi syndrome have been reported
- Use with tenofovir DF: Assess urine glucose and urine protein at baseline and monitor CLcr, urine glucose, and urine protein. Monitor serum phosphorus in patients with or at risk for renal impairment.
- Cobicistat in combination with more than one antiretroviral that requires pharmacokinetic enhancement (i.e., two protease inhibitors or elvitegravir in combination with a protease inhibitor) is not recommended
- Use with HIV-1 protease inhibitors other than atazanavir or darunavir administered once daily is not recommended.
- Coadministration with drugs or regimens containing ritonavir is not recommended.

CONTRAINDICATIONS:
Coadministration with certain drugs for which altered plasma concentrations are associated with serious and/or life-threatening events or loss of therapeutic effect.

ADVERSE REACTIONS:

Adverse Reactions	Cobicistat coadministered with atazanavir and truvada	Ritonavir coadministered with atazanavir and truvada
Jaundice	6%	3%
Rash	5%	4%
Ocular icterus	4%	2%
Nausea	2%	2%
Diarrhea	2%	1%
Headache	2%	1%

Less common adverse reactions: vomiting, upper abdominal pain, fatigue, rhabdomyolysis, depression, abnormal dreams, insomnia, nephropathy, Fanconi syndrome acquired, nephrolithiasis

Lab abnormalities: Cobicistat causes increases in serum creatinine and decreases in estimated creatinine clearance due to inhibition of tubular secretion of creatinine without affecting actual renal glomerular function

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:
Cobicistat is an inhibitor of CYP3A and CYP2D6. The transporters that cobicistat inhibits include p-glycoprotein (P-gp), BCRP, OATP1B1, and OATP1B3. The plasma concentration of drugs that are primarily metabolized by CYP3A or CYP2D6, or are substrates of P-gp, BCRP, OATP1B1, or OATP1B3 may be increased if those drugs are coadministered with cobicistat.

Based on in vitro data, cobicistat is not expected to induce CYP1A2 or CYP2B6 and based on in vivo data, cobicistat is not expected to induce MDR1 or, in general, CYP3A to a clinically significant extent. The induction effect of cobicistat on CYP2C9, CYP2C19, or UGT1A1 is unknown, but is expected to be low based on CYP3A in vitro induction data.

Coadministration of cobicistat with atazanavir or darunavir with drugs highly dependent on CYP3A for clearance and for which elevated plasma concentrations are associated with serious and/or life-threatening events is contraindicated. Coadministration with other CYP3A substrates may require a dose adjustment or additional monitoring.

DOSING AND ADMINISTRATION:

Cobicistat dosage	Coadministered Agent Dosage	Patient Populations
150 mg orally once daily	atazanavir 300mg orally once daily	Treatment-naïve or experienced
	darunavir 800 mg orally once daily	Treatment-naïve Treatment-experienced with no darunavir resistance associated substitutions

RECOMMENDED MONITORING:
CBC with differential, reticulocyte count, CD4 count, HIV RNA plasma levels, and serum creatinine at baseline and when clinically indicated during therapy; when coadministered with tenofovir disoproxil fumarate, serum creatinine, urine glucose and urine protein prior to initiation and as clinically indicated during therapy; assess serum phosphorus in patients with or at risk for renal impairment. Patients who experience a confirmed increase in serum creatinine >0.4 mg/dL from baseline should have renal function monitored closely. Testing for HBV is recommended prior to the initiation of antiretroviral therapy.

PHARMACOECONOMICS/COST:
Tybost 150 mg tabs (30 count) = $244.78 = $8.16/tab

CONCLUSION:
When designing an antiretroviral (ARV) regimen for a treatment-naive patient, it generally consists of two nucleoside reverse transcriptase inhibitors (NRTIs) administered in combination with a third active ARV drug from one of three drug classes: an integrase strand transfer inhibitor (INSTI), a non-nucleoside reverse transcriptase inhibitor (NNRTI), or a protease inhibitor (PI) with a

pharmacokinetic (PK) enhancer. The regimens are designed specifically for a patient, keeping in mind safety profile, drug- disease state interactions, drug-drug interactions, pill burden, and adherence. Modification of therapy occurs because of virologic failure, suboptimal response, or drug toxicity. Changing a drug regimen in a hospitalized HIV patient is not in the best interest of patient safety and therapeutics. Assuring anti-retroviral therapy (ART) is available and continued is important.

Cobicistat is a PK enhancer for certain PIs and INSTIs. It is coformulated with atazanavir and darunavir and is also available in several combination antiretroviral regimens. While ritonavir is also utilized as a PK enhancer and is on formulary, there are important pharmacokinetic distinctions between the two agents. One of the primary differences between cobicistat and ritonavir is the impact on other CYP isoenzymes. Cobicistat and ritonavir have similar inhibitory effects on CYP3A4, CYP2D6, P-gp, and other transporters. Similar exposures of elvitegravir, atazanavir, and darunavir are achieved when combined with either booster. However, in the presence of inducers such as etravirine, rifamycins or anticonvulsants, cobicistat may not be as effective as ritonavir in terms of inhibiting CYP3A4. Furthermore, ritonavir induces CYP1A2, CYP2B6, CYP2C9, CYP2C19, and UGT, whereas cobicistat is not known to induce these enzymes. Significant issues can arise when switching from cobicistat to ritonavir in certain patients with multiple comorbidities and concomitant medications.

Please see the following link for more information regarding recommended HIV regimens.
https://clinicalinfo.hiv.gov/en/guidelines/adult-and-adolescent-arv/whats-new-guidelines

RECOMMENDATION:
It is recommended to approve cobicistat (Tybost) to formulary with restrictions as follows:

- Ordering or approval by Infectious Disease for new therapy initiation
- Any provider may order to continue a patient's established home medication

FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)

Medication Management Step	Identified Risk	Steps for Prevention
Selection & Procurement		
Therapeutic interchange?	n/a	
Special Ordering Requirements?	n/a	
Storage		
LASA* separation of stock?	n/a	
Special storage (e.g. refrigeration, protect from light, controlled substance)?	n/a	
Pharmacist/Technician Education?	n/a	
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	ID restricted for initiation. Any provider may order to continue home medication	Pharmacy education
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	n/a	
Drug Interactions?	alfuzosin hydrochloride carbamazepine cisapride colchicine dronedarone hydrochloride drospirenone/ethinyl estradiol dihydroergotamine mesylate ergotamine tartrate indinavir irinotecan methylergonovine maleate lovastatin lurasidone midazolam nevirapine phenobarbital phenytoin	Include warnings upon order entry notifying interaction

Medication Management Step	Identified Risk	Steps for Prevention
	pimozide ranolazine rifampin sildenafil simvastatin St. John's wort triazolam	
Pregnancy?	Use during pregnancy only if the potential benefit justifies the potential risk	Pharmacy education
Absolute Contraindications?	The concomitant use of cobicistat with medications listed in the drug interaction column are contraindicated due to the potential for serious and/or life threatening events or loss of therapeutic effect	Staff education
Requires Order Set, Protocol, concomitant therapy with another drug?	No	
LASA* nomenclature issues?	No	
Prescriber education?	No	
Processing, Preparing, & Dispensing		
High-risk drug double check?	n/a	
Drug Interaction check in place?	Drug interaction checks in EMR	
LASA* computer warnings?	n/a	
Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)?	Take w/ food	Add instructions to EHR
Packaging/Labeling (e.g. prepacking)?	Pre-package for inpatient dispensing	
Dispensing (e.g. auxiliary labeling, light protection, refrigeration)?	n/a	
Documentation required (e.g. double check, worksheet)?	n/a	
Pharmacist/Technician Education?	n/a	
Administration		
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	n/a	
Special delivery system (e.g. pump)?	No	
Documentation required? (e. g. double check)	No	
Nurse education?	No	
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?	Monitor closely for toxicities related to DDIs and common adverse effects	Staff education
Follow-up laboratory tests?	CBC with differential, reticulocyte count, CD4 count, HIV RNA plasma levels, and serum creatinine at baseline and when clinically indicated during therapy	

FORMULARY UPDATE

THERAPEUTIC CLASS: Oral rifamycin antibiotic

GENERIC NAME: Rifaximin

PROPRIETARY NAME: Xifaxan®

BACKGROUND/RATIONALE:

Later this month, the CommonSpirit Health P&T committee will be voting on the conversion of rifaximin 550 mg doses to 600 mg doses (three 200 mg tablets) as a cost saving initiative. The 550 mg tablet will be non-formulary.

There is no expected clinical impact with a 50 mg dose difference, or an additional 100 mg per day per patient.

Rifaximin Utilization:

From October 2021 to April 2022, the three campuses of CHI Memorial administered a combined **1,800** doses of rifaximin 550 mg.

Provider Specialty	Percentage of prescribed orders
Hospitalist	58%
Gastroenterology	24%
Pulmonary medicine	9%

PHARMACOECONOMICS/COST:

Product	Cost per tablet	Cost per dose	Cost per day of therapy
Rifaximin (Xifaxan®) 550 mg tablet	$45.37	$45.37	$90.74
Rifaximin (Xifaxan®) 200 mg tablet	$8.82	$26.46	$52.92

Cost savings per dose	$18.91
Anticipated annual cost savings (based on 6 month utilization Oct 21-April 22)	**$68,000**

RECOMMENDATION/DISCUSSION:

It is 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.

FORMULARY REVIEW

GENERIC NAME: Anifrolumab-fnia

PROPRIETARY NAME: *Saphnelo®*

INDICATIONS:

FDA Approved
Adults with moderate to severe systemic lupus erythematosus (SLE) already receiving standard therapy

THERAPEUTIC CATEGORY: Immune globulin; type 1 interferon antagonist; monoclonal antibody

PHARMACOKINETICS:

Vd (L/kg)	0.0902 L/kg
Elimination	0.193 L/day

SPECIAL POPULATIONS:

Pregnancy	There is insufficient data to inform on drug-associated birth defects, miscarriage or adverse maternal or fetal outcome.
Lactation	There is no data available regarding the presence of anifrolumab-fnia in human milk, its effects on breastfeed children or effects on milk production.
Pediatrics	Safety and efficacy have not been established in patients <18 years of age.
Geriatrics	There is insufficient data to determine efficacy in patients >65 years of age due to limited participation in clinical trials.
Hepatic Impairment	While no studies have been performed to assess the effect of hepatic impairment, IgG1 monoclonal antibodies are predominately eliminated via catabolism.
Renal Impairment	Based on population PK analyses, clearance was comparable in patients with mild (eGFR 60-89) and moderate (eGFR 30-59) renal impairment to patients with normal renal function. Patients with severe (eGFR<30) renal impairment were not included in clinical trials

CLINICAL STUDIES:

TULIP-1 Trial	
METHODS	
Study Design	Double-blind, randomized, placebo-controlled, multicenter, phase 3 trial
Study Funding	AstraZeneca
Patient Enrollment Inclusion	● Aged 18-70 years ● Diagnosis of pediatric or adult SLE according to the ACR 1982 revised criteria ≥24 weeks prior to enrollment ● Currently receiving one of the following medications: prednisone or equivalent, azathioprine, an antimalarial, mycophenolate, methotrexate, mizoribine ● Fulfills at least 4 of the 11 ACR modified 1982 classification criteria for SLE with at least 1 of which being: o Positive antinuclear antibody test o Elevated anti-dsDNA antibodies o Elevated anti-Smith antibody ● SLEDAI-2K score ≥4 points ● OCS dose stable for at least 2 weeks prior to randomization ● Stable SLE SOC treatment ● Negative serum b-hcg test and negative urine pregnancy test
Patient Enrollment Exclusion	● Receipt of any investigational produce within 4 weeks or 5 half-lives of signing ICF ● Receipt of intra-articular, IM, or IV glucocorticoids within 6 weeks prior to Day 1 of study ● History of clinically significant non SLE-related vasculitis syndrome ● Active severe or unstable neuropsychiatric SLE ● Active severe SLE-driven renal disease ● Diagnosis of mixed connective tissue disease or overlap syndromes of SLE or SSc ● History of inflammatory joint or skin disease ● Receipt of oral or parenteral corticosteroids for >2 weeks within the past 24 weeks

- History of primary immunodeficiency, splenectomy, or any underlying condition that predisposes subject to infection
- Hepatitis B or hepatitis C
- Severe herpes infection
- Opportunistic infection requiring hospitalization or IV antimicrobials within 3 years of randomization
- History of cancer except successfully treated squamous or basal cell carcinoma or cervical cancer in situ

Baseline Characteristics

	Placebo (n=184)	**Anifrolumab 150 mg (n=93)**	**Anifrolumab 300 mg (n=180)**
Sex, female - no. (%)	171 (92.9)	86 (92.5)	165 (91.7)
Age - yrs (SD)	41.0 (12.3)	40.8 (12.05)	42.0 (11.99)
Race - no. (%)			
White	137 (74.5)	64 (68.8)	125 (69.4)
African American	23 (12.5)	14 (15.1)	29 (16.1)
Asian	5 (2.7)	8 (8.6)	11 (6.1)
American Indian/Alaskan Native	1 (0.5)	0	0
Native Hawaiian or other Pacific Islander	0	0	0
Other	18 (9.8)	7 (7.5)	15 (8.3)
Hispanic - no. (%)	35 (19.0)	20 (21.5)	32 (17.8)
Time from initial SLE diagnosis to randomization (mo.), median - range	79.5 (4-503)	87.0 (6-458)	88.0 (0-450)
SLEDAI-2K			
Global score - mean (SD)	11.5 (3.5)	11.0 (3.5)	11.3 (4.04)
Score ≥10 - no. (%)	135 (73.4)	68 (73.1)	125 (69.4)
BILAG-2004			
≥A - no (%)	84 (45.7)	40 (43.0)	93 (51.7)
No A and ≥2 B - no. (%)	84 (45.7)	48 (51.6)	79 (43.9)
CLASI activity score - mean (SD)	8.1 (6.66)	7.7 (6.71)	8.5 (7.26)
SDI global score - mean (SD)	0.6 (0.98)	0.5 (0.96)	0.7 (1.16)
Swollen joint count - mean (SD)	7.0 (4.80)	7.4 (6.20)	7.4 (5.79)
Tender joint count - mean (SD)	10.6 (7.17)	11.3 (8.03)	11.7 (7.50)
Elevated anti-dsDNA antibodies - no. (%)	82 (44.6)	44 (47.3)	81 (45.0)

Baseline SLE treatments - no. (%)				
OCS (prednisone or equivalent) ≥10 mg/d	153 (83.2)	78 (83.9)	150 (83.3)	
Antimalarials	102 (55.4)	48 (51.6)	103 (57.2)	
Azathioprine	134 (72.8)	76 (81.7)	124 (68.9)	
Methotrexate	34 (18.5)	16 (17.2)	32 (17.8)	
Mycophenolate	38 (20.7)	14 (15.1)	22 (12.2)	
NSAIDs	22 (12.)	9 (9.7)	31 (17.2)	
	35 (19.0)	16 (17.2)	31 (17.2)	

Treatment Plan	Eligible patients were randomly assigned in a 1:2:2 ratio to receive a fixed intravenous dose of 150 mg anifrolumab, 300 mg anifrolumab or placebo every 4 weeks for a total of 13 doses.

RESULTS

Primary Endpoint

Endpoint	Placebo (n=184)	Anifrolumab 300 mg (n=180)	Difference (95% CI)	Nominal P-value
SRI(4) at wk 52 - no. (%)	74/184 (40.4)	65/180 (36.2)	-4.2 (-14.2-5.8)	**0.41**

Secondary Endpoint

SRI(4) at wk 52 in IFNGS test-high patients - no. (%)	59/151 (39.3)	53/148 (35.9)	-3.4 (-14.4-7.6)	0.55
Sustained OCS reduction to target ≤7.5 mg/d at wk 52	33/102 (32.1)	50/103 (48.8)	16.7 (3.5-29.8)	**0.013**
≥50% reduction in CLASI activity score at wk 12 - no. (%)	14/54 (24.9)	25/58 (43.6)	18.7 (1.4-36.0)	**0.034**
Annualized flare rate through wk 52	0.72	0.60	0.83 (0.60-1.14)	0.258
BICLA response at wk 52 - no. (%)	54/184 (29.6)	83/180 (46.1)	16.4 (6.7-26.2)	N/A

Adverse Events

Adverse Event Category	Placebo (n=184)	Anifrolumab 150 mg (n=93)	Anifrolumab 300 mg (n=180)
Any adverse event	144 (78.3)	79 (84.9)	161 (89.4)
Serious adverse event	30 (16.3)	10 (10.8)	25 (13.9)
Death	0	0	1 (0.6)
Adverse event leading to discontinuation of study medication	5 (2.7)	5 (5.4)	11 (6.1)

	Adverse event of special interest			
	Non-opportunistic serious infection	8 (4.3)	2 (2.2)	9 (5.0)
	Opportunistic infection	1 (0.5)	0	1 (0.6)
	Anaphylaxis	0	1 (1.1)	0
	Malignancy	1 (0.5)	1 (1.1)	3 (1.7)
	Herpes zoster	3 (1.6)	5 (5.4)	10 (5.6)
	Tuberculosis	1 (0.5)	0	1 (0.6)
	Influenza	2 (1.1)	1 (1.1)	2 (1.1)
	Vasculitis	0	0	0
	Major adverse cardiovascular event	0	1 (1.1)	0
	Adverse event with frequency 5% or higher in the combined anifrolumab 150 mg and 300 mg group			
	Nasopharyngitis	22 (12.0)	14 (15.1)	36 (20.0)
	Upper respiratory tract infection	18 (9.8)	16 (17.2)	22 (12.2)
	Urinary tract infection	27 (14.7)	9 (9.7)	22 (12.2)
	Infusion-related reaction	13 (7.1)	9 (9.7)	16 (8.9)
	Bronchitis	10 (5.4)	7 (7.5)	16 (8.9)
	Headache	16 (8.7)	6 (6.5)	17 (9.4)
	Pharyngitis	13 (7.1)	6 (6.5)	12 (6.7)
	Herpes zoster	3 (1.6)	5 (5.4)	10 (5.6)
	Hypersensitivity	2 (1.1)	4 (4.3)	11 (6.1)

TULIP-2 Trial	
METHODS	
Study Design	Phase 3, randomized, double-blind, placebo-controlled, parallel-group trial
Study Funding	AstraZeneca
Patient Enrollment Inclusion	● 18 to 70 years of age ● SLEDAI-2K score of 6 or higher and a clinical SLEDAI-2K score of 4 or higher ● Fulfilled ACR classification criteria for SLE ● Severe disease in ≥1 organs or moderate disease in ≥2 organs ● Seropositive for antinuclear antibodies or anti-Smith antibodies ● Receiving stable treatment with at least one of the following: prednisone or equivalent, an antimalarial agent, azathioprine, mizoribine, mycophenolate mofetil, mycophenolic acid, or methotrexate
Patient Enrollment Exclusion	● Receipt of any investigational produce within 4 weeks or 5 half-lives of signing ICF ● Receipt of intra-articular, IM, or IV glucocorticoids within 6 weeks prior to Day 1 of study ● History of clinically significant non SLE-related vasculitis syndrome ● Active severe or unstable neuropsychiatric SLE ● Active severe SLE-driven renal disease ● Diagnosis of mixed connective tissue disease or overlap syndromes of SLE or SSc ● History of inflammatory joint or skin disease ● Receipt of oral or parenteral corticosteroids for >2 weeks within the past 24 weeks ● History of primary immunodeficiency, splenectomy, or any underlying condition that predisposes subject to infection ● Hepatitis B or hepatitis C ● Severe herpes infection ● Opportunistic infection requiring hospitalization or IV antimicrobials within 3 years of randomization ● History of cancer except successfully treated squamous or basal cell carcinoma or cervical cancer in situ

Baseline Characteristics

Characteristic	Placebo (n=182)	Anifrolumab 300 mg (n=180)
Age - yr	41.1 (11.5)	43.1 (12.0)
Female sex – no. (%)	170 (93.3)	168 (93.3)
Race – no. (%)		
White	107 (58.8)	110 (61.1)
Black	25 (13.7)	17 (9.4)
Asian	30 (16.5)	30 (16.7)
Other	20 (29.7)	23 (12.8)
Hispanic or Latino – no. (%)	54 (29.7)	54 (30.0)
Geographic region – no. (%)		
United States or Canada	68 (37.4)	64 (35.6)
Europe	46 (25.3)	51 (28.3)
Latin America	32 (17.6)	35 (19.4)
Asia-Pacific	26 (14.3)	27 (15.0)
Other	10 (5.5)	3 (1.7)
Median time from initial SLE diagnosis to randomization (range) – mo.	78.0 (6-494)	94.4 (6-555)
SLEDAI-2K		
Global score	11.5 (3.9)	11.4 (3.6)
Score ≥10 – no. (%)	131 (72.0)	129 (71.7)
BILAG-2004 – no. (%)		
≥1 A item	95 (52.2)	81 (45.0)
No A items and ≥2 B items	78 (42.9)	91 (50.6)
PGA score	1.76 (0.40)	1.68 (0.41)
CLASI activity	7.6 (7.8)	8.3 (7.9)
SDI global score	0.5 (0.8)	0.5 (0.9)
No. of swollen joints	7.4 (6.6)	6.2 (5.7)
No. of tender joints	11.0 (7.9)	9.0 (7.1)
High type I interferon gene signature – no. (%)	151 (83.0)	150 (83.3)
Baseline treatment for SLE – no. (%)		
Glucocorticoid	151 (83.0)	141 (78.3)
Antimalarial agent	133 (73.1)	199 (66.1)
Immunosuppressant agent	86 (47.3)	88 (48.9)

Treatment Plan

- Patients were randomly assigned in a 1:1 ratio to receive IV infusions of anifrolumab 300 mg every 4 weeks for 48 weeks.
- Other treatments were stable throughout the trial except as resulting from protocol determined intent to taper glucocorticoids.
- Glucocorticoid doses were required to be stable for the last 12 weeks of the trial

RESULTS

Primary Endpoint

End point	Placebo (n=182)	Anifrolumab 300 mg (n=180)	Difference (95% CI)	Adjusted P Value
BICLA response at wk 52	57/182 (31.5)	86/180 (47.8)	16.3 (6.3-26.3)	**0.001**

Key Secondary Endpoints

BICLA response at wk 52 in patients with a high type 1 interferon gene signature	46/151 (30.7)	72/150 (48.0)	17.3 (6.5-28.2)	**0.002**
Glucocorticoid reduction to target	25/83 (30.2)	45/87 (51.5)	21.2 (6.8-35.7)	**0.01**

	dose, sustained from wk 40 to wk 52				
	≥50% reduction in CLASI activity from baseline to wk 12	10/40 (25.0)	24/49 (49.0)	24.0 (4.3-43.6)	**0.04**
	≥50% reduction in both swollen and tender joints from baseline to wk 52	34/90 (37.5)	30/71 (42.2)	4.7 (-10.6-20.0)	0.55
	Annualized flare rate through wk 52	0.64	0.43	0.67 (0.48-0.94)	0.08

Adverse Events

Event	Placebo (n=182)	Anifrolumab 300 mg (n=180)
Any adverse event	153 (84.1)	159 (88.3)
Serious adverse event	31 (17.0)	15 (8.3)
Death	0	1 (0.6)
Adverse event leading to discontinuation of intervention	13 (7.1)	5 (2.8)
Adverse events of special interest	18 (9.9)	25 (13.9)
Herpes zoster	2 (1.1)	13 (7.2)
Non-opportunistic serious infections	10 (5.5)	5 (2.8)
Influenza	6 (3.3)	4 (2.2)
Tuberculosis	0	3 (1.7)
Major adverse cardiovascular event	0	1 (0.6)
Cancer	1 (0.5)	0
Serious adverse events occurring in ≥2 patients in the trial		
Pneumonia	7 (3.8)	3 (1.7)
Gastroenteritis, viral	0	2 (1.1)
Worsening of SLE	6 (3.3)	1 (0.6)
Radius fracture	2 (1.1)	0
Adverse events with frequency of >5% in the anifrolumab group		
Upper respiratory tract infection	18 (9.9)	39 (21.7)
Nasopharyngitis	20 (11.0)	28 (15.6)
Infusion-related reaction	14 (7.7)	25 (13.9)
Bronchitis	7 (3.8)	22 (12.2)
Urinary tract infection	25 (13.7)	20 (11.1)
Herpes zoster	2 (1.1)	13 (7.2)
Sinusitis	9 (4.9)	12 (6.7)
Arthralgia	6 (3.3)	10 (5.6)
Back pain	3 (1.6)	10 (5.6)
Cough	6 (3.3)	10 (5.6)

COMPARATIVE EFFICACY:

Currently there are no head-to-head trials comparing anifrolumab-fnia to other therapies. Anifrolumab-fnia is the first type 1 IFN antagonist approved for the treatment of SLE. In both of the phase 3 clinical trials, anifrolumab-fnia was used with standard of care therapies for SLE. Anifrolumab may be considered in patients with moderate to severe SLE who meet the following criteria:

- Individual is 18 years of age or older
- Documentation of positive autoantibody test
- Individual meets one of the following:
    - The medication is being used concurrently with at least one other standard therapy (i.e hydroxychloroquine, a systemic corticosteroid, azathioprine, mycophenolate mofetil, or methotrexate).
- The individual is determined to be intolerant to standard therapy due to a significant toxicity, as determined by the prescriber.
- Medication is being prescribed by, or in consultation with, a rheumatologist, clinical immunologist, nephrologist, neurologist, or dermatologist.

WARNING AND PRECAUTIONS:

- Increased risk of respiratory infections and herpes zoster
- Avoid initiating treatment during active infection
- Consider individual benefit in patients with severe or chronic infection
- Consider interrupting therapy with anifrolumab-fnia if patients develop a new infection during treatment
- Serious hypersensitivity including anaphylaxis and angioedema have been reported
- Consider individual benefit-risk in patients with known risk factors for malignancy prior to initiating therapy
- Avoid use of live or live-attenuated vaccines
- Not recommended for concomitant use with other biologic therapies

CONTRAINDICATIONS:

Patients with a history of anaphylaxis with anifrolumab-fnia

ADVERSE REACTIONS:

Adverse Reactions	Intervention Group (N=459) %	Placebo or Standard of Care Group (N=466) %
Upper respiratory tract infection	34	23
Bronchitis	11	5.2
Infusion-related reactions	9.4	7.1
Herpes zoster	6.1	1.3
Cough	5.0	3.2
Respiratory tract infection	3.3	1.5
Hypersensitivity	2.8	0.6
Malignancies	0.7	0.6

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:

Interacting Drug	Effect
Other biologics	Even though no formal drug interaction studies have been conducted, Saphnelo has not been evaluated in combination with other biologic therapies, including B-cell-targeted therapies; therefore, use of Saphnelo is not recommended for use in combination with biologic therapies.

DOSING AND ADMINISTRATION:

Recommended dosing is 300 mg IV infusion over 30 minutes every 4 weeks. If an infusion is missed, administer as soon as possible. Maintain a minimum interval of 14 days between infusions.

RECOMMENDED MONITORING:

A pregnancy exposure registry monitors pregnancy outcomes in women exposed to SAPHNELO during pregnancy.

PHARMACOECONOMICS/COST:

Product (Drug, Strength, Form)	NDC	Size	Contract/GPO Price	Cost/Year
Anifrolumab-fnia (Saphnelo) 150 mg/mL	00310-3040-00	1x2 mL	$4,600.54	$55,206.48 (12 doses annually)

Medication specific billing codes: J0491 (assigned 4/1/22)

CONCLUSION & RECOMMENDATION:

Saphnelo is indicated for the treatment of adults with moderate to severe systemic lupus erythematosus (SLE), who are receiving standard therapy including hydroxychloroquine in combination with glucocorticoids with or without immunosuppressive agents. Saphnelo is currently the only IFN antagonist FDA approved for the treatment of SLE and the first therapy to be approved for SLE within the past decade. Based on the results from the clinical trials, Saphnelo was superior to placebo at improving BICLA response, reducing OCS use and improving skin lesions. Saphnelo has the potential to address significant unmet medical needs in SLE.

It is recommended to approve to formulary with the following restrictions:

- 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		
Therapeutic interchange?	No	N/A
Special Ordering Requirements?	No	N/A
Storage		
LASA* separation of stock?	No	N/A
Special storage (e.g. refrigeration, protect from light, controlled substance)?	Yes	
Pharmacist/Technician Education?	No	N/A
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	Yes	
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	No	N/A
Drug Interactions?	Yes	Saphnelo has not been studied and is not recommended in combination with other biologics.
Pregnancy?	No	There are insufficient data on the use of Saphnelo in pregnant women to establish whether there is drug associated risk for major birth defects or miscarriage.
Absolute Contraindications?	Yes	Known history of anaphylaxis with Saphnelo
Requires Order Set, Protocol, concomitant therapy with another drug?	Yes	Saphnelo should be used in combination with standard of care treatments for SLE
LASA* nomenclature issues?	No	N/A
Prescriber education?	No	N/A
Processing, Preparing, & Dispensing		
High-risk drug double check?	No	N/A
Drug Interaction check in place?	No	N/A
LASA* computer warnings?	No	N/A
Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)?	No	N/A
Packaging/Labeling (e.g. prepacking)?	No	N/A
Dispensing (e.g. auxiliary labeling, light protection, refrigeration)?	Yes	Store in a refrigerator at 36°F to 46°F (2°C to 8°C) in the original carton to protect from light. Do not freeze. Do not shake.
Documentation required (e.g. double check, worksheet)?	No	N/A
Pharmacist/Technician Education?	No	N/A
Administration		
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	No	N/A
Special delivery system (e.g. pump)?	No	N/A
Documentation required? (e. g. double check)	No	N/A
Nurse education?	No	N/A
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?	No	N/A
Follow-up laboratory tests?	No	N/A

Medication Management Step	Identified Risk	Steps for Prevention
Education?	No	N/A
Operational Impact		
Unique procurement process? (e.g. orphan medication)	No	N/A
Unique equipment required?	No	N/A
Complex preparation process required	No	N/A

FORMULARY REVIEW

GENERIC NAME: Pafolacianine (On Target Laboratories)

PROPRIETARY NAME: *Cytalux®*

INDICATIONS:

FDA Approved
Optical imaging agent (ovarian cancer): Adjunct for intraoperative identification of malignant lesions in adult patients with ovarian cancer

THERAPEUTIC CATEGORY: Imaging agent

PHARMACOKINETICS:

Absorption	Not studied
Distribution	Mean (± SD) volume of distribution is 17.1 (± 5.99) liters
Metabolism	Not metabolized by cytochrome P450 (CYP) enzymes
Elimination	Mean (± SD) plasma clearance is 28.6 (± 4.97) L/hr and the elimination half-life is 0.44 (± 0.23) hours.

SPECIAL POPULATIONS:

Pregnancy	There are no specific recommendations for using pafolacianine in pregnant women, however, the manufacturer recommends obtaining a pregnancy test and verifying the absence of pregnancy prior to administration. Based on its mechanism of action, pafolacianine may cause fetal harm when administered to a pregnant woman.
Lactation	There are no data on the presence of pafolacianine in either human or animal milk, the effects on the breastfed infant, or the effects on milk production.
Pediatrics	Not studied
Geriatrics	No clinically significant differences in pharmacokinetics based on age 18 - 89 years
Hepatic Impairment	No clinically significant differences in pharmacokinetics based on mild to moderate hepatic impairment (total bilirubin < 3 ULN and AST > ULN). The effect of severe hepatic impairment (total bilirubin > 3 ULN and any AST value) has not been studied.
Renal Impairment	No clinically significant differences in pharmacokinetics based on mild to moderate renal impairment (CrCl 30 - 89 mL/min). The effect of severe renal impairment (CrCl < 30 mL/min) has not been studied.

CLINICAL STUDIES:

OTL38 for Intra-operative Imaging of Folate Receptor Positive Ovarian Cancer	
METHODS	
Study Design	Phase 3, single dose, randomized, multicenter, open-label study
Study Funding	On Target Laboratories, LLC
Patient Enrollment Inclusion	Nonpregnant females 18 years or older Have a primary diagnosis, or at high clinical suspicion, of primary ovarian cancer (of epithelial type), planned for primary surgical cytoreduction, interval debulking, or have recurrent ovarian cancer surgery, and: ● Scheduled to undergo laparotomy for the debulking surgery OR ● Scheduled to undergo laparoscopy and pre-authorized to undergo laparotomy for the debulking surgery if cancer is detected on the laparoscopy Able and agree to use contraception from time of signing informed consent until 30 days after administration (for female patients of childbearing potential)
Patient Enrollment Exclusion	Previous treatment with pafolacianine Pregnancy or positive pregnancy test Impaired renal function defined as eGFR< 50 mL/min/1.73m2 Impaired liver function defined as values > 3x the upper limit of normal (ULN) for alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), or total bilirubin.
Baseline Characteristics	Total of 140 participants. Median age was 60.8 years (range 33-81 years).

	119 participants (85%) were White, 7 participants (5%) were Black or African American, and 17 participants (12.1%) were Hispanic or Latino
Outcome Measures	Primary: Percentage of patients with at least one evaluable FR+ ovarian cancer lesion confirmed by central pathology (Standard of truth) that was detected using the combination of OTL38 and fluorescent light but not under normal light or palpation Secondary: False Positive Rate at the patient level (FPRp) will be a major secondary efficacy endpoint and is defined as the percentage of women who underwent both normal light and fluorescent light (Intent-to-Image Set)
Statistical Analyses	Statistical analyses have not been made available at this time
Treatment Plan	Pafolacianine 0.025 mg/kg IV infused over 60 minutes
RESULTS	
Outcomes Summary	26.9% of patients had an ovarian cancer lesion detected after pafolacianine administration that was not detected prior to pafolacianine administration. The patient-level false-positive rate was 20.2%.
Primary Endpoint	Patients with at least one confirmed ovarian cancer evaluable lesion (N=134): 36 (26.9%)
Secondary Endpoint	Patient-level false positive rate (N=134): 27 (20.2%)
Adverse Events	Most common adverse events were nausea, vomiting, abdominal pain, flushing, dyspepsia, chest discomfort, pruritus, and hypersensitivity. All-cause mortality: 2/150 patients (undisclosed cause of death)
Limitations	Small population size, low proportion of ethnic and racial minorities
Author's Conclusion	This study has not been published, therefore there is no available conclusion from the author.

A phase II, multicenter, open-label trial of OTL38 injection for the intraoperative imaging of folate receptor-alpha positive ovarian cancer	
METHODS	
Study Design	Single-arm, open label, multicenter, prospective phase II trial
Study Funding	On Target Laboratories, LLC
Patient Enrollment Inclusion	Nonpregnant females 18 years or older Known or suspected ovarian cancer planned for cytoreductive surgery by laparotomy Able and agree to use contraception from time of signing informed consent until 30 days after administration (for female patients of childbearing potential)
Patient Enrollment Exclusion	Pregnancy or positive pregnancy test Impaired renal function defined as eGFR< 50 mL/min/1.73m2 Impaired liver function defined as values > 3x the upper limit of normal (ULN) for alanine aminotransferase (ALT), aspartate aminotransferase (AST), or total bilirubin. Abnormal ECG
Baseline Characteristics	Total of 48 participants. Median age was 63.8 years (range 37–82 years). 35 participants(75.9%) were White, 1 participant (2.3%) was Black or African American, and no participants were Hispanic or Latino
Outcome Measures	Determine safety and efficacy of pafolacianine Decision to increase dose and/or expand cohort
Statistical Analyses	Both an Intention to Treat and modified Intention to Treat (mITT) population were used, along with two different statistical models. The mITT population only included patients with a confirmed ovarian cancer lesion: 29/48 (60.4%)
Treatment Plan	Pafolacianine 0.025 mg/kg IV infused over 60 minutes
RESULTS	
Outcomes Summary	225 lesions were obtained from 29 patients. Pafolacianine had an estimated sensitivity of 96.82%.
Primary Endpoint	225 total lesions obtained from 29 patients 171 (76%) true positives 23 (10%) false positives 28 (12.4%) false negatives 3 (1.3%) true negatives
Adverse Events	N = 44 5 (11.4%) gastrointestinal disorders (nausea, vomiting, abdominal pain) 5 (11.4%) infusion-related reaction 8 (18.2%) severe adverse events (infection, postoperative wound infection, sepsis)
Limitations	Small population size, low proportion of ethnic and racial minorities, removal of normal tissues was not built into the study design and prevented calculating specificity

COMPARATIVE EFFICACY:
Pafolacianine is a folate analog conjugated to a near-infrared (NIR) fluorescent dye. It is a novel imaging agent that targets folate receptor (FR), which may be overexpressed in ovarian cancer. The drug binds to FR-expressing cancer cells, internalizes via receptor mediated endocytosis, and concentrates in FR-positive cancer tissues. Pafolacianine is an adjunct for intraoperative identification of malignant lesions in adult women with a diagnosis, or high clinical suspicion, of ovarian cancer. It works in real-time, which allows the surgeon to remove the lesion at the time of surgery. Pafolacianine assists optical imaging during surgery by absorbing light in the NIR region and emitting fluorescence.

There are currently no other drugs on the market with this mechanism of action or that has the same indication.

The Food and Drug Administration (FDA) approved pafolacianine in adult patients with ovarian cancer as an adjunct for intraoperative identification of malignant lesions. Pafolacianine was granted priority review, fast-track designation, and orphan drug designation.

Pafolacianine is not included in the NCCN ovarian cancer guidelines, which was recently updated January 18th, 2022.

WARNING AND PRECAUTIONS:
- Infusion reaction: Interrupt the infusion and treat as necessary with antihistamines and/or nausea medications.
- Risk of misinterpretation: Non-fluorescing tissue in the surgical field does not rule out the presence of tumor. Fluorescence may be seen in non-cancerous tissues.
- Embryo-Fetal toxicity: Pafolacianine may cause fetal harm. Advise females of reproductive potential of the potential risk to a fetus.
- Risk of Pafolacianine Aggregation and Infusion Reactions: Use only 5% Dextrose Injection for dilution. Do not use other diluents.

CONTRAINDICATIONS: None

ADVERSE REACTIONS:

Adverse Reactions	Intervention Group (N=150*)
Cardiovascular	Sinus tachycardia (1/150) and Supraventricular tachycardia (1/150)
Central Nervous System	Ischemic stroke (1/150)
Gastrointestinal	Abdominal pain (7/150), Diverticular perforation (1/150), Gastric perforation (1/150), Nausea (27/150), Vomiting (8/150)
Hematologic and Oncologic	Anemia (1/150)
Hepatic	Cholelithiasis (1/150)
Infection	Septic shock (2/150), Abscess (1/150), *Clostridium difficile* infection (1/150), Peritonitis (1/150), Pneumonia (1/150), Sepsis (1/150), Post-operative wound infection (1/150)
Metabolic	Metabolic acidosis (1/150)
Neuromuscular & Skeletal	Not reported
Renal	Acute kidney injury (3/150) and Renal impairment (1/150)
Respiratory	Pleural effusion (2/150), Acute respiratory distress syndrome (1/150), Acute respiratory failure (1/150), Hypoxia (1/150)
Skin	Not reported
Systemic	Not reported
*10 participants received the study drug but were not randomized to either arm due to withdrawal prior to randomization	

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:
- Folic acid: May diminish the diagnostic effect of Pafolacianine

DOSING AND ADMINISTRATION:
- Optical imaging agent for ovarian cancer: 0.025 mg/kg (actual body weight) IV over 60 minutes given 1 hour to 9 hours prior to surgery
- Consider administration of antihistamines and/or antiemetic medication for prophylaxis against infusion-related reactions

RECOMMENDED MONITORING:
- Verify pregnancy status prior to therapy (in patients who could become pregnant)
- Monitor for signs/symptoms of infusion-related reactions.

PHARMACOECONOMICS/COST:
Must be purchased directly from the manufacturer; no wholesaler contract pricing/discounts. The manufacturer has reported that there have been manufacturing delays that will limit the availability of the product once it is available for purchase.

There is no method for drug-specific billing for reimbursement of drug expense.

Product (Drug, Strength, Form)	NDC	Contract/GPO Price
CYTALUX (pafolacianine) solution for injection, 3.2 mg /1.6 mL (2 mg/mL)	81052-138-10	$4250/vial (Minimum purchase of 10 vials)

Product (Drug, Strength, Form)	Cost/Day	Cost/Defined Course of Therapy	Cost per patient/Year
CYTALUX (pafolacianine) solution for injection, 3.2 mg /1.6 mL (2 mg/mL)	~$33.20/kg Ex: ~$1,992 (60 kg)	Single dose treatment ~$33.20/kg	Single dose treatment ~$33.20/kg (1 vial = $4,250)

Additional Expense(s) Required: A near infrared (NIR) imaging device is required intraoperatively to visualize the cancer cells following Cytalux administration. The anticipated price for this device is around $120,000.

CONCLUSION & RECOMMENDATION:
Ovarian cancer is the deadliest type of gynecologic cancer. It is the 11th most common type of cancer in women, however, it is the 5th leading cause of cancer-related death in women. In 2022, the American Cancer Society estimates that in the United States there will be about 19,880 new cases of ovarian cancer diagnosed and 12,810 deaths in women caused by ovarian cancer. While there have been significant improvements in survival in other types of cancer over the past few decades, there has only been a slight decline in mortality associated with ovarian cancer.

The National Comprehensive Cancer Network (NCCN) guidelines recommend surgical staging as the most complete and accurate way to stage ovarian cancer. The staging of ovarian cancer is usually done by removing the uterus, both ovaries, and fallopian tubes for laboratory testing. During surgery, surgeons will feel for tumors and use bright lights and imaging done prior to surgery to determine where cancer is located in the body and remove it. Intraoperative imaging is also sometimes used to help locate cancer. Pafolacianine is not included in the NCCN ovarian cancer guidelines.

A phase three, randomized, multi-center, single dose, open label, pivotal study in patients diagnosed with, or with high clinical suspicion of, ovarian cancer demonstrated the safety and efficacy of pafolacianine. The study assessed the proportion of patients who had at least one ovarian cancer lesion that was not detected under light prior to pafolacianine administration, however, was detected after pafolacianine administration. 26.9% of patients in the study had a confirmed ovarian cancer lesion detected after pafolacianine administration. Results were confirmed by central pathology. The patient-level false-positive rate was 20.2% for the study.

Based on unknown and limited drug supply, need for a capital purchase of equipment, and limitations in current evidence, pafolacianine should not be added to the formulary at this time. Formulary status may be revisited once the supply chain issues are addressed. The CommonSpirit Health System P&T committee is anticipated to vote as non-formulary later this month.

It is recommended that pafolacianine (Cytalux) be non-formulary.

FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)

Medication Management Step	Identified Risk	Steps for Prevention
Selection		
Therapeutic interchange?	N/A	
Special Ordering Requirements?	N/A	
Storage		
LASA* separation of stock?	Yes	Drugs will be stored according to generic name
Special storage (e.g. refrigeration, protect from light, controlled substance)?	Yes	Store frozen between -25° to -15°C (-13° to 5°F) in the original carton to protect from light.
Pharmacist/Technician Education?	Yes	Educate on storage
Ordering & Prescribing		

Medication Management Step	Identified Risk	Steps for Prevention
Restriction to particular specialty, indication, or particular patient population?	Yes	Restrict to only Heme/Onc or OB/GYN providers/surgeons
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	Yes	Not studied in severe liver or renal impairment
Drug Interactions?	Yes	Build into Epic Warning about interaction with folic acid. Folic Acid: May diminish the diagnostic effect of Pafolacianine. Risk X: Avoid combination. Manufacturer recommends discontinuing folic acid supplements 48 hours before administration of pafolacianine
Pregnancy?	Yes	Build into Epic Obtain negative pregnancy test prior to administration
Absolute Contraindications?	No	
Requires Order Set, Protocol, concomitant therapy with another drug?	No	
LASA* nomenclature issues?	Yes	Drugs will be stored according to generic names. Medication labels will include generic drug name
Prescriber education?	No	
Processing, Preparing, & Dispensing		
High-risk drug double check?	No	
Drug Interaction check in place?	Yes	Build into Epic
LASA* computer warnings?	No	
Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)?	Yes	Administer over 60 minutes using a dedicated infusion line, 1 hour to 9 hours prior to surgery
Packaging/Labeling (e.g. prepacking)?	No	
Dispensing (e.g. auxiliary labeling, light protection, refrigeration)?	Yes	Protect from light Complete infusion within 3 hours of removal from refrigeration. Use only 5% Dextrose Injection for dilution. Do not use other diluents.
Documentation required (e.g. double check, worksheet)?	No	
Pharmacist/Technician Education?	Yes	Storage, preparation, administration
Administration		
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	Yes	Administer over 60 minutes using a dedicated infusion line, 1 hour to 9 hours prior to surgery
Special delivery system (e.g. pump)?	Yes	Build specific rates into pump
Documentation required? (e. g. double check)	No	
Nurse education?	Yes	Administration instructions
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?	Yes	Infusion reactions
Follow-up laboratory tests?	No	
Education?	Yes	Infusion reactions
Operational Impact		
Unique procurement process? (e.g. orphan medication)	No	
Unique equipment required?	No	
Complex preparation process required	No	

FORMULARY REVIEW

GENERIC NAME: Olanzapine and samidorphan

PROPRIETARY NAME: *Lybalvi®*

INDICATIONS:

FDA Approved
● Schizophrenia in adults ● Bipolar I disorder in adults ○ Acute treatment of manic or mixed episodes as monotherapy and as adjunct to lithium or valproate ○ Maintenance monotherapy treatment

THERAPEUTIC CATEGORY: Antimanic Agent; Opioid Antagonist; Second Generation (Atypical) Antipsychotic

PHARMACOKINETICS:

	Olanzapine	**Samidorphan**
Absorption	Tmax Oral: 4.5-7 hrs	Tmax Oral: 1-2 hrs
Distribution	Protein binding: 93%	Protein binding: 23-33%
Metabolism	Hepatic metabolism, primarily through UGT1A4, CYP1A2	Hepatic metabolism, primarily through CYP3A4
Excretion	Oral, 57% in urine, 30% in feces. 7% in urine as unchanged drug	Oral, 67% in urine, 16% in feces. 18% in urine as unchanged drug
Cmax (mg/L)	64.6	45.1
Bioavailability (%)	N/A	69%
t ½ (hr)	35-52	7-11
AUC (ng*h/L) at Steady State	1,086	346

SPECIAL POPULATIONS:

	Olanzapine	**Samidorphan**
Pregnancy	Studies of pregnant women exposed to olanzapine have not established a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Neonates exposed to antipsychotic drugs, including olanzapine, during the third trimester are at risk for extrapyramidal and/or withdrawal symptoms after delivery.	There are no available data on the use of samidorphan or the combination of olanzapine and samidorphan in pregnant women to determine a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.
Lactation	Olanzapine is present in human milk. There are reports of excess sedation, irritability, poor feeding and extrapyramidal symptoms (tremors and abnormal muscle movements) in infants exposed to olanzapine through breast milk. There is no information on the effects of olanzapine on milk production.	There is no data on the presence of samidorphan in human milk, the effects on the breastfed infant or the effects on milk production.
Pediatrics	The safety and effectiveness of olanzapine/samidorphan has not been established in pediatric patients.	
Geriatrics	In a study involving 24 healthy patients, the mean elimination half-life of olanzapine was ~1.5 times greater in patients 65 years or older than in patients younger than 65 years.	No effect of age on samidorphan pharmacokinetics was found in a study involving 12 elderly (aged 66-80 years old) and 24 young (aged 18-39 years old) healthy subjects administered a single oral dose of 10 mg samidorphan.
Hepatic Impairment	Olanzapine and samidorphan plasma exposures were found to be higher in subjects with moderate hepatic impairment than in subjects with normal hepatic function. The effect of severe hepatic impairment was not studied. The higher plasma exposure in patients with moderate hepatic impairment was not expected to be clinically relevant and there are no dose adjustments recommended for patients with hepatic impairment.	
Renal Impairment	Plasma exposure to olanzapine and samidorphan was higher in patients with severe renal impairment (eGFR 15 to 29 mL/minute/1.73 m2) compared to those with normal renal function. The effect of olanzapine/samidorphan in patients with end-stage renal disease was not studied and its use is not recommended.	

Other – Tobacco Smoking	Olanzapine clearance was approximately 40% higher in smokers than in non-smokers.	Samidorphan pharmacokinetics were not affected by smoking.

CLINICAL STUDIES:

Efficacy and Safety of a Combination of Olanzapine and Samidorphan in Adult Patients With an Acute Exacerbation of Schizophrenia: Outcomes From the Randomized, Phase 3 ENLIGHTEN-1 Study (NCT02634346)	
METHODS	
Study Design	Phase 3, multinational, multicenter, randomized, double-blind, placebo controlled study
Patient Enrollment Inclusion	● Ages 18-70 years ● DSM-5 diagnosis of schizophrenia who meet pre-specified symptom severity criteria ● Meet criteria for an acute exacerbation of schizophrenia symptoms ● Have a stable living environment (when not hospitalized) ● Have a designated caregiver or informant in countries where a caregiver is required
Patient Enrollment Exclusion	● Diagnosis of additional psychiatric conditions ● Use of prohibited or contraindicated drugs and medications ● Pre-existing medical conditions ● Abnormal lab results during screening ● Pregnancy ● Relationship to an employee of the study sponsor
Baseline Characteristics	● Mean age: 41.1 years ● 60.8% male, 28.2% black, 38.4% in the United States ● Mean weight: 78.9 kg ● Mean BMI: 26.6 kg/m2 ● 25.9% obese ● 89.0% had taken at least 1 antipsychotic prior to study entry; the most common were risperidone (n = 124, 30.9%) and haloperidol (n = 122, 30.4%)
Outcome Measures	● Primary - Change from baseline in Positive and Negative Syndrome Scale (PANSS) total score at week 4 ● Secondary - Change from baseline in Clinical Global Impressions-Severity of Illness Scale (CGI-S) score at week 4
Treatment Plan	● Randomized 1:1:1 to olanzapine/samidorphan, olanzapine, or placebo administered orally, once daily for up to 4 weeks ● Olanzapine/Samidorphan: Goal of 20 mg/10 mg daily. Patients were given 10 mg/10 mg daily on days 1 and 2, then 20 mg/10 mg daily starting on day 3. At the end of week 1, doses could be decreased for tolerability to 10 mg/10 mg at the discretion of the investigator. Thereafter, no dose adjustments were permitted from weeks 2 to 4. ● Olanzapine: Goal of 20 mg daily. Patients were given 10 mg daily on days 1 and 2, then 20 mg daily starting on day 3. At the end of week 1, doses could be decreased for tolerability to 10 mg at the discretion of the investigator. Thereafter, no dose adjustments were permitted from weeks 2 to 4. ● Placebo: one tablet daily
RESULTS	
Primary Endpoint	Mean difference in change from baseline at week 4 in PANSS total score versus placebo ● Olanzapine/samidorphan: −6.4 ± 1.8 ($P < .001$) ● Olanzapine: −5.3 ± 1.8 ($P = .004$) A statistically significant mean difference from placebo in the olanzapine/samidorphan group was observed from week 2 onward
Secondary Endpoint	Mean difference in change from baseline at week 4 in CGI-S score ● Olanzapine/samidorphan: −0.38 ± 0.12 ($P = .002$) ● Olanzapine: −0.44 ± 0.12 ($P < .001$)
Adverse Events	● ≥1 Adverse event: 73 patients (51.4%) in Olanzapine/samidorphan, 73 (54.9%) in Olanzapine, and 60 (44.8%) in Placebo ● Serious adverse events: 1 in Olanzapine/samidorphan, 1 in Olanzapine, 0 in placebo ● AEs reported in ≥ 5% of patients in the olanzapine/samidorphan group and that occurred at a rate of at least 2-fold greater than in placebo group: weight gain, somnolence, dry mouth, and headache ● Weight gain (most common AE): 25/134 (18.7%) in Olanzapine/samidorphan, 19/133 (14.3%) in Olanzapine, 4/134 (3%) in Placebo group ● Discontinuation of treatment: 2/134 (1.5%) in the Olanzapine/samidorphan, 3/133 (2.3%) in Olanzapine, and 7/134 (5.2%) in the Placebo group

Limitations	● Study was funded by the drug manufacturer who was involved in the design, collection, and analysis of the data and provided the study medications ● Short duration of 4 weeks - long-term efficacy and safety was not assessed ● Study was only designed to assess the antipsychotic efficacy of olanzapine/samidorphan and not to assess the relative weight gain or other adverse effects ● High placebo response observed at week 4 (mean improvement in PANSS total score: −17.5)
Effects of Olanzapine Combined With Samidorphan on Weight Gain in Schizophrenia: A 24-Week Phase 3 Study (NCT02694328)	
METHODS	
Study Design	Phase 3 multicenter, randomized, double-blind study conducted in the United States
Patient Enrollment Inclusion	● Ages 18–55 years ● Meet DSM-5 criteria for a primary diagnosis of schizophrenia ● Body mass index (BMI) between 18–30 ● Stable body weight for at least 3 months prior to study initiation
Patient Enrollment Exclusion	● History of treatment resistant schizophrenia ● Over 1 year since initial onset of symptoms ● Naïve to antipsychotic medication ● Active alcohol or substance use disorders (excluding marijuana/ tetrahydrocannabinol) ● Clinically significant or unstable medical illness (e.g., diabetes, hypo- or hypertension, thyroid dysfunction, and history of seizure disorder or brain tumor) that might compromise patient safety or study endpoint assessments or interfere with the ability to fulfill study requirements ● Opioid agonist use within 14 days of screening, opioid antagonist use within 60 days of screening, or anticipated need for opioid treatment during the study
Baseline Characteristics	● Mean age: olanzapine/samidorphan = 40.3 years, olanzapine = 40.1 ● Sex: Olanzapine/samidorphan = 70.4% male, olanzapine = 75.0% male ● Race: Olanzapine/samidorphan = 72.6% African American, olanzapine = 69.9% African American ● Mean weight: Olanzapine/samidorphan = 77.14 kg, olanzapine = 77.57 kg ● Mean BMI: Olanzapine/samidorphan = 25.38, olanzapine = 25.52
Outcome Measures	● Primary endpoints – Percent change from baseline at week 24 in body weight, Proportion of patients with >10% weight gain from baseline at week 24 ● Secondary endpoint – proportion of patients with >7% weight gain at week 24
Treatment Plan	● Randomized 1:1 ratio to either olanzapine/samidorphan or olanzapine for 24 weeks ● Olanzapine/samidorphan: Patients took 10 mg/10 mg daily for one week, then 20 mg/10 mg daily starting at week 2. At the end of week 2, 3, or 4, the olanzapine dosage could be lowered to 10 mg/day for tolerability reasons. No dosage adjustments were permitted beyond week 4. ● Olanzapine: Patients took 10 mg daily for one week, then 20 mg daily starting at week 2. At the end of week 2, 3, or 4, the dosage could be lowered to 10 mg/day for tolerability reasons. No dosage adjustments were permitted beyond week 4.
RESULTS	
Primary Endpoint	Mean percent increase from baseline in body weight at week 24 ● Olanzapine/samidorphan: 4.21% ● Olanzapine: 6.59% ● Mean difference between the combined olanzapine/samidorphan group and the olanzapine group was −2.38% (P = 0.003) Number of patients with ≥10% weight gain at week 24 ● Olanzapine/samidorphan: 47 (17.8%) ● Olanzapine: 81 (29.8%) ● Odds ratio = 0.50 (95% CI=0.31, 0.80; p=0.003) ● Number needed to treat (NNT) = 7.29
Secondary Endpoint	Percentage of patients with ≥7% weight gain at week 24 ● Olanzapine/samidorphan: 27.5% ● Olanzapine: 42.7% ● Odds ratio = 0.50 (95% CI=0.33, 0.76; p=0.001) ● NNT=6.29
Adverse Events	● Any adverse event: 74.1% of patients in Olanzapine/samidorphan group, 82.2% in the Olanzapine group

	● Serious adverse event: 3.6% of patients in Olanzapine/samidorphan group, 2.5% in the Olanzapine group ● Most common adverse events (>10%): Weight increase (24.8% in Olanzapine/samidorphan group, 36.2% in Olanzapine group), somnolence (21.2% and 18.1%), dry mouth (12.8% and 8.0%), and increased appetite (10.9% and 12.3%) ● Discontinuation of treatment: 12% percent of patients in olanzapine/samidorphan group, 9.8% in the olanzapine group ● Most common reasons for discontinuation: Adverse events (12.0% and 9.8%, respectively), withdrawal by participant (8.4% and 9.8%), and lost to follow-up (8.0% and 9.4%)
Limitations	● High number of patients that discontinued the study early ● Restrictive inclusion criteria: BMI criterion (BMI 18-30), age <55, patients with long illness and antipsychotic treatment histories o May have selected patients who were relatively resistant to antipsychotic-associated weight gain and metabolic dysregulation ● The study was funded and sponsored by the drug manufacturer who assisted in the preparation of the methods and manuscript

COMPARATIVE EFFICACY:
Olanzapine/samidorphan is the only second generation (atypical) antipsychotic and opioid antagonist combination medication, and was formulated to decrease weight gain seen with existing medications. In the clinical trials that led to the drugs approval, olanzapine/samidorphan was shown to have comparable efficacy to olanzapine monotherapy, as assessed by the PANSS and CGI-S scale scores, but resulted in significantly less weight gain after 24 weeks.

Olanzapine/samidorphan is also approved for the treatment of adults with bipolar I disorder, as a maintenance monotherapy or for the acute treatment of manic or mixed episodes, as monotherapy or an adjunct to lithium or valproate. Studies for the combination therapy were only conducted on patients with schizophrenia, and all recommendations for the treatment of bipolar I disorder was established from pre-existing studies using olanzapine monotherapy.

BLACK BOX WARNING(S):
- Increased mortality in elderly patients with dementia-related psychosis:
    - Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Olanzapine/samidorphan is not approved for the treatment of patients with dementia-related psychosis

WARNING AND PRECAUTIONS:
- Increased mortality in elderly patients with dementia-related psychosis
- Cerebrovascular adverse reactions, including stroke in elderly patients with dementia-related psychosis
- Precipitation of severe opioid withdrawal in patients who are physiologically dependent on opioids
- Vulnerability to life-threatening opioid overdose
- Neuroleptic malignant syndrome
- Drug reaction with eosinophilia and systemic symptoms
- Metabolic changes
- Tardive dyskinesia
- Orthostatic hypotension and syncope
- Falls
- Leukopenia, neutropenia, and agranulocytosis
- Dysphagia
- Seizures
- Potential for cognitive and motor impairment
- Body temperature dysregulation
- Anticholinergic (antimuscarinic) effects
- Hyperprolactinemia
- Risks associated with combination treatment with lithium or valproate

CONTRAINDICATIONS:
- Patients who are receiving opioids, including those treated with opioids for opioid use disorder
- Patients undergoing acute opioid withdrawal

ADVERSE REACTIONS:

Adverse Reactions	Olanzapine/Samidorphan (10 mg/10 mg, 20 mg/10 mg) (N=134)	Placebo Group (N=134)

Weight increased	19%	3%
Somnolence	9%	2%
Dry mouth	7%	1%
Headache	6%	3%
Blood insulin increased	3%	1%
Sedation	2%	0%
Dizziness	2%	1%
Neutrophil count decreased	2%	0%

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:

Interacting Drug	Effect
Opioids	Lybalvi contains samidorphan, an opioid antagonist, opioid treatment may be less effective or ineffective shortly after olanzapine/samidorphan discontinuation because of the presence of samidorphan. Olanzapine/samidorphan is contraindicated in patients who are using opioids or undergoing acute opioid withdrawal.
Strong CYP3A4 Inducer	Coadministration of olanzapine/samidorphan with a strong CYP3A4 inducer decreases the AUC of olanzapine and samidorphan, which may reduce efficacy. Concomitant use of olanzapine/samidorphan with strong CYP3A4 inducers is not recommended.
Strong CYP1A2 Inhibitor	Concomitant use of olanzapine/samidorphan with a strong CYP1A2 inhibitor increases olanzapine AUC and Cmax, which may increase the risk of olanzapine/samidorphan adverse reactions. Consider reducing the dosage of the olanzapine component when used concomitantly with strong CYP1A2 inhibitors.
CYP1A2 Inducer	Concomitant use of olanzapine/samidorphan with CYP1A2 inducers decreases olanzapine exposure, which may reduce olanzapine/samidorphan efficacy. Consider increasing the dosage of the olanzapine component in olanzapine/samidorphan when used concomitantly with CYP1A2 inducers.
Diazepam, Alcohol, and Other CNS Acting Drugs	Concomitant use of diazepam, alcohol, or other CNS acting drugs with olanzapine/samidorphan may potentiate the orthostatic hypotension observed with olanzapine. Olanzapine/samidorphan should be used with caution in patients receiving concomitantly diazepam or other CNS acting drugs, or using alcohol.
Anticholinergic Drugs	Concomitant treatment with olanzapine and other drugs with anticholinergic activity can increase the risk for severe gastrointestinal adverse reactions related to hypomotility. Olanzapine/samidorphan should be used with caution in patients receiving medications having anticholinergic (antimuscarinic) effects.
Antihypertensive Agents	Olanzapine/samidorphan may enhance the effects of certain antihypertensive agents. Monitor blood pressure and reduce dosage of antihypertensive drug in accordance with its approved product labeling
Levodopa and Dopamine Agonists	Olanzapine/samidorphan may antagonize the effects of levodopa and dopamine agonists. Concomitant use is not recommended with levodopa and dopamine agonists.

DOSING AND ADMINISTRATION:

- Initiation In Patients who have used Opioids
    - In patients who use opioids, delay initiation of olanzapine/samidorphan for a minimum of 7 days after last use of short-acting opioids and 14 days after last use of long-acting opioids
- Schizophrenia
    - 5 mg/10 mg or 10 mg/10 mg orally once daily.
    - The recommended dosage is 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg once daily
    - Dosage may be adjusted at weekly intervals of 5 mg (based on the olanzapine component) depending upon clinical response and tolerability, up to the maximum recommended dosage of olanzapine/samidorphan 20 mg/10 mg once daily
- Bipolar I Disorder (Manic or Mixed Episodes)
    - Monotherapy
        - 10 mg/10 mg or 15 mg/10 mg once daily. The recommended dosage is 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg once daily. The maximum recommended dosage is 20 mg/10 mg once daily.
        - Dosage adjustments should occur at intervals of not less than 24 hours. When dosage adjustments are necessary, dose increments/decrements of 5 mg (based on the olanzapine component) are recommended.
    - Maintenance Monotherapy
        - Administer olanzapine/samidorphan at 5 mg/10 mg, 10 mg/10 mg, 15 mg/10 mg, or 20 mg/10 mg once daily.
    - Adjunctive to lithium or valproate

        - Initiate olanzapine/samidorphan at 10 mg/10 mg once daily. The recommended dosage is 10 mg/10 mg, 15 mg/10 mg or 20 mg/10 mg, once daily.
        - Dosage may be adjusted at weekly intervals of 5 mg (based on the olanzapine component), depending upon clinical response and tolerability, up to the maximum recommended dosage of 20 mg/10 mg once daily.
- Administration
    - Administer orally with or without food as a single tablet.
    - Do not divide tablets or combine strengths.

RECOMMENDED MONITORING:

- Neurologic function - Symptoms of neuroleptic malignant syndrome
- Blood glucose, serum lipid profile
- Weight prior to initiation and frequently thereafter
- Heart rate, blood pressure, and orthostatic vital signs
- CBC for patients with a pre-existing low WBC or a history of drug induced leukopenia/neutropenia
- Pregnancy testing - Pregnancy exposure registry that monitors outcomes in pregnant patients exposed to atypical antipsychotics, including olanzapine/samidorphan

PHARMACOECONOMICS/COST:

Product (Drug, Strength, Form)	Cost per dose	Cost per 7 days
Lybalvi (5-10 mg, 10-10 mg, 15-10 mg, or 20-10 mg) oral tablet (30 tablets/bottle)	$38.16 per tablet ($1,144.67 per bottle)	$267.12
Olanzapine 5 mg tablet (100 ct)	$0.19 per tablet ($19.14 per bottle)	5 mg dose: $1.34
		10 mg dose: $2.68
		15 mg dose: $4.02
		20 mg dose: $5.36

CONCLUSION & RECOMMENDATION:

Olanzapine/samidorphan (Lybalvi) is a newly approved once daily medication indicated for the treatment of adults with schizophrenia and bipolar I disorder. Lybalvi is the first medication that combines olanzapine, a commonly used second generation antipsychotic, with samidorphan, an opioid antagonist. Previous therapies, including olanzapine alone, have been shown to be effective in managing schizophrenia and bipolar 1 disorder, but can be associated with adverse effects such as weight gain. Pre-clinical data suggested a decrease in weight gain when opioid receptors were inhibited, so olanzapine with samidorphan was formulated to provide an effective treatment option with decreased weight gain compared to olanzapine monotherapy.

Because the efficacy of olanzapine/samidorphan treatment was found to be similar in both studies, the main place in therapy is decreasing weight gain from long term antipsychotic treatment. Olanzapine/samidorphan is contraindicated in patients taking opioids or those who are undergoing acute opioid withdrawal.
Based on the specialized place in therapy, lower cost treatment options with similar efficacy, and contraindications with opioids, it is recommended to classify olanzapine/samidorphan as non-formulary. An automatic therapeutic interchange from olanzapine/samidorphan to olanzapine monotherapy is also recommended (see below).

THERAPEUTIC INTERCHANGE:

Ordered	**Provided** (olanzapine 5 mg tablets are stocked)
Lybalvi (olanzapine/samidorphan) 5 mg/10 mg	Olanzapine 5 mg
Lybalvi (olanzapine/samidorphan) 10 mg/10 mg	Olanzapine 10 mg (2 x 5 mg tab)
Lybalvi (olanzapine/samidorphan) 15 mg/10 mg	Olanzapine 15 mg (3 x 5 mg tab)
Lybalvi (olanzapine/samidorphan) 20 mg/10 mg	Olanzapine 20 mg (4 x 5 mg tab)

FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)

Medication Management Step	Identified Risk	Steps for Prevention
Selection & Procurement		
Therapeutic interchange?	N/A	
Special Ordering Requirements?	N/A	
Storage		
LASA* separation of stock?	N/A	
Special storage (e.g. refrigeration, protect from light, controlled substance)?	Store and dispense in original package	

Pharmacist/Technician Education?	N/A	
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	No	
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	Yes	-Use not recommended in eGFR of <15 mL/minute/1.73 m2 -Initiate at a lower dose in patients at risk of hypotension, have slower olanzapine metabolism, or pharmacodynamic sensitivity, such as the geriatric adult
Drug Interactions?	Yes	-Contraindicated: with opioids -Avoid using: with CYP3A4 inducers, levodopa and dopamine agonists -Decrease dose of olanzapine/samidorphan: with CYP1A2 inhibitors -Increase dose of olanzapine/samidorphan: with CYP1A2 inducers -Use with caution: with diazepam, alcohol, other CNS acting drugs, anticholinergics
Pregnancy?	Yes – with patient discussion and understanding of risks versus benefits	There are risks to the mother associated with untreated schizophrenia or bipolar I disorder and with exposure to antipsychotics, including olanzapine/samidorphan, during pregnancy.
Absolute Contraindications?	Yes	Contraindicated in patients who are using opioids or are undergoing acute opioid withdrawal.
Requires Order Set, Protocol, concomitant therapy with another drug?	No	
LASA* nomenclature issues?	N/A	
Prescriber education?	Yes	Medication cannot be started within 7 days of last short-acting opioid dose or 14 days from last long-acting opioid dose. Medication has multiple drug-drug interactions.
Processing, Preparing, & Dispensing		
High-risk drug double check?	No	
Drug Interaction check in place?	Yes	
LASA* computer warnings?	N/A	
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)?	No	
Documentation required (e.g. double check, worksheet)?	No	
Pharmacist/Technician Education?	Yes	Medication cannot be crushed or split. Medication cannot be started within 7 days of last short-acting opioid dose or 14 days from last long-acting opioid dose.
Administration		
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	Yes	Administer with or without food
Special delivery system (e.g. pump)?	No	
Documentation required? (e. g. double check)	No	

Nurse education?	No	
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?	Yes	Blood pressure, orthostatic vitals, heart rate, weight, neurologic function
Follow-up laboratory tests?	Yes	Serum lipid profile, blood glucose, CBC, pregnancy testing
Education?	Yes	Take this medication with or without food. Do not take opioids while on this medication.

FORMULARY UPDATE

THERAPEUTIC CLASS: Erythropoiesis stimulating agents (ESAs)

BACKGROUND/RATIONALE:

Retacrit (epoetin alfa-epbx), a biosimilar to Epogen and Procrit, is currently the formulary preferred erythropoiesis stimulating agent (ESA). Recently, the manufacturer of Retacrit, Pfizer, communicated an expected supply disruption of Retacrit. The supply disruption is expected to begin in June 2022 with a return to market in October 2022. Specifically, Pfizer placed order limits with wholesalers starting in January 2022.

Epogen and Procrit are currently non-formulary with an approved automatic therapeutic interchange to the equivalent Retacrit dose. Due to the expected longevity of the Retacrit supply disruption, in order to maintain patient care Epogen and Procrit procurement will be necessary.

PHARMACOECONOMICS/COST:

Product	Cost per unit	Cost per 4000 unit vial
Retacrit®	$0.083	$332.16
Procrit®	$0.154	$615.94
Epogen®	$0.159	$636.87

RECOMMENDATION/DISCUSSION:

It is 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, is recommended while Retacrit is in short supply.

FORMULARY UPDATE

THERAPEUTIC CLASS: Histamine H1 Antagonist, Second Generation

GENERIC NAME: Azelastine

PROPRIETARY NAME: Astelin® nasal spray

BACKGROUND/RATIONALE:

Azelastine nasal spray is currently a non-formulary medication at CHI Memorial and CommonSpirit Health, but the patient may use their own home supply, if available, in alignment with policies on non-formulary drug use at CHI Memorial.

Utilization:

The past 3 months of utilization includes only 10 orders to continue azelastine nasal spray as a home medication.

This is a workflow constraint; on a daily basis for each patient, pharmacists must coordinate with nursing staff and patients to obtain their home supply for inpatient use.

RECOMMENDATION/DISCUSSION:

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 order verification.

Medications for COVID-19: Update

Emergency Use Authorization (EUA) Medications		
	Current Process	**Recommended Action**
Tocilizumab (Actemra)	Pharmacist automatic therapeutic interchange to either product based on product availability	Maintain current process
Baricitinib (Olumiant)		
Bamlanivimab/etesevimab	Federal government (HHS) manages supply and determines which product will be shipped to each state. State of TN then allocates mAb to select sites.	Maintain current process
Casirivimab/imdevimab (Regen-COV)		
Sotrovimab		
Nirmatrelvir and ritonavir (Paxlovid)*	Non-formulary. Federal government (HHS) manages supply and determines which product will be shipped to each state. State of TN then allocates products to select sites.	Add to formulary. Allow continuation of the patient's own home supply upon hospital admission, if ordered to continue by the admitting physician.
Molnupiravir		Maintain non-formulary status

*Per the PAXLOVID fact sheet: "Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID, the patient should complete the full 5-day treatment course per the healthcare provider's discretion."

COVID-19 Vaccines		
	Current Process	**Recommended Action**
Pfizer-BioNTech COVID-19 Vaccine (gray top)	Formulary for inpatient use; includes booster doses	Maintain current process
Moderna COVID-19 Vaccine	Non-formulary for inpatient use	Maintain current process
Janssen (J&J) COVID-19 Vaccine	Non-formulary for inpatient use	Maintain current process

Use/Restriction Criteria Approved by COVID-19 Medications Subcommittee

Remdesivir Criteria: Inpatients (updated 2/1/22)**:** 5 (FIVE) day course of IV remdesivir (200 mg IV x 1 dose, followed by 100 mg IV daily x 4 days) or until hospital discharge, whichever comes first.

Inclusion criteria:
- COVID-19 (+)
- ≤5 days since symptom onset or positive test (whichever comes first)

Exclusion criteria:
- No greater than 5L of supplemental oxygen to maintain an O2 Sat of 92%
- ALT > 5x ULN
- If the provider determines the patient has end stage comorbidities, it is reasonable to withhold remdesivir and the palliative care screening tool is available to assist with decision making regarding therapy initiation.

-Renal function must be tested prior to starting remdesivir. Remdesivir should be used with caution in patients with an eGFR <30 mL/min (dose has not been studied & the infusion may cause further injury)

-If patient does not meet the specified criteria but you feel your patient may benefit from remdesivir, ID approval must be obtained.

Ritonavir-boosted nirmatrelvir (Paxlovid) Criteria: Inpatients (approved 4/12/22):

Inclusion criteria:
- COVID-19 (+) with mild to moderate symptoms
- <= 5 (FIVE) days since symptom onset or positive test (whichever comes first)
- High risk of progressing to severe COVID-19

Exclusion criteria:
- Hospitalized due to COVID-19
- eGFR < 30mL/min (dosage adjustment required for eGFR < 60mL/min)
- Severe Hepatic Impairment (Child-Pugh Class C)
- High risk for serious toxicity due to drug interactions unmanageable via therapy modification

Remdesivir Criteria: Incidental COVID+ (symptomatic) while admitted for non-COVID diagnosis (updated 4/12/22)**: (SOTROVIMAB preferred, when available/effective against VOC)**

3 (THREE) day course of IV remdesivir (200 mg IV x 1 dose, followed by 100 mg IV daily x 2 days) or until hospital discharge, whichever comes first.

Inclusion criteria:
- COVID-19 (+) with mild to moderate symptoms
- ≤7 (SEVEN) days since symptom onset or positive test (whichever comes first)
- High risk of progressing to severe COVID-19
- Patient is not a candidate for sotrovimab or ritonavir-boosted nirmatrelvir due to specific patient factors and/or drug availability

Exclusion criteria:
- Hospitalized due to COVID-19
- ALT > 5x ULN
- If the provider determines the patient has end stage comorbidities, it is reasonable to withhold remdesivir and the palliative care screening tool is available to assist with decision making regarding therapy initiation.

-Renal function must be tested prior to starting remdesivir. Remdesivir should be used with caution in patients with an eGFR <30 mL/min (dose has not been studied & the infusion may cause further injury)

-If patient does not meet the specified criteria but you feel your patient may benefit from remdesivir, ID approval must be obtained.

Sotrovimab Criteria (approved 4/12/22):
Update [4/5/2022] 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
Inclusion criteria:
- COVID-19 (+) with mild to moderate symptoms
- <= 10 (TEN) days since symptom onset or positive test (whichever comes first)
- High risk of progressing to severe COVID-19

Exclusion criteria:
- Hospitalized due to COVID-19

Bebtelovimab Criteria (approved 4/12/22):
Inclusion criteria:
- COVID-19 (+) with mild to moderate symptoms
- <=7 (SEVEN) days since symptom onset or positive test (whichever comes first)
- ONLY if none of the preferred therapies are available, feasible to deliver, or clinically appropriate (e.g., due to drug-drug interactions, concerns related to renal or hepatic function)

Exclusion criteria:
- Hospitalized due to COVID-19

Medication use evaluation on collagenase ointment inpatient utilization following implementation of restriction criteria and unit dosing at a community hospital

BACKGROUND:
Collagenase (Santyl™) is an FDA-approved enzymatic debridement ointment that helps clean wounds by removing necrotic tissue so that the wound can begin to heal, allowing new healthy tissues to form. The active ingredient is the enzyme that contributes towards the formation of granulation tissue and subsequent epithelization of dermal ulcers and severely burned areas. Santyl is generally not beneficial in hospitalized patients due to its long onset of action. In March of 2021, our institution implemented restriction criteria *(see below)* for inpatient use of Santyl and predicted a 25% decrease in utilization.

CHI approved inpatient restriction criteria for Santyl, which is as follows:

- Necrotic tissue or severe burns in need of enzymatic therapy, or
- Not a candidate for other debridement therapy (if available); assess cost-effectiveness of debridement therapy:

Autolytic Debridement	Mechanical Debridement
• Hydrocolloids • Hydrogels • Alginates • Iodosorb • Mesalt • Antiseptics • Silver dressings	• Larval therapy • Pulsatile Lavage and Hydrotherapy • Ultrasound therapy • Ultrasonic Mist • Debrisoft • Wet to dry gauze dressings (not recommended)

PHARMACOECONOMICS:
At the time of this evaluation, a 30-gram tube of Santyl cost our institution $234.35. To help prevent unnecessary waste, a 30-gram tube can be divided into twelve 2.5-gram unit doses, averaging $19.53 per dose. Of note, the price of Santyl has since increased to $245.92.

OBJECTIVE:
To assess the adherence to the newly implemented restriction criteria for prescribing and the cost savings associated with dispensing 2.5-gram unit doses of Santyl.

METHODS:
A retrospective chart review was performed. Data was collected from the electronic health records (EHR) for patients who had an order for Santyl from April 1, 2021 through July 31, 2021. Santyl average monthly utilization and spend data from 2021 was compared to data from 2020, prior to the implementation of Santyl restriction criteria and unit dosing. Patients from all three of our campuses (CHI Memorial Hospital Chattanooga, Hixson, and Georgia) who had an order for Santyl from April to July 2021 were included in this review. Those receiving Santyl as a home medication prior to admission were excluded from following the restriction criteria (but they were still included for the cost analysis). Primary outcomes included adherence to restriction criteria and cost savings. Data evaluated included clinical documentation to support inclusion criteria, any unreconciled dispenses, and if any pharmacist-driven interventions occurred.

RESULTS:

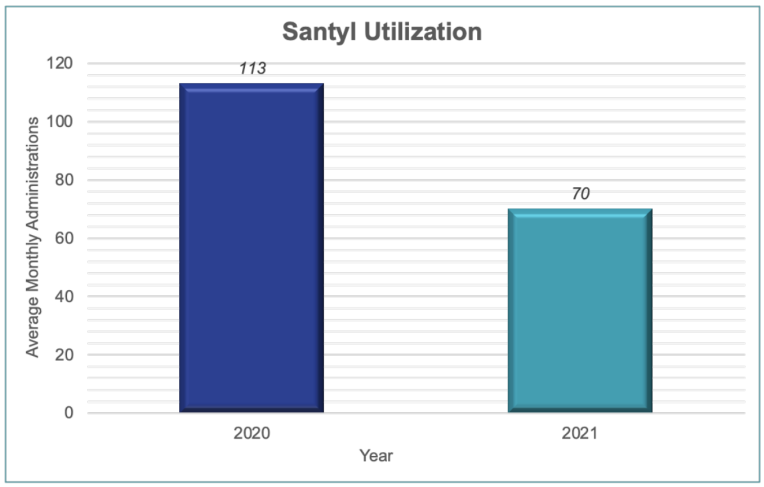


Figure 1. Overall Utilization: average monthly administrations pre and post-implementation of restriction criteria and unit dose dispensing of Santyl

Month	Budgeted Savings
April 2021	$3,000
May 2021	$3,000
June 2021	$3,000
July 2021	$3,000
	$12,000

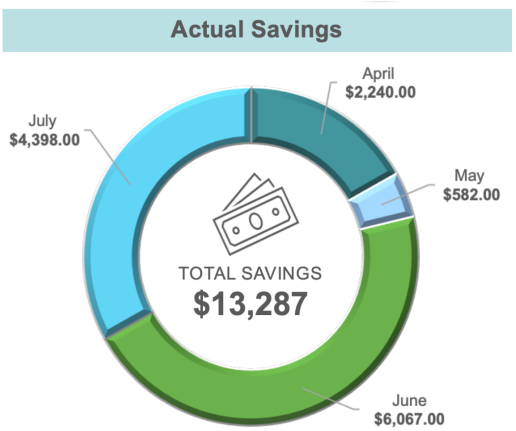


Figure 2. Cost Savings: monthly savings post-implementation of restriction criteria and unit dose dispensing of Santyl

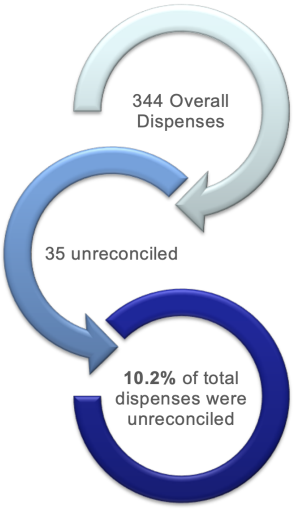


Figure 3. Unreconciled Dispenses: number of times Santyl was dispensed more than it was administered

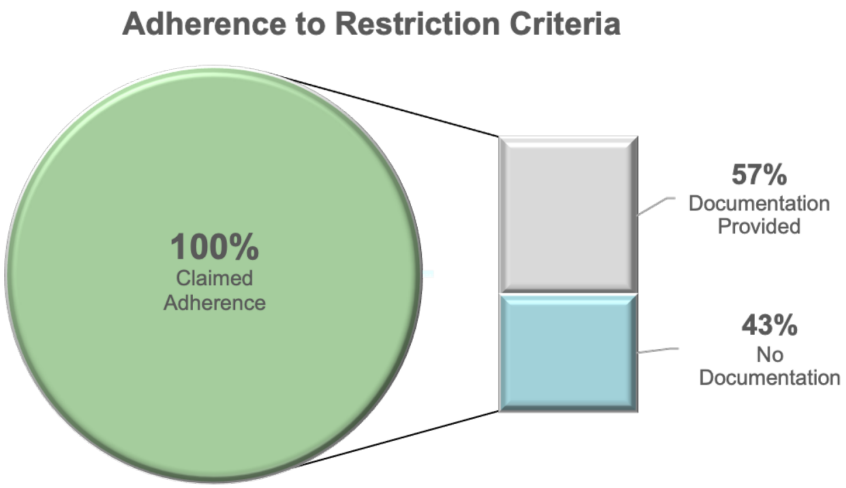


Figure 4: Adherence to Santyl Restriction Criteria

DISCUSSION:
After implementing the restriction criteria for inpatient use, monthly administrations decreased by 38.1%, surpassing the 25% decrease in utilization predicted *(see Figure 1)*. Implementation of the restriction criteria helped reduce unnecessary prescribing.

The average monthly savings is $3,322 following implementing Santyl restriction criteria and unit dose dispensing *(see Figure 2)*. Predicted annualized sayings is $39,861.

Our hospital average of unreconciled medication dispenses is 1.8%. Santyl unreconciled dispenses were considerably higher at 10.2% *(see Figure 3)*. Further nursing education is necessary to help minimize this.

As a requirement to order Santyl, users must select “yes” or “no” to the following statement, “This medication is restricted. Are you with or have you consulted with one of the approved service lines and/or does the patient meet the specified criteria?” Although 100% of ordering users claimed adherence to restriction criteria, only 57% had supporting documentation of the specific criteria met in the patient’s EHR *(see Figure 4)*. Zero interventions were made by pharmacists to discontinue potentially inappropriate orders. Complete accuracy of adherence to restriction criteria cannot be concluded.

CONCLUSION:
Implementation of restriction criteria for prescribing and dispensing 2.5-gram unit doses of Santyl was a cost-effective choice for our institution. The findings from this evaluation were discussed with Dr. Gwin who assisted in the creation of our restriction criteria and unit-dose dispensing.

REFERENCES:

1. Santyl. Package insert. Smith & Nephew, Inc; 2016.

Evaluation of Prescriber Compliance with Initiation Criteria and Nursing Adherence to Titration Protocol for Angiotensin II in Vasodilatory Shock at a Community Hospital

Jessica A. Duke, PharmD, Jenny Parnell, PharmD

Background:

The ATHOS-3 trial showed that angiotensin II was associated with a 45% absolute increase in mean arterial pressure (MAP) in patients with severe vasodilatory shock when compared to placebo. Despite increasing MAP, angiotensin II was not associated with a statistically significant difference in all-cause mortality at 7 or 28 days. Several drawbacks to utilizing angiotensin II include its high cost, complex titration parameters, and risk of thromboembolic events. The complex titration parameters required for angiotensin II create opportunities for nursing errors, which could negatively impact clinical outcomes.

Objective:

The primary objective of this medication use evaluation (MUE) was to assess our institution's provider compliance to restriction criteria and nursing adherence to the titration protocol for angiotensin II. In-hospital mortality for patients who received angiotensin II was also assessed.

Methods/Results

A retrospective chart review was performed to identify patients in the intensive care unit (ICU) who received angiotensin II between January 1, 2020 and July 31, 2021. A total of 31 patients who received angiotensin II were identified. Adult patients with vasodilatory shock were included into the analysis (n=12). Patients were excluded from the evaluation if they received angiotensin II for less than 3 hours (n=12) or were diagnosed with vasoplegic shock (n=7).

Nursing adherence to the titration protocol was suboptimal **(Figure 2)**. The majority of errors occurred during the initial titration phase. **Figure 1** highlights the most commonly identified titration errors that occurred during the first 3 hours of initiation. Fifty percent of titration errors occurred by increasing the infusion rate by more than 5 ng/kg/min every 5 minutes based on our hospital's protocol. During the maintenance phase, angiotensin infusions were commonly continued at rates greater than maximum rate of 40 ng/kg/min.

Overall, prescribers were compliant with initiation criteria **(Figure 2)**; however, 3 patients did not receive pharmacological deep vein thrombosis (DVT) prophylaxis per the current ordering instructions. Hospital mortality occurred in 100% (n=12) of patients who received angiotensin II for vasodilatory shock.

Figure 1:

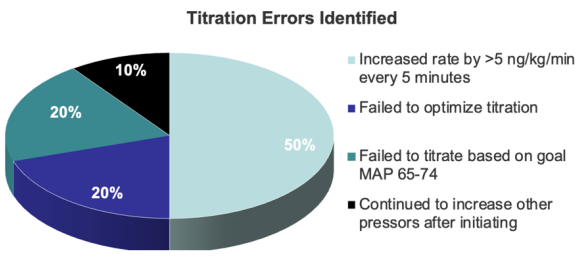
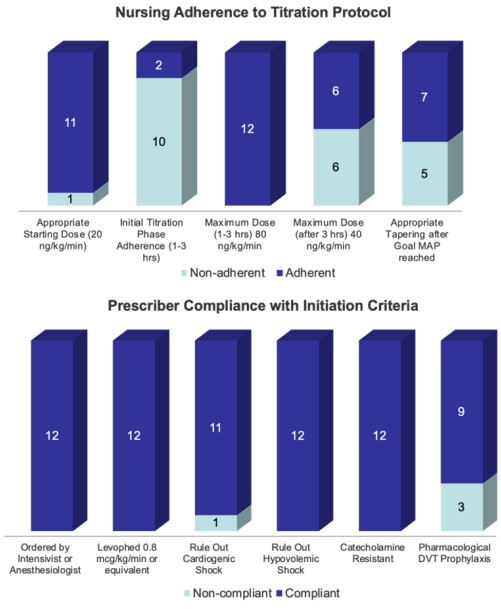


Figure 2:



Discussion/Conclusion

Opportunity exists to improve our institution's angiotensin II titration protocol adherence through ongoing nursing education and engagement. Factors that may have influenced titration non-adherence are high nursing turnover, unfamiliarity with the medication and/or instructions by the provider that were not documented in the electronic medical record (EMR). It is important to note that the accuracy of the titration errors identified are dependent on appropriate nursing documentation.

Currently at our institution, angiotensin II serves as a last line vasopressor in patients with vasodilatory shock. Although not evaluated in this MUE, because the ATHOS-3 trial excluded patients with an expected lifespan of <12 hours, this agent may provide more benefit when initiated earlier in patients with severe vasodilatory shock. However, its high cost limits use and influences selection bias, which may have contributed to the high in-hospital mortality rates observed in this evaluation.

Notably, hospital expenditure on angiotensin II has totaled $44,998.95 from July 2021 to April 2022.

Finally, while providers were compliant with our institution's initiation criteria, opportunity exists to improve the concomitant use of pharmacological DVT prophylaxis when clinically indicated.

Recommendations

After discussing the results of this MUE with the intensivists and nursing education teams, we recommend incorporating an angiotensin II order panel that embeds a DVT prophylaxis ordering panel to optimize provider ordering compliance. Additionally, this order panel would clarify the maximum infusion rates during the initial and maintenance phases to ease nursing workload and improve titration adherence. Additionally, administration instructions have been revised to further limit titration errors.

References

1. Khanna A, English S, Wang X, et al. Angiotensin II for the Treatment of Vasodilatory Shock. *N Engl J Med*. 2017;377(5):419-430.

ADR Summary
January-March 2022

IRIS ADRs/ADEs

Inpatient ADRs/ADEs reported through IRIS Jan-Mar 2022

Incident Number	Event Date	Drug	Reaction	Level of Harm	Facility	Unit
220034406	3/31/2022	Amiodarone	infiltration	2	GW	CVICU
220032245	3/25/2022	Metoprolol	low BP	2	GW	IMCU

Level of Harm as defined in IRIS:

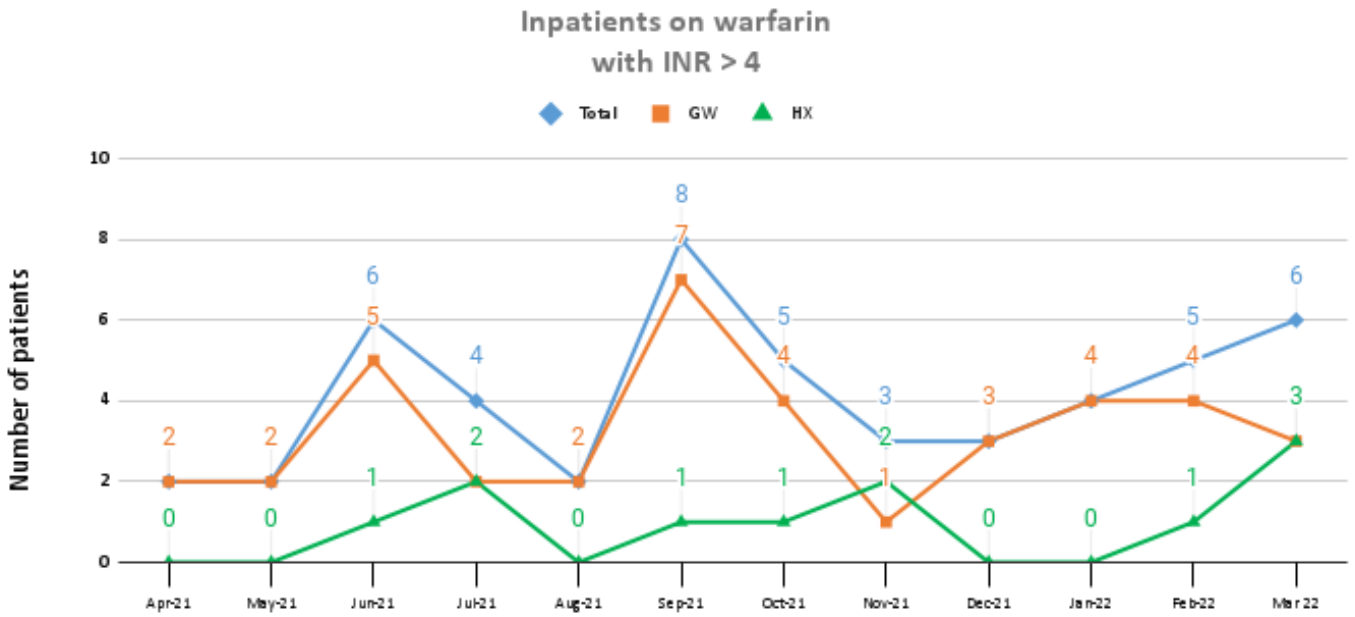
Level 00 – Near Miss
Level 01 – No Detectable Harm
Level 02 – Minimal Harm
Level 03 – Moderate Harm
Level 04 – Severe Harm
Level 05 – Death

EPIC ADRs/ADEs

Inpatient ADRs/ADEs reported through EPIC Jan-Mar 2022

Patient HAR	Event Date	Drug	Reaction	Level of Harm	Unit/Floor	Facility
20140342778	1/12/2022	Clonazepam	lethargy	2	HXNU3	HX
20991426546	1/18/2022	Propofol	Unexplained lactic acidosis	2	5 NO	GW

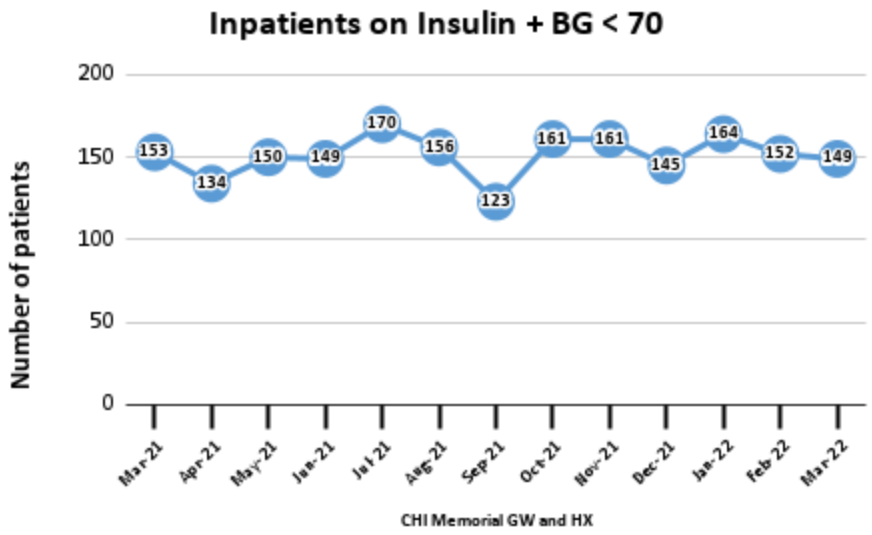
ADRs/ADEs for patients receiving warfarin with INR > 4



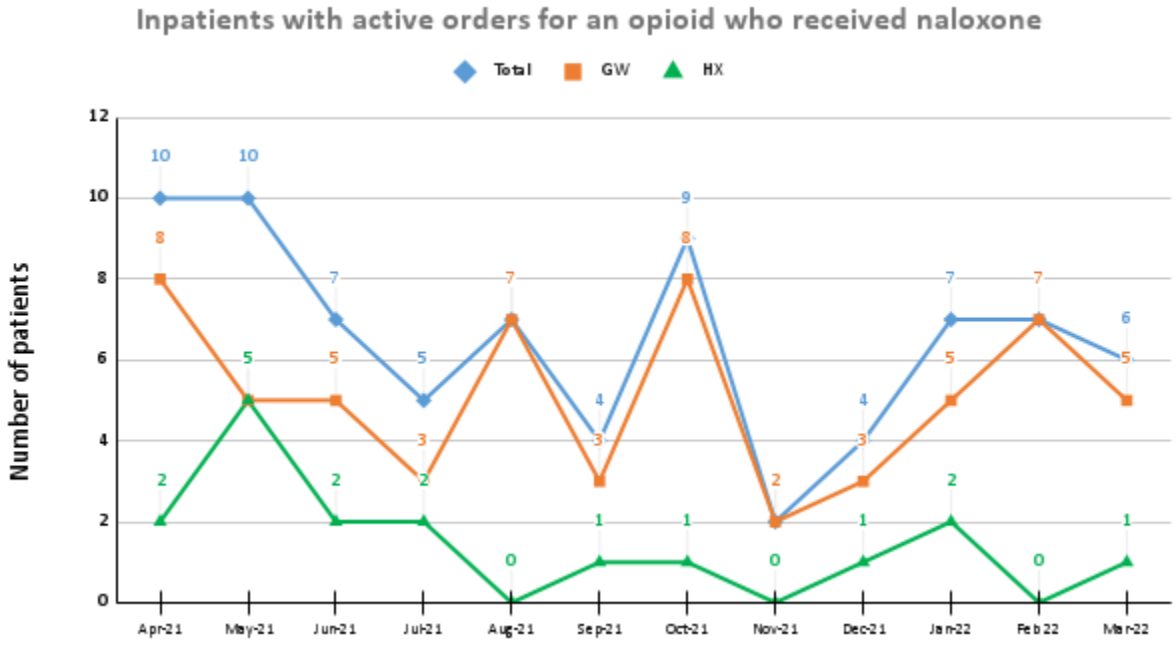
INPATIENT elevated INRs also receiving warfarin Jan-Mar 2022*			
Date	MRN	Location	Notes
1/15 & 1/16	5708464	3 South	On warfarin at home, admitted for fractured femoral neck
1/9, 1/10, 1/11	5665722	CDU	On warfarin at home, admitted for shoulder injury
1/27 & 1/28	5806382	IMCU	Admitted for femur fracture, COVID +, started on bridge therapy + warfarin
2/8/2022	6754422	4 South	Covid + patient. Therapeutic INR on admission, but question about whether INR goal was 2.5-3.5 or 2-3
2/25/2022	5731365	NPU2 & ICU	On warfarin at home, subtherapeutic INR on admission, gave 25% increase dose which caused INR to go supratherapeutic two days later.

*Note: These are the patients that Pharmacy was NOT consulted to follow.

ADRs/ADEs for patients on Insulin + BG less than 70



ADRs/ADEs for inpatients with active orders for an opioid who received naloxone



Performance Improvement Chapter PI.01.01.01 for The Joint Commission:

- *The hospital collects data on the following: adverse events related to using moderate or deep sedation or anesthesia.*

We are reviewing naloxone administrations to determine if given within 12 hours of anesthesia and sharing them with anesthesia.

Naloxone administrations Jan-Mar 2022				
Date	MRN	Location	Notes	**Given within 12hrs of anesthesia?**
1/29/2022	5625498	4 SO	MS 4mg at 1130, MS 2mg at 1441, Oxy 10mg at 2200, Naloxone administered at 2300 "due to low BP/low O2 Sat".	N

1/21/2022	6405616	5 SO	Ketorolac 15mg at 1816 (no pain score), Oxy IR 15mg at 1817 (no pain score), Ketorolac 15mg IV at 2330 (pain 8), Oxycontin 30mg at 2002 (no pain score), Oxy IR 15mg at 2330 (pain 8), Naloxone given at 0027 on 1/21. Patient with high demand for pain medications, was also on Dilaudid PCA until 01/20 at 1400, suspect wife gave patient "something" even though she denies.	N
1/22/2022	5639163	4 EA	Dilaudid 0.2mg 0032, 0343, 2224, Phenergan at 1009	N
1/31/2022	5671465	7 NO	Dilaudid 0.4mg at 0323, 0921, Hospice pt	N
1/30/2022	5688119	MICU	Dilaudid 0.5mg at 1525, Naloxone at 1736	N
1/18/2022	5610418	NPU2	Dilaudid 0.2mg at 0206, Naloxone at 0853	N
1/23/2022	5731813	NPU2	Dilaudid 1mg at 1926, 2226, Naloxone at 0100	N
2/16/2022	5622124	3SO2	Patient had changes to mental status (no change after administration, encephalopathy continues). RN held sedating meds. Last opioid given was oxycodone 5 mg @ 1459 for pain scale of 9	N
2/5/2022	5628887	6NO	This patient also received a dose in MICU on 2/5. Pt had been somnolent after receiving Klonopin and Lyrica at 2015, then Seroquel and Pamelor @ 2141. Pt was still verbal until 1 AM. Narcan given at 0605,0630 with no changes.	N
2/2/2022	5703932	6NO	Drowsy after HD, Dilaudid 0.5mg at 0954, nothing else	N
2/13/2022	5737193	7NO	Two fentanyl patches added at 1304 (pain score 10), Norco 7.5 @ 1544 (pain score 10), Norco 5 mg @ 2252 (pain score 9). Narcan administered for "drowsy and oversedation".	N
2/5/2022	5648817	7NO	Hydromorphone 0.4 mg @ 1007 (pain score 8) ,1820 (no pain score). Pt had decline in mental status and was hypotensive. After Narcan administered, pt became more alert.	N
2/21/2022	5602342	CVICU	Post-Op CABG. Several Fentanyl boluses given: 200 mcg @0700, 250 mcg @ 0837, 100 mcg @1408, 150 mcg @1604. Patient extubated (pain score 9), given 50 mcg @ 2211, O2 sat dropped into the 70's and he was very sleepy but was arousable. When awake his sats climbed back into the 90s. Narcan given, he became responsive and able to maintain his airway with sats in the 90s.	**Y**
2/5/2022	5611033	CVICU	Norco 7.5 given @ 1703 (no pain scale), Mentation declined and neuro recommended trial of narcan. Mentation did not improve after administration.	N
3/30/2022	5659074	1 South	dilaudid 0.5 given @ 0104 (pain score 9), given due to somnolence	N
3/31/2022	6092789	4 East	Morphine 15 mg given @ 2118 (pain score 6), patient late found unresponsive and hypotensive, narcan given at rapid response	N
3/22/2022	5696038	6 North	Post-Op foot amputation. Patient was given Fentanyl, Versed, Propofol, and Precedex during the procedure. Then on a PCA with morphine 1 mg q 1hr prn breakthrough pain. Narcan given for lethargy. Also receives sufentanil/hydromorphone pain med intrathecal daily for back pain.	**Y**
3/15/2022	5668987	2 South	no pain score or meds given around this time. Patient was found to be less responsive and unable to follow commands, rapid response was initiated	N
3/2/2022	5672536	CVICU	dilaudid 1 mg given @ 1237, fentanyl 25 mcg given @1357, they intubated patient since she was hypoxic and hyperventilating	N
3/30/2022	5743733	NPU3	dilaudid 0.5 mg given @ 1700 (not pain score documented), pt was extremely lethargic. Suspicion that use of Zanaflex in combination with her MS Contin, prn Percocet, use of prn IV Dilaudid (for acute on chronic post op pain) likely contributed to the event	N

Definitions:

Adverse Drug Reaction: any unexpected, unintended, undesired, or excessive response to a drug that
a. Requires discontinuing the drug (therapeutic or diagnostic)
b. Requires changing the drug therapy
c. Requires modifying the dose (except for minor dosage adjustments)
d. Necessitates admission to a hospital

e. Prolongs stay in a health care facility
f. Necessitates supportive treatment
g. Significantly complicates diagnosis
h. Negatively affects prognosis
i. Results in temporary or permanent harm, disability, or death
Consistent with this definition, an allergic reaction (an immunologic hypersensitivity, occurring as the result of unusual sensitivity to a drug) and an idiosyncratic reaction (an abnormal susceptibility to a drug that is peculiar to the individual) are also considered ADRs.

Adverse Drug Event: A patient injury resulting from a medication, where the patient outcome is death, life threatening (real risk of dying), hospitalization (initial or prolonged), disability (significant, persistent, or permanent), congenital anomaly, or required intervention to prevent permanent impairment or damage.1

ADR reports may be generated by different mechanisms as deemed appropriate by Pharmacy and the Medication Safety Committee, such as:

a. Suspected ADRs will be reported in IRIS when they occur by any physician or hospital employee who handles or administers medications.
b. Potential ADRs may be identified by monitoring utilization of trigger medications, such as naloxone, phytonadione, flumazenil, etc.
c. Occurrence rates of specific patient care events (ie. INRs >4, BG <70 + insulin, etc), may be monitored to evaluate safety of specific treatment modalities.

ASHP Guidelines on Adverse Drug Reaction Monitoring and Reporting, Medication Safety—Guidelines, pg 264-266

CHI Memorial

POLICY

Title: HYPERTONIC SODIUM CHLORIDE FOR ADULTS			
		Page 1 of 2	
Policy Number: MM-05465		Date Last reviewed/Revised: 5/22	Valid Until: 5/25
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 outline the necessary requirements for the safe ordering, dispensing and administration of hypertonic sodium chloride (HTS), which is a concentrated electrolyte solution and a high risk medication.

POLICY:

Ordering Requirements and Restrictions

1.) Hyponatremia Treatment
HTS may be ordered by any prescriber for the treatment of symptomatic hyponatremia although any orders from providers other than nephrology or critical care must use the hospital approved "Hypertonic Saline (3% NS) IV Infusion– Hyponatremia Treatment" order set. All orders must have total volume/dose or duration in the order. All orders must comply with minimum requirements for laboratory monitoring.

2.) Acute Neurologic Indications
HTS (**3%** NS) for acute neurological indications other than hyponatremia treatment (increased intracranial pressure or other acute neurological deficits, etc.) should be ordered using the Hyperosmolar Therapy order set. Mandatory laboratory monitoring is required as indicated below.
   a. Undiluted **23.4%** hypertonic saline may be ordered emergently by a Neurology or Neurosurgery provider through a central line as a single 15 to 60 mL bolus dose infused over 10 to 20 minutes. Emergent short-term administration via peripheral IV access is permissible in the setting of acute ICP elevation, however, while central access is obtained.

3.) Maximum infusion rates:
   a. Peripheral line: ≤ 30 ml/hr
   b. Central line:
      i. ≤ 50 ml/hr (Hyponatremia)
      ii. ≤ 70 ml/hr (Acute Neurologic Indications)
         1. Bolus doses of 3% NS of 250 ml or less may be infused over 20 minutes (if ordered by a Neurology or Neurosurgery provider per the Hyperosmolar Therapy order set).

4.) Maximum order volume:
   a. No more than 500 ml of HTS may be ordered for treatment of hyponatremia. If the ordered volume exceeds 500 ml, prescriber will be contacted after initial infusion of 500 ml for continuation order.
   b. HTS for acute neurologic indications may be ordered as a continuous infusion exceeding 500 ml if ordered by neurology provider. Mandatory laboratory monitoring is still required for duration of infusion.

Laboratory and Patient Assessment Monitoring

1.) Required labs*:
   a. Baseline serum sodium required prior to treatment initiation
   b. BMP at least every 4 hours for duration of HTS infusion (if not already ordered). May be ordered more frequently at discretion of provider.

   ** If labs are not ordered by provider these may be ordered by pharmacy.*

2.) The infusion must be held and provider notified for the following conditions:

   Hyponatremia Treatment:
   a. Serum sodium increases by more than 2 mEq/L in any 4 hour period
   b. Serum sodium increases by more than 8 mEq/L during 24 hour period.
   c. Serum sodium ≥ 130 mEq/L

   Neurologic Indications:
   a. Serum sodium ≥ 155 mEq/L or < 135 mEq/L
   b. Serum osmolality > 320

3.) Nursing - patient assessment:
   a. Strict input and output every 4 hours
   b. Neurological checks Q 4 hours for duration of infusion

Storage and Dispensing

1.) Only pharmacy will stock pre-mixed HTS for intravenous use. Pharmacy will dispense the exact volume to be administered (transferred to an empty IV bag) and no more than a 500 ml premix bag at one time.

2.) Specific for hyponatremia indication: Further doses will only be sent after pharmacist review of sodium levels to prevent overly rapid correction (as outlined above).

Administration

1.) Administration via central line is preferred. If central line is not available, infusion via the largest peripheral vein available is acceptable for durations < 24 hours. If prolonged infusion is required, central line administration is highly recommended.

2.) HTS is a High Alert medication. An independent double check (documentation of 2nd nurse verification) is required and will be performed/documented with every new bag administration and at shift change (verification of pump setting and drug).

Key Contact: Pharmacy Review Team
Approved/Reviewed by: P & T Committee, Director of Pharmacy
Related Document(s): HIGH ALERT MEDICATIONS (MM-05402)
Date First Effective & Revision/Review dates: 5/17, (9/20), 12/21, 5/22

CHI Memorial

POLICY

Title: THERAPEUTIC DUPLICATION OF PRN MEDICATION ORDERS			
		Page **1** of **2**	
Policy Number: MM-05475		Date Last reviewed/Revised: 5/22	Valid Until: 5/25
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. **Physician order sets will instruct that one choice only be ordered for a specific PRN indication.** In situations where the prescriber enters orders for the same PRN indication or fails to select one medication for a PRN indication in the 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 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 (most potent agent will be used). 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 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 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 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.
    - Prescription PRN pain home medications, if ordered without indication will be assigned a PRN moderate pain indication.
5. The prescriber will be contacted for clarification of orders or situations not covered in this policy.

Prioritization of Route
When multiple routes are ordered for the same medication (example: promethazine 12.5 mg IV/PO/PR Q 4 hours PRN), based on the patient's condition (e.g. IV in place, or tolerating oral medications), the least invasive route will be used as the first choice (Oral, before IV, before SQ/IM, before PR). The exception is in the case of acute or breakthrough pain where a parenteral route of administration (if ordered and available) is preferred and specified on the order.

Key Contact: Pharmacy Review Team
Approved/Reviewed by: P&T Committee, Nursing Professional Practice Council
Joint Commission Chapter: Medication Management
Date First Effective & (Revision/Review dates): 4/16, (9/19) (5/22)