Pharmacy & Therapeutics Committee Meeting
Private Dining Room
April 14, 2016 7:00 a.m.

Agenda Items	Individual Responsible
1. Call to Order	Richard Pesce, MD
2. Approval of February, 2016 Minutes	Richard Pesce, MD
3. Therapeutic Interchanges and Formulary Decisions	Page
A. CHI MUE Committee – March meeting	……..Patrick Ellis, PharmD……..6-9
B. Exparel® (liposomal bupivacaine).....	…….....
C. Kengreal® (cangrelor)	…….....
D. Veltassa® (patiromer)....	……....10-12
E. Movantik® (naloxegol)	……13-17
F. Bridion® (sugammadex)	Erin Massarello, PharmD..…..18-22
G. Opthalmic Antihistamines Class Review.....	Patrick Ellis, PharmD…….23-24
H. Meningococcal Vaccines ……	Linda Johnson, PharmD……25-27
I. Cefazolin, Cefepime – Dose Adjustments….....	……28
J. Aranesp® (darbepoetin alfa)	…..Patrick Ellis, PharmD..…….
4. MUE	
A. PPI Stress Ulcer Prophylaxis.. ...	Sean Bergeron/Whitney Williams, PharmD..29-31
5. JCAHO/Regulatory	
A. Therapeutic Duplication Policy	Patrick Ellis, PharmD….32
6. Adjournment	

Next Meeting will be June 9, 2016 at 7:00 AM in the Private Dining Room

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PHARMACY AND THERAPEUTICS COMMITTEE
Minutes of Meeting

DATE: February 11, 2016 CALLED TO ORDER: 7:00 A.M.
LOCATION: Private Dining Room ADJOURNED: 8:00 A.M.

Members Present:			**Members Absent**:		**Guests**:
Richard Pesce, M.D.	Karen Babb, PharmD	Sandy Vredeveld, DPh	Diona Brown, RN	Nan Payne, RN	Sean Bergeron, PharmD
David Dodson, M.D.	Patrick Ellis, PharmD	Patty Hicks, RN	Michael Harper, M.D.	Shannon Harris, RN	Camellia Davis, PharmD
Mark Anderson, M.D.	Susan Fuchs, RD	Rodney Elliott, PhT	Kevin Lewis, CMO		Erin Massarrello, PharmD
Allen Atchley, M.D.	Michelle Denham, RN	Melissa Roden, RN	Michael Stipanov, M.D.		Whitney Williams, PharmD
Nathan Chamberlain, M.D.	Rhonda Poulson, CNO	Scott Harbaugh, Finance	Nathan Schatzman, M.D.		Linda Johnson, PharmD
Sam Currin, M.D.			Lila Heet, PharmD		Eric Nelson, MD

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 November 12, 2015 minutes were approved as submitted.		Complete
Therapeutic Interchanges and Formulary Decisions	The following medications were reviewed: 1. **Keytruda®** – Immune modulating monoclonal antibody indicated for the treatment of advanced melanoma and refractory NSCLC. Although similar to Opdivo, Dr. Stipanov recommended that this be added to formulary (non-stock) for outpatient use for the approved indications. 2. **Blincyto®** – Monoclonal antibody indicated for treatment of relapsed or refractory Philadelphia chromosome negative B-cell acute lymphoblastic leukemia (ALL). This represents a treatment option for what would otherwise be a condition with little to no other viable options. Due to the risk of serious adverse reactions Patrick explained to the committee that for the inpatient portion of Blincyto therapy that pharmacy would develop a detailed reaction guide to help nursing identify signs/symptoms of adverse reactions. Despite the safety concerns it was recommended to approve this to formulary (non-stock) for this rare condition. 3. **Voraxaze®** – Therapy indicated for treatment of toxic plasma MTX concentrations in patients who develop impaired renal function resulting in delayed clearance of MTX. Although this is a rare situation, cases of severe MTX toxicity can be fatal and leucovorin and dialysis are ineffective at preventing ongoing toxic side effects. Voraxaze rapidly	1. Approved for Formulary Non-Stock 2. Approved for Formulary Non-Stock 3. Approved for Formulary Non-Stock	Complete Complete Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	hydrolyzes MTX and is the only known therapy for this condition. It was recommended to approve to formulary (non-stock).		
	4. **Nucala**® – New monoclonal antibody (once monthly SQ injection) indicated for add-on maintenance therapy for treatment of severe asthma in patients with an eosinophilic phenotype. Clinical trials have shown that this medication has the ability to decrease the rate of exacerbations and reduce steroid requirements in patients with this asthma phenotype. Scott Harbaugh reviewed the outpatient reimbursement details with the committee and explained that the hospital could expect a modest profit based on expected payments from the hospital's normal payer mix. Due to the unique mechanism of action it was recommended to approve this therapy to formulary (non-stock) as an outpatient only medication formulary item.	4. Approved for outpatient infusion use only	Complete
	5. **Cresemba**® – Azole antifungal agent indicated for invasive aspergillosis and invasive mucormycosis. Linda explained that although this would not be commonly utilized it would be useful for patients who are intolerant of voriconazole or who are on concomitant drugs with severe drug-drug interactions with voriconazole prohibiting its use and for patients with mucormycosis who are intolerant of amphotericin B or who need salvage therapy. It was recommended by Dr. Anderson to approve to formulary (restriction to ID service) and with the formulary addition of Cresemba to remove Noxafil (posaconazole) from formulary.	5. Approved	Complete
	6. **Exparel®** – Dr. Nelson presented his request for Exparel to be allowed for utilization as a TAP block in colorectal procedures. Questions surrounding the efficacy of Exparel TAP blocks in comparison to other local anesthetics were raised by members of the committee in addition to the lack of data demonstrating prolonged efficacy of Exparel. Dr. Pesce recommended to table the discussion and allow Dr. Nelson the opportunity to further discuss the available literature on this topic with a small sub-set of the committee at a later date.	6. Sub-committee to review data from Dr. Nelson	Tabled
CHI Medication Use and Evaluation Committee	Patrick updated the committee on CHI's plans to form a national MUE (P&T) committee that will be utilized to vet formulary decisions at a national level. The committee will consist of physicians from the various CHI regions and Dr. Pesce will represent Memorial at these meetings. Patrick reviewed the charter with the committee and explained to them how this process will work in relation to the local Memorial P&T. The first meeting is scheduled for March and Exparel is a confirmed agenda item at the first meeting.	Information	Complete
Medication Safety/Quality	**Opioid Safety Work Group –** *update* Patrick updated the committee on the progress of this work group including the recent	Information Only	Tabled

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	implementation of mandatory/automatic sedation assessments following the administration of any opioid medication. Upon review of patients requiring naloxone following opioid over-sedation the question was posed by Lori Hammon (quality) if a standing order for opioid reversal would be beneficial to direct nurses upon identification of over-sedation to expedite reversal. Patrick explained that the POSS sedation scale is very objective and that if this was pursued that we would likely need to utilize some objective measures (respiratory rate, etc.) in addition to the subjective findings of the POSS scale to prevent reversal in patients that may not clinically need naloxone. After much discussion it was decided for Patrick to develop a draft of potential reversal orders and bring this back for further discussion at the April meeting.		
Policy, Procedure & Protocols	1. **Antimicrobial Stewardship Policy** Patrick reviewed a policy formally outlining the responsibilities, tasks, and leadership of the hospital's antimicrobial stewardship program. 2. **Seadative/Hypnotics for Sleep** This policy was reviewed as required every 3 years. The pharmacy reviewed 70 patients that experienced inpatient falls to assess for any contribution of sedatives or hypnotics. Based on this small review it appears that the policy as designed is continuing to positively impact falls in patients ≥ 65 years of age with only two patient in this category experiencing falls who received a hypnotic for sleep. In both of these situations these were continuation of home medications and not newly started medications as part of order sets. Patrick mentioned that benzodiazepines appear to be a contributing factor in many falls and the pharmacy will continue this retrospective evaluation to determine if any other changes may be necessary to further minimize the risk of medication related patient falls. 3. **Medication Administration – Timeliness of Meds** Modifications to this policy were suggested in order to limit the number of "time critical" medications to those that are truly felt to represent a patient safety risk if administration is greater than 30 minutes before or after the scheduled dosing time. After collaboration with clinical informatics it was recommended to only include the following in this category: antimicrobials in which serum levels are frequently utilized (vancomycin, gentamicin, amikacin), and therapeutic doses of oral and injectable anticoagulants (excluding warfarin and prophylactic doses of injectable anticoagulants such as enoxaparin 40 mg and fondaparinux 2.5 mg). It was recommended to approve these changes in order to minimize the number of	1. Approved 2. Approved 3. Approved	Complete Complete Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	medications impacted by this policy and to improve compliance with the CMS requirement for designation of time critical medications. 4. **Look Alike/Sound Alike Med List** Approved with no changes needed.	4. Approved	Complete

There being no further business, the meeting was adjourned at 8:00 A.M. The next P&T meeting is **April 14, 2016 at 7:00 a.m.**

Respectfully submitted,
Sandy Vredeveld, D.Ph. Director of Pharmacy
Patrick Ellis, Pharm.D Pharmacy Clinical Coordinator

Approved by,
Richard Pesce, M.D. Chairman

Catholic Health Initiatives

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Medication Use and Evaluation Committee

DECISION BRIEF

Date: March 15, 2016

Members Present:

CHI National:	Venita Papillion (Clinical Pharmacist), Ryan Ramaekers (National Oncology Service Line), Jerome Granato (Cardiovascular Service Line)
CHI SE:	Tom Cummins (Co-Chair, SE Division CMO (Arkansas)), Shalena McWilliams (Division Pharmacy Director), Don Meacham (P&T Physician), Richard Pesce (P&T Physician)
CHI Pacific NW:	Tim Lynch (Co-Chair, National VP Pharmacy (Interim)), John Luber (P&T Physician), Mike Bonck (Division Pharmacy Director-Interim)
CHI Health:	Jason Lambrecht (Hospital Medicine Service Line), Sunil Jagadesh (P&T Physician), Mike Tiesi (Division Pharmacy Director)
CHI IOWA:	Dan Gervich **(**P&T Physician), Greg Young (Division Pharmacy Director)
CHI Texas:	Victor Narcisse **(**P&T Physician), Kim Oas (Advanced Practice Clinician), Lorie Shoemaker (Division CNO), Craig Frost (Division Pharmacy Director)
CHI Fargo:	Gaylord Kavlie **(**P&T Physician), Keith Horner (Division Pharmacy Director)
CHI KYOne:	Nancy Morris **(**P&T Physician), Greg Rennirt (Ortho-Spine Service Line), Jim O'Donnell (Division Pharmacy Director)

Co-Chairs Tom Cummins, MD, CHI St. Vincent and Tim Lynch, CHI Franciscan Health

Executive Sponsor: Kathy Sanford, SVP and Chief Nursing Officer

Adhoc Members: Robynn Pruett, National Pharmacy staff member

Others Present: Mike Kimbel, Orthopedics Service Line

FORMULARY CONSIDERATIONS

A. Cangrelor (Kengreal™)

Drug Summary

Cangrelor (Kengreal™) is a P2Y12 platelet inhibitor indicated for use as thromboembolic prophylaxis in percutaneous coronary intervention (PCI). Clinical trials of cangrelor show mixed results. In the largest study to date, cangrelor reduced the odds of composite death, myocardial infarction (MI), ischemia-driven revascularization (IDR), or stent thrombosis (ST) by around 22% vs. clopidogrel in patients undergoing PCI. However, other research suggests that cangrelor and clopidogrel are equally efficacious. While cangrelor provides several

advantages over oral agents in terms of intravenous administration and rapidly reversible effects, it has not been studied as a solo agent and instead has been studied only when used in conjunction with clopidogrel. Further research is needed to determine its ability to replace clopidogrel for PCI thromboprophylaxis.

MUE COMMITTEE DECISION – MARCH 14, 2016

1. The MUE Committee approved the addition of cangrelor to the CHI formulary as formulary, restricted to the following indications for use:
   - STEMI patients when oral loading is not feasible
   - PCI patients that cannot be loaded orally (example: intubated)
   - Selected ACS/NSTEMI cases where likelihood of urgent* CABG is high [**Urgent procedure: Defined as a procedure required during same hospitalization in order to minimize chance of further clinical deterioration. Examples include, but not limited to, worsening sudden chest pain, CHF, AMI, unstable angina with IV NTG, or rest angina (NCDR)]*
2. Use restricted to Catheterization Laboratory and only by interventional cardiologists
3. Use in bridging is discouraged due to lack of indication and documented benefit

ACTION: A motion was made and seconded to add Cangrelor to the formulary with the above restrictions.

Voting: FOR: 13; AGAINST: 10; ABSENT: 1

B. Liposomal Bupivacaine (Exparel™)

Drug Summary

Liposomal bupivacaine liposomal injectable suspension (Exparel™) is an amide-type local anesthetic in an encapsulated liposomal formulation developed with the goal of providing a longer duration of anesthesia compared with its non-liposomal counterpart, bupivacaine hydrochloride or other local anesthetics. The product utilizes the DepoFoam drug delivery system consisting of an aqueous suspension of multivesicular liposomes containing bupivacaine in a honeycomb-like structure that allows for a more gradual release. The FDA approved bupivacaine liposomal in October 2011 for single-dose infiltration into the surgical site for postoperative analgesia.

Three phase 3 pivotal trials were reviewed by the FDA for final approval, two of them comparing liposomal bupivacaine to placebo and one comparing liposomal bupivacaine to unencapsulated bupivacaine HCl/epinephrine (unpublished). In each of the trials, the primary endpoint was pain intensity and duration using the numeric pain rating score through a predetermined period of time postoperatively (24, 72 and 96 hrs). In the placebo-controlled trials (1-bunionectomy, 1-hemorrhoidectomy), liposomal bupivacaine was associated with statistically less intense pain through the stated time period compared to placebo. In addition, opioid consumption was statistically less in favor of liposomal bupivacaine versus placebo, but the clinical significance of the difference is unknown (Golf-3.8 vs. 4.7 tabs of oxycodone 5 mg/APAP 325 mg tablets at 24 hrs, p=0.008 and Gorfine-22.3 mg vs. 29.1 mg morphine equivalents at 72 hrs, p=0.0006). However, the only phase III active control trial failed to show superiority over conventional bupivacaine. The primary efficacy endpoint (AUC of the NRS pain intensity scores through 96 hours) between treatment groups was not found to be statistically significant (P=0.15). There were also over 60 secondary endpoints evaluated and only 2 of these differed significantly between treatment groups, and in both cases, the difference favored conventional bupivacaine over LB (mean NRS-R and opioid utilization at 84 hour time point, P=0.04).

Liposomal bupivacaine has yet to demonstrate significant efficacy over alternative multimodal opioid sparing therapies for postsurgical analgesia in clinical trials. Its high cost in comparison to standard bupivacaine with epinephrine and other possible alternatives, prompts further discussion regarding its appropriate place in current post-surgical analgesia.

MUE COMMITTEE DECISION

The MUE Committee rejected the addition of liposomal bupivacaine to the CHI formulary with the decision to make liposomal bupivacaine a non-formulary product.

ACTION: A motion was made and seconded to not add liposomal bupivacaine to the formulary.

Voting: FOR: 16; AGAINST: 6; ABSENT: 2

In addition, the MUE Committee recommended that the MUE co-chairs will work to create a reference document for physicians and other stakeholders that includes data and alternatives to the indicated uses of liposomal bupivacaine.

C. Sugammadex (Bridion™)

Drug Summary
Sugammadex (Bridion™) is a modified gamma cyclodextrin that forms a complex with rocuronium and vecuronium to reduce the amount of neuromuscular blocking agent that is available to bind to nicotinic cholinergic receptors. In the clinical studies, the time to recovery and the cumulative recovery rate were significantly improved with sugammadex when compared to neostigmine. Sugammadex is only used for the reversal of rocuronium or vecuronium, which may limit its use. Sugammadex works faster and has better recovery times, but is slightly more expensive than some of the current neuromuscular blockade reversal agents.

MUE COMMITTEE DECISION
The MUE Committee approved the addition of sugammadex to the CHI inpatient and outpatient formulary, as formulary, restricted with the following indications for use:

1. Immediate reversal of neuromuscular blockade in a "cannot intubate/cannot ventilate" or other emergency situation
2. Dense residual block after conventional reversal
3. Residual block in PACU that could lead to re-intubation
4. Procedures requiring fast onset-short duration, where succinylcholine is contraindicated
5. Reversal of intubation doses of rocuronium to shorten anesthesia time for abandoned or cancelled procedures
6. Each facility that adds sugammadex to local formulary will need to implement an appropriate compliance monitoring process

ACTION: A motion was made and seconded to add sugammadex to the formulary with the above restrictions

Voting: FOR: 22; AGAINST: 0; ABSENT: 2

D. Daratumumab (Darzalez™)

Drug Summary
Daratumumab (Darzalex™) is an anti-CD38 monoclonal antibody indicated for the treatment of multiple myeloma in patients who meet the following criteria: 1) have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or 2) who are double-refractory to a PI and an immunomodulatory agent. In one study of 106 patients, 29% experienced a complete or partial reduction in tumor burden, with an average response duration of 7.4 months. Overall, daratumumab has been shown to be a safe and effective medication for use in the treatment of multiple myeloma.

MUE COMMITTEE DECISION
The MUE Committee approved the addition of daratumumab to the CHI formulary as formulary, restricted with the following indications for use:

1. Restricted to use in the outpatient infusion clinics by oncologists for the treatment of patients with multiple myeloma who have received at least 3 prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.
2. Daratumumab will be added to the Hazardous Drug List at a facility level as a Biotherapy/Non-Hazardous medication.

ACTION: A motion was made and seconded to add daratumumab to the formulary with the above restrictions

Voting: FOR: 22; AGAINST: 0; ABSENT: 2

Meeting Record Form **March 14-15, 2016**

Voting Committee Member Role		Individual Name	Cangrelor (Kengreal ™)		Liposomal bupivacaine (Exparel™)	Sugammadex (Bridion™)	Daratumumab (Darzalex™)
Southeast	Co-Chair, SE Division CMO (Arkansas)	Tom Cummins	Y	N	Y	Y	Y
CHI National	Co-Chair , National VP Pharmacy (Interim)	Tim Lynch	N	N	Y	Y	Y
CHI National	National Oncology Service Line	Ryan Ramaekers	N	Y	N	Y	Y
CHI National	Cardiovascular Service Line	Jerome Granato	Y	Y	----	----	-----
CHI National/ Market	Ortho-Spine Service Line	Greg Rennirt	Y	Y	N	Y	Y
CHI National/ Market	Hospital Medicine Service Line	Jason Lambrecht	N	N	Y	Y	Y
Pacific Northwest	P&T Physician	John Luber	Y	N	Y	Y	Y
Iowa	P&T Physician	Dan Gervich	Y	N	Y	Y	Y
Texas	P&T Physician	Victor Narcisse	N	----	Y	Y	Y
CHI Health (Nebraska)	P&T Physician	Sunil Jagadesh	Y	Y	N	Y	Y
Fargo	P&T Physician	Gaylord Kavlie	Y	Y	Y	Y	Y
Southeast (Arkansas)	P&T Physician	Don Meacham	Y	N	Y	Y	Y
Southeast (Tennessee)	P&T Physician	Richard Pesce	---	---	Y	Y	Y
KYOne	P&T Physician	Nancy Morris	Y	N	N	Y	Y
Texas	Advanced Practice Clinician	Kim Oas	Y	N	Y	Y	Y
Texas	Division CNO	Lorie Shoemaker	Y	N	---	---	---
Pacific Northwest	Division Pharmacy Director (see Interim above)	*Tim Lynch **Mike Bonck**	N	N	Y	Y	Y
CHI Health	Division Pharmacy Director	Mike Tiesi	N	N	N	Y	Y
Iowa	Division Pharmacy Director	Greg Young	Y	N	Y	Y	Y
Southeast	Division Pharmacy Director	Shalena McWilliams	N	N	Y	Y	Y
Texas	Division Pharmacy Director	Craig Frost	N	N	Y	Y	Y
KYOne	Division Pharmacy Director	Jim O'Donnell	N	N	N	Y	Y
Fargo	Division Pharmacy Lead	Keith Horner	Y	N	Y	Y	Y
CHI National	Clinical Pharmacist	Venita Papillion	N	N	Y	Y	Y

FORMULARY REVIEW

GENERIC NAME: PATIROMER

PROPRIETARY NAME: *Veltassa (Relpysa)*

INDICATION: Veltassa is a potassium binder indicated for the treatment of hyperkalemia.

While kayexalate is commonly used for non-urgent reversal of hyperkalemia in the hospital or ambulatory setting, patiromer is intended to serve as a long term maintenance medication in patients with chronic kidney disease who need to continue renin-angiontensin-aldosterone-system (RAAS) inhibition therapy while controlling associated hyperkalemia. This is based on the clinical data that accompanied it.

CLINICAL PHARMACOLOGY: Patiromer is a non-absorbed, cation exchange polymer that contains a calcium sorbitol counterion, which increase fecal potassium excretion through binding of potassium to the GI lumen. Binding of potassium reduces the concentration of free potassium in the GI lumen, resulting in a reduction of serum potassium concentrations. Based on the available data; patiromer is shown to be safe and effective in reducing serum potassium concentrations.

PHARMACOKINETICS: In radiolabeled ADME studies in rats and dogs, patiromer was not systemically absorbed and was excreted in the feces. Quantitative whole-body utoradiography analysis in rats demonstrated that radioactivity was limited to the gastrointestinal tract, with no detectable level of radioactivity in any other tissues or organs.

SPECIAL POPULATIONS:

- ***Pregnancy:*** Veltassa is not absorbed systemically following oral administration and maternal use is not expected to result in fetal risk.
- ***Lactiation:*** Veltassa is not absorbed systemically by the mother, so breastfeeding is not expected to result in risk to the infant.
- ***Geriatric Use***: Of the 666 patients treated with Veltassa in clinical studies, 59.8% were age 65 and over, and 19.8% were age 75 and over. No overall differences in effectiveness were observed between these patients and younger patients. Patients age 65 and older reported more gastrointestinal adverse reactions than younger patients.
- ***Renal Impairment***: Of the 666 patients treated with Veltassa in clinical studies, 93% had chronic kidney disease (CKD). No special dosing adjustments are needed for patients with renal impairment.

DRUG INTERACTIONS: No formal drug interaction studies have been conducted in humans. In in vitro binding studies, Veltassa was shown to bind about half of the oral medications that were tested. Binding of Veltassa to other oral medications could cause decreased gastrointestinal absorption and loss of efficacy when taken close to the time Veltassa is administered. Administer other oral medications at least 6 hours before or 6 hours after Veltassa. Monitor for clinical response and/or blood levels where possible.

ADVERSE REACTIONS:

Adverse reactions reported in ≥ 2% of patients:

Adverse Reactions	**Patients treated with Velatassa (N=666)**
Constipation	7.2%
Hypomagnesemia	5.3%
Diarrhea	4.8%
Nausea	2.3%
Abdominal Discomfort	2.0%
Flatulence	2.0%

During the clinical studies, the most commonly reported adverse reactions leading to discontinuation of Veltassa were gastrointestinal adverse reactions (2.7%), including vomiting (0.8%), diarrhea (0.6%), constipation (0.5%) and flatulence (0.5%). Mild to moderate hypersensitivity reactions were reported in 0.3% of patients treated with Veltassa in clinical trials. Reactions have included edema of the lips.

CLINICAL STUDIES:

Weir et al. NEJM 2015 – OPAL-HK		
METHODS		
Study design	Two phase study: 1. 4-week single-group, single-blind initial treatment phase 2. 8-week placebo-controlled, single-blind, randomized withdrawal phase.	
Patient enrollment	Inclusion (n=243): • 18-80 yo • Stage 3 or 4 chronic kidney disease (est. GFR 15 to < 60 ml/min • Serum K+ 5.1 to < 6.5 mmol/L • Receiving stable dose of one or more RAAS inhibitors for at least 28 days. • Stable doses of antihypertensives, loop and thiazide diuretics, and beta blockers for at least 28 days.	Exclusion: • K+ related echocardiogram changes • Severe GI disorders • Uncontrolled/unstable arrhythmias or clinically significant ventricular arrhythmias • Recent cardiac surgery • Kidney or heart transplant • ACS • TIA or stroke within previous 2 months • SBP >180 or <110, or DBP >110 or <60 • DM-I • Emergency treatment of DM-II or exacerbation of acute heart failure in previous 3 months • NYHA Class IV heart failure

Treatment Plan	• PART A – Initial Treatment Phase:
	  • 243 patients were treated with patiromer for 4 weeks. Patients with a baseline serum potassium of 5.1 mEq/L to 5.5 mEq/L received a starting patiromer dose of 8.4g daily given in divided doses and patients with a baseline serum potassium of 5.5 mEq/L to 6.5 mEq/L received a starting dose of 16.8g daily given in divided doses. The dose of patiromer was titrated, as needed, based on the serum potassium level. The level was assessed starting on Day 3 and then at weekly visits (Weeks 1, 2 and 3) until the end of the 4-week treatment period. The goal of this portion of the study was to maintain serum potassium at a target range of 3.8 mEq/L to 5.1 mEq/L.
	• PART B – Randomized Withdrawal Phase:
	  • 107 patients with a Part A baseline serum potassium of 5.5 mEq/L to 6.5 mEq/L with levels in the target range of 3.8 mEq/L to 5.1 mEq/L at Week 4 and still receiving RAAS inhibitor medication were randomized to continue patiromer or to receive placebo to evaluate the effect of withdrawing patiromer on serum potassium. In patients randomized to patiromer, the mean daily dose was 21g at the start of Part B and during Part B.	

RESULTS		
Summary of outcomes	Primary Endpoint for Initial Treatment Phase: Mean change in serum potassium from baseline to week 4.	The mean change in the serum K+ level was -1.01±0.03 mmol/L. At week 4, 76% of the patients had reached the target potassium level (3.8 to < 5.1).
	Primary Endpoint for Randomized Withdrawal Phase: Difference between patiromer group and placebo group in the median change in serum potassium level from start of this phase to week 4 of the phase, or to the earliest visit at which the patient's serum potassium level was < 3.8 mmol/L or > 5.5 mmol/L.	Serum potassium rose by 0.72 mEq/L in patients who were switched to placebo versus no change in patients who remained on patiromer ($p < 0.001$).

Bakris et al. NEJM 2015 – AMETHYST-DN	
METHODS	
Study design	Phase 2, multicenter, open-label, dose-ranging, randomized clinical trial, conducted at 48 sites in Europe from June 2011 to June 2013 evaluating patiromer in 306 outpatients with type 2 diabetes (estimated glomerular filtration rate, 15 to <60 mL/min/1.73 m2 and serum potassium level >5.0 mEq/L). All patients received RAAS inhibitors prior to and during study treatment.
Outcome Measures	The primary efficacy end point was mean change in serum potassium level from baseline to week 4 or prior to initiation of dose titration. The primary safety end point was adverse events through 52 weeks. Secondary efficacy end points included mean change in serum potassium level through 52 weeks.
Treatment Plan	Patients were stratified by baseline serum potassium level into mild or moderate hyperkalemia groups and received 1 of 3 randomized starting doses of patiromer (4.2 g [n = 74], 8.4 g [n = 74], or 12.6 g [n = 74] twice daily

	[mild hyperkalemia] or 8.4 g [n=26], 12.6 g [n=28], or 16.8 g [n=30] twice daily [moderate hyperkalemia]). Patiromer was titrated to achieve and maintain serum potassium level 5.0 mEq/L or lower.
RESULTS	
Summary of outcomes	In patients with a baseline serum potassium of 5.0 to 5.5 mEq/L who received an initial dose of 8.4g patiromer per day (as a divided dose), the mean daily dose was 14g; in those with a baseline serum potassium of 5.5 to 6.0 mEq/L who received an initial dose of 17g patiromer per day (as a divided dose), the mean daily dose was 20g during the entire study.

WARNINGS AND PRECAUTIONS

- *Binding To Other Orally Administered Agents:* Veltassa binds many orally administered medications, which could decrease their gastrointestinal absorption and lead to reduced efficacy. Administer other oral medications at least 6 hours before or 6 hours after Veltassa. Choose Veltassa or the other oral medication if adequate dosing separation is not possible.
- *Worsening of Gastrointestinal Motility:* Avoid use of Veltassa in patients with severe constipation, bowel obstruction or impaction, including abnormal post-operative bowel motility disorders, because Veltassa may be ineffective and may worsen gastrointestinal conditions. Patients with a history of bowel obstruction or major gastrointestinal surgery, severe gastrointestinal disorders, or swallowing disorders were not included in the clinical studies.
- *Hypomagnesemia:* Veltassa binds to magnesium in the colon, which can lead to hypomagnesemia. In clinical studies, hypomagnesemia was reported as an adverse reaction in 5.3% of patients treated with Veltassa.

DOSING/ADMINISTRATION:

- ***General Information*:** Administer Veltassa at least 6 hours before or 6 hours after other oral medications. Administer Veltassa with food. Do not heat Veltassa (e.g., microwave) or add to heated foods or liquids. Do not take Veltassa in its dry form.
- ***Recommended Dosing and Titration:*** The recommended starting dose of Veltassa is 8.4 grams patiromer once daily. Monitor serum potassium and adjust the dose of Veltassa based on the serum potassium level and the desired target range. The dose may be increased or decreased, as necessary, to reach the desired serum potassium concentration, up to a maximum dose of 25.2 grams once daily. The dose can be up-titrated based on serum potassium level at 1-week or longer intervals, in increments of 8.4 grams.

COST:

Vetlassa 8.4 gm 4-packets/box = $119.00; $29.75 per 8.4 gm packet
Comparator cost (kayexalate) = $0.55 per 15 gm dose

Based upon mean doses reported in dose ranging studies performed on this agent, it is expected most patients will often require 2 packets per day to maintain desirable serum potassium levels. Therefore the cost of therapy for most patients would be approximately $60.00 per day.

CONCLUSION

Patiromer is a non-absorbed, cation exchange polymer that contains a calcium sorbitol counterion, which increases fecal potassium excretion through binding of potassium to the GI lumen. Binding of potassium reduces the concentration of free potassium in the GI lumen, resulting in a reduction of serum potassium concentrations. Based on the available data; patiromer is shown to be safe and effective in reducing serum potassium concentrations.
However it is not anticipated patiromer is an agent that needs to be initiated as new therapy for hospitalized patients. This anticipated role of patiromer is different from kayexalete. While kayexalate is commonly used for non-urgent reversal of hyperkalemia in the hospital setting, patiromer is intended to serve as a long term maintenance medication in patients with chronic kidney disease who need to continue renin-angiontensin-aldosterone-system (RAAS) inhibition therapy while controlling associated hyperkalemia.

RECOMMENDATION

This medication will be discussed at the April 19th national MUE committee and the recommendation that will be presented to this meeting will be to designate this as a non-formulary medication. This medication was discussed with Dr. Nathan Chamberlain and he agreed that due to the cost that designating this non-formulary was a reasonable decision based on cost, etc. Patients that are stabilized this as a home medication may be allowed to utilize their own medication per the hospital's formulary policy.

FORMULARY REVIEW

GENERIC NAME: NALOXEGOL

PROPRIETARY NAME: *Movantik* (Astra Zeneca)

THERAPEUTIC CLASS: Peripheral Mu-Opioid Receptor Antagonist (PAMORA)

SIMILAR DRUGS: Alvimopan (Entereg®), Methylnaltrexone (Relistor®), Eluxadoline (Viberzi®)

INDICATIONS: Naloxegol is an opioid antagonist indicated for the treatment of opioid-induced constipation (OIC) in adult patients with chronic non-cancer pain.

CLINICAL PHARMACOLOGY: Naloxegol is a pegylated derivative of the mu-opioid receptor antagonist naloxone. Pegylation confers p-glycoprotein transporter substrate properties, reduces passive permeability, and therefore limits the ability of naloxegol to cross the blood-brain barrier. As a result, Naloxegol binds to peripheral mu-opioid receptors located in tissues such as the gastrointestinal tract where it decreases the constipating effects of opioids.

PHARMACOKINETICS: Following oral administration, naloxegol is absorbed with peak concentrations (Cmax) achieved at less than 2 hours. In a majority of patients, a secondary plasma concentration peak of naloxegol was observed approximately 0.4 hours to 3 hours after the first peak. Accumulation was minimal following multiple daily doses. A high-fat meal increases the extent and rate of drug absorption (dosed on an empty stomach in clinical trials).

Naloxegol is metabolized primarily by the CYP3A4 enzyme system. Following oral administration, 68% and 16% of total administered dose were recovered unchanged in the feces and urine, respectively. Parent naloxegol excreted in the urine accounted for less than 6% of the total administered dose. The half-life of naloxegol at therapeutic doses ranged from 6-11 hours

SPECIAL POPULATIONS:
Pregnancy (Category C): There are no adequate and well-controlled studies with naloxegol in pregnant women. The use of naloxegol during pregnancy may precipitate opioid withdrawal in a fetus due to the immature fetal blood-brain barrier.

Nursing mothers: It is not known whether naloxegol is excreted in human milk. Since the potential for serious adverse reactions is present, including opioid withdrawal, in nursing infants, a decision should be made to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Geriatrics: Of the total number of subjects in clinical studies, 11% were 65 years of age and older, while 2% were 75 years of age and older. No overall differences in safety or effectiveness were observed between these patients and young patients, and other reported clinical experience has not identified differences in responses.

Hepatic Impairment: The effect of severe hepatic impairment (Child-Pugh Class C) on the pharmacokinetics of naloxegol has not been evaluated. Avoid use in patients with severe hepatic impairment, as the dosage in these patients has not been determined.

Renal Impairment: Some subjects with creatinine clearance (CrCl) < 60 mL/min (i.e., moderate, severe, or end-stage renal disease) were shown to exhibit markedly higher systemic exposure of naloxegol compared to subjects with normal renal function. The reason for these high exposures is not understood. The risk of adverse reactions increases with systemic exposure, so a lower initial dose is recommended (12.5mg daily). No dosage adjustment is needed in patients with mild renal impairment.

CLINICAL STUDIES:

KODIAC-04 & KODIAC-05
Study Design: two identical multicenter, randomized, double-blind, parallel-group, placebo-controlled studies
Patients: Patients were 18 to 84 years of age and receiving oral opioids for non-cancer pain at a morphine equivalent dose of 30 to 1000 mg/day for at least four weeks. Patient eligibility was confirmed during a 2-week screening period.

Methods: Patients meeting study criteria kept a diary to record symptoms of active opioid-induced constipation for two additional weeks. Constipation was defined as less than three spontaneous bowel movements per week with one or more of the following: hard or lumpy stools, straining, or incomplete evacuation for at least 25% of bowel movements.

Major exclusion criteria included uncontrolled pain despite opioid analgesic therapy, cancer within five years of study enrollment, medical conditions associated with diarrhea or constipation, evidence of gastrointestinal obstruction or conditions that increase risk of bowel perforation. The trial protocols included a randomization procedure to ensure at least 50% of each study arm contained patients with an inadequate laxative response which required patients to have utilized one or more laxative classes for a minimum of four days within two weeks before screening and have stool-symptoms rated as moderate or greater on a baseline laxative-response questionnaire. Throughout the confirmation and treatment period laxatives and other bowel treatments were not allowed; however, patients were allowed bisacodyl rescue if a bowel movement had not occurred within 72 hours.

Primary Endpoint: The response rate over 12 week treatment period, defined as three or more spontaneous bowel movements (bowel movements without the use of rescue laxative treatment in the previous 24 hours) per week, and an increase of one or more spontaneous bowel movements over baseline for at least 9 of 12 treatment weeks, and at least 3 of the final 4 treatment weeks.

Study Results	KODIAC-04			KODIAC-05		
Response rate over 12-wk treatment*	29.4%	40.8%	44.4%	29.3%	34.9%	39.7%
Difference vs. placebo (95% CI), bowel movements per week		11.4 (2.4-20.4)	15 (5.9-20.4)		5.6 (- 2.9-14.1	10.3 (1.7-18.9)
NNT (95% CI), bowel movements per week		9 (5-42)	7 (4-17)		18 (7-34)	10 (5-59)
Response rate over 12-wk treatment in patients with Inadequate response to laxatives	28.8%	42.6%	48.7%	31.4%	42.4%	46.8%
Difference vs. placebo (95% CI), bowel movements per week		13.8 (1.6-26)	19.9 (7.7-32.1)		11 (- 1-23)	15.4 (3.3-27.4)
NNT (95% CI), bowel movements per week		7 (4-63)	5 (3-13)		10 (4-100)	7 (4-30)
Median time to first SBM (hours)	35.8	20.4	5.9	37.2	19.3	12
Change from baseline, number of SBM per week, mean ± SE	2.02 ± 0.18	2.56 ± 0.18	3.02 ± 0.18	2.1 ± 0.18	2.62 ± 0.18	3.14 ± 0.19
Patients using bisacodyl rescue at least once	72%	63.4%	54.7%	70.7%	57.3%	57.3%

*Primary endpoint

- In both trials, the 25 mg dose showed statistically significant benefit for the primary endpoints of response over 12-weeks and response in inadequate laxative responders over 12 weeks. The 12.5 mg dose was statistically significant for both the primary endpoints only in KODIAC-04 trial.
- There is moderate quality evidence that naloxegol is efficacious in patients who have a history of inadequate response to laxatives.
- Both naloxegol treatment groups in both studies had bisacodyl rescue utilization at least once over the 12-week treatment in at least 50% of patients. No subgroup analysis (pre-hoc or post-hoc) were reported for patients who used bisacodyl for rescue.
- There are not any published studies that compare the efficacy of naloxegol with usual care or other treatment modalities, nor any Cochrane systematic reviews or meta-analysis for naloxegol available.

Author's Conclusion: The studies showed that treatment with naloxegol achieved response rates that were increased by 10-15%, as compared to placebo, in patients with chronic non-cancer pain and opioid-induced constipation.

KODIAC-08:
Study Design: 52-week, multicenter, open-label, randomized, parallel-group phase 3 safety and tolerability study
Study Funding: AstraZeneca (naloxegol manufacturer)
Patients: Patients were 18 to 84 years of age and were enrolled as new patients or rollover patients from KODIAC-05 or KODIAC-04. All patients were receiving oral opioids for non-cancer pain at a morphine equivalent dose of 30 to 1000 mg/day for at least four weeks. Patient eligibility was confirmed during a 2-week screening period where use of laxative (other than rescue medication) was not permitted.

Methods: Patients meeting study criteria were randomized 2:1 to open-label naloxegol 25mg once daily (n=563) or usual-care (UC) treatment (n=281) using laxatives available for use in constipation or OIC. Peripheral mu-opioid antagonists including methylnaltrexone or naloxone-containing products were not allowed in the UC arm. The UC treatment could be modified at any point during the 52 week study period. No specific rescue protocol was determined for the UC group. The naloxegol group was allowed rescue bisacodyl 10-15 mg every 12 hours for a total of three doses when 72 hours had passed without a bowel movement.

Safety and tolerability were assessed at the OIC confirmation visit, baseline, weeks 1 and 2 of treatment, every month up to 12 months, and at the follow-up visit (2 weeks after the month 12 visit). Vital signs and laboratory, clinical, and ECG assessments were performed at screening, baseline, weeks 1 and 2, months 1, 3, 6, 9, 12, and follow-up. Physical examinations were conducted at screening, baseline and months 6 and 12. Treatment-emergent AEs were defined as those occurring during the treatment period. AEs of special interest included selected cardiovascular events, AEs with a potential relationship to blood pressure changes or opioid withdrawal, and serious GI events adjudicated for bowel perforation. In addition, the mean bisacodyl dose per week for naloxegol-treated patients was assessed from randomization to month 1, months 1 to 3, months 3 to 6, months 6 to 9 and months 9 to 12.

Primary Endpoint: A majority of patients in each group had an adverse event (naloxegol 81.8% vs UC 72.2%). Additionally, a majority of patients in each group had a treatment-emergent adverse event, however abdominal pain (17.8% vs 3.3%), diarrhea (12.9% vs 5.9%), nausea (9.5% vs 4.1%), headache (9.0% vs 4.8%), flatulence (6.9% vs 1.1%), bronchitis (5.6% vs 4.4%), and upper abdominal pain (5.1% vs 1.1%) occurred more frequently with naloxegol that usual care.

Secondary Endpoints: The number of patients with AE related to decreased blood pressure, serious GI adverse effects, and opioid withdrawal adverse effects were similar between groups. Two patients in each group met criteria for a major adverse cardiac event, upon independent adjudication neither were considered to be related to the study medication.

Authors Conclusions: Long-term administration of naloxegol 25 mg was generally safe and well tolerated, with preservation of opioid analgesia in patients with non-cancer pain and OIC. The most common AEs observed in the naloxegol group were GI, as would be expected based on the underlying mechanism of action at enteric l-opioid receptors. Treatment with naloxegol is a viable option for the management of OIC in this patient population.

COMPARATIVE EFFICACY: NO ACTIVE COMPARATOR TRIALS ARE AVAILABLE.

Due to similar mechanisms of action on peripheral mu-opioid receptors, comparative safety and efficacy between naloxegol and methylnaltrexone may be questioned. While no head to head comparative trials have been performed the following data is available for both products:

	Naloxegol (Movantik)	Methylnaltrexone (Relistor)
Time to peak concentration	<2 hours with secondary plasma peak 0.4-3 hrs after initial peak	30 minutes
Efficacy Onset	**Median time to first SBM:** KODIAC-04: 25mg – 5.9 hrs 12.5 mg – 20.4 hrs KODIAC-05: 25 mg – 12 hrs 12.5 mg – 19.3 hrs	**% of patients with SBM within 4 hrs of first dose:** Study 1: Methylnaltrexone 12 mg daily - 33% (~50% of patients had SBM within 24 hours) Study 3: Methylnaltrexone 0.15 mg/kg – 62% Methylnaltrexone 0.3 mg/kg – 58% Study 4: Methylnaltrexone 0.15 mg/kg – 48%
Adverse Effects	Abdominal Pain: 12-21% Diarrhea: 6-9% Nausea: 7-8% flatulence 3-6% vomiting 3-5%	Abdominal Pain: 21-29% Nausea: 9-12% Diarrhea: 6% Flatulence: 13% Hyperhidrosis: 6% Dizziness: 7%

CONTRAINDICATIONS:
Naloxegol is contraindicated for patients with known or suspected gastrointestinal obstruction and patients at increased risk of recurrent obstruction due to the potential for gastrointestinal perforation. Patients concomitantly using strong CYP3A4 inhibitors

(e.g., clarithromycin, ketoconazole) because these medications can significantly increase exposure to naloxegol which may precipitate opioid withdrawal symptoms such as hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, irritability, and yawning.

WARNINGS AND PRECAUTIONS:
Gastrointestinal Perforation: Cases of gastrointestinal perforation have been reported with use of another peripherally acting opioid antagonist in patients with conditions that may be associated with localized or diffuse reduction of structural integrity in the wall of the gastrointestinal tract (e.g., peptic ulcer disease, Ogilvie's syndrome).

Opioid Withdrawal: Clusters of symptoms consistent with opioid withdrawal, including hyperhidrosis, chills, diarrhea, abdominal pain, anxiety, and irritability have occurred in patients treated with naloxegol. In addition, patients receiving methadone as therapy for their pain condition were observed to have a higher frequency of gastrointestinal adverse reactions that may have been related to opioid withdrawal than patients receiving other opioids.

ADVERSE REACTIONS:
Gastrointestinal related adverse reactions for patients receiving 25 mg or 12.5 mg naloxegol were reported relative to placebo: abdominal pain (21%, 12%, vs. 7%), diarrhea (9%, 6%, vs. 5%), nausea (8%, 7%, vs. 5%), flatulence (6%, 3%, vs. 3%), and vomiting (5%, 3%, vs. 4

DRUG INTERACTIONS:
Naloxogel is contraindicated with concomitant administration of strong CYP3A4 inhibitors (ketoconazole, itraconazole, clarithromycin) and use should be avoided if possible with moderate CYP3A4 inhibitors (diltiazem, erythromycin, verapamil).

DOSING AND ADMINISTRATION:
Adult Dosing: 25 mg once daily by mouth in the morning and if patients are not able to tolerate naloxegol or if the CrCl is less than 60 ml/min, reduce to dosage to 12.5 mg once daily. If this dose is well tolerated but opioid-induced constipation symptoms continue, the dosage may be increased to 25 mg by mouth once daily.

Administration: Take naloxegol on an empty stomach without crushing the tablet at least one hour prior to the first meal of the day or two hours after the meal. Discontinue naloxegol if treatment with the opioid pain medication is also discontinued. Discontinue all maintenance laxative therapy prior to initiation of naloxegol. Laxative(s) can be used as needed if there is suboptimal response to naloxegol after 3 days.

PHARMACOECONOMICS:

	HT Contract	Cost per unit	Cost per Dose
Movantik (Naloxegol) 12.5mg tablets	YES	$248.01/#30	$8.27
Movantik (Naloxegol) 25 mg tablets	YES	$248.01/#30	$8.27
Reslistor (chronic non-cancer OIC) 12 mg SC daily	YES	$95.16/EACH	$95.16
Relistor (38-61 kg)* 8mg SC q24-48 hrs	YES	$95.16/EACH	$95.16
Relistor (62-114 kg)* 12 mg SC q 24-48 hrs	YES	$95.16/EACH	$95.16
Relistor (>114kg)* 0.15mg/kg q24-48 hrs	YES	$95.16/EACH	MIN $190.32

*dosing for Adults with advanced illness and opioid-induced constipation

SUMMARY & RECOMMENDATION:
- Current Relistor restrictions: ED, hospice, GI, and oncology
- Annual Relistor Spend: $40,000

The similar mechanism of actions of naloxegol and methylnaltrexone make these two agents interesting comparator agents despite the differing modes of administration. Due to the similar mechanisms and onset of actions as demonstrated in the clinical studies, the possibility exists to utilize naloxegol as an alternative for some patients with OIC who normally would utilize Relistor. The acquisition cost difference of $86.89 per dose offers an intriguing cost savings opportunity within this class of medications.

If added to formulary the below restrictions should likely be considered:
1. Taking naloxegol prior to admission for chronic opioid induced constipation (OIC)
2. Receiving chronic (>4 weeks) opioid therapy with failure to respond to oral and rectal laxative therapy
3. Candidates for methylnaltrexone (Relistor) subcutaneously for OIC but who can tolerate oral therapy

POTENTIAL **THERAPEUTIC INTERCHANGE:** For the treatment of opioid induced constipation with failure of laxative therapy, in patients who can tolerate oral medications methylnaltrexone should be converted to naloxegol according to the following:

When you order this	**You will receive**
Methylnaltrexone (Relistor) 12 mg subcutaneously	Naloxegol (Movantik) 25 mg po same frequency
Methylnaltrexone (Relistor) 8 mg subcutaneously	Naloxegol (Movantik) 12.5 mg po same frequency
Methylnaltrexone (Relistor) weight based dosing (0.15 mg/kg) Weight based dose < 12 mg Weight based dose ≥ 12 mg	 Naloxegol (Movantik) 12.5 mg po same frequency Naloxegol (Movantik) 25 mg po same frequency

**discontinue all maintenance laxative therapy prior to initiation of naloxegol

**adjust initial naloxegol dose for CrCl ≤60 ml/min to 12.5 mg daily, may increase to 25 mg if ineffective

**for use with concomitant moderate CYP3A4 inhibitors reduce dose to 12.5 mg daily (use with strong CYP3A4 inhibitors is contraindicated)

FORMULARY REVIEW

GENERIC NAME: SUGAMMADEX

PROPRIETARY NAME: BRIDION (Merck)

INDICATIONS: FDA approved for the reversal of neuromuscular blockade induced by rocuronium bromide and vecuronium bromide in adults undergoing surgery.

CLINICAL PHARMACOLOGY: Sugammadex is a modified gamma cyclodextrin with a lipophilic cavity and hydrophilic exterior. The positively charged ammonium groups of rocuronium and vecuronium are attracted to the negatively charged sugar groups in the center of sugammadex, binding in a 1 to 1 ratio. Removal of the free blocking agent from the plasma creates a concentration gradient that draws the agent out of the neuromuscular junction, rapidly reducing the amount of blocking agent available to bind nicotinic cholinergic receptors and reversing the neuromuscular blockade.

PHARMACOKINETICS: Sugammadex exhibits linear kinetics in the dosage range of 1 to 16 mg/kg when administered as an IV bolus dose. No metabolites of sugammadex have been observed in clinical studies and only renal excretion of the unchanged product was observed as the route of elimination. Greater than 90% of the dose is excreted within 24 hours and at least 95% could be attributed to unchanged sugammadex. Administration of sugammadex to healthy volunteers resulted in increased renal elimination of rocuronium in complex. The half-life of sugammadex in patients with mild, moderate and severe renal impairment is 4, 6, and 19 hours, respectively.

ADVERSE REACTIONS:

Adverse reactions reported in at least 10% of subjects receiving 2, 4, or 16 mg/kg sugammadex in pooled phase I-III clinical trials.

Adverse Reaction	Sugammadex	Placebo
Pain	36-52%	38%
Nausea	23-25%	23%
Vomiting	11-15%	10%
Headache	5-10%	8%
Hypotension	4-13%	4%

WARNINGS AND PRECAUTIONS:

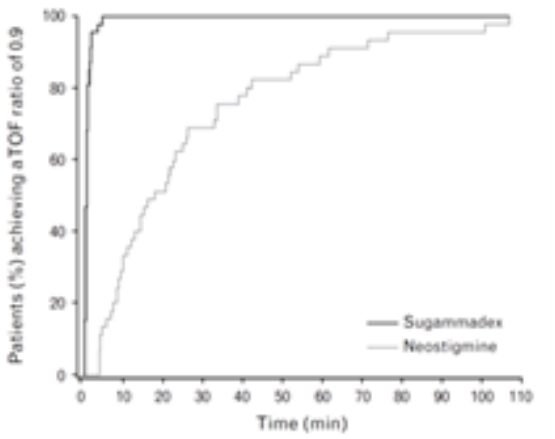
- Anaphylaxis: Anaphylaxis has occurred in 0.3% of healthy volunteers. Observe patients for an appropriate period of time after administration.
- Cardiovascular: Marked bradycardia, which may result in cardiac arrest, has been reported within minutes of administration; monitoring recommended and administration of anticholinergic agents should be administered if significant bradycardia is observed.
- Respiratory: Ventilatory support is mandatory until adequate spontaneous respiration is restored.
- Waiting times for re-administration of neuromuscular blocking agent: If re-administration of a neuromuscular blocking agent is required after reversal with Bridion, waiting times should be based on the dose of Bridion and the renal function of the patient. Consider use of a non-steroidal neuromuscular blocking agent.
- Neuromuscular blockade reversal: Do not use to reverse blockade induced by non-steroidal neuromuscular blockers or steroidal neuromuscular blockers other than rocuronium and vecuronium.

DRUG INTERACTIONS:

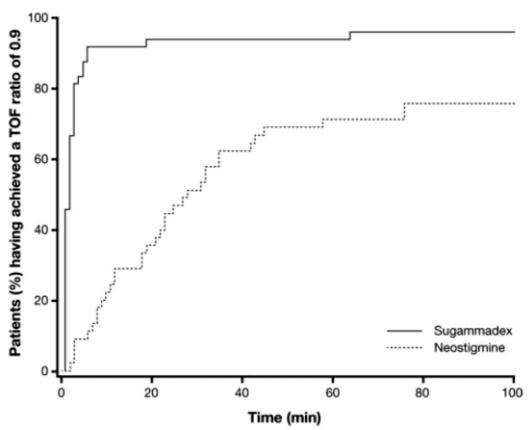
- Hormonal Contraceptives
  - Concomitant use may decrease serum contraceptive concentrations and efficacy.
  - Recommend using an additional, non-hormonal method of birth control for 7 days following the use of sugammadex.
- Toremifene
  - May result in recurrence of or delayed recovery from neuromuscular blockade

CLINICAL STUDIES:

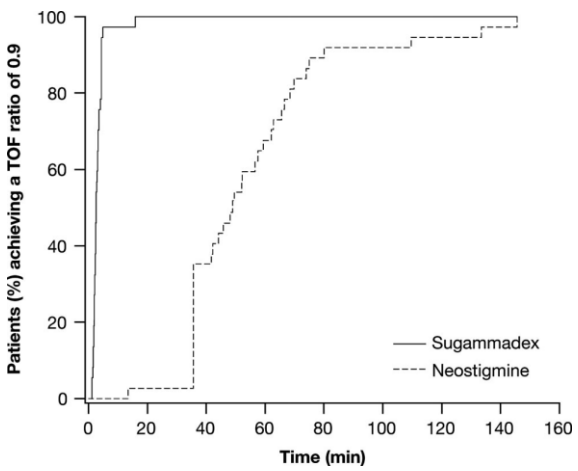
Moderate Neuromuscular Blockade Studies

Blobner et. al. *Eur J Anaesthesiol* 2010;27:874–881		
	METHODS	
Study design	multicenter, randomized, parallel-group, active-controlled, safety-assessor blinded, phase III trial (rocuronium arm of the AURORA trial)	
Patient enrollment	Inclusion (n=98): • 18 years or older • ASA class I–III • Any body weight • scheduled for elective surgery under general anesthesia were enrolled	Exclusion: • expected difficult intubation • receiving medication known to interact with rocuronium • having neuromuscular or significant renal disease • a history of malignant hyperthermia • allergy or other contraindication to medications used during the study • Females if pregnant, of childbearing potential not using a mechanical method of birth control or if breast-feeding
Baseline characteristics	55 men, 41 women of comparable height, weight and age between groups. 96% of patients in each group were ASA physical status I or II. Surgery type: endocrine, ocular, ENT, abdominal (gynecological, colorectal, urological), or orthopedic	
Treatment Plan	• 0.6mg/kg rocuronium-induced moderate NMB monitored by acceleromyography and TOF • Maintenance rocuronium 0.1–0.2mg/kg doses administered according to clinical need during surgery • **Sugammadex 2mg/kg** (n=48) vs. **neostigmine 50 mcg/kg + glycopyrrolate** (n=48) single bolus injection after the last dose of rocuronium at reappearance of T2	
	RESULTS	
Summary of outcomes	Primary Endpoint: time from start of administration of intervention to recovery of TOF ratio to 0.9: Geometric mean time • **Sugammadex 1.5 min vs.** • **Neostigmine 18.6 min (p<0.0001)** Predictability of response greater with sugammadex: 98% of sugammadex versus 11% of neostigmine patients recovering to a TOF ratio of 0.9 within 5 min. Authors noted that even 60 minutes after administration of reversal agent, less than 90% of the patients in the neostigmine group had reached the recommended recovery level for safe extubation (Fig. 1).	Figure 1. (see next page) 
Adverse Events	All drug-related adverse events were mild or moderate in intensity, except for one case of severe abdominal pain in a sugammadex treated patient and one case of severe bradycardia in a neostigmine-treated patient.	

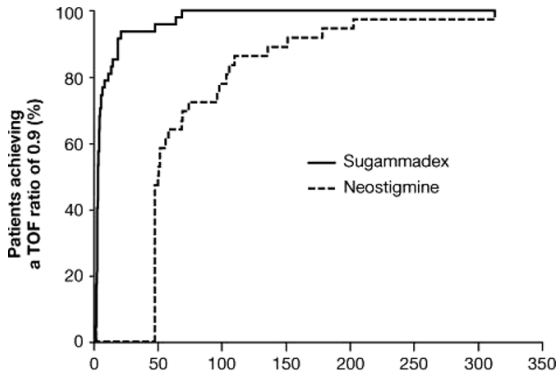
Khuenl-Brady et. al. *Anest Analg* 2010; 110:64 –73	
METHODS	
Study design	multicenter, randomized, parallel-group, active-controlled, safety-assessor blinded, phase III trial
Patient enrollment	Vecuronium arm of the AURORA trial. Inclusion/exclusion criteria identical to Blobner et al above.
Baseline characteristics	47 men, 46 women of comparable height, weight and age between groups. 94% of patients in each group were ASA physical status I or II. Surgery type: endocrine, ocular, ENT, abdominal (gynecological, colorectal, urological), or orthopedic
Statistical analyses	46 patients needed in each group, for a power of 95% to detect a difference of at least 5 min between treatment groups – **power was not met**
Treatment Plan	• 0.1 mg/kg vecuronium-induced NMB monitored by acceleromyography and TOF mode of stimulation. ○ Maintenance doses of 0.02– 0.03 mg/kg at reappearance of T2 if needed • **Sugammadex 2mg/kg** (n=48) vs. **neostigmine 50 mcg/kg + glycopyrrolate** (n=45) single bolus injection after the last dose of rocuronium at reappearance of T2

RESULTS		
Summary of outcomes	Primary Endpoint: time from start of administration of intervention to recovery of TOF ratio to 0.9: Geometric mean time • **Sugammadex 2.7 min vs.** • **Neostigmine 17.9 min (p<0.0001)**	 Figure 1.
Adverse Events	Treatment-related adverse events were similar between groups (14.6% sugammadex and 22.2% neostigmine) and included dry mouth, nausea, vomiting, and procedural hypertension	

Profound Neuromuscular Blockade Studies

Jones et. al *Anesthesiology* 2008		
METHODS		
Study design	Phase III, multicenter, randomized, parallel-group, safety assessor– blinded study (Rocuronium arm of SIGNAL trial)	
Patient enrollment	Inclusion (n=88): • 18 years or older • ASA physical status I–IV • scheduled for elective surgery using rocuronium for tracheal intubation and maintenance of neuromuscular blockade	Exclusion: • expected difficult intubation • receiving medication known to interact with rocuronium • having neuromuscular or significant renal disease • a history of malignant hyperthermia • allergy or other contraindication to medications used during the study • Females if pregnant, of childbearing potential not using a mechanical method of birth control or if breast-feeding
Baseline characteristics	No significant differences	
Statistical analyses	To achieve 95% power to detect a difference of 5 min or more, 30 patients were needed per group	
Treatment Plan	• The median intubating dose of rocuronium was 0.6 mg/kg for both groups ○ Mean maintenance doses of 0.15 mg/kg were administered when needed • **Sugammadex 4mg/kg** (n=37) vs. **neostigmine 70 mcg/kg + glycopyrrolate** (n=37) single bolus injection after the last dose of rocuronium at reappearance of T2	
Mean		
Summary of outcomes	One sugammadex and 15 neostigmine treated patients had missing times for recovery of the TOF ratio to 0.9, because it was not reached during the observation period. Primary Endpoint: intervention to recovery of TOF ratio to 0.9 geometric mean time • **Sugammadex 2.7 min vs.** • **Neostigmine 49 min (p<0.0001)** Based on available patient data (sugammadex n=30; neostigmine n=22), 70% of sugammadex patients recovered within 3 min of administration and all but one recovered within 5 min. (Fig 1)	Figure 1. 

Jones et. al *Anesthesiology* 2008	
Adverse Events	Serious AEs were reported for 2 sugammadex and 3 neostigmine patients; none were considered study drug related

Lemmens et. al *BMC Anesthesiology* 2010		
METHODS		
Study design	Phase III, multicenter, randomized, parallel-group, safety assessor-blinded study, (Vecuronium arm of SIGNAL trial)	
Patient enrollment	Enrollment criteria outlined above in Lee et. al study (identical to rocuronium arm of SIGNAL trial)	
Baseline characteristics	More women (63% vs 42%), more ASA status I-II (87% vs 64%), and younger mean age (50 vs 57 years) in sugammadex group. Surgery type: gynecologic, urologic, open abdominal, and laparoscopic abdominal	
Statistical analyses	To achieve 95% power to detect a difference of 5 min or more, 30 patients were needed per group	
Treatment Plan	• **Sugammadex 4mg/kg** (n=47) vs. **neostigmine 50 mcg/kg + glycopyrrolate** (n=36) single bolus injection after the last dose of rocuronium at reappearance of T2 - 44 patients received vecuronium induction and maintenance doses	
Results		
Summary of outcomes	Primary endpoint: time from start of administration of intervention to recovery of TOF ratio to 0.9: Geometric mean time • Sugammadex 4.5 minutes versus • Neostigmine 66.2 minutes ($p < 0.0001$) Sugammadex: reversal after vecuronium intubation vs. intubation plus 1 or more maintenance doses (4.2 v 4.5 min).	Figure 1. (see next page) 
Adverse Events	19.6% sugammadex patients with drug-related AEs vs. 27.8% in neostigmine group: nausea or post-procedural nausea (sugammadex, n = 5; neostigmine, n = 3) and leukocytosis (n=1 and n=2 respectively). There were no deaths or serious drug related AEs in either treatment group	

DOSING/ADMINISTRATION:
Dosing is based on actual body weight, given as an IV bolus over 10 seconds

Routine reversal of rocuronium- or vecuronium-induced blockade
•Deep block (at least 1 to 2 post-tetanic counts but prior to appearance of T2): 4 mg/kg IV as a single dose
•Moderate block (after appearance of T2): 2 mg/kg IV as a single dose

Immediate reversal of rocuronium-induced blockade
•16 mg/kg as a single dose administered soon (~3 minutes) after administration of a single dose of 1.2 mg/kg of rocuronium.
Note: This dose of sugammadex has not been evaluated following administration of vecuronium.

Flush the infusion line with 0.9% NaCl between administration of sugammadex and other medicinal agents. Do not mix sugammadex with other products.

DOSE ADJUSTMENTS:
- Pediatric Use – Safety and efficacy of sugammadex in pediatric patients have not been established.
- Geriatric Use – No dose adjustments necessary
- Renal Impairment – Use is not recommended in patients with CrCl< 30ml/min or those on dialysis

COST/COST COMPARISON:

- Sugammadex 200 mg/2 ml – **$90.40** (adequate for 100 kg patient with 2 mg/kg dosing) – moderate block reversal
- Neostigmine 3 mg + Glycopyrrolate 1.2 mg (typical adult dose) – **$28.28**

CONCLUSION:

Sugammadex is a potent neuromuscular blockade reversal agent for rocuronium and vecuronium with a novel mechanism of action. It has a faster time to recovery and a higher cumulative recovery rate than neostigmine. It also may have less adverse effects since it is not an acetylcholinesterase inhibitor and does not require the use of an anticholinergic agent (such as glycopyrrolate) to reduce side effects. Therefore, it also reduces the chance for errors to occur due to the administration of fewer medications needed for reversal. Sugammadex was not studied for reversal following rocuronium or vecuronium administration in the ICU, so it should be used with caution. It should not be used to reverse blockade induced by steroidal neuromuscular blocking agents other than rocuronium or vecuronium. It should also not be used to reverse non-steroidal neuromuscular blocking agents (such as succinylcholine or benzylisoquinolium compounds).

RECOMMENDATION:

The following recommendations were recommended and supported by anesthesia and are in concordance with the recent national MUE committee recommendations for use approved at the March 2016 meeting.

- Immediate reversal of neuromuscular blockage in a "cannot intubate/cannot ventilate" or other emergency situation
- For intubation doses of rocuronium/vecuronium to shorten anesthesia time for shorter than expected, abandoned or cancelled procedures.
    - Examples:
        - Situations in which a surgery is started and the patient was recently administered rocuronium or vecuronium but the surgery is quickly aborted due to multiple tumors or other reasons.
        - Surgeries that end quicker than expected and significant neuromuscular block still present and they have 1 or no twitches at the end of the case – To allow the turnover of the room in times of heavy surgery volumes versus waiting for twitch return and neostigmine being an option

FORMULARY CLASS REVIEW

THERAPEUTIC CLASS: OPTHALMIC ANTIHISTAMINES

GENERIC/PROPRIETARY NAME: Azelastine Hydrochloride (Optivar), Epinastine Hydrochloride (Elestat), Ketotifen Fumarate (Zaditor), Olopatadine Hydrochloride (Patanol, Pataday), Emedastine Difumarate (Emadine)

THERAPEUTIC CLASS: Multiple action histamine antagonists

INDICATIONS: Allergic conjunctivitis, seasonal allergic rhinitis, itching prophylaxis

CLINICAL PHARMACOLOGY:
The multiple action histamine antagonists all exhibit selective H(1) receptor antagonistic properties blocking the release of histamine from cells involved in the allergic response. They also demonstrate inhibition of other mediators involved in allergic reactions. Azelastine also inhibits leukotrienes and platelet-aggregating factor (PAF), and reduces chemotaxis and eosinophil activation. Epinastine has additional affinity for histamine H(2)-, gamma(1)-, gamma(2)-, and 5-HT(2) receptors. Ketotifen, is also mast cell stabilizer that acts by inhibiting the release of mediators from cells involved in hypersensitivity reactions and also prevents chemotaxis and activation of eosinophils. Olopatadine also blocks the type 1 immediate hypersensitivity reactions including prevention of histamine-mediated effects on human conjunctival epithelial cells. It has no activity on dopamine, alpha-adrenergic and muscarinic type 1 and type 2 receptors. Emedastine is a pure H(1) receptor antagonist without additional allergy preventing properties.

PHARMACOKINETICS:

Ophthalmic Agent	Onset	Duration	Directions for use
Azelastine	3 minutes	8 hrs	Twice daily
Epinastine	3-5 minutes	8 hrs	Twice daily
Ketotifen	Minutes	Up to 12 hrs	Twice daily (every 8-12 hrs)
Olopatadine	Less than 30 minutes	8 hrs	0.1% Twice daily (every 6-8 hrs) 0.2%: Once daily
Emedastine	3 minutes	3-4 hrs	Up to four times daily

COMPARATIVE EFFICACY: Several studies have been done to show similar efficacy and side effects among the multiple action antihistamines. In one comparison study of ketotifen and olopatadine, olopatadine showed only slightly better results over 2 weeks of treatment. In another, ketotifen was shown to be more effective than olopatadine in reducing conjunctival edema and vascular permeability of the eyelids and eyeball although reported to cause mild stinging. Azelastine has been shown to significantly improve itching and conjunctival redness compared with placebo, but has a noticeable bitter taste and some stinging with application. In an animal model of histamine induced vascular leakage, epinastine, azelastine, and ketotifen had a shorter duration of effect than olopatadine. In a final study comparing the clinical efficacy and ocular surface variables of olopatadine, ketotifen, epinastine, emedastine and fluorometholone ophthalmic solutions in preventing the signs and symptoms of seasonal allergic conjunctivitis all products were found to be significantly more effective than placebo with fluorometholone (an adrenal glucocorticoid) being the least effective of the group.

CONTRAINDICATIONS: Hypersensitivities to the antihistamines or other components of the product.

PRECAUTIONS: Not for contact lens related irritation. Do not use while wearing contact lenses. Remove contact lenses prior to instillation; may reinsert 10 min after administration.

ADVERSE REACTIONS: The most common adverse reactions associated with use of ophthalmic antihistamines include dry eye, eye irritation or burning sensation in the eye.

DOSING: See directions for use listed above.

PREGNANCY/LACTATION: Pregnancy category C. Infant risk cannot be ruled out in breastfeeding.

PEDIATRICS: Safety and effectiveness in children below 3 years of age has not been established. In age greater than 3, adult dosing is appropriate.

RECOMMENDED MONITORING: Monitor for relief of ocular itchiness and irritation.

PRODUCT AVAILABILITY, COST, USAGE:

Drug	Acquisition Cost	Usage (annual)
Azelastine	$22.84 / 6mL	4
Epinastine 0.05%	$81.46 / 5mL	Non-Formulary
Ketotifen 0.025%	$6.08 / 5mL	15
Olopatadine 0.1%	$36.15 / 5mL	30
Olopatadine 0.2%	$149.81 / 2.5mL	Non-Formulary
Emedastine 0.05%	$102.70 / 5mL	Non-Formulary

CONCLUSION: The multiple action histamine antagonists vary slightly with their mechanism of action but are comparable in efficacy and side effect profile. A decision for use of an individual ophthalmic agent should likely be based upon acquisition cost.

RECOMMENDATION: Therapeutically interchange all other ophthalmic antihistamines to a therapeutically equivalent dose of ketotifen.

THERAPEUTIC INTERCHANGE:

Drug/Dose Ordered	Drug/Dose Interchanged
Azelastine 1 drop in each eye twice daily	Ketotifen 1 drop in each eye twice daily
Epinastine 1 drop in each eye twice daily	Ketotifen 1 drop in each eye twice daily
Olopatadine 0.1% 1 drop in each eye twice daily	Ketotifen 1 drop in each eye twice daily
Olopatadine 0.2% 1 drop in each eye once daily	Ketotifen 2 drops in each eye twice daily
Emedastine 1 drop in each eye four times daily	Ketotifen 1 drop in each eye twice daily

FORMULARY CLASS REVIEW
MENINGOCOCCAL VACCINES

BACKGROUND:
- Meningococcal disease: bacterial infection caused by *Neisseria meningitidis*
- 0.3 cases per 100,000 population (CDC, 2012)
- Case-fatality ratio: is 10%–15%, and 20% of survivors
- *N. meningitidis*: classified into at least 13 serogroups
  - Serogroups B, C, and Y are most frequent cases in U.S.

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES (ACIP) RECOMMENDATIONS 2016:
MPSV4 [Menomune]; MenACWY [Menactra, Menveo]; MenB [Trumenba, Bexsero]
- All patients aged 11-18 [MenACWY; MenB]
- **Persons ≥ 2 months with anatomical/ functional asplenia, complement component deficiency or microbiologists with occupational exposure [MenACWY; MenB]**
- Special populations such as first-year college students living in residence halls & military recruits [MenACWY]
- Persons ≥ 9 months who travel to or reside in countries in which meningococcal disease is hyperendemic or endemic [MenACWY]

VACCINE COMPARISONS:
*** Randomized controlled clinical trials for meningococcal vaccines are unable to evaluate clinical efficacy because of the low incidence of meningococcal disease. Because efficacy cannot be measured, immunogenicity data are used as a surrogate for efficacy.*

Menomune®:
- No longer routinely recommended per ACIP guidelines
  - Only for patients ≥ 56 who have not received MenACWY previously AND who require a single dose only (i.e. people at risk b/c of an outbreak or travelers)
- Cost: $117.26/dose

Menactra® vs. Menveo®

	Menactra® (2005)	**Menveo®** (2010)
Indication	Active immunization to prevent invasive disease caused by *N. meningitidis* serogroups A,C,W, & Y	
Pharmacology	Provides protection against invasive meningococcal disease by complement-mediated antibody-dependent killing of *N. meningitidis*	
Manufacturer	Sanofi Pasteur	GSK
Dosing (asplenia)	2 doses (month apart); revaccinate q5yrs	2 doses (month apart); revaccinate q5yrs
Clinical Efficacy	1) RCT (U.S.) – children 9-12 months ≥ 86% had titers ≥ 1:8 for all serogroups. Similar results when extended to 12-15 months of age 2) 3 RCTs comparing Menactra® to Menomune® (immunogenicity): 28 days post vaccination, same or higher percentage of patients in all age groups achieved hSBA titers in the Menactra® group when compared to Menomune® and it was deemed to be non-inferior	1) RCT (U.S.) – children 2-12 months compared to Menactra®, response was non-inferior (% ≥1:8 hSBA titer) for all the serogroups. 2) Similar responses seen in adolescent and adult populations
Contraindications	Hypersensitivity to any component of the vaccine	
Pregnancy	Category C	Category B
Adverse Reactions	• Injection site pain • Erythema • Swelling	• Injection site pain • Erythema • Headache

	• Headache • Fatigue • Muscle pain	• Myalgia • Malaise • Nausea
Admin w/ other vaccines	• Non-inferior immune responses to dTAP, and MMR, but not PCV7/PCV13 (decreased immunogenicity of pneumococcal vaccine). • It's recommended to administer Menactra® at least 4 weeks after PCV13 or PCV7	• Non-inferior immune responses to HPV, HepB, HIB, & PCV7 • Co-administration with Tdap may result in lower immune response to pertussis antigens • No recommendations to space vaccines
Cost	$481.76/dose	$553.36/dose

Trumenba® vs. Bexsero®:

	Trumenba® (2014)	**Bexsero®** (2015)
Indication	Active immunization to prevent invasive disease caused by *N. meningitidis* serogroup B	
Pharmacology	Provides protection against invasive meningococcal disease by complement-mediated antibody-dependent killing of *N. meningitidis*	
Manufacturer	Pfizer Pharmaceuticals	GSK
Dosing	3 doses at 0, 2, and 6 months	2 doses 1 month apart
Clinical Efficacy	Nine clinical trials: six randomized controlled trials and 3 open label studies. 1) MC RCT (U.S.) – 11-17 years old received 3 doses; 83% subjects had an hSBA response to all four test strains. Only 50% subjects had an hSBA response after 2nd dose. 2) RCT (Europe – 11-18 year olds received 3 doses; >80% hSBA responses to all four test strains after 3rd dose as above	Six randomized controlled trials evaluated the safety and immunogenicity of MenB-4C in individuals aged ≥ 10 years. 1) RCT (UK) - students aged 18-24 years old received two doses. One month after the second dose, 88% of the students had a composite hSBA response to all three strains tested 2) RCT (Australia and Canada), 63% of subjects aged 11-17 had a composite hSBA response to all three test strains one month after receiving the second dose.
Contraindications	Hypersensitivity to any component of the vaccine	
Pregnancy	Category B	Category B
Adverse Reactions	• Injection site pain (≥ 85%) • Fatigue (≥ 40%) • Headache (≥ 35%) • Muscle pain (≥ 30%) • Chills (≥15%)	• Injection site pain (≥ 83%) • Muscle pain (≥ 48%) • Erythema (≥ 45%) • Fatigue (≥ 35%) • Headache (≥ 33%) • Induration (≥ 28%) • Nausea (≥ 18%) • Arthralgia (≥ 13%)
Admin w/ other vaccines	Non-inferior immune responses to all Tdap, MenACWY antigens and MenB test strains when administered concomitantly	Expert opinion that it may be co-administered with MenACWY vaccines No specific clinical data
Cost	$94.80/dose	$142.37/dose

RECOMMENDATION:

- Add to formulary – keep single dose at both Glenwood and Hixson campuses
    - **Preferred:** Menveo® and Bexsero®
    - **Alternative:** Menactra® and Trumenba® or Bexsero®

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.

Overview:

- Patients should be vaccinated at least **2 weeks before** elective splenectomy or **2 weeks after** emergent splenectomy.
    - If discharged prior to 2 weeks, can consider administering first doses on day of discharge in an attempt to improve compliance rate.
- Patients who have received Pneumovax 23® in the past year should wait at least 1 year to receive Prevnar 13® vaccine, followed by Pneumovax 23® at least 8 weeks later.
- Patients who have received Prevnar 13® should wait at least 8 weeks before receiving Pneumovax 23®.

Vaccine Schedule:

	Initial vaccination	2 month follow-up	Long-term follow-up
Pneumococcal 13-valent conjugate (Prevnar 13®)	√		
Pneumococcal vaccine polyvalent (Pneumovax 23®)		√	√ (Every 5 yrs.)
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.

ANTIBIOTIC DOSE ADJUSTMENTS

UPDATES – Cefazolin, Cefepime

Cefazolin (Ancef®)			
CrCl (ml/min)	**UTI (no sepsis); Uncomplicated ABSSSI**	**All other indications**	**Treatment of confirmed GNR from a non-urinary source and MIC > 2**
> 30	1g IV q8h	2g IV q8h	Contact stewardship pharmacist as cefazolin may not be the best drug for the patient
10-30	1g IV q12h	2g IV q12h	
<10	1g IV q24h		
HD	2g post HD only		
CRRT	2g IV q12h		

Note: The MIC > 2 comment in the last column only applies to gram-negative infections.
Continue using the dosing strategies listed in the first two columns for gram-positive infections.

Cefepime (Maxipime®) Dose Optimization			
CrCl (ml/min)	**Febrile Neutropenia or Treatment of recent or confirmed infection with a GNR with an MIC of 8**	**UTI, no sepsis**	**All other indications**
> 50	2 gm Q 8 hrs	1 gm Q 12 hrs	1 gm Q 6 hrs
30-49 or CRRT	2 gm Q 12 hrs	1 gm Q 24 hrs	1 gm Q 8 hrs
11-29	2 gm Q 24 hrs	500 mg Q 24 hrs	1 gm Q 12 hrs
≤ 10 or HD	1 gm Q 24 hrs (give after dialysis)	500 mg Q 24 hrs (give after dialysis)	1 gm Q 24 hrs (give after dialysis)

PPI (pantoprazole) Medication Use Evaluation
CHI Memorial & CHI Memorial Hixson

The purpose of this evaluation was to evaluate usage of pantoprazole hospital wide to identify opportunities to reduce inappropriate use while still properly treating patients in need of acid suppression therapy.

Background:

Stress ulcer prophylaxis (SUP) has become a routine medical practice among healthcare practitioners. Up until the last 10 years, it was thought that utilization of Proton Pump Inhibitors (PPIs) were relatively benign. Studies have shown that up to 73% of patients in the hospital under general medicine care are on acid suppression therapy without an appropriate indication. In 2009 Heidelbaugh, et al published a systematic review[1] detailing the major complications associated with PPI usage. PPIs have been shown to contribute to pneumonia, *Clostridium difficile* associated diarrhea, and osteoporosis. Another literature review[2] in 2013 also details the risks associated with PPI overuse. As a result of these findings, a medication use evaluation was conducted to determine pantoprazole usage trends at Memorial Hospital.

With an increase in gastric acid pH, more aerobic bacteria are able to grow. Many patients in the hospital are considered high risk for aspiration. Aspiration and even microaspiration events can lead to pulmonary colonization with potential to cause pneumonia. Three meta-analyses show an increased risk of pneumonia, both CAP and HAP, with long- and short-term (<30 days) use of PPIs. A case-control study also showed increased risk of CAP in patients currently on PPI therapy and those on short-term (1-15 days) therapy.

Along similar lines, an increase in gastric pH can lead to less inhibition of enteric bacteria, such as *Clostridium difficile*, allowing for clinically significant *C. diff* - associated diarrhea. A meta-analysis of 30 trials showed PPIs were associated with increased risk of *C. diff* infection regardless of antibiotic use ($p < 0.00001$). The risk was also higher even if the patient was on an H_2RA, daily PPI, or a dose larger than daily.

Acid suppression can lead to decreased calcium absorption, due to the needed acidic environment for ionization and absorption of calcium. Decreased calcium can lead to increased parathyroid hormone, which causes increased production of osteoclasts for bone resorption. With prolonged use and higher dosage of PPIs, increased risk of bone fracture can occur. While this may not be considered an acute problem, many patients started on PPI therapy as inpatient are continued indefinitely as outpatients. A randomized, double-blind, placebo-controlled crossover trial with omeprazole demonstrated a significantly decreased rate of calcium absorption from 9.1% to 3.5% after 7 days of therapy. After 6-12 months or longer on PPI therapy, a retrospective study found an association of osteoporosis medication prescribing and PPI usage. The FDA has issued a warning about risk of developing fractures on PPIs.

Other small studies and case reports have also shown an association with hypomagnesemia, Vitamin B12 deficiency, and rare incidence of rhabdomyolysis with long-term PPI use.

Data Analysis/Methods:

All doses of pantoprazole given at CHI-Memorial Glenwood and CHI-Memorial Hixson during October 2015 were collected. Patients were excluded if they were on home PPI therapy or if they had a GI bleed at or during admission. Patients were then separated based on ICU or floor status when the PPI was initiated.

The ASHP Guidelines for Stress Ulcer Prophylaxis from 1999 were used to determine if ICU stress ulcer prophylaxis was initiated appropriately. Patients with one of the following risk factors were considered appropriately treated: mechanical ventilation > 48 hours, history of GI ulceration or bleeding within the past year, coagulopathy (Plt < 50, INR > 1.5 , PTT > 2x control), traumatic brain, spinal cord or burn injury (burns > 35 % BSA), sepsis.

Table 1: Floor Patient Risk Factors	
Age > 60	2
Male	2
Acute Renal Failure	2
Liver disease	2
Sepsis	2
Prophylactic anticoagulation	2
Coagulopathy	3
Medicine Service	3

Table 2. Percent Bleeding and NNT per Risk Group		
Risk Group	Percent with Bleeding	NNT
Low risk (≤ 7 points)	0.10	> 1000*
Without prophylaxis	0.04	
With prophylaxis	0.16	
Low-Medium risk (8-9 points)	0.54	556
Without prophylaxis	0.67	
With prophylaxis	0.49	
High-medium risk (10-11 points)	0.68	159
Without prophylaxis	1.16	
With prophylaxis	0.53	
High risk (≥ 12 points)	1.47	48
Without prophylaxis	3.24	
With prophylaxis	1.14	

*Estimated NNT based on the results of the Low Risk group and confounding by indication.

Floor patient charts were assessed for gastrointestinal bleeding risk based on the SURGIB risk criteria recently published in Hong et al. and Herzig et al. Hong et al. was a cohort study that evaluated patients with nosocomial gastrointestinal bleeding. These patients were reviewed in order to establish a set of criteria to determine need/appropriateness of stress ulcer prophylaxis. The investigators evaluated and compiled characteristics that made patients more susceptible to gastrointestinal bleeding and established scoring criteria and risk categories (Table 1). They then determined the percentage of patients likely to bleed within each risk category and the number needed to treat (NNT) (Table 2). We utilized this scoring system in our evaluation of pantoprazole usage at CHI-Memorial. Scores < 10 were considered inappropriate and further analyzed. Other data points collected included ordering physician and length of stay.

Results:

Table 3. Usage of PPI in the ICU and on the floor		
ICU		**Percentage of Evaluated Patients**
Total Patients	77	
Appropriate*	27	56%
Inappropriate	21	44%
Excluded	29	
Floor		
Total Patients	720	
Appropriate**	56	20%
Inappropriate	223	80%
Excluded	441	

*Appropriateness in the ICU is based on the 1999 ASHP SUP Guidelines. If the patient meets any one of the following, PPI is considered appropriate: Mechanical ventilation > 48hrs, history of GI ulceration in past year, coagulopathy, trauma, sepsis, ICU LOS > 1 week, or occult GI bleed ≥ 6 days.
** Scores > 10 were considered to be at an increased risk for gastrointestinal bleed and PPI use was determined to be appropriate.
***Exclusion Criteria: patients with a PPI home medication or GI bleed

Floor Patients: Of the patients inappropriately treated (score < 10), the median risk score was 6.58. The most common risk factors seen were age > 60 (41%), prophylactic anticoagulation (52%), and care by general medicine service (64%).

Table 4: Percentage of PPI ordered by physician specialty	
ICU	
Hospitalist	57%
Emergency Medicine	19%
Intensivists/Pulmonologists	14%
Surgery (Cardiovascular & General)	10%
Floor	
Hospitalist	75%
Surgery (Cardiovascular & General)	6%
GI/GE	5%
Nephrology/Urology	3%
All other disciplines	< 3%

Summary & Conclusion:

ICU

This analysis has demonstrated the extent of PPI overuse at this institution. ICU PPI use was more judicial with about 56.3% of patients evaluated determined to be appropriate. It would be prudent to note that over half of inappropriate PPI usage was ordered by a general medicine physician (57%) prior to transfer to the ICU. With this smaller sample size demonstrating more appropriate usage, it may be difficult to draw conclusions from this data. Interventions should likely focus more on floor patients until further evidence suggests the need to evaluate ICU PPI usage further.

Floor

As shown above, only 20% of all floor patients evaluated were initiated on SUP appropriately. The majority of patients were initiated on PPI upon admission utilizing the admission order sets. Using the scoring system, the most common risk factors leading to initiation of PPI were age > 60, prophylactic anticoagulation, and the general medicine service. The median score for risk of stress ulcer bleeding was 6.58. According to Table 2, patients with a score ≤ 7 were associated with a negligent risk for bleeding. The hospital as a whole would need to treat over 1000 patients in this risk category, in order to prevent 1 patient from developing a GI bleed. Coupled with the cost per dose of IV and PO protonix that would be considered inappropriate, this a significant cost that could be saved per month.

In light of this data, it may be practical to evaluate the admission order sets. Removal of, or stipulations for protonix may need to be enacted to decrease the amount of inappropriate PPI use. Through observation only, written orders for protonix were determined to be appropriate more often than when checked on admission order sets. While pharmacy is capable of evaluating the appropriateness for patients already on PPI and discontinuing per approved protocols, more proactive measures should be taken to avoid PPI use altogether to prevent short- and long-term complications as described earlier. Education of SUP indications and risks of PPI use should be initiated to prevent further overuse.. With proper education, PPI use should decrease and lead to an added cost savings per month.

References:

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POLICY

Title: **THERAPEUTIC DUPLICATION OF PRN MEDICATION ORDERS**			
		Page 1 of 2	
Policy Number: MM- 01000		Date Last reviewed/Revised: 4/16	Valid Until: 4/19
Department(s) Affected: All Clinical Areas		Review Period: every 3 years	

OUTCOME:

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

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

POLICY:

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

1. If the prescriber's orders already provide direction for prioritizing the order of use, they will be implemented as written.
2. Of the medications ordered for a specific given indication (example: moderate pain), the first agent written in the list of orders for that indication will be considered to be the provider's choice. If the patient is intolerant/allergic to the medication ordered and another medication is listed for the same indication, that medication will be considered the provider's choice.
    - Multiple PRN medications for the same indication and same route of administration will not be allowed to exceed one option (e.g. one oral 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).
    - Additional medication is allowable for breakthrough pain if patients are on a PCA and the PCA is ineffective at the maximum dose ordered.
3. If a new medication is ordered for the same specific indication as a currently ordered medication, the newly ordered medication will be considered the new choice for that indication and the previous medication will be automatically discontinued.
4. Home PRN medications ordered from a medication reconciliation form will be implemented if continued by the prescriber only if other prescriber orders are not ordered for the same PRN indication.
    - Whenever possible, patients will be assessed for preference of PRN home medication when multiple home medications are taken for the same PRN indication, and this information noted on the medication reconciliation form.
    - 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 (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.