Pharmacy & Therapeutics Committee Meeting
Private Dining Room
December 12, 2019 7:00 a.m.

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

Next Meeting will be Feb 13, 2020 at 7:00 AM in the Private Dining Room

Conflict of Interest Disclosure

CHI Memorial P&T Committee members (voting and non-voting) and any guests are expected to carefully review the agenda prior to the start of the meeting and determine if any conflicts of interest or any possibility for perceived conflicts of interest exist related to the agenda topics.

If so, please announce yourself at the beginning of the meeting (when asked) and recuse yourself from the discussion of that topic when it is discussed.

PHARMACY AND THERAPEUTICS COMMITTEE

DATE: October 10, 2019 CALLED TO ORDER: 7:01 A.M.
LOCATION: Private Dining Room ADJOURNED: 8:00 A.M.

Members Present:		**Members Absent**:	**Guests**:
Nathan Schatzman, MD David Dodson, MD Mark Anderson, MD Richard Yap, MD F. Lee Hamilton MD	Patrick Ellis, PharmD Jessica Stanley, FNP-BC Susan Fuchs, RD Karen Babb, PharmD Rhonda Hatfield, CNO Rachel Kile, PharmD	Allen Atchley, MD Matthew Kodsi, MD Nathan Chamberlain, MD Chad Paxson, MD Jamie Barrie, PharmD Shannon Harris, RN Rodney Elliott	Casey O'Neal, Resident Kameron Blair, Resident Bradley Proctor, Resident Jessica Tyler, MD

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
Minutes	The August 2019 minutes were approved as submitted.	Approved	Complete
CHI System P&T Committee	**September 2019 Decision Brief-** The medications that were reviewed at the September CHI system P&T committee meeting were reviewed. All new system formulary medications or changes were either consistent with existing Memorial formulary decisions or are described in the "Therapeutic Interchanges and Formulary Changes" section of the minutes below.	Information	Complete
Old Business	**1. Alternatives to Opioids (ALTO) protocol for inpatient expansion-** Rachel shared inpatient data on total opioid doses dispensed per month from August 2016 through July 2019. The data showed a trend toward decreasing opioid doses. The ALTO rollout to inpatient use is expected to further impact this downward trend in opioid doses. Rachel also shared that nursing and hospitalist education has begun for inpatient ALTO expansion.	Information	Complete
Therapeutic Interchanges and Formulary Decisions	**1. SGLT2 Inhibitor Class Review-** The CHI System P&T committee voted in September to modify the formulary status of the SGLT2 inhibitors by adding only empagliflozin as "formulary, with restrictions"; all other SGLT2 inhibitors are to remain non-formulary. Our local P&T committee concluded that mirroring our formulary status to the system P&T decision will allow for continuation of home regimens, if the provider chooses to order. All home medication orders will be interchanged to empagliflozin as listed below. New orders for SGLT2 inhibitors should not be initiated and empagliflozin will be withheld from the facility preference list. **SGLT2 Inhibitor Ordered** — **SGLT2 Inhibitor Substitution** Canagliflozin 100 mg daily — Empagliflozin 10 mg daily Canagliflozin 300 mg daily — Empagliflozin 25 mg daily Dapagliflozin 5 mg daily — Empagliflozin 10 mg daily Dapagliflozin 10 mg daily — Empagliflozin 25 mg daily Ertugliflozin 5 mg daily — Empagliflozin 10 mg daily Ertugliflozin 15 mg daily — Empagliflozin 25 mg daily **2. Rituximab biosimilars-** The committee reviewed the monograph for Truxima (rituximab-abbs), a	Approved Approved	Complete Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	biosimilar for the reference product, Rituxan. Truxima has demonstrated similar clinical efficacy as Rituxan. Rituximab-abbs is not yet available on the market (anticipated Q4 2019) and the cost is unknown, although a 10% or more price reduction, when compared to the reference product, is anticipated. Truxima and other rituximab biosimilars were approved to formulary for outpatient use for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization. Rituxan will now have the following restrictions: If a rituximab biosimilar is not available or payer-approved, may be used outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization. The Epic ordering panel for Rituxan will have the following order instructions added: "Pharmacy may substitute biosimilar product per P&T committee approved restriction criteria." Rituxan Hycela (rituximab and hyaluronidase) is non-formulary.		
	3. **Cyclosporine ophthalmic emulsion to artificial tear product –** Due to upcoming NIOSH hazardous drug regulations, the committee voted to remove cyclosporine 0.05% ophthalmic emulsion (Restasis) from formulary and interchange all new and home medication orders to artificial tears 1.4% ophthalmic drops. Restasis is a NIOSH category 2B medication that will require extensive steps for staff handing and administration.	Approved	Complete
	4. **Fluconazole IV Dosing Interchange –** Fluconazole IV is also on the NIOSH hazardous drug list. To avoid unnecessary IV compounding, low dose IV fluconazole (doses <= 100 mg) will be interchanged to a higher dose (based on renal function) of a premixed bag, when the oral formulation is not an option.	Approved	Complete
Protocols & Orders	1. **Phenobarbital for Alcohol Withdrawal Syndrome –** Dr. Jessica Tyler, Hospitalist, presented data on the use of phenobarbital for alcohol withdrawal syndrome (AWS) as she has prior experience using it for this indication. The committee had a robust discussion on the efficacy, safety, and role of phenobarbital for our patients with AWS. The committee discussed incorporating a protocol for phenobarbital use into the existing BZD-sparing protocol. It was suggested that input from our critical care colleagues is necessary in order to move forward with protocol development. Rachel will coordinate a smaller workgroup of critical care physicians, hospitalists, and pharmacy to work on a protocol and this will be discussed at the next P&T meeting in December.	In progress- update to be shared at next meeting	Pending
	2. **HIT Ab Assay Ordering with 4T score calculation –** Rachel shared with the committee that the proposal for pharmacist calculation of 4T score when a HIT Ab Assay is ordered was passed at the Med Exec meeting. With Epic go-live, all orders for HIT Ab assays will be paired with a consult to pharmacy. The pharmacist will calculate the 4T score and if 3 or less, will contact the ordering provider to discuss canceling the order. If 4 or higher, the test will be performed without contacting the ordering provider.	Information	Complete
Policies	1. **Renal Dose Adjustment Policy –** Rachel reviewed updates to the renal dose adjustment policy which included changes to the ciprofloxacin pharmacy automatic renal dose adjustment.	Approved	Complete
	2. **Timeliness of Scheduled Medications Policy –** Patrick reviewed updates to the timeliness of scheduled medication policy which now includes our new standard dosing times to reflect required changes with the conversion to Epic.	Approved	Complete

There being no further business, the meeting was adjourned at 8:00 A.M. The next P&T meeting is **December 12, 2019 at 7:00 a.m.**

Respectfully submitted,
Patrick Ellis, PharmD, Director of Pharmacy; Rachel Kile, PharmD, Pharmacy Clinical Manager

Approved by,
Nathan Schatzman, M.D. Chairman

CHI SYSTEM PHARMACY AND THERAPEUTICS COMMITTEE DECISION BRIEF

November 2019 Decisions

NOTE: Markets may implement more restrictive formulary statuses.

Medication Name	Medication Used for	Decision				Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary	Do Not Stock		
Intravenous Fat Emulsion	*Nutrition*	Fat emulsions IV 20% (Nutrilipid)					90 days from 11/19/2019
		Fat emulsions IV 20% (Intralipid)					
		Fat emul/soy/ mct/oliv/fish oil IV (Smoflipid)					
		Fat emulsions IV 30 % (Intralipid)					
				Aa 3.31 %/d9.8w /fat/e-lytes 10 IV (Kabiven)			
				Aa 2.36%/d6.8w /fat/e-lytes no9 IV (Perikabiven)			
				Intravenous fat emulsion (Omegaven)			
				Intravenous fat emulsion (Clinolipid)			
Brodalumab (Siliq)	*Plaque psoriasis*			brodalumab (Siliq)			60 days from 11/19/2019

Medication Name	Medication Used for	Decision				Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary	Do Not Stock		
Mometasone Furoate Nasal Implant 1350 MC (Sinuva)	*Chronic sinusitis with nasal polyps*		Mometasone furoate nasal implant 1350 mc (sinuva asd)			• Patients must be diagnosed with chronic sinusitis with nasal polyps • Patients must be 18 years or older who have had ethmoid sinus surgery • Implanted by physicians trained in otolaryngology • Outpatient surgery for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization	90 days from 11/19/2019
Nusinersen (Spinraza)	*Spinal Muscular Atrophy*				nusinersen (Spinraza)		60 days from 11/19/2019
Onasemnogene abeparvovec-xioi (Zolgensma)	*Spinal Muscular Atrophy*				onasemnogene abeparvovec-xioi (Zolgensma)		60 days from 11/19/2019
Cerliponase alfa (Brineura)	*Neuronal ceroid lipo-fuscinoses*				cerliponase alfa (Brineura)		60 days from 11/19/2019
Avatrombopag (Doptelet)	*Thrombo-cytopenia*				avatrombopag (Doptelet)		90 days from 11/19/2019
Revefenacin (Yupelri)	*Chronic obstructive pulmonary disease*			Revefenacin inhalation vial-neb 175mcg/3 (Yupelri)		**Therapeutic Interchange** **Ordered:** **Revefenacin** (Yupelri) 175 mcg once daily via nebulizer **Provided:** **Glycopyrrolate (Seebri Neohaler)** 15.6 mcg (1 cap) via oral inhalation twice daily OR **Ipratropium** SVN q6 hours	60 days from 11/19/2019
Esketamine nasal spray	*Depression*		Esketamine HCL nasal spray 56 mg (Spravato)			• Facilities willing to pilot the operational logistics to deliver this medication to patients after the permanent billing code is available. Re-review with the System P&T Committee in 12 months. • Restricted to sites that have registered through the REMS program. Sites must be able to complete required monitoring.	120 days from 11/19/2019

Medication Name	Medication Used for	Decision				Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary	Do Not Stock		
						• Patient must have failed two prior antidepressant medications • Psychiatrist must be on site when administrating to a patient • Outpatient psychiatric setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization. Prior authorization should determine if/how this medication is covered (retail pharmacy benefit vs. medical benefit).	
			Esketamine HCL nasal spray 84 mg (Spravato)			• Facilities willing to pilot the operational logistics to deliver this medication to patients after the permanent billing code is available. Re-review with the System P&T Committee in 12 months. • Restricted to sites that have registered through the REMS program. Sites must be able to complete required monitoring. • Patient must have failed two prior antidepressant medications • Psychiatrist must be on site when administrating to a patient • Outpatient psychiatric setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization. Prior authorization should determine if/how this medication is covered (retail pharmacy benefit vs. medical benefit).	
Hexaminolevulinate (Cysview)	*Bladder cancer detection*		hexaminolevulinate (Cysview)			• Outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization • Urology and oncology patients with suspected bladder lesions	90 days from 11/19/2019

Medication Name	Medication Used for	Decision				Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary	Do Not Stock		
Valbenazine (Ingrezza)	*Tardive dyskinesia*			Tetrabenazine oral tab 12.5 mg (Xenazine)			60 days from 11/19/2019
				Tetrabenazine oral tab 25 mg (Xenazine)			
				Deutetrabenazine oral tab 6 mg (Austedo)			
				Deutetrabenazine oral tab 9 mg (Austedo)			
				Deutetrabenazine oral tab 12 mg (Austedo)			
				Valbenazine 40mg capsule (Ingrezza)			
				Valbenazine 80mg capsule (Ingrezza)			
Avelumab (Bavencio)	*Cancer*		Avelumab intraven vial 200mg/10ml (Bavencio)			• Utilize only after first line therapies with higher levels of evidence or deemed inaccessible via toxicities (based on NCCN guidelines) • Outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization • This drug should not be routinely stocked	120 days from 11/19/2019
Telotristat (Xermelo)	*Carcinoid syndrome diarrhea*				telotristat (Xermelo)		60 days from 11/19/2019
Generic fosaprepitant inj	*Nausea/ vomiting*			Fosaprepitant dimeglumine intraven vial (Emend)		See Fosaprepitant/Aprepitant Therapeutic Interchange	60 days from 11/19/2019
				Aprepitant intraven vial 130mg/18ml (Cinvanti)			

Medication Name	Medication Used for	Decision				Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary	Do Not Stock		
			Fosaprepitant dimeglumine intraven vial (fosaprepitant dimeglumine)			Based on CINV risk: Use in combination with 5HT3 antagonist + dexamethasone with high risk for CINV and with moderate risk to improve coverage for experienced delayed CINV	
Mepivacaine	*Local anesthesia*	Mepivacaine HCL/PF vial 10 mg (Carbocaine)					60 days from 11/19/2019
		Mepivacaine HCL vial 10 mg/ml (Carbocaine)					
		Mepivacaine HCL/PF vial 15 mg (Carbocaine)					
		Mepivacaine HCL/PF vial 20 mg (Carbocaine)					
		Mepivacaine HCL vial 20 mg/ml (Carbocaine)					
		Mepivacaine HCL/PF vial 10 mg/ (Polocaine)					
		Mepivacaine HCL/PF vial 15 mg (Polocaine)					
		Mepivacaine HCL/PF vial 20 mg (Polocaine)					

Medication Name	Medication Used for	Decision				Comments/Restrictions/ Therapeutic Interchange	Timeline to Implementation
		Formulary Unrestricted	Formulary Restricted	NonFormulary	Do Not Stock		
		Mepivacaine HCL injection vial 20 mg/ml (Polocaine)					
Restasis	*Increased tear production*			Cyclosporine ophthalmic drops 0.05 % (Restasis multi)		See Restasis/Cequa Therapeutic Interchange	90 days from 11/19/2019
				Cyclosporine ophthalmic droperette 0.05 (Restasis)			
				Cyclosporine ophthalmic droperette 0.09% (Cequa)			
acetaminophen injectable	*Pain*			Acetaminophen intraven vial 1000mg/100 (Ofirmev)		IV acetaminophen appeal	60 days from 11/19/2019

Fosaprepitant/Aprepitant Therapeutic Interchange

Ordered	Provided
Aprepitant 130mg IV	Fosaprepitant 150mg IV
Aprepitant 125 mg, 80 mg x2 PO	Fosaprepitant 150mg IV
Netupitant/ Palonosetron 300-0.5mg PO	Inpatient: Fosaprepitant 150mg IV + Ondansetron 8 mg IV
	Outpatient: Fosaprepitant 150mg IV+ Palonosetron 0.25mg IV
Fosnetupitant/ Palonosetron 235-0.25mg IV	Inpatient: Fosaprepitant 150mg IV + Ondansetron 8 mg IV
	Outpatient: Fosaprepitant 150mg IV+ Palonosetron 0.25mg IV
Rolapitant 180 mg PO	Fosaprepitant 150mg IV
Rolapitant 166.5mg IV	Fosaprepitant 150mg IV
Palonosetron 0.25mg IV (inpatient only)	Ondansetron 8 mg IV

Restasis/Cequa Therapeutic Interchange

Ordered	Provided
Restasis 0.05% Ophthalmic Emulsion *Instill 1 drop into affected eye(s) BID*	Polyvinyl alcohol (artificial tears) 1.4% ophthalmic sol **OR** most cost-effective artificial tear product available *Instill 1-2 drops into affected eye(s) 2 to 4 times daily as needed*
Cequa Ophthalmic Solution *Instill 1 drop into affected eye(s) BID*	Polyvinyl alcohol (artificial tears) 1.4% ophthalmic sol **OR** most cost-effective artificial tear product available *Instill 1-2 drops into affected eye(s) 2 to 4 times daily as needed*

November 2019 CHI System P&T Meeting Documents

Meeting Packet: CHI System PT Committee November 2019 Packet
Meeting Slides: System P.T Presentation 11.19.19
Motion Slides: CHI System PT Motion Slides 2019 11
Attendance Roster: 2019 System PT Attendance Roster Cumulative 11.19.2019
Voting Record: Voting Record November 2019

Items for which decisions were made are listed in same order as they appear in the P&T Committee Meeting Packet.

FORMULARY REVIEW

GENERIC NAME: Revefenacin

PROPRIETARY NAME: *Yupelri*

INDICATIONS:

FDA Approved
Maintenance treatment of chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema

THERAPEUTIC CATEGORY: Long-acting muscarinic antagonist

PHARMACOKINETICS:

Absorption	Rapid
Distribution	-
Metabolism	Hydrolysis of primary amide to carboxylic acid to active metabolite
Elimination	Primarily feces

SPECIAL POPULATIONS:

Pregnancy	Currently, there are no adequate controlled studies of this drug in pregnant women. No evidence of fetal harm was found during animal reproductive studies with subcutaneous administration to rats and rabbits. It is recommended that women contact their physician if they become pregnant while on revefenacin.
Lactation	There is no current information regarding the presence of revefenacin in breast milk or the effects it has on breast-fed infants. The drug was found to be present in the milk of lactating rats, although there are differences in lactation physiology between rats and humans. Risk versus benefit should be considered when using revefenacin in lactating women.
Pediatrics	Safety and efficacy have not been established.
Geriatrics	No dosage requirements required
Hepatic Impairment	Not recommended in patients with any degree of hepatic impairment. Safety has not been evaluated.
Renal Impairment	No dosage adjustments required

CLINICAL STUDIES:

A Phase 3, 12-week, Randomized, Double-blind Placebo-controlled Parallel Group Study of Nebulized TD-4208 in Subjects With Chronic Obstructive Pulmonary Disease (Study 0126)	
METHODS	
Study Design	Double-blinded, randomized, placebo-controlled, parallel clinical trial
Patient Enrollment Inclusion	• Subject is a male or female subject 40 years of age or older • Documented COPD history • Smoking history of at least 10 pack years • Post-ipratropium FEV1 OF <80% of predicted normal, but at least 700mL at visit 1B • Met criteria for moderate to severe COPD
Patient Enrollment Exclusion	• Females who are pregnant, lactating, breast-feeding or planning to become pregnant during the study • History of myocardial infarction or unstable angina in the past 6 months • Unstable or life-threatening cardiac arrhythmia requiring intervention within the previous 3 months • NYHA Class IV heart failure prior to start of study • Exhibited and abnormal and clinically significant 12-lead ECG finding at study entry
Outcome Measures	• Primary: change from baseline in trough FEV1 on Day 85 • Secondary:

<table>
<tr><td></td><td>

Summary of trough FEV1 overall treatment effect from day 15 to day 85
Summary of change from baseline to peak FEV1 after first dose
Summary of rescue medication use: puffs per day
Percentage of albuterol rescue-free 24-hour periods
St. George’s Respiratory Questionnaire (SGRQ) proportion of responders on day 85

</td></tr>
<tr><td>Statistical Analyses</td><td>Intention to treat analysis, including all randomized patients who received at least 1 dose of the study drug</td></tr>
<tr><td>Treatment Plan</td><td>Randomized 1:1:1 to receive one of the following:

Revefenacin 88 mcg
Revefenacin 175 mcg
Placebo

Each to be administered once daily in the morning via nebulizer</td></tr>
<tr><td colspan="2">RESULTS</td></tr>
<tr><td>Outcomes Summary</td><td>Both strengths of Revefenacin (88 mcg and 175 mcg) showed a statistical difference in mean trough FEV1 compared to placebo. Both strengths also showed improvement in OTE FEV1 and increased trough FEV1 by ≥100 mL</td></tr>
<tr><td>Primary Endpoint</td><td>

Mean increase in trough FEV1 with revefenacin 88 mcg = 79.2 mL (p=0.0003)
Mean increase in trough FEV1 with revefenacin 175 mcg = 146.3 mL (p<0.0001)

</td></tr>
<tr><td>Secondary Endpoints</td><td>
<table>
<tr><th></th><th>REV 88 mcg</th><th>REV 175 mcg</th><th>Placebo</th><th>p-value</th></tr>
<tr><td>Change in Trough OTE FEV1 from placebo</td><td>103.8 mL</td><td>155.6 mL</td><td>-</td><td>-</td></tr>
<tr><td>Change from baseline to peak FEV1 after 1st dose</td><td>126.35 mL</td><td>132.67 mL</td><td>-</td><td><0.0001</td></tr>
<tr><td>Rescue medication use: puffs per day</td><td>2.26</td><td>2.27</td><td>2.72</td><td>>0.05</td></tr>
<tr><td>% of albuterol rescue-free 24-hour periods</td><td>48.35</td><td>43.57</td><td>45.21</td><td></td></tr>
<tr><td>SGRQ proportion of responders on day 85</td><td>70 (47.3%)</td><td>68 (48.9%)</td><td>46 (33.8%)</td><td></td></tr>
</table>
</td></tr>
<tr><td>Adverse Events</td><td>

Serious adverse events

Revefenacin 88 mcg: 10/212 (4.72%) patients
Revefenacin 175 mcg: 10/198 (5.05%)
Placebo: 14/209 (6.7%)
Most common: serious COPD worsening/exacerbation

Non-serious adverse events

Revefenacin 88 mcg: 51/212 (24.06%)
Revefenacin 175 mcg: 46/198 (23.23%)
Placebo: 51/209 (24.4%)
Most common: non-serious COPD worsening/exacerbation

</td></tr>
<tr><td>Limitations</td><td>

Some patients were on concomitant LABA or LABA/ICS combination
Study was only 12 weeks in duration
Albuterol was allowed to be used

</td></tr>
<tr><td>Author’s Conclusion</td><td>Both revefenacin 88 mcg and 175 mcg resulted in clinically significant improvements in trough FEV1 and OTE FEV1. This drug has the potential to be the first once-daily, long-acting bronchodilator in patients that need or prefer antimuscarinic therapy via nebulizer.</td></tr>
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<tr><td colspan="2">A Phase 3, 12-week, Randomized, Double-blind Placebo-controlled Parallel Group Study of Nebulized TD-4208 in Subjects With Chronic Obstructive Pulmonary Disease (Study 0127)</td></tr>
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Subject is a male or female subject 40 years of age or older
Documented COPD history
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Post-ipratropium FEV1 OF <80% of predicted normal, but at least 700mL at visit 1B

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o Summary of trough FEV1 overall treatment effect from day 15 to day 85
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<tr><td>Primary Endpoint</td><td>• Mean increase in trough FEV1 with revefenacin 88 mcg = 160.5 mL (p=<0.0001)
• Mean increase in trough FEV1 with revefenacin 175 mcg = 147.0 mL (p<0.0001)</td></tr>
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<tr><td>Rescue medication use: puffs per day</td><td>2.00</td><td>2.38</td><td>2.54</td><td>>0.05</td></tr>
<tr><td>% of albuterol rescue-free 24-hour periods</td><td>44.79</td><td>43.26</td><td>37.23</td><td>-</td></tr>
<tr><td>SGRQ proportion of responders on day 85</td><td>67 (46.2%)</td><td>67 (45.0%)</td><td>54 (38.6%)</td><td>-</td></tr>
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COMPARATIVE EFFICACY:

- There are very few studies that compare revefenacin to other drugs on the market currently.
- There was a study comparing revefenacin and tiotropium, but analysis has yet to be performed. Results have shown that an overall reduced percentage of adverse events with revefenacin compared to tiotropium, but statistical or clinical significance have yet to be determined.

WARNING AND PRECAUTIONS:

- Acute bronchospasms:
  - Not indicated for acute bronchospasms
  - Revefenacin is not to be initiated with acutely deteriorating or potentially life-threatening exacerbations of COPD.
- Paradoxical bronchospasm: discontinue revefenacin if this occurs as it can be life-threatening
- Use with caution in patients with narrow-angle and closed-angle glaucoma
- Urinary Retention: use with caution in patients that are predisposed to urinary retention.
- Hepatic disease/impairment
  - Not recommended in patients with any degree of hepatic disease or impairment.
- Cardiac Disease
  - Patients with unstable cardiac disease were excluded from pre-marketing clinical trials.
- Geriatrics
  - Geriatric patients are at an increased susceptibility to anti-cholinergic effects; therefore, careful monitoring should take place.
- Pregnancy
  - No adequate controlled trials to establish safety during pregnancy.
  - Women should contact their physician if they become pregnant while taking revefenacin.
- Lactation
  - There is no current information regarding the presence of revefenacin in breast milk or the effects it has on breast-fed infants.
  - Risk versus benefit should be considered when using revefenacin in lactating women.

BLACK BOX WARNINGS: None

CONTRAINDICATIONS: Hypersensitivity to revefenacin or any inactive ingredients

ADVERSE REACTIONS:

Adverse Reactions	**Study 0126**		**Study 0127**	
	REV 175 mcg	**Placebo**	**REV 175 mcg**	**Placebo**
Cardiovascular, N (%)				
Hypertension	3 (1.5)	3 (1.4)	4 (2.0)	2 (1.0)
Chest pain	1 (0.5)	0	0	0
Non-cardiac chest pain	1 (0.5)	1 (0.5)	0	0
Acute MI	1 (0.5)	0	0	0
Central Nervous System, N (%)				
Dizziness	-	-	4 (2.0)	0
Headache	8 (4.0)	5 (2.4)	8 (4.1)	6 (2.9)
Gastrointestinal, N (%)				
Vomiting	3 (1.5)	2 (1.0)	-	-
Constipation	2 (1.0)	0	0	1 (0.5)
Diarrhea	1 (0.5)	3 (1.4)	3 (1.5)	2 (1.0)
Upper GI hemorrhage	1 (0.5)	0	0	0
Hematologic and Oncologic	-	-	-	-
Hepatic	-	-	-	-
Infection, N (%)				
Nasopharyngitis	6 (3.0)	5 (2.4)	9 (4.6)	4 (1.9)
Sinusitis	5 (2.5)	6 (2.9)	4 (2.0)	4 (2.0)
Acute sinusitis	3 (1.5)	2 (1.0)	-	-
Upper respiratory tract infection	1 (0.5)	4 (1.9)	10 (5.1)	5 (2.4)
Urinary tract infection	2 (1.0)	3 (1.4)	2 (1.0)	4 (1.9)

Cellulitis	0	0	0	1 (0.5)
Metabolic	-	-	-	-
Neuromuscular & Skeletal, N (%)				
Back pain	-	-	7 (3.6)	3 (1.4)
Muscle spasms	1 (0.5)	2 (1.0)	-	-
Renal	-	-	-	-
Respiratory, N (%)				
COPD (worsening/exacerbation)	**4 (2.0)**	**2 (1.0)**	**1 (0.5)**	**4 (1.9)**
Dyspnea	**4 (2.0)**	**11 (5.3)**	**8 (4.1)**	**12 (5.7)**
Acute respiratory failure	0	0	0	0
Respiratory failure	0	1 (0.5)	0	0
Skin	-	-	-	-
Systemic	-	-	-	-
Miscellaneous, N (%)				
Oropharyngeal pain	4 (2.0)	1 (0.5)	2 (1.0)	5 (2.4)
Cough	7 (3.5)	8 (3.8)	10 (5.1)	9 (4.3)
Nasal congestion	-	-	2 (1.0)	2 (1.0)
Dysuria	0	0	0	0
Dry mouth	2 (1.0)	0	1 (0.5)	0

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:

Interacting Drug	Effect
Anticholinergics	Potential for additive anticholinergic effects
Atazanavir, macrolides (except azithromycin), cobicistat, cyclosporine, gemfibrozil, isoniazid, rifampin, leflunomide	Increased systemic exposure of active metabolite of revefenacin; increased risk for anticholinergic adverse effects

DOSING AND ADMINISTRATION:

Adult Dosing/Indication and Administration

- Inhale 175 mcg once daily via nebulizer
- Max dose: 175 mcg daily

RECOMMENDED MONITORING: Pulmonary function tests (PFTs)

PHARMACOECONOMICS/COST:

Product (Drug, Strength, Form)	Cost/Day	Cost/3-Day Course3-Day
Yupelri 175mcg vial for inhalation	$13.01	$39.04
Seebri (glycopyrrolate) Neohaler	$6.23	$18.69

CONCLUSION & RECOMMENDATION:

Revefenacin is the first long-acting muscarinic antagonist available as a nebulized medication. Glycopyrrolate (Seebri) Neohaler is a twice daily inhaler and is the formulary long-acting muscarinic antagonist currently stocked at CHI Memorial. Given that there is limited data comparing revefenacin to other long-acting bronchodilators, it is recommended to adopt the CHI System formulary decision to interchange orders for revefenacin to glycopyrrolate inhalation as follows:

Ordered	Provided
Revefenacin (Yupelri) 175 mcg once daily via nebulizer	**Glycopyrrolate (Seebri Neohaler)** 15.6 mcg (1 cap) via oral inhalation twice daily

FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)

Medication Management Step	Identified Risk	Steps for Prevention
Selection & Procurement		
Therapeutic interchange?	No	
Special Ordering Requirements?	No	
Storage		

Medication Management Step	Identified Risk	Steps for Prevention
LASA* separation of stock?	No	
Special storage (e.g. refrigeration, protect from light, controlled substance)?	Yes	Protect from direct sunlight and excessive heat
Pharmacist/Technician Education?	No	
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	Non-formulary	
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	Yes	Not recommended to use in patients with any degree of hepatic impairment
Drug Interactions?	Yes	Avoid co-administration of revefenacin with other anticholinergic drugs. Co-administration of OATP1B1 and OATP1B3 inhibitors with revefenacin is not recommended.
Pregnancy?	No	No adequate and well-controlled studies have been conducted in pregnant women.
Absolute Contraindications?	Yes	Hypersensitivity to revefenacin or any component of this product
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?	No	
Drug interaction check in place?	No	
LASA* computer warnings?	No	
Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)?	No	
Packaging/Labeling (e.g. prepacking)?	Yes	Prepackaged
Dispensing (e.g. auxiliary labeling, light protection, refrigeration)?	Yes	Sunlight protection
Documentation required (e.g. double check, worksheet)?	No	
Pharmacist/Technician Education?	No	
Administration		
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	No	
Special delivery system (e.g. pump)?	Yes	Must be given via nebulizer
Documentation required? (e. g. double check)	No	
Nurse education?	No	
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?		
Follow-up laboratory tests?	Yes	Pulmonary function tests (PFTs)
Education?	Yes	-Not for acute symptoms -Review warning signs/symptoms of paradoxical bronchospasms, acute narrow-angle glaucoma, urinary retention -Administration technique

FORMULARY INTERCHANGE

Aprepitant (Cinvanti) IV to fosaprepitant IV

Background:

At the November 2018 CHI System P&T committee meeting, it was decided to remove Emend (fosaprepitant) from formulary and add Cinvanti (aprepitant) to formulary, with restrictions based on CINV risk. The NK1 receptor antagonists were then reviewed locally at the February 2019 P&T committee meeting, where aprepitant (Cinvanti) was added to formulary and all orders for fosaprepitant were interchanged to aprepitant due to cost-effectiveness.

	Usual Sig per Course of Therapy	**Cost per vial**	**Cost per 6 months usage**
Fosaprepitant IV (generic)	150 mg IV x 1	**$103.45**	**$6,000.10**
Aprepitant IV (Cinvanti)	130 mg IVx1	**$233.05**	**$13,516.90**
Fosaprepitant IV (Emend)	150 mg IV x 1	$250.37	n/a

Conclusion/Recommendation:

Aprepitant IV 130 mg and fosaprepitant IV 150 mg have been shown to be similar in efficacy and safety. However, now fosaprepitant is available generically. With its improved cost-effectiveness, it is recommended that generic fosaprepitant be our preferred formulary product. The anticipated cost savings annually will be ~$15,000. It is recommended that the following therapeutic interchange be adopted.

Recommended Formulary Interchange:

Ordered	**Provided**
Aprepitant 130 mg IV	Fosaprepitant 150 mg IV x 1
Aprepitant 125 mg, 80 mg x 2 PO	Fosaprepitant 150 mg IV x 1
Netupitant/ Palonosetron 300-0.5 mg PO	Inpatient: Fosaprepitant 150 mg IV x 1 + ondansetron 8 mg IV
	Outpatient: Fosaprepitant 150 mg IV x 1 + palonosetron 0.25 mg IV
Fosnetupitant/ Palonosetron 235-0.25 mg IV	Inpatient: Fosaprepitant 150 mg IV x 1 + ondansetron 8 mg IV
	Outpatient: Fosaprepitant 150 mg IV x 1 + palonosetron 0.25 mg IV
Rolapitant 180 mg PO	Fosaprepitant 150 mg IV x 1
Rolapitant 166.5 mg IV	Fosaprepitant 150 mg IV x 1
Palonosetron 0.25 mg IV (inpatient only)	Ondansetron 8 mg IV

FORMULARY REVIEW

GENERIC NAME: Hexaminolevulinate hydrochloride

PROPRIETARY NAME: *Cysview®*

INDICATIONS:

FDA Approved
• Detection of bladder cancer • Detection of non-invasive bladder cancer (carcinoma in situ) • Used with Karl Storz D-Light C Photodynamic Diagnostic system to perform Blue Light Cystoscopy as an adjunct to the white light cystoscopy

THERAPEUTIC CATEGORY: Contrast Agent, Optical Imaging Agent

PHARMACOKINETICS:

	Hexaminolevulinate hydrochloride (Cysview®)
Metabolism	In vitro study showed rapid metabolism in human blood
Bioavailability (%)	Intravesical: 7%
t ½ (hr)	Initial elimination: 39 minutes; Terminal elimination: 76 hours (biphasic)
Elimination	Voided/evacuated from the bladder prior to the procedure

SPECIAL POPULATIONS:

	Hexaminolevulinate hydrochloride (Cysview®)
Pregnancy	There are currently no data available to inform a drug associated risk of adverse developmental outcomes. There are no studies conducted to show adequate reproductive and developmental toxicity in animals. Systemic absorption after administration of the medication is expected to be minimal.
Lactation	There are currently no data available on the presence of the medication in breast milk, the effects on a breastfed infant, or the effects on milk production. Systemic absorption after administration of the medication is expected to be minimal. Development and health benefits of breastfeeding, any potential adverse effects on the breastfed infant, and benefits of diagnostic imaging to the mother should be considered when deciding to continue or discontinue breastfeeding following administration.
Pediatrics	Safety and effectiveness in pediatric patients have not been established.
Geriatrics	There are no differences in safety and efficacy between older and younger patients in the controlled study. 67% of 2127 subjects in clinical studies were 65 years old and over.
Hepatic Impairment	No dose adjustments necessary
Renal Impairment	No dose adjustments required

CLINICAL STUDIES:

A comparison of hexaminolevulinate fluorescence cystoscopy and white light cystoscopy for the detection of carcinoma in situ i patients with bladder cancer: a phase III, multicenter study	
METHODS	
Study Design	• Open label, comparative, controlled, phase III multicenter study
Patient Enrollment Inclusion	• Age $\geq$ 18 and fulfilled $\geq$ 1 of certain criteria: o Prior multiple bladder lesions o Bladder lesion > 3 cm in diameter o Bladder tumor at stage T1 or less o Grade 2 or 3 bladder tumor o Positive urine cytology o Recurrent bladder cancer at follow-up examination
Patient Enrollment Exclusion	• Gross hematuria • Porphyria • Known allergy to hexaminolevulinate (HAL) or any derivative of aminolevulinic acid • Participation in other clinical studies within the last 30 days

<table>
<tr><td></td><td>• Pregnancy or lactation and intravesical bacillus Calmette-Guerin or chemotherapy within 3 months before HAL instillation</td></tr>
<tr><td>Baseline Characteristics</td><td>
<table>
<tr><td></td><td>Safety (n=298)</td><td>Intent-to-treat (n=196)</td></tr>
<tr><td>Mean Age</td><td>67± 11</td><td>67 ± 11</td></tr>
<tr><td>Male (%)/Female (%)</td><td>223 (75%)/75 (25%)</td><td>148 (76%)/48 (24%)</td></tr>
<tr><td>White (%)</td><td>274 (92%)</td><td>187(95%)</td></tr>
<tr><td>Black (%)</td><td>15 (5%)</td><td>5 (2.6%)</td></tr>
</table>
</td></tr>
<tr><td>Treatment Plan</td><td>• HAL HCl in phosphate buffered saline solution, 50mL of a 2.0mg/mL solution, was instilled into the patients' bladder using a standard catheter 1 to 3.5 hours before cystoscopy.
• The bladder was evacuated and inspected by white light cystoscopy using Karl Storz™. Afterwards a band filter on a lamp was used to supply blue light for fluorescence cystoscopy.
• Biopsies of all flat mapped lesions and suspicious areas were collected after both white and blue light examinations.
• Papillary lesions detected were resected and collected separately for histological examinations.</td></tr>
<tr><td colspan="2">RESULTS</td></tr>
<tr><td>Outcomes Summary</td><td>• Carcinoma in situ lesions were found in 58 patients (29.6%) of the 196 ITT patients and only 5 of the CIS lesions were not detected using either cystoscopy examinations but by biopsy. Therefore, of the 53 patients, only 18 patients (34%) had CIS alone and 35 patients (66%) had concomitant papillary disease.</td></tr>
<tr><td>Primary Endpoint</td><td>• HAL cystoscopy in 22 patients (41.5%, 95% CI 28-56%) detected more CIS lesions, whereas white light cystoscopy detected more CIS lesions in 8 patients (15.1%, 95% CI 7-28%).
• HAL cystoscopy detected 104 of 113 CIS lesions (92%, 95% CI 85-96) and white light cystoscopy detected 77 of 113 CIS lesions (68%, 95% CI 59-77).
<table>
<tr><td></td><td>HAL Fluorescence Cystoscopy</td><td>White Light Cystoscopy</td></tr>
<tr><td>Sensitivity (patient/lesion level)</td><td>87% / 92%</td><td>83% / 68%</td></tr>
<tr><td>Specificity (patient level)</td><td>82%</td><td>72%</td></tr>
</table>
</td></tr>
<tr><td>Secondary Endpoint</td><td>• HAL cystoscopy's false-positive detection rate at biopsy level was 39% (95% CI 35-43%), whereas white light cystoscopy's false-positive detection rate was 31% (95% CI 2-36%)
o The main source of the false-positive biopsies were areas of inflammation
• Safety of HAL → see adverse events</td></tr>
<tr><td>Adverse Events</td><td>• 800 adverse events were reported by 240 of 298 patients, where 19 events were related to HAL instillation and 20 patients reported a total of 23 serious adverse events, including 1 death caused by an aortic aneurysm.
• Most common adverse event was hematuria in 129 patients (43.3%)
• 38 adverse events were rated severe, where 11 cases were HAL instillation related, causing penile infection, penile pain, blood in urine, bladder pain, bladder spasm, and urinary frequency.</td></tr>
<tr><td>Author's Conclusion</td><td>• HAL fluorescence cystoscopy is an effective, well-tolerated method that may offer superior detection of bladder lesions, may improve the diagnosis of CIS lesions and bladder cancer, and is easy to perform as an adjunct to white light cystoscopy</td></tr>
<tr><td colspan="2"></td></tr>
<tr><td colspan="2">A comparison of hexaminolevulinate (Hexvix®) fluorescence cystoscopy and white-light cystoscopy for detection of bladder cancer: results of the HeRo observational study</td></tr>
<tr><td colspan="2">METHODS</td></tr>
<tr><td>Study Design</td><td>• Observational, open-label, comparative, controlled, multicenter study</td></tr>
<tr><td>Patient Enrollment Inclusion</td><td>• History of bladder tumor undergoing cystoscopy during follow-up or with suspicion of bladder lesion after bladder ultrasonography or urine cytology</td></tr>
<tr><td>Patient Enrollment Exclusion</td><td>• Gross hematuria
• Porphyria
• Known allergy to hexaminolevulinate (HAL) or any derivative of aminolevulinic acid
• Participation in other clinical studies within the last 30 days
• Pregnancy or lactation and intravesical bacillus Calmette-Guerin or chemotherapy within 3 months before HAL instillation</td></tr>
<tr><td>Baseline Characteristics</td><td>• Male (%)/Female (%): 80 (83.3%) /16 (16.7%)
• Mean Weight (range): 77.7 kg (39-105)
• Mean Height (range): 172 cm (155-185)
• BMI (range): 26.2 kg/m^2 (12.-36.7)</td></tr>
</table>

	• Primary diagnosis (%): 35 (36.5%) • Previous history of bladder cancer (%): 61 (63.5%)
Treatment Plan	• HAL HCl in phosphate buffered saline solution, 50mL of a 2.0mg/mL solution, was instilled into the patients' bladder using a standard catheter 1 hour before cystoscopy. • The bladder was evacuated and examined by white light cystoscopy followed by blue light cystoscopy. • Biopsies and resection of each positive lesions or suspicious areas were collected after inspection of both lights for histological analysis.
RESULTS	
Outcomes Summary	• 96 patients were enrolled, and no side-effects were detected after HAL administration. • Overall, 243 suspicious lesions were detected, where 39 (16.7%) from WLC alone, 71 (30.3%) from BLC alone, and 124 (53%) from WLC plus BLC. • 108 (46.2%) of the lesions were histologically confirmed to be bladder tumor/carcinoma in situ, with 82 (75.9%) were detected by WLC plus BLC, 1 (0.9%) by WLC only, and 25 (23.2%) by BLC only.
Primary Endpoint	• Sensitivity of BLC biopsies (99.1%) was significantly higher than WLC technique (76.8%), 22.3%; 95% CI, 12.6-31.9%; p<0.00001 o Relative sensitivity of BLC showed a superiority to WLC of 28.9%, 95% CI, 16.4-41.5% • Specificity of BLC biopsies (36.5%) was not significantly different compared with WLC (30.2%), -6.3%; 95% CI, -22.6-9.9% o Relative specificity BLC showed an inferiority to WLC of 17.4%; 95% CI, 27.2-62.0% • The correct diagnosis was achieved in 83 patients by both WLC plus BLC, 11 (11.5%) patients by BLC alone, and 2 (2%) patients by WLC alone. o BLC reached the correct diagnosis in 97.9% vs 88.5% with WLC, which was statistically significant; 9.4; 95% CI 1.1-17.7%; p=0.0265
Adverse Events	• No side-effects were detected after HAL administration.
Author's Conclusion	• HAL PDD is a well-tolerated procedure that can exceed the threshold of WLC for diagnosis of CIS and increase the detection rate and diagnostic accuracy of standard WLC for Ta/T1 bladder tumors, which will decrease the number of transurethral resections of bladder tumor in the follow-up period and increase the disease-free interval.

COMPARATIVE EFFICACY:
Cysview® is approved for use in cystoscopic detection of non-muscle invasive papillary cancer of the bladder among patients suspected or known to have lesions based on prior cystoscopy. It is also used with Karl Storz D-Light C Photodynamic Diagnostic system to perform cystoscopy with blue light setting as an adjunct to white light setting. Cysview® is not a replacement for random bladder biopsies or other procedures used for detecting bladder cancer.

WARNING AND PRECAUTIONS:
- Anaphylaxis
  - Hypersensitivity reactions (e.g. anaphylaxis and anaphylactoid shock) have been reported following administration.
- Appropriate Use
  - To enhance the diagnostic utility of Cysview®, bladder must be emptied of urine before instillation of fluids for cystoscopy and biopsy or resect the bladder mucosal lesion after completion of blue and white light rigid cystoscopy.
- Failed Detection
  - May fail to detect some bladder tumors, malignant lesions. Cysview® is not a replacement for random biopsies or other procedures usually performed in cystoscopic evaluation for cancer. Both blue and white light settings of the Karl Storz D-Light C Photodynamic Diagnostic system must be used for optimal accuracy in detecting malignancies.
- False Positive Fluorescence
  - Fluorescent areas detected during blue light cystoscopy may not indicate a bladder mucosal lesion. False positive areas may result from inflammation, cystoscopic trauma, scar tissue, or bladder mucosal biopsy from a recent cystoscopic examination as well as bacillus Calmette-Guerin (BCG) immunotherapy or intravesical chemotherapy. Presence of urine and/or blood in the bladder may interfere with detection results.

BLACK BOX WARNINGS: None

CONTRAINDICATIONS:

- Porphyria
- Gross Hematuria
- BCG immunotherapy or intravesical chemotherapy within the past 90 days
- Known hypersensitivity to hexaminolevulinate or any derivative of aminolevulinic acid

ADVERSE REACTIONS:

Adverse Reactions	HAL Fluorescence Cystoscopy (N=298)	White Light Cystoscopy*
Cardiovascular		-
Hypotension	9 (3.0)	
Central Nervous System		-
Headache	25 (8.4)	
Insomnia	11 (3.7)	
Gastrointestinal		
Nausea	42 (14.1)	-
Vomiting	12 (4.0)	-
Abdominal Pain	17 (5.7)	-
Lower Abdominal Pain	7 (2.3)	-
Constipation	7 (2.3)	-
Renal		
Hematuria	129 (43.3)	-
Dysuria	53 (17.8)	-
Bladder Spasm	42 (14.1)	-
Bladder Pain	29 (9.7)	-
Urinary Retention	25 (8.4)	-
Pubic Pain	21 (7.0)	-
Urinary Frequency	21 (7.0)	-
Penile Pain	11 (3.7)	-
Urinary Urgency	10 (3.4)	-
Miscellaneous		
Unspecified Pain	30 (10.1)	-
Post-Procedural Pain	19 (6.4)	-
Pelvic Pain	13 (4.4)	-
Pharyngolarngeal pain	7 (2.3)	-
Back Pain	7 (2.3)	-

**There were no recordings for adverse effects for patients who underwent white light cystoscopy in the trial*

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:

Interacting Drug	Effect
BCG (intravesical)	May diminish the diagnostic effect of Cysview®

DOSING AND ADMINISTRATION:

Cysview® Kit 100 mg/50 mL (2 mg/mL)

- Detection of bladder cancer: Intravesical instillation: 100mg (50mL) instilled into empty bladder via urinary catheter

RECOMMENDED MONITORING: Signs and symptoms of hypersensitivity

PHARMACOECONOMICS/COST:

Product (Drug, Strength, Form)	NDC	Contract/GPO Price
Hexaminolevulinate 100 mg Kit	10511-3001-1	$945

CONCLUSION & RECOMMENDATION:

Studies demonstrated favorable results of Cysview® over white light cystoscopy or in conjunction with white light cystoscopy for identifying malignant tissues or lesions in patients with suspected or confirmed bladder cancer. It is recommended to add Cysview® to formulary, with the following restrictions for use:

1. Outpatient surgery setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization, and
2. Urology and/or oncology patients with suspected bladder lesions

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?	No	
Special storage (e.g. refrigeration, protect from light, controlled substance)?	Yes	Store hexaminolevulinate kits at 20°-25°C (68°-77°F). Reconstituted solution can be stored for up to 2 hours under refrigeration 2°-8°F (36°-46°F).
Pharmacist/Technician Education?	No	
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	Yes	Restrict to outpatient use by oncology or urology departments for patients with suspected or confirmed bladder cancer.
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	No	
Drug Interactions?	Yes	
Pregnancy?	No	
Absolute Contraindications?	Yes	Patients with porphyria, gross hematuria, use of BCG immunotherapy or intravesical chemotherapy within the past 90 days, or have known hypersensitivity to hexaminolevulinate or any derivative of aminolevulinic acid.
Requires Order Set, Protocol, concomitant therapy with another drug?	No	
LASA* nomenclature issues?	No	
Prescriber education?	Yes	Patient will require a straight or intermittent urethral catheter that will accommodate the Luer Lock adapter for administration of Cysview. Can use Foley catheters if they are inserted shortly prior to administration and are removed following Cysview instillation. Do not use catheters coated or embedded with silver or antibiotics. Cysview imaging requires the use of the Karl Storz D-Light C PDD system.
Processing, Preparing, & Dispensing		
High-risk drug double check?	No	
Drug Interaction check in place?	Yes	BCG (intravesical)
LASA* computer warnings?	No	
Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)?	Yes	Avoid skin contact with Cysview. Wash skin immediately with soap and water and dry off if skin comes in contact with Cysview.
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	Reconstitute in aseptic conditions. Use 50 mL syringe with a Luer Lock tip throughout the process. Withdraw 50 mL of the diluent and inject 10 mL into the powder vial. Without withdrawing the needle from the vial, gently shake the powder vial with the syringe until the powder dissolves. Then withdraw all the dissolved solution from the vial, disconnect the needle from the syringe and discard to appropriate sharps container, and place a syringe cap. The expiration is 2 hours after reconstitution.
Administration		

Medication Management Step	Identified Risk	Steps for Prevention
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	Yes	Avoid skin contact with Cysview. Wash skin immediately with soap and water and dry off if skin comes in contact with Cysview.
Special delivery system (e.g. pump)?	Yes	Patient will require a straight or intermittent urethral catheter that will accommodate the Luer Lock adapter for administration of Cysview. Can use Foley catheters if they are inserted shortly prior to administration and are removed following Cysview instillation. Do not use catheters coated or embedded with silver or antibiotics.
Documentation required? (e. g. double check)	No	
Nurse education?	Yes	After solution is instilled, remove the catheter and instruct the patient to retain the solution within the bladder for at least 1 hour. Patients may stand, sit, and move around during the time period before the start of cystoscopic procedure. After the patient voids the bladder of Cysview, routinely wash the patient's perineal skin region with soap and water and dry.
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?	Yes	Monitor for anaphylactic reaction following exposure to Cysview.
Follow-up laboratory tests?	No	
Education?	Yes	Retain Cysview in the bladder for at least 1 hour after instillation to void prior to cystoscopy procedure.

FORMULARY REVIEW

GENERIC NAME: Caplacizumab-yhdp

PROPRIETARY NAME: *Cablivi®*

INDICATIONS:

FDA Approved
Adult patients with acquired thrombotic thrombocytopenic purpura (aTTP) in combination with plasma exchange and immunosuppressive therapy

THERAPEUTIC CATEGORY: Monoclonal Antibody; parenteral von Willebrand factor-directed antibody fragment

PHARMACOKINETICS:

Absorption	The bioavailability of subcutaneous caplacizumab-yhdp is approximately 90%.
Distribution	Caplacizumab-yhdp central volume of distribution is 6.33 L in patients with aTTP.
Metabolism	The available data suggest target-bound caplacizumab-yhdp is metabolized within the liver. Because caplacizumab-yhdp is a monoclonal antibody fragment, it is expected to be catabolized by various proteolytic enzymes.
Elimination	The half-life of caplacizumab-yhdp is concentration and target-level dependent. The available nonclinical data suggest unbound caplacizumab-yhdp is cleared renally.

SPECIAL POPULATIONS:

Pregnancy	There is no data regarding caplacizumab use in pregnant women. However, there are potential risks of hemorrhage in the mother and fetus associated with the use of caplacizumab.
Lactation	There is no information regarding the presence of caplacizumab-yhdp in human milk, the effects on the breastfed child or the effects on milk production.
Pediatrics	The safety and effectiveness of caplacizumab in pediatric patients have not been established.
Geriatrics	Clinical studies of caplacizumab did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently.
Hepatic Impairment	No formal studies with caplacizumab have been conducted in patients with hepatic impairment. Closely monitor for bleeding.
Renal Impairment	No formal studies with caplacizumab have been conducted in patients with renal impairment.

CLINICAL STUDIES:

HERCULES trial- Phase III Trial With Caplacizumab in Patients With Acquired Thrombotic Thrombocytopenic Purpura	
METHODS	
Study Design	Phase 3, double-blinded, randomized, placebo-controlled, parallel group
Patient Enrollment Inclusion	• Adult male or female ≥ 18 years of age at the time of signing the informed consent form (ICF). • Clinical diagnosis of acquired thrombotic thrombocytopenic purpura (aTTP) (initial or recurrent), which included thrombocytopenia and microscopic evidence of red blood cell fragmentation (e.g., schistocytes). • Required initiation of daily plasma exchange treatment and had received 1 plasma exchange treatment prior to randomization • Others as defined in the protocol
Patient Enrollment Exclusion	• Platelet count ≥100×10E9/L. • Serum creatinine level >200 µmol/L in case platelet count is > 30×10E9/L • Known other causes of thrombocytopenia • Congenital TTP (known at the time of study entry). • Pregnancy or breast-feeding. • Subjects who were previously enrolled in a clinical study with caplacizumab and received caplacizumab or for whom the assigned treatment arm is unknown • Others as defined in the protocol
Outcome Measures	• Primary outcome: time to normalization of the platelet count

	• Secondary outcomes: composite of TTP-related death, recurrence of TTP, or a thromboembolic event during the trail treatment period
Statistical Analyses	• The primary outcome was evaluated using a two-sided stratified log-rank test. • Secondary outcomes were mostly analyzed using the Cochran-Mantel-Haenszel test
Treatment Plan	Both groups received daily plasma exchange (until at least 2 days after the normalization of the platelet count) and glucocorticoids. Caplacizumab group • First day of treatment: 10 mg intravenous injection prior to plasma exchange (PE) followed by a 10 mg subcutaneous injection (in the abdominal region) after completion of PE on that day. • Subsequent days of treatment during PE: daily 10 mg s.c. injection following PE. • Treatment after PE period: daily 10 mg s.c. injections for 30 days. If the underlying immunological disease was not resolved, treatment could be extended for a maximum of 4 additional 1-week periods (i.e., 28 days) and was to be accompanied by optimization of immunosuppression. Placebo group • First day of treatment: IV injection prior to plasma exchange (PE) followed by a s.c. injection (in the abdominal region) after completion of PE on that day. • Subsequent days of treatment during PE: daily s.c. injection following PE. • Treatment after PE period: daily s.c. injections for 30 days. If the underlying immunological disease was not resolved, treatment could be extended for a maximum of 4 additional 1-week periods (i.e., 28 days) and was to be accompanied by optimization of immunosuppression.
RESULTS	
Outcomes Summary	• The rate ratio for normalization of the platelet count was 1.55 times as likely to have a normalization compared to standard of care. • Death from aTTP did not occur in any patients in the caplacizumab group, although it occurred in 3 patients in the standard of care group.

Primary & Secondary Endpoint

Outcome	Caplacizumab (N=72)	Placebo (N=73)	P-Value
Primary outcome			
Time to normalization of platelet count			
25th Percentile (95% CI) – days	1.75 (1.65-1.87)	1.94 (1.70-2.64)	
50th Percentile (95% CI) – days	2.69 (1.89-2.83)	2.88 (2.68-3.56)	
75th Percentile (95% CI) – days	2.95 (2.85-3.81)	4.50 (3.78-7.79)	
Rate ratio for normalization of platelet count, caplacizumab vs placebo (95% CI)	1.55 (1.09-2.19)		0.01
Key secondary outcomes			
Composite of TTP-related death, recurrence of TTP, or major thromboembolic event during the double-blind treatment period	9 (12)	36 (49)	<0.001
TTP-related death	0	3 (4)	
Recurrence of TTP: exacerbation	3 (4)	28 (38)	
Major thromboembolic event	6 (8)	6 (8)	
Recurrence of TTP at any time during the trial	9 (12)	28 (38)	<0.001
Refractory TTP	0	3 (4)	0.06
Mean time to normalization of organ-damage markers in days	2.86 (1.93-3.86)	3.36 (1.88-7.71)	
Other Secondary Outcomes			
Number of days of plasma exchange	5.8	9.4	
Volume of plasma exchange – in liters	21.3	35.9	
No. of days of hospitalization	9.9	14.4	
Patients admitted to the ICU	28	27	
No. of days ICU	3.4	9.7	

Adverse Events	• Serious adverse events were reported in 23 patients (32%) in the caplacizumab group and in 12 patients (16%) in the placebo group during the overall trial period. • Bleeding related adverse events were reported in 46 patients (65%) in the caplacizumab group and in 35 patients (48%) in the placebo group. o The most common bleeding events included epistaxis and gingival bleeding
Author's Conclusion	Overall, caplacizumab showed value when added to the standard treatment for acquired TTP. It significantly lowered the time to normalization of platelet count and the reoccurrence rate which lead to shorter stays in the hospital and intensive care units.
TITAN trial- Study to Assess Efficacy and Safety of Anti-von Willebrand Factor Nanobody in Patients With Acquired Thrombotic Thrombocytopenic Purpura	
METHODS	
Study Design	Phase 2, single-blind, randomized, placebo controlled
Patient Enrollment Inclusion	• 18 years of age or older or aged 12 to < 18 years • Male or female subject, willing to accept an acceptable contraceptive regimen • Subject with a clinical diagnosis of TTP • Requiring PE (one single PE session prior to randomization into the study was allowed) • Subject accessible to follow-up • Subject able to provide signed and dated informed consent and assent (if applicable, for adolescents)

Patient Enrollment Exclusion	• Platelet count ≥ 100,000/μL
	• Severe active infection indicated by sepsis (requirement for pressors with or without positive blood cultures)
	• Clinical evidence of enteric infection with Escherichia coli 0157 or related organism
	• Anti-phospholipid syndrome
	• Diagnosis of disseminated intravascular coagulation (DIC)
	• Pregnancy or breast-feeding
	• Hematopoietic stem cell or bone marrow transplantation-associated thrombotic microangiopathy
	• Known with congenital TTP
	• Active bleeding or high risk of bleeding
	• Uncontrolled arterial hypertension
	• Known chronic treatment with anticoagulant treatment that cannot be stopped safely, including but not limited to:
	  o vitamin K antagonists
	  o heparin or low molecular weight heparin
	  o non-acetyl salicylic acid non-steroidal anti-inflammatory molecules
	• Severe or life threatening clinical condition other than TTP that would impair participation in the study
	• Subjects with malignancies resulting in a life expectation of less than 3 months
	• Subjects with known or suspected bone marrow carcinosis
	• Subjects who cannot comply with study protocol requirements and procedures
	• Known hypersensitivity to the active substance or to excipients of the study drug
	• Severe liver impairment, corresponding to grade 3 toxicity defined by the CTCAE scale. For the key liver parameters, this is defined as follows:
	  o bilirubin > 3 ULN (needed to differentiate isolated increase in indirect bilirubin due to hemolysis, this was not an exclusion parameter but disease-related)
	  o ALT/AST > 5 x ULN
	  o ALP > 5 x ULN
	  o GGT > 5 x ULN
	• Severe chronic renal impairment, as defined by glomerular filtration rate < 30 mL/min

Outcome Measures	• The primary outcome was the time to confirmed normalization of the platelet count. • Key secondary endpoints included exacerbations, relapse, complete remission after the initial course of daily plasma exchange, duration and volume of plasma exchange, mortality, and safety.

<table>
<tr><td>Statistical Analyses</td><td>• The primary outcome was evaluated using a one-sided log-rank test stratified for the absence or presence of one-plasma exchange session before randomization, with a 2.5% significance level.</td></tr>
<tr><td>Treatment Plan</td><td>Caplacizumab group
• Subjects received a first IV bolus of 10 mg caplacizumab via push injection within 6 hours to 15 minutes prior to the first PE on study. The first PE on study could either be the very first PE session for the current episode of aTTP (if the subject was randomized prior to the initiation of PE) or the second PE session (if the subject was randomized after a single PE session).
• The first PE on study was followed by subcutaneous (s.c.) administration of 10 mg study drug within 30 minutes after the end of the PE procedure.
• All subsequent study drug administrations were daily s.c. injections within 30 minutes after the end of the PE procedure (if applicable) or within 24 hours of the previous dose.
• Subjects received caplacizumab up to 30 days after the last PE session.
Placebo group
• Subjects received a first IV bolus of placebo via push injection within 6 hours to 15 minutes prior to the first PE on study. The first PE on study could either be the very first PE session for the current episode of aTTP (if the subject was randomized prior to the initiation of PE) or the second PE session (if the subject was randomized after a single PE session).
• The first PE on study was followed by s.c. administration of placebo within 30 minutes after the end of the PE procedure.
• All subsequent study drug administrations were daily s.c. injections within 30 minutes after the end of the PE procedure (if applicable) or within 24 hours of the previous dose.
• Subjects received placebo up to 30 days after the last PE session.</td></tr>
<tr><td colspan="2">RESULTS</td></tr>
<tr><td>Outcomes Summary</td><td>On the basis of the stratified log-rank test, caplacizumab significantly reduced the time to a response, as compared with placebo (39% reduction in median time to response; event rate ratio, 2.20; 95% CI, 1.28 to 3.78; P = 0.005).</td></tr>
<tr><td>Primary & Secondary Endpoint</td><td>
<table>
<tr><th>Outcome</th><th>Caplacizumab (N=36)</th><th>Placebo (N=39)</th><th>P-value</th></tr>
<tr><td>Primary endpoint</td><td></td><td></td><td></td></tr>
<tr><td>Time to response: caplacizumab vs placebo</td><td></td><td></td><td></td></tr>
<tr><td>Event rate ratio (95% CI)</td><td colspan="2">2.20 (1.28-3.78)</td><td>0.005</td></tr>
<tr><td>Patient with no PE before randomization</td><td></td><td></td><td></td></tr>
<tr><td>Median time to response (95% CI)—days</td><td>3.0 (2.7-3.9)</td><td>4.9 (3.2-6.6)</td><td></td></tr>
<tr><td>Confirmed response—no. (%)</td><td>29 (81)</td><td>24 (62)</td><td></td></tr>
<tr><td>Patients with one PE before randomization</td><td></td><td></td><td></td></tr>
<tr><td>Median time to response (95% CI)—days</td><td>2.4 (1.9-3.0)</td><td>4.3 (2.9-5.7)</td><td></td></tr>
<tr><td>Confirmed response—no. (%)</td><td>2 (6)</td><td>4 (10)</td><td></td></tr>
<tr><td>Secondary endpoint</td><td></td><td></td><td></td></tr>
<tr><td>Exacerbation of TTP—no. (%)</td><td>3(8)</td><td>11 (28)</td><td></td></tr>
<tr><td>Relapse—no.(%)</td><td></td><td></td><td></td></tr>
<tr><td>During 1-month follow-up</td><td>8 (22)</td><td>0</td><td></td></tr>
<tr><td>During 12 month follow-up</td><td>11 (31)</td><td>3 (8)</td><td></td></tr>
<tr><td>Complete remission after initial daily PE—no. (%)</td><td>29 (81)</td><td>18 (46)</td><td></td></tr>
<tr><td>Mean no. of PE days (range)</td><td></td><td></td><td></td></tr>
<tr><td>During daily PE period</td><td>5.9 (3-15)</td><td>7.9 (2-35)</td><td></td></tr>
<tr><td>During overall study-drug treatment period</td><td>7.7 (3-21)</td><td>11.7 (2-43)</td><td></td></tr>
<tr><td>During the first 30 days of follow-up</td><td>10.2 (4-29)</td><td>11.7 (2-43)</td><td></td></tr>
</table>
</td></tr>
<tr><td>Adverse Events</td><td>• The most common adverse events were headache and epistaxis.
• Adverse events considered to be related to the study drug were reported in 6 patients (17%) receiving caplacizumab and 4 patients (11%) receiving placebo, and events that were possibly related to the study drug were reported in 19 patients (54%) and 3 patients (8%) in the two groups, respectively.</td></tr>
</table>

	• The number of bleeding-related adverse events was higher in the caplacizumab group (19 patients) than in the placebo group (14 patients).
Author's Conclusion	This trial showed a more rapid resolution of TTP episodes. As ndicated by faster platelet count normalization, caplacizumab prevents further consumption of platelets into microthrombi and the consequent progression of tissue ischemia.

COMPARATIVE EFFICACY: Caplacizumab is currently the first and only FDA-approved therapy for adult patients with acquired thrombotic thrombocytopenic purpura (aTTP).

WARNING AND PRECAUTIONS:
- Increased risk of bleeding
- Hold caplacizumab 7 days prior to elective surgery, dental procedures, and other invasive interventions.

BLACK BOX WARNINGS: None

CONTRAINDICATIONS: Caplacizumab is contraindicated in patients with a previous severe hypersensitivity reaction to caplacizumab-yhdp or to any of the excipients. Hypersensitivity reactions have included urticaria.

ADVERSE REACTIONS:

Adverse Reactions	**Intervention Group (N=106) n (%)**	**Placebo or Standard of Care Group (N=110) N (%)**
Gastrointestinal disorders		
Gingival bleeding	17 (16)	3 (3)
Rectal hemorrhage	4 (4)	0 (0)
Abdominal wall hematoma	3 (3)	1 (1)
General disorders and administration side conditions		
Fatigue	16 (15)	10 (9)
Pyrexia	14 (13)	12 (11)
Injection side hemorrhage	6 (6)	1 (1)
Catheter site hemorrhage	6 (6)	5 (5)
Injection site pruritus	3 (3)	0 (0)
Musculoskeletal and connective tissue disorders		
Back pain	7 (7)	4 (4)
Myalgia	6 (6)	2 (2)
Nervous system disorders		
Headache	22 (21)	15 (14)
Paresthesia	13 (12)	11 (10)
Renal and urinary disorders		
Urinary tract infection	6 (6)	4 (4)
Hematuria	4 (4)	3 (3)

CLINICALLY SIGNIFICANT DRUG INTERACTIONS:
- Anticoagulants- Concomitant use of caplacizumab with any anticoagulant may increase the risk of bleeding.

DOSING AND ADMINISTRATION:
- Caplacizumab should be administered upon the initiation of plasma exchange therapy. The recommended dose of caplacizumab is as follows:
  - **First day of treatment: 11 mg bolus intravenous injection at least 15 minutes prior to plasma exchange followed by an 11 mg subcutaneous injection after completion of plasma exchange on day 1.**
  - Subsequent treatment during daily plasma exchange: 11 mg subcutaneous injection **once daily following plasma exchange.**
  - Treatment after the plasma exchange period: 11 mg subcutaneous injection **once daily for 30 days beyond the last plasma exchange.**
    - If after initial treatment course, sign(s) of persistent underlying disease such as suppressed ADAMTS13 activity levels remain present, treatment may be extended for a maximum of 28 days.
  - Discontinue caplacizumab if the patient experiences more than 2 recurrences of aTTP, while on caplacizumab.
- **The first dose should be administered by a healthcare provider as a bolus intravenous injection.** Administer subsequent doses subcutaneously in the abdomen.

RECOMMENDED MONITORING: Signs and symptoms of bleeding

PHARMACOECONOMICS/COST:

Product Purchase Price

Product (Drug, Strength, Form)	NDC	Contract/GPO Price
Cablivi Injection Kit 11 mg Kit	58468-0225-01	$7,300 per each

Product (Drug, Strength, Form)	Cost/Day	Cost/Defined Course of Therapy	Cost/Year
Cablivi Injection Kit 11 mg Kit	$7,300	$204,400/28 days	unknown

CONCLUSION & RECOMMENDATION:

The addition of caplacizumab to current standard of care could improve the care of those who develop acquired thrombotic thrombocytopenic purpura. It is recommended that caplacizumab should be added to formulary with the following restrictions for use, which have been previously reviewed by TN Oncology providers:

- ✓ Ordering restricted to hematology/oncology physicians
- ✓ Patients with confirmed, high-risk acquired thrombotic thrombocytopenic purpura (neurologic or cardiac involvements)
- ✓ Patient must receive one treatment of plasma exchange, in addition to immunosuppressive therapy, prior to initiation of caplacizumab.
- ✓ Must be given in conjunction with plasma exchange and immunosuppression therapy.
- ✓ Prior to ordering the first dose of caplacizumab, a case management consult to begin the prior authorization approval process and to determine cost to the patient for outpatient therapy is required.
- ✓ Caplacizumab will not be routinely stocked unless available via consignment.
- ✓ Discharge of patient should occur as soon as medically stable, with therapy to continue on an outpatient basis.

FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)

Medication Management Step	Identified Risk	Steps for Prevention
Selection & Procurement		
Therapeutic interchange?	NA	NA
Special Ordering Requirements?	NA	NA
Storage		
LASA* separation of stock?	NA	NA
Special storage (e.g. refrigeration, protect from light, controlled substance)?	Yes	Store refrigerated at 2° to 8°C in the original carton to protect from light. Do not freeze. Unopened vials may be stored in the original carton at room temperature up to 30°C (86°F) for a single period of up to 2 months. Do not return caplacizumab to the refrigerator after it has been stored at room temperature.
Pharmacist/Technician Education?	No	NA
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	Yes; Hematology/Oncology	Indicated to aTTP only.
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	None known	NA
Drug Interactions?	Increased risk of bleeding when used with anticoagulants.	Monitor bleeding
Pregnancy?	None known	NA
Absolute Contraindications?	Yes	Do not use in patients with a previous severe hypersensitivity reaction to caplacizumab or to any of the excipients.
Requires Order Set, Protocol, concomitant therapy with another drug?	Yes	Used in combination with plasma exchange and immunosuppressive therapy. Administer initial bolus at least 15 minutes prior to plasma exchange.
LASA* nomenclature issues?	No	NA
Prescriber education?	Prescribers should be educated on appropriate clinical utilization.	Provide provider education from pharmacy and medication manufacturer.
Processing, Preparing, & Dispensing		
High-risk drug double check?	NA	NA

Medication Management Step	Identified Risk	Steps for Prevention
Drug Interaction check in place?	Yes	Check for concomitant use of an anticoagulant.
LASA* computer warnings?	No	NA
Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)?	No	NA
Packaging/Labeling (e.g. prepacking)?	Caplacizumab Carton contains: 1 vial of caplacizumab 1 prefilled syringe containing 1 mL Sterile Water for Injection (diluent for caplacizumab) 1 sterile vial adapter 1 sterile needle 2 alcohol swabs	Additional supplies needed includes sharps disposable container and cotton balls.
Dispensing (e.g. auxiliary labeling, light protection, refrigeration)?	Yes	Dispense in original carton to protect from light.
Documentation required (e.g. double check, worksheet)?	No	NA
Pharmacist/Technician Education?	No	NA
Administration		
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	No	NA
Special delivery system (e.g. pump)?	No	NA
Documentation required? (e. g. double check)	No	NA
Nurse education?	Yes	Nursing education to explain the instructions for use.
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?	Yes	Monitor for bleeding
Follow-up laboratory tests?	Yes	If suppressed ADAMTS13 activity levels remain 30 days beyond the last plasma exchange, treatment may be extended for a maximum of 28 days.
Education?	Pharmacists, providers, and nurses should be educated on appropriate clinical utilization.	Educate coworkers.

SUGAMMADEX MEDICATION USE EVALUATION

BACKGROUND:

Sugammadex (Bridion) is a cyclodextrin molecule that binds rocuronium and vecuronium allowing for rapid reversal of neuromuscular blockade in adults undergoing surgery. Sugammadex provides a more effective means for reversing these medications as compared to neostigmine/glycopyrrolate for patients with deep neuromuscular blockade although at an increased cost of $81 per day.

Sugammadex was added to formulary at CHI Memorial in April 2016 with restriction criteria for use. The P&T committee voted that usage would be monitored to ensure compliance with these restrictions and education provided for anesthesia staff. The CHI Memorial expense report from FY2019, paired with early FY20 expenses, revealed that sugammadex (Bridion) is on track to be the 4th highest inpatient drug expenditure, which prompted a medication use evaluation.

The CHI System P&T is also preparing for a review of the current restriction criteria for sugammadex use in order to ensure appropriate clinical indications supported by literature are included for use. CHI Memorial utilization of sugammadex is currently restricted to the following indications:

- Immediate reversal of NMB in a "cannot intubate/cannon ventilate" or other emergency situation.

- For intubation doses of rocuronium/vecuronium to shorten anesthesia time for shorter than expected, abandoned or cancelled procedures in which neostigmine/glycopyrrolate would be ineffective (deep block).

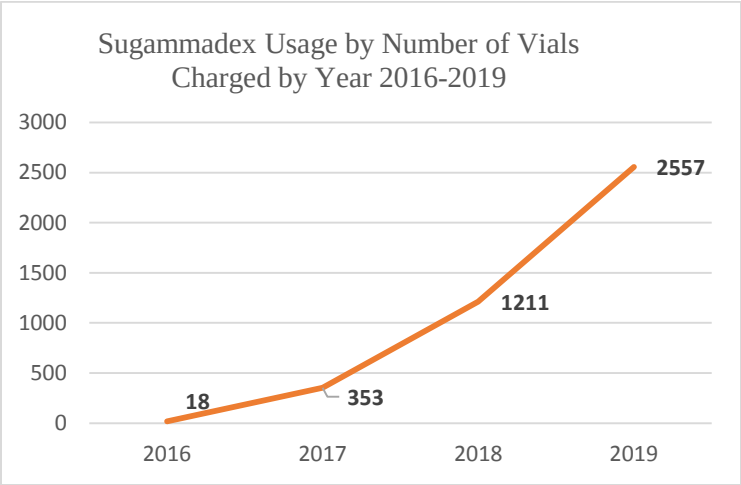
PHARMACOECONOMICS – SUGAMMADEX

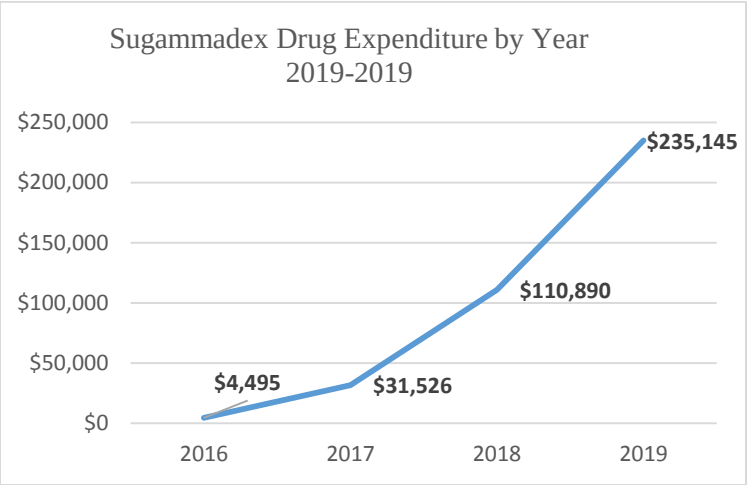
FY19 Total Drug Spend: **$235,135**

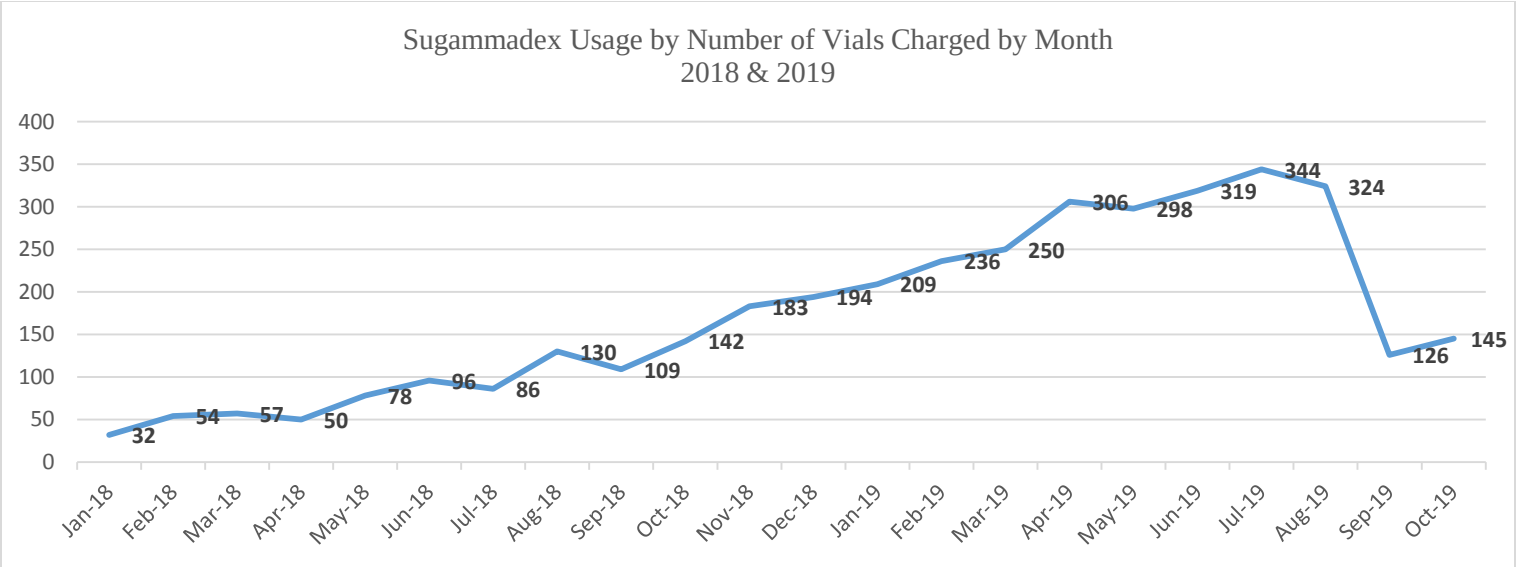
Sugammadex 200 mg/2 ml – **$92.69** (adequate for 100 kg patient with 2 mg/kg dosing) – moderate block reversal
Neostigmine 5 mg + Glycopyrrolate 1 mg (typical adult dose) – **$12**

LITERATURE REVIEW:

In all clinical trials, sugammadex was compared with the combination of neostigmine and glycopyrrolate. Sugammadex produces a significantly faster reversal of neuromuscular blockade, with the biggest difference seen in deep neuromuscular paralysis (post-tetanic count 1 to 2 twitches) vs moderate neuromuscular block (train of four count 1-2 twitches). Data regarding other benefits of sugammadex such as lower risk of adverse events are limited. A retrospective study looked at differences in pulmonary outcomes in patients that received at least one dose of a neuromuscular blocker prior to surgery. Patients older than 60 and patients considered American Society of Anesthesiologists Class III and IV had better pulmonary outcomes when reversed with sugammadex compared to patients who did not receive sugammadex. However, only 212 of the 722 patients in the non-sugammadex group received neostigmine.


Sugammadex Usage by Number of Vials Charged by Year 2016-2019
3000
2500
2000
1500
1000
500
0
2016
2017
2018
2019
18
353
1211
2557


Sugammadex Drug Expenditure by Year 2019-2019
$250,000
$200,000
$150,000
$100,000
$50,000
$0
2016
2017
2018
2019
$4,495
$31,526
$110,890
$235,145


Sugammadex Usage by Number of Vials Charged by Month 2018 & 2019
400
350
300
250
200
150
100
50
0
Jan-18
Feb-18
Mar-18
Apr-18
May-18
Jun-18
Jul-18
Aug-18
Sep-18
Oct-18
Nov-18
Dec-18
Jan-19
Feb-19
Mar-19
Apr-19
May-19
Jun-19
Jul-19
Aug-19
Sep-19
Oct-19
32
54
57
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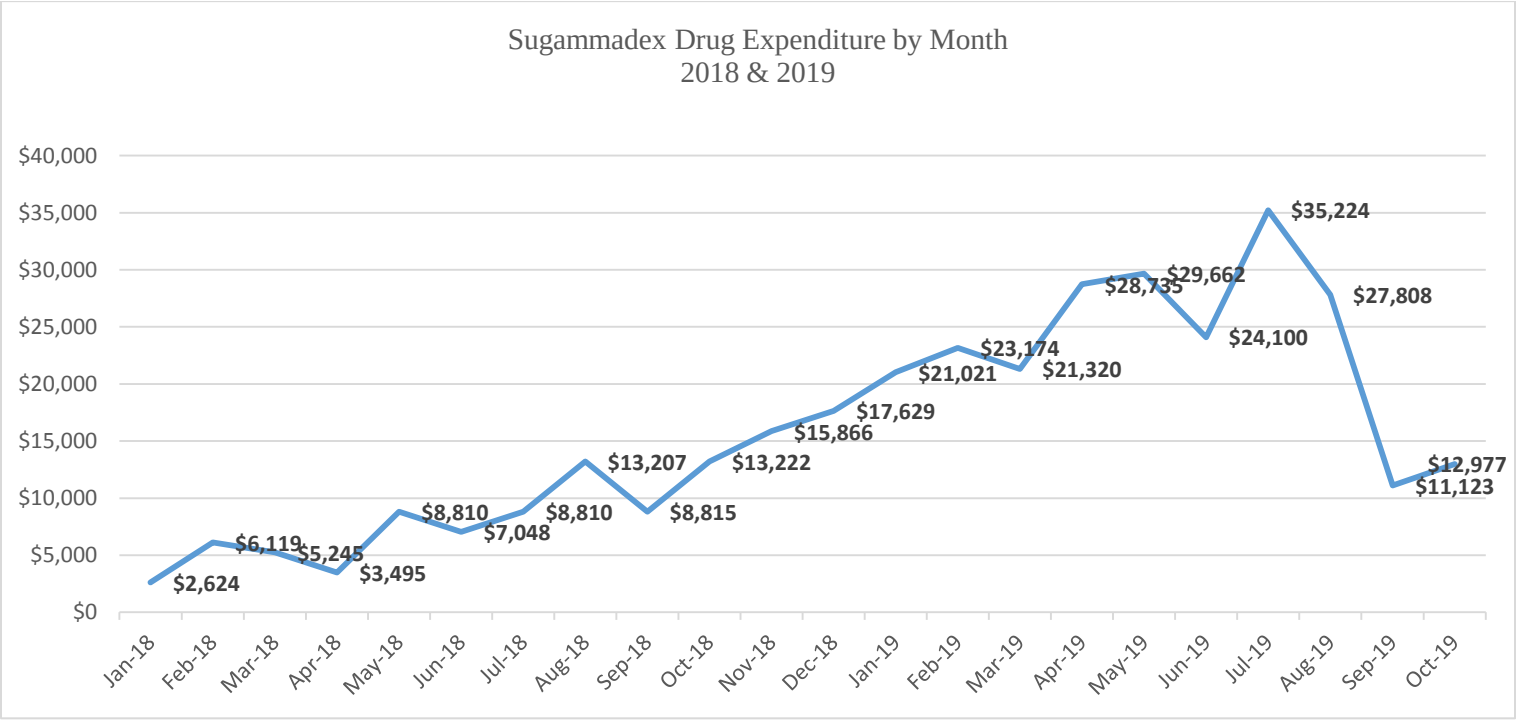
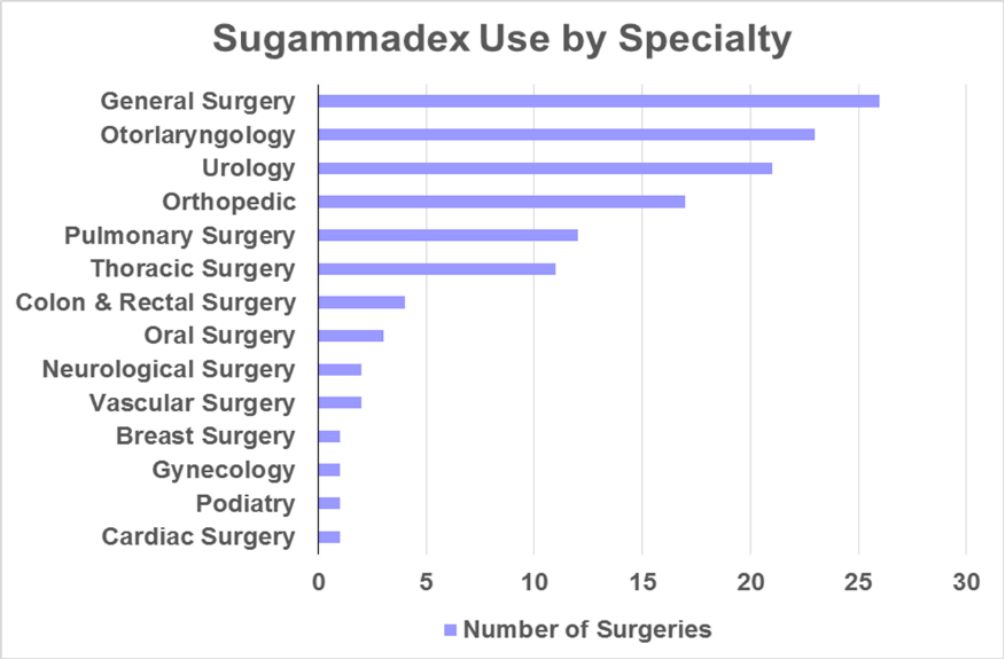
86
130
109
142
183
194
209
236
250
306
298
319
344
324
126
145


Sugammadex Drug Expenditure by Month 2018 & 2019
$40,000
$35,000
$30,000
$25,000
$20,000
$15,000
$10,000
$5,000
$0
Jan-18
Feb-18
Mar-18
Apr-18
May-18
Jun-18
Jul-18
Aug-18
Sep-18
Oct-18
Nov-18
Dec-18
Jan-19
Feb-19
Mar-19
Apr-19
May-19
Jun-19
Jul-19
Aug-19
Sep-19
Oct-19
$2,624
$6,119
$5,245
$3,495
$8,810
$7,048
$8,810
$13,207
$8,815
$13,222
$15,866
$17,629
$21,021
$23,174
$21,320
$28,735
$29,662
$24,100
$35,224
$27,808
$11,123
$12,977

MEDICATION USE SUMMARY:

Two recent evaluations of sugammadex use were performed:

1. May to June 2019: chart review of 129 patients
    a. Inclusion Criteria:
        i. ≥ 18 years old, undergoing a surgical procedure
        ii. Received a non-depolarizing NMB
        iii. Received at least one dose of Sugammadex
    b. Exclusion Criteria:
        i. Less than 18 years of age
    c. Results/Conclusions:
        i. Documentation of requirement for sugammadex use did not align with approved restriction criteria due to lack of intraoperative documentation, which was paper-based during the time of this evaluation.
        ii. The majority of patients received 1 vial (200 mg) of sugammadex.
        iii. Utilization based on surgery type was evaluated:



2. Fall 2019, Anesthesiology championed and collected prospective documentation of sugammadex indication:

Documented Indication	Count of Indication	Meets Current Restriction Criteria?	Percentage of Use
"Weak"	3		
Aborted procedure	*1*	Yes	
Bradycardia	1		
COPD	4		
Deep blockade	17	Unknown	**21%**
Deep blockade after brief procedure	*2*	Yes	
Deep blockade after quick case	*2*	Yes	
Deep blockade after short case	*3*	Yes	
Deep blockade after short case (cancel case intraop)	*1*	Yes	
EBUS	5		
Emergent intubation- weaning trial	*1*	Yes	
Failed reversal	26	No, but appropriate	**21%**
Failed reversal	1	No, but appropriate	
Frailty	2		
h/o PONV	1		
High dose rocuronium	1		
History of postop weakness	1		
Hypoxemia	1		
Interscalene block	1		
MD Request	2		
Morbid obesity	13	No	**11%**
Morbid obesity, OSA	1	No	
Multiple sclerosis	1		
Myasthenia gravis	3		
Pericardial window	1		
Preop nausea	1		
Pulmonary compromise	1	No	**18%**
Pulmonary cripple	13	No	
Pulmonary hypertension	1		
Pulmonary insufficiency	5	No	
Respiratory failure	1	No	
Rocuronium RSI reversal	1		
Severe GERD/Hiatal Hernia	1		
Short case	2		
Sjogren's Syndrome	1		
Thoracic surgery	8		
Grand Total	**130**		

SUMMARY:

Sugammadex utilization since 2016 has risen substantially, with use peaking in July 2019 with 344 vials used that month. Approximately 40% of recent sugammadex use is in alignment with approved restriction criteria for use. Common uses that do not align with current criteria are for patients with existing pulmonary disease (~18%) and those with morbid obesity (~11%). This suggests that there may be room for improvement in order to decrease sugammadex usage for indications that are not supported by literature. Due to the high annualized cost of sugammadex at CHI facilities it is important to evaluate our use for areas of potential decreased use where clinically appropriate, and to provide recommendations for use restrictions to the CHI System P&T committee in advance of the January CHI System P&T committee meeting.

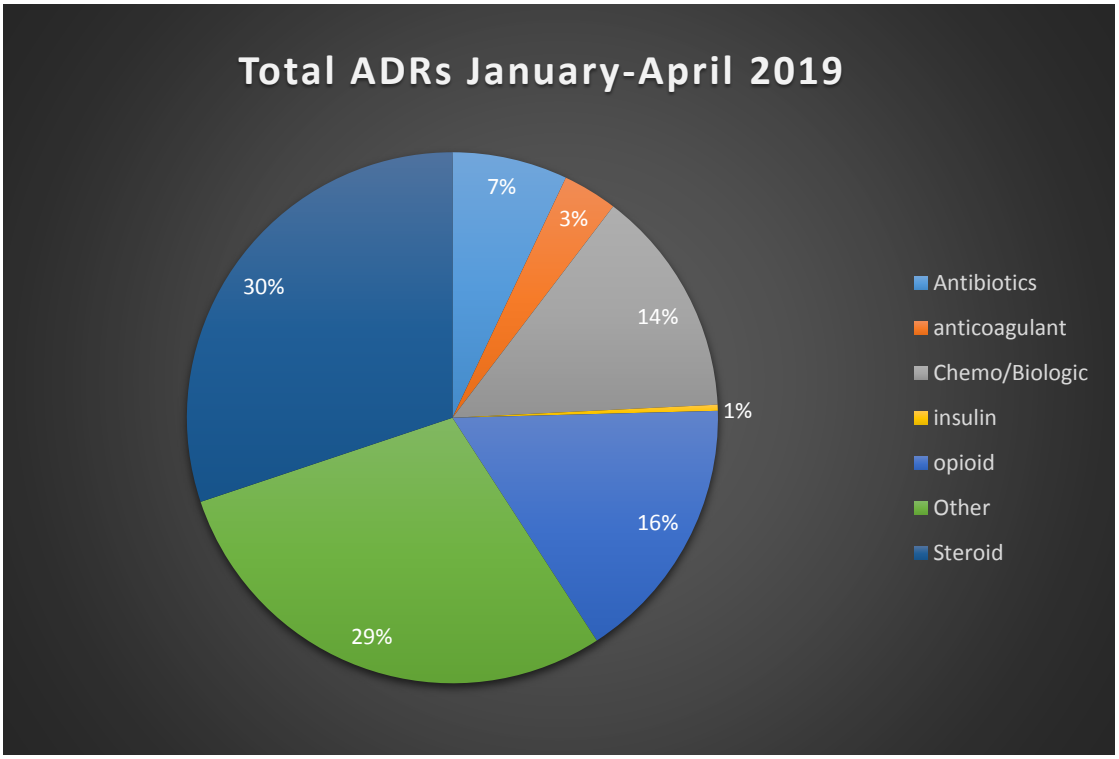
Category 1: Commonly recognized ADR's which are expected and do not result in serious medical consequences or extended hospitalization (e.g. antibiotic rash, nausea, mild hypokalemia).

Category 2: Significant ADR's which extend hospitalization and/or require extensive therapeutic measures (e.g. gastrointestinal bleed secondary to NSAIDs, Aminoglycoside nephrotoxicity.

Category 3: A serious or rare ADR which has abnormal characteristics compared with published reports of the reaction (e.g. heparin induced platelet aggregation resulting in limb amputation). ADR's from this category should be reported to the manufacturer and/or the FDA (MedWatch or the Vaccine Adverse Event Reporting System).

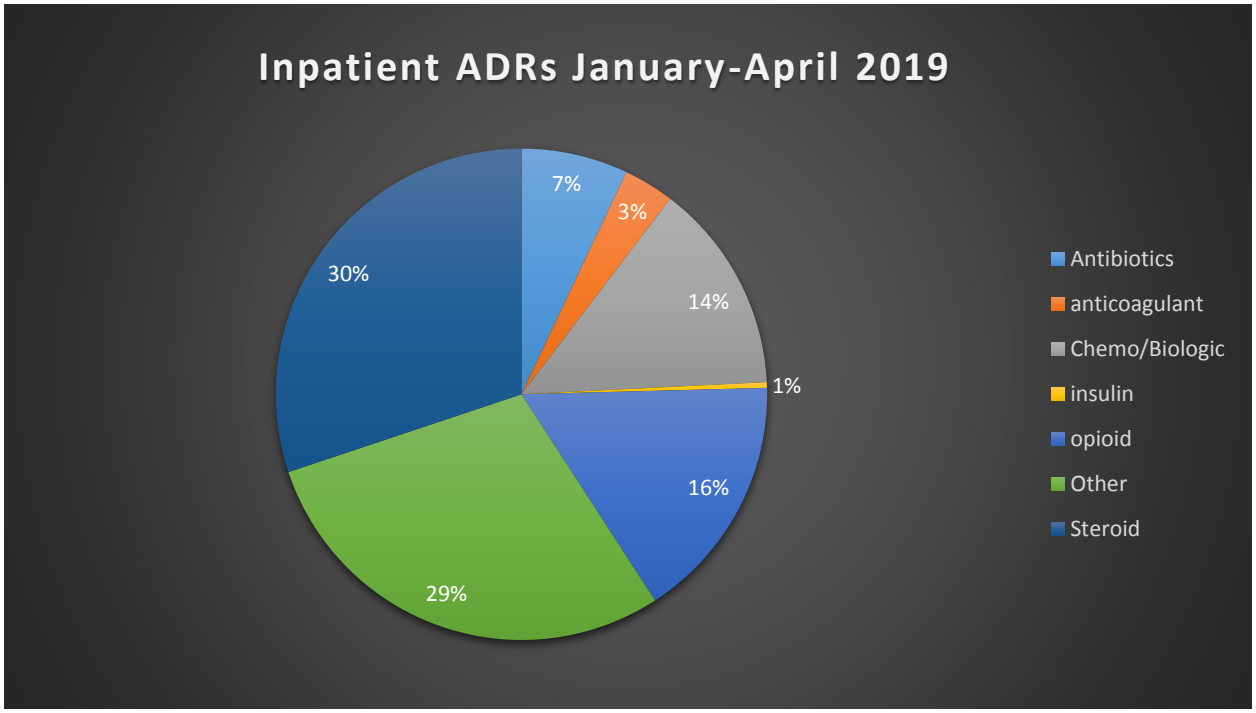
Inpatient: 199 (29.1%)
Prior to hospitalization: 485 (70.9%)
Total: 684

Category 1: 547 (80%)
Category 2: 132 (20%)
Category 3: 0



Most Common Total Adverse Drug Reactions:

- Steroid: Hyperglycemia (87), Leukocytosis (61)
- Opioid**:** Constipation (65), Altered Mental Status (16)
- Anticoagulant**:** GI Bleeding (11), Supratherapeutic INR (11)
- Antibiotics: Rash/Itching (20), Diarrhea (9)
- Chemo/Biologics: Pancytopenia (26), Nausea/Vomiting/Diarrhea (11)
- Other Medications**:** Hypotension due to Antihypertensive (18), Encephalopathy due to Centrally Active Medication (13)



Most Common Inpatient Adverse Drug Reactions:

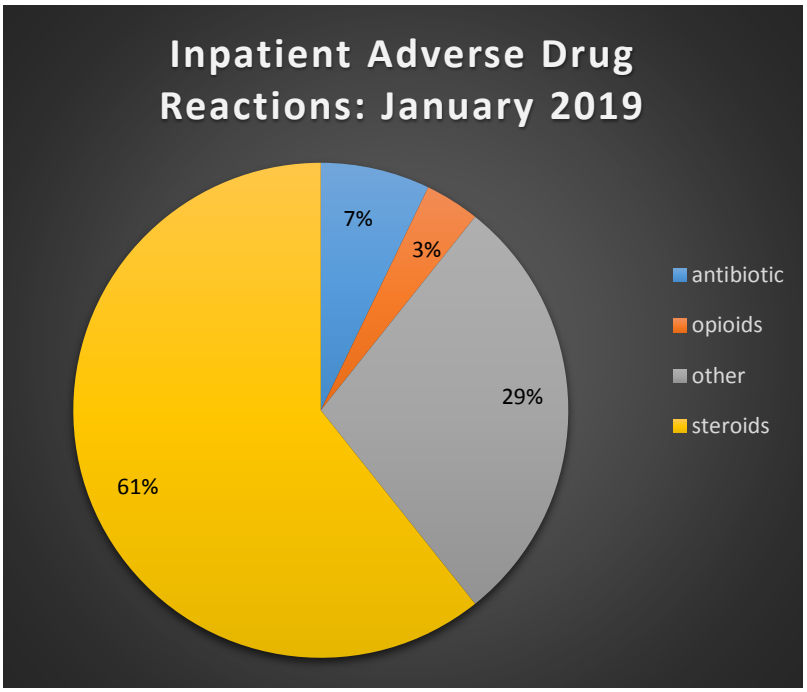
- Steroid: hyperglycemia (54), leukocytosis (38)
- Opioid: constipation (11)
- Anticoagulant: elevated INR (1), hemothorax (1)
- Antibiotics: diarrhea (7)
- Chemo/Biologics: nausea/vomiting/diarrhea (2)
- Other Medications: hypotension due to antihypertensive (7), electrolyte abnormalities (5)

Category 1: Commonly recognized ADR's which are expected and do not result in serious medical consequences or extended hospitalization (e.g. antibiotic rash, nausea, mild hypokalemia).

Category 2: Significant ADR's which extend hospitalization and/or require extensive therapeutic measures (e.g. gastrointestinal bleed secondary to NSAIDs, Aminoglycoside nephrotoxicity.

Category 3: A serious or rare ADR which has abnormal characteristics compared with published reports of the reaction (e.g. heparin induced platelet aggregation resulting in limb amputation). ADR's from this category should be reported to the manufacturer and/or the FDA (MedWatch or the Vaccine Adverse Event Reporting System).

January 2019	Total Adverse Drug Reactions	Category 1 Reactions	Category 2 Reactions	Category 3 Reactions
Inpatient				
Anticoagulant	0	0	0	0
Antibiotic	6	4	2	0
Insulin	0	0	0	0
Chemo/Biologic	0	0	0	0
Steroids	34	34	0	0
Opioids	2	2	0	0
Other	3	2	1	0
Outpatient				
Anticoagulant	14	4	10	0
Antibiotic	17	7	10	0
Insulin	0	0	0	0
Chemo/Biologic	21	12	9	0
Steroids	12	11	1	0
Opioids	28	23	5	0
Other	43	30	13	0



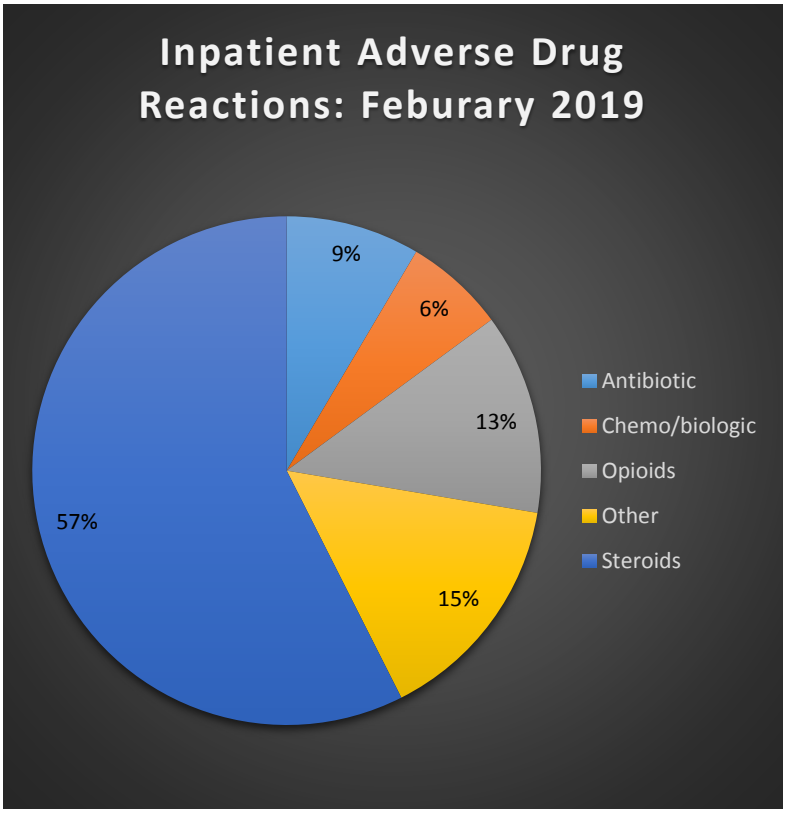
Antibiotics:
- Doxycycline, Azithromycin, and other: rash,nausea and vomiting (5)
- Levaquin: seizure (1)
- Cefepime: encephalopathy (1)

Opioids: Constipation (1), Over-sedation (1)

Steroids: Hyperglycemia (23), Leukocytosis (9), agitation (1), hallucinations (1)

Other: Hypotension associated with antihypertensives (5), Bradycardia associated with Precedex and Lopressor (2), QT Prolongation associated with Haldol (1)

February 2019	Total Adverse Drug Reactions	Category 1 Reactions	Category 2 Reactions	Category 3 Reactions
Inpatient				
Anticoagulant	0	0	0	0
Antibiotic	4	4	0	0
Insulin	0	0	0	0
Chemo/Biologic	3	2	1	0
Steroids	27	27	0	0
Opioids	6	6	0	0
Other	7	5	2	0
Outpatient				
Anticoagulant	12	0	12	0
Antibiotic	2	2	0	0
Insulin	0	0	0	0
Chemo/Biologic	22	16	6	0
Steroids	11	8	3	0
Opioids	11	9	2	0
Other	18	7	11	0



Antibiotic:
- Bactrim: Hyperkalemia (1)
- Unasyn: Rash (1), Diarrhea (1)
- Vancomycin: Rash (1)

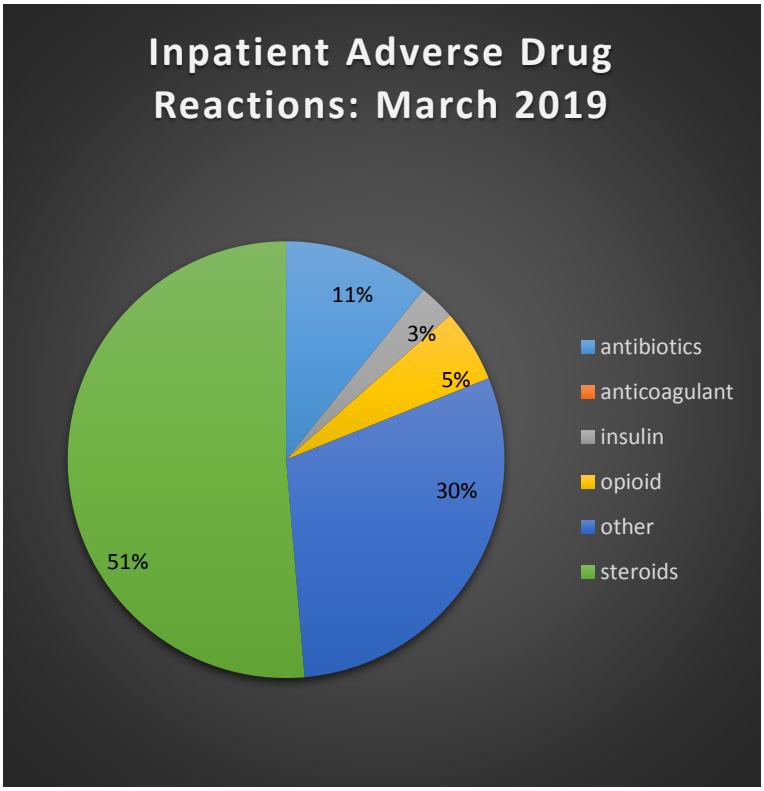
Chemo/Biologic:
- Bendamustine: SIRS (1)
- Velcade: Thrombocytopenia (1)
- Blinatumomab: Facial Nerve Disorder (1)

Opioids:
- Oxycodone: itching (1), rash (1)
- Fentanyl: Encephalopathy (1), Constipation(1)
- Morphine: Encephalopathy (1), Constipation (1), Nausea/Vomiting (1)

Steroids:
- Hyperglycemia (15)
- Leukocytosis (12)

Other:
- Zolpidem: Delirium (1)
- Hydrochlorothiazide: Hyponatremia (1)
- Zometa: Electrolyte Abnormalities (1)
- Dextrose: Hyperglycemia (2)
- Xanax: Aphasia (1)
-Ambien: Encephalopathy (1)

March 2019	Total Adverse Drug Reactions	Category 1 Reactions	Category 2 Reactions	Category 3 Reactions
Inpatient				
Anticoagulant	1	0	1	0
Antibiotic	5	4	1	0
Insulin	1	1	0	0
Chemo/Biologic	0	0	0	0
Steroids	19	19	0	0
Opioids	3	2	1	0
Other	12	11	1	0
Outpatient				
Anticoagulant	10	8	2	0
Antibiotic	9	9	0	0
Insulin	0	0	0	0
Chemo/Biologic	26	23	3	0
Steroids	34	32	2	0
Opioids	24	22	2	0
Other	52	46	6	0



Antibiotic:
- Vancomycin: Nausea/Diarrhea (1)
- Zyvox: Leukopenia (1)
- Azithromycin: Diarrhea (1)
- Levaquin: Diarrhea (1)
- Rocephin: Angioedema (1)

Anticoagulant:
- tPA: acute right hemothorax (1)

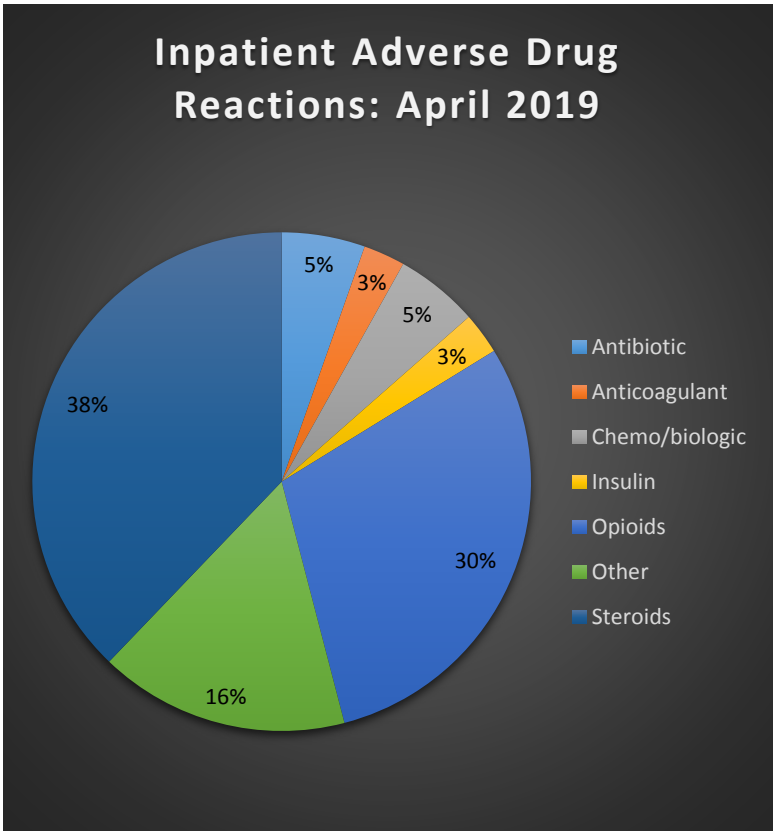
Insulin:
- Hypoglycemia (1)

Opioid:
- Dilaudid: nausea (1)
- Oxycodone: encephalopathy (1)
- Other: Constipation (1)

Steroids:
- Hyperglycemia (5)
- Hypertension (1)
- Confusion (1)
- Leukocytosis (12)
- Myopathy (1)
- Rash (1)

Other:
- Beta blockers: Bradycardia (1), SOB (1), Dizziness (1)
- Bumex: Hyponatremia (1)
- Amiodarone: Itching (1), Liver Disease (1)
- Fosphenytoin: Itching (1)

April 2019	Total Adverse Drug Reactions	Category 1 Reactions	Category 2 Reactions	Category 3 Reactions
Inpatient				
Anticoagulant	1	1	0	0
Antibiotic	2	2	0	0
Insulin	1	1	0	0
Chemo/Biologic	2	2	0	0
Steroids	22	22	0	0
Opioids	13	12	1	0
Other	8	6	2	0
Outpatient				
Anticoagulant	11	5	1	0
Antibiotic	9	6	3	0
Insulin	0	0	0	0
Chemo/Biologic	20	20	0	0
Steroids	12	10	2	0
Opioids	15	12	3	0
Other	46	37	9	0



Antibiotic:
- Amoxicillin: diarrhea (1)
- Vancomycin: rash (1)

Anticoagulant:
- Warfarin: supratherapeutic INR (1)

Chemo/Biologic:
- diarrhea (1)
- nausea/vomiting (1)

Insulin:
- hypoglycemia (1)

Opioids:
- Percocet: constipation (3)
- Methadone: constipation (1)
- Hydrocodone: constipation (1)
- MS Contin: confusion (1), nausea (1)
- Unlisted Opioid: lethargy (1), encephalopathy (1), constipation (5)

Steroids:
- leukocytosis (7)
- hyperglycemia (12)
- delirium (2)
- increased BUN (1)

Others:
- Ativan: over sedation (1)
- Metoprolol: bronchospasm (1), hypotension (2)
- Motrin: acute kidney injury (1)
- Ambien: encephalopathy (1)
- Lorazepam: delirium (1)
- Lactulose: diarrhea (1)