Pharmacy & Therapeutics Committee Meeting
Private Dining Room
August 11, 2016 7:00 a.m.

Next Meeting will be October 13, 2016 at 7:00 AM in the Private Dining Room

PHARMACY AND THERAPEUTICS COMMITTEE
Minutes of Meeting

DATE: April 14, 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. David Dodson, M.D. Mark Anderson, M.D. Nathan Chamberlain, M.D. Sam Currin, M.D. Michael Stipanov, M.D. Richard Yap, M.D. Avni Kapadia, M.D.	Karen Babb, PharmD Patrick Ellis, PharmD Susan Fuchs, RD Lila Heet, PharmD	Sandy Vredeveld, DPh Patty Hicks, RN Melissa Roden, RN Linda Johnson, PharmD	Nathan Schatzman, M.D. Michael Harper, M.D. Jeffrey Mullins, M.D. Nan Payne, RN Shannon Harris, RN Rhonda Poulson, CNO Michelle Denham, RN Scott Harbaugh, Finance	Sean Bergeron, PharmD Camellia Davis, PharmD Erin Massarrello, PharmD Whitney Williams, PharmD Adam Henderson, RN

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

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
Minutes	The February 11, 2016 minutes were approved as submitted.		Complete
Therapeutic Interchanges and Formulary Decisions	The following medications were reviewed: 1. CHI MUE Committee Decision Brief: The medications that were reviewed at the first national MUE committee meeting from March 15, 2016 were reviewed with the committee. Updates to the Memorial formulary will be required for the following medications based on the national committee's formulary decisions: • **Kengreal®:** This was approved to CHI national formulary with restrictions as recommended by the CVSL. Since this was previously approved to local formulary in August 2015 the nationally approved use restrictions will be communicated to the Cardiology Invasive Committee at their next scheduled meeting. • **Exparel®:** This was voted to be removed from all CHI hospital formularies. The committee recommended that this be removed from local formulary by the end of April to comply with this national decision. Dr. Pesce stated that one physician may file an exception request to the national decision. A motion was passed to have the P&T chair and CMO review the exception request along with hospital administration to decide if the exception should be considered at a later date by the full committee and removal from local formulary by 4/30/16. 2. **Veltassa®** – Potassium binding agent indicated for the treatment of hyperkalemia. Although similar to kayexalate, Veltassa is intended to serve as a long term maintenance therapy for patients with CKD who need to continue RAAS inhibition therapy while controlling associated hyperkalemia. The cost per day of therapy is ~ $60 per day versus $5 per day for kayexalate. Due to the cost difference and the unlikely need to start this therapy during inpatient hospitalization it was recommended to designate this	Use restrictions approved Removed from formulary effective 4/30/16 Not approved for formulary addition	Complete Complete Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	as a non-formulary medication. Patients that are stabilized on this as a home medication will be allowed to utilize their own medication per the hospital's formulary policy.		
	3. **Movantik®** – Oral peripheral acting mu-opioid receptor antagonist (PAMORA) indicated for the treatment of opioid-induced constipation (OIC). The use of the other formulary PAMORA agents (Relistor) was also discussed along with the current Relistor restrictions of use. Due to an increasing prevalence of OIC it was recommended by Drs. Dodson and Yap to consider the addition of Movantik to formulary for use by any specialty. Due to similar clinical efficacy and cheaper cost associated with Movantik as compared to Relistor it was recommended to add this to formulary and allow this to be used by any physician as long as the following criteria are met. Education will be provided to hospitalists on appropriate use and other current prescribers of Relistor due to cost savings opportunity if Movantik is utilized as an alternative. ✓ Taking Movantik prior to admission for OIC ✓ Receiving chronic (> 4 weeks) opioid therapy with failure to respond to oral and rectal laxative therapy. ✓ Candidates for SQ Relistor for OIC but who can tolerate oral therapy	Approved with restrictions for use	Pending education
	4. **Bridion®** – Cyclodextrin molecule that binds rocuronium and vecuronium allowing for rapid reversal of neuromuscular blockade in adults undergoing surgery. Bridion 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 $79 per day. This has been discussed with Drs. Clanton and Schatzman from anesthesia and the following situations were recommended as approved restrictions of use for Bridion. Usage will be monitored to ensure compliance with these restrictions and education provided for anesthesia staff. ✓ 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).	Approved with restrictions for use	Complete
	5. **Opthalmic Antihistamines** – A class review of this class of medications were reviewed. Patrick explained that the limited clinical data indicates that all of the available products are likely interchangeable from a therapeutic efficacy standpoint with no significant safety or tolerability differences as well. Due to the cost advantage with using Ketotifen, it was recommended to only utilize this product and automatically interchange other ophthalmic antihistamine orders to a therapeutically equivalent dose of ketotifen.	Therapeutic interchange approved	Approved
	6. **Meningococcal Vaccines** – Linda reviewed updated ACIP recommendations for post-splenectomy vaccines that will require formulary changes in order to provide the recommended vaccinations to our patients needing these vaccinations while hospitalized. The recommendation was to remove Menomune (MPSV4) from formulary and add a MenACWY meningococcal vaccination (Menactra or Menveo) and MenB meningococcal vaccination (Trumenba or Bexsero) to formulary. Dr. Anderson recommended that Trumenba and Bexsero be added due to more convenient dosing	Menomune removed from formulary; alternative agents approved pending CHI contracting decision	Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	regimens and a lack of vaccine interactions with the Pneumococcal vaccinations. Patrick explained that CHI is currently in contract negotiations with the vaccine manufacturers and at this time it was unclear which vaccines would be preferred. Patrick agreed to try if at all possible to utilize the vaccines that Dr. Anderson recommended for formulary inclusion. 7. **Post Splenectomy Vaccines** – Patrick reviewed with the committee the updated post-splenectomy vaccine recommendations. Education will be provided to physicians once the vaccine contracts are finalized and pharmacy will help develop a process to assist with writing the appropriate follow up prescriptions to help with patient compliance post hospital discharge. 8. **Antibiotic dose adjustments (cefepime, cefazolin)** – Due to changes related to susceptibility breakpoints modifications are necessary to the automatic dose adjustment process performed by pharmacy to ensure optimal therapy based on MIC values and renal function. Dr. Anderson supported Linda's recommendations and recommended these changes be approved.	Approved Approved	Complete Complete
MUE – Medication Use Evaluation	**Stress Ulcer Prophylaxis (PPI's)** – A MUE was conducted to evaluate the usage of PPI's as stress ulcer prophylaxis. The evaluation revealed that patients admitted to the non-ICU areas were most commonly inappropriate (80% inappropriate) when evaluated against a literature evaluated risk stratification model. The majority of the inappropriate orders for SUP were generated from admission order sets with the hospitalist admission orders being the most commonly implicated. The hospitalist representatives on the committee (Drs. Yap, Dodson, Kapadia) all recommended that their group consider the removal of SUP agents from their admission order sets. Additional strategies (pharmacy initiated auto-discontinuation) may be considered based on follow up reviews in 4-6 months following order set modifications.	Information – to be further discussed with Hospitalist group	Complete
Patient Safety & Regulatory (JCAHO)	**Therapeutic Duplication of PRN Medication Orders Policy** Patrick reviewed a draft policy that was created to provide resolution to the most commonly encountered issues related to therapeutic duplication of PRN orders. Patrick explained that > 350 physician standing orders have been reviewed and edited. The most commonly encountered issues were PRN pain medications that did not clearly indicate pain severity or contained duplications for the same level of pain severity. The policy was reviewed with the committee and the process for executing this policy and resolving discrepancies if duplicate PRN meds are ordered was explained in detail to the committee. The policy was recommended for approval by Dr. Pesce and no further suggestions to the policy were recommended by the members of the committee.	Policy approved	Complete

There being no further business, the meeting was adjourned at 8:00 A.M. The next P&T meeting is June 9, 2016.

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
Imagine better health.℠

CHI Medication Use and Evaluation Committee
Meeting: April 19, 2016
DECISION BRIEF

Members Present (Bold)

MUE Co-Chairs	**Tom Cummins (Co-Chair, SE Division CMO (Arkansas)); Tim Lynch, CHI Franciscan Health (for National VP Pharmacy (Interim))**
National	**Ryan Ramaekers (National Oncology Service Line); Jerome Granato (Cardiovascular Service Line); Greg Rennirt (Ortho-Spine Service Line); Jason Lambrecht (Hospital Medicine Service Line); Venita Papillion (Clinical Pharmacist)**
Southeast	**Shalena McWilliams (Division Pharmacy Director); Don Meacham (P&T Physician (Arkansas)); Richard Pesce (P&T Physician (Tennessee))**
Pacific Northwest	**Tim Lynch (Co-Chair, National VP Pharmacy (Interim)), John Luber (P&T Physician), Eric Wymore (Division Pharmacy Representative)** for Mike Bonck (Division Pharmacy Representative)
CHI Health	**Sunil Jagadesh (P&T Physician); Mike Tiesi (Division Pharmacy Director)**
Iowa	**Dan Gervich (P&T Physician); Greg Young (Division Pharmacy Director)**
Texas	**Victor Narcisse (P&T Physician); Kim Oas (Advanced Practice Clinician); Lorie Shoemaker (Division CNO); Craig Frost (Division Pharmacy Director)**
Fargo	**Gaylord Kavlie (P&T Physician); Keith Horner (Division Pharmacy Representative)**
KentuckyOne	**Nancy Morris (P&T Physician); Jim O'Donnell (Division Pharmacy Director)**
Executive Sponsor	Kathy Sanford, SVP and Chief Nursing Officer
AdHoc Members	**Susan Lorkovic; Tamara Hill; Carl Middleton; Manoj Pawar; Robynn Pruett**
Physician Guests	**David McCowen; Douglas Koch**
PCC Members	**David Schmidt; Kim Putney; Kevin Poe; Patrick Ellis; Rebecca Brannan; Dawn Mayer; Katie Palmer**

Link to Complete Committee Meeting Packet: April 2016 MUE

FORMULARY DECISION SUMMARY

A. Basal insulin (Lantus® to Levemir®)

Drug Summary
Lantus® (insulin glargine U-100), Toujeo® (insulin glargine U-300) and Levemir® (insulin detemir) are all long-acting human insulin analogues approved for subcutaneous injection in diabetes mellitus types 1 and 2. They are absorbed slowly with a stable plateau effect that lasts most of the day. Consequently, they are used to control blood sugar overnight, while fasting and between meals. Lantus® and Toujeo® are FDA approved for once daily dosing; Levemir® is FDA approved for once and twice daily dosing.

Note: The Decision Brief summarizes the decisions of the national CHI Medication Use and Evaluation (MUE) Committee. Local P&Ts may act on MUE Decisions in one of four ways: 1) approve with no changes 2) approve with more restrictions 3) appeal the MUE decision (apply to entire organization) 4) request an exception to the MUE decision (request for variance).

There are no head to head inpatient trials comparing the two long-acting insulins (glargine vs detemir). A systematic review of 187 literature citations concluded there were no significant differences in efficacy or safety with the long acting insulins.

These basal insulin agents have comparable safety, efficacy, pharmacokinetic and pharmacodynamic considerations, thus they are therapeutically interchangeable at a 1:1 ratio. In addition, the unit-to-unit dose conversion is supported in the insulin detemir package insert. Therefore, the basal insulins should be interchangeable to the most cost-effective agent.

Tresiba® (insulin degludec) is a long-acting insulin analogue for use as basal insulin in the treatment of patients with type 1 and type 2 diabetes mellitus. It has a duration of action exceeding 24 hours, and may have a lower pharmacodynamic variation than insulin glargine. In comparative studies with insulin glargine, insulin degludec has exhibited comparable reductions in HbA1c, with lower insulin doses and less confirmed nocturnal hypoglycemia.

Insulin glargine (Lantus®) and insulin detemir (Levemir®) are interchangeable in a 1:1 ratio. The current recommendation is to therapeutically substitute insulin glargine (U-100 and U-300) to insulin detemir (Levemir®) while the patient is hospitalized. A therapeutic interchange has been provided for converting insulin degludec (Tresiba®) to insulin detemir (Levemir®) for patients being hospitalized who currently use insulin degludec (Tresiba®). (See April 2016 Packet for Therapeutic Interchange Details)

MUE COMMITTEE DECISION

The decision is to classify insulin detemir (Levemir®) as formulary as the primary basal insulin for CHI hospitals. The decision is to classify insulin glargine (Lantus®) as non-formulary for CHI hospitals. Therapeutic interchanges will be used to achieve the conversion.

A grace period of 60-90 days will be afforded to hospitals to make the conversion.

ACTION: A motion was made and seconded for insulin detemir to have formulary status and insulin glargine to be non-formulary. Conversion will be achieved through use of appropriate therapeutic interchange.

Voting: FOR: 23
AGAINST: 0
ABSENT: 1

B. naloxegol (Movantik™)

Drug Summary

Naloxegol (Movantik™) is a pegylated derivate of the μ-opioid receptor antagonist naloxone. Pegylation confers p-glycoprotein transporter substrate properties and limits the ability of naloxegol to cross the blood-brain barrier. The Food and Drug Administration (FDA) has approved the drug for opioid-induced constipation in adults with chronic noncancer related pain. Two identical phase III, multicenter,

randomized, double-blind, parallel-group, placebo-controlled studies investigated the efficacy and safety of naloxegol. KODIAC-04 (N=652) and KODIAC-05 (N=700) subjects were randomly assigned to receive a daily dose of 12.5 or 25 mg of naloxegol or placebo. The primary endpoint was the 12-week response rate. A shorter time to the first post-dose spontaneous bowel movement and a higher mean number of days per week with one or more spontaneous bowel movements were observed with 25 mg of naloxegol versus placebo in both studies and with 12.5 mg of naloxegol in KODIAC-05. Adverse events, primarily gastrointestinal, occurred most frequently in the groups treated with 25 mg of naloxegol. Overall, 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.

Therapeutic Interchange: methylnaltrexone to naloxegol
For the treatment of opioid induced constipation with failure of laxative therapy, patients who can tolerate oral medications methylnaltrexone should be converted to naloxegol according to the following table:

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
Notes: 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)	

MUE COMMITTEE DECISION

The decision is to classify this agent as formulary, restricted for use in patients who are:

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. Appropriate therapeutic interchange will be used to convert therapy from methylnaltrexone to naloxegol.

ACTION: A motion was made and seconded to add naloxegol as formulary, restricted based on the listed restrictions using a therapeutic interchange where applicable.

Voting: FOR: 24
AGAINST: 0
ABSENT: 0

C. phenylephrine 1% and ketorolac 0.3% ophthalmic (Omidria®)

Drug Summary

Intraoperative lens replacement during cataract extraction and lens replacement and for clear or refractive lens exchange is the most common surgical procedure performed in the United States.3 Adequate pupil

dilation during these procedures is needed for visualization of the field, adequate room for intraocular maneuvering of surgical instruments, and to decrease the risk of complications.

Iris expansion can be accomplished in various ways. Commonly, preoperative mydriatic agents such as phenylephrine, tropicamide, and cyclopentolate are utilized in combination with nonsteroidal anti-inflammatory agents, which minimize prostaglandin release, prolonging mydriasis. Some surgeons find mechanical expansion with iris retractors or pupil expansion rings to be the most reliable means of maintaining a safe pupil diameter during surgery. Pharmacologic expansion with intracameral administration of phenylephrine or epinephrine have been used with success as well. Most recently Omidria® was developed to manage intraoperative pupil diameter and reduce post-operative ocular pain.

Within the CHI system, there have been requests from ophthalmologists in the Fargo and Texas divisions for the addition of Omidria to formulary specifically requesting the medication for patients with Intraoperative Floppy Iris Syndrome (IFIS). The overall incidence of IFIS among patients undergoing cataract surgery is 1.1–2.3%, but 37.9–73.0% in patients receiving tamsulosin. Unfortunately, the use of Omidria in patients with prior or current use of alpha 1 adrenergic agents has not been studied as this specific patient population was excluded in Phase 3 trial design. However, there is data to support that the intracameral use of phenylephrine can be effective for prophylaxis against IFIS in patients receiving tamsulosin.

MUE COMMITTEE DECISION
The decision is to classify this agent as non-formulary for inpatient and outpatient setting.

ACTION: A motion was made and seconded to assign non-formulary status to phenylephrine 1% and ketorolac 0.3% ophthalmic (Omidria®)

Voting: FOR: 22
AGAINST: 1
ABSENT: 1

D. patiromer (Veltassa®)

Drug Summary
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.

It is not anticipated that patiromer is an agent that needs to be initiated as new therapy for hospitalized patients. The anticipated role of patiromer is different from kayexalate. 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.

Note: The Decision Brief summarizes the decisions of the national CHI Medication Use and Evaluation (MUE) Committee. Local P&Ts may act on MUE Decisions in one of four ways: 1) approve with no changes 2) approve with more restrictions 3) appeal the MUE decision (apply to entire organization) 4) request an exception to the MUE decision (request for variance).

Date: May 17, 2016

Members Present (Bold)

MUE Co-Chairs	**Tom Cummins (Co-Chair, SE Division CMO (Arkansas)); Tim Lynch, CHI Franciscan Health (for National VP Pharmacy (Interim))**
National	**Ryan Ramaekers (National Oncology Service Line);** Jerome Granato (Cardiovascular Service Line); **Greg Rennirt (Ortho-Spine Service Line); Jason Lambrecht (Hospital Medicine Service Line); Venita Papillion (Clinical Pharmacist)**
Southeast	**Shalena McWilliams (Division Pharmacy Director); Don Meacham (P&T Physician (Arkansas)); Richard Pesce (P&T Physician (Tennessee))**
Pacific Northwest	**Tim Lynch (see above: Co-Chair, National VP Pharmacy (Interim)), John Luber (P&T Physician), Mike Bonck (Division Pharmacy Representative)**
CHI Health	**Sunil Jagadesh (P&T Physician); Mike Tiesi (Division Pharmacy Director)**
Iowa	**Dan Gervich (P&T Physician); Greg Young (Division Pharmacy Director)**
Texas	**Victor Narcisse (P&T Physician); Kim Oas (Advanced Practice Clinician);** Lorie Shoemaker (Division CNO); **Craig Frost (Division Pharmacy Director)**
Fargo	**Gaylord Kavlie (P&T Physician); Keith Horner (Division Pharmacy Representative)**
KentuckyOne	**Nancy Morris (P&T Physician); Ashley Ross / Jim O'Donnell (Division Pharmacy Director),**
Executive Sponsor	**Kathy Sanford, SVP and Chief Nursing Officer**
AdHoc Members	**Susan Lorkovic; Teri Gaskin** (for Tamara Hall)**; Carl Middleton; Manoj Pawar**
Guests	**Mike Kimbel, Dr. Gallentine, Greg Schardt**
PCC Members	**David Schmidt; Kimberly Putney; Kevin Poe; Rebecca Brannan; Katie Palmer, Laura Parsons, Eric Wymore**
Support	**Roseanna Picerno**

Link to complete Committee Meeting Packet with references: 2016 May MUE

MEDICATION USE AND EVALUATION COMMITTEE DECISION SUMMARY

A. eribulin (Halaven®)

Drug Summary

Eribulin is a microtubule inhibitor that has activity against refractory breast cancer and liposarcoma. Food and Drug Administration (FDA) approved indications include locally advanced or metastatic breast cancer and prior exposure to an anthracycline and a taxane, and in unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen.[1] The open-label, randomized,

Note: The Decision Brief summarizes the decisions of the national CHI Medication Use and Evaluation (MUE) Committee. Local P&Ts may act on MUE Decisions in one of four ways: 1) approve with no changes 2) approve with more restrictions 3) appeal the MUE decision (apply to entire organization) 4) request an exception to the MUE decision (request for variance).

1

multicenter EMBRACE (Eisai Metastatic Breast Cancer Study Assessing Physician's Choice Versus E7389) trial demonstrated an additional 2.5 months in overall survival versus treatment of physician's choice.2 Results from a phase 3 randomized, controlled trial in patients with liposarcoma or leiomyosarcoma showed a 2 month overall survival benefit compared with dacarbazine therapy.[3] The toxicity profile of eribulin includes neutropenia, anemia, and peripheral neuropathy.[1-3] These side effects were more common in patients with underlying hepatic dysfunction. Eribulin has favorable administration requirements (2-5 minute infusion) and provides an option for treatment refractory patients.

MUE COMMITTEE DECISION

The decision is to classify eribulin as Formulary, Restricted. The product will be restricted to outpatient use in patients meeting the following FDA-approved indications:
1) metastatic breast cancer as a single agent after prior therapy with two chemotherapy agents for metastatic disease (patients should have had prior treatment with both a taxane and an anthracycline in either the adjuvant or metastatic setting); or,
2) unresectable or metastatic liposarcoma who have received a prior anthracycline-containing regimen based on the updated FDA approval.

ACTION: A motion was made and seconded for eribulin to have Formulary, Restricted status with the recommended restrictions.

Voting: FOR: 22
AGAINST:
ABSENT: 2

B. Echinocandin Class Review

Drug Summary

The three commercially available echinocandins are similar in clinical efficacy for the treatment of fungal infections, specifically Candida and Aspergillus infections. However, it is important to note that there are differences in drug-drug interactions (more with caspofungin), loading dose requirements (caspofungin and anidulafungin), and dose adjustments for hepatic impairment (caspofungin). All three agents have favorable adverse effect profiles compared to alternative antifungal agents. However, there may be slightly higher rates of adverse effects for caspofungin, specifically higher incidence of increased liver enzymes as well as infusion-related reactions.

MUE COMMITTEE DECISION

The decision is to select the most cost-effective echinocandin (one of three) as Formulary, Unrestricted.

caspofungin	micafungin	anidulafungin
70 mg on day 1, followed by 50 mg daily	100 mg daily	200 mg on day 1, followed by 100 mg daily

ACTION: A motion was made and seconded to approve the most cost-effective echinocandin as Formulary, Unrestricted as recommended.

Voting: FOR: 22
AGAINST:
ABSENT: 2

C. ertapenem (Invanz®) Criteria for Appropriate Use

Drug Summary

The purpose of this initiative is to provide general guidance for appropriate use of ertapenem (Invanz®) in the acute care hospital setting. The goal is to conserve ertapenem (Invanz®) for multi-drug resistant (MDR) organisms and prevents over-usage that leads to resistance. An added benefit of the conversion is cost savings by transitioning to a more cost-effective agent. The choice between cefotetan (Cefotan®) and cefoxitin (Mefoxin®) is based on a preference of frequency of administration versus cost variance and local resistance pattern assessment.

Postoperative wound infections have an enormous impact on patients' quality of life and contribute substantially to the financial cost of patient care. The goal of prophylactic antibiotics is to prevent an infection from developing. Ertapenem (Invanz®), cefotetan (Cefotan®) and cefoxitin (Mefoxin®) are approved by the FDA for surgical prophylaxis in adult patients undergoing elective colorectal procedure. The cost of surgical prophylaxis treatment with ertapenem (Invanz®) compared with cefotetan (Cefotan®) or cefoxitin (Mefoxin®) is approximately is 2-3 times higher.

MUE COMMITTEE DECISION

The decision is to select the establish ertapenem as Formulary, Restricted with the following restrictions:

1. Restrict to use in suspected or proven infection with a multi-drug resistant Gram-negative pathogen where a carbapenem is preferred (e.g. pathogens producing ESBLs, Amp-Cs, etc.)
2. Restrict to use in confirmed infection requiring broad spectrum coverage where other antibiotics are not appropriate due to severe allergy
3. Allow a one-time dose within 24 hours of expected discharge to support transition to outpatient IV antibiotic therapy
4. Avoid use of ertapenem for:
   a. MSSA infections
   b. Pseudomonas or Acinetobacter infections: lacks adequate coverage
   c. Enterococcus: lacks adequate coverage
   d. Surgical prophylaxis: not recommended due to broad spectrum of activity, development of carbapenem resistance and higher rates for C. diff infection. If the patient does not meet the defined criteria, consider ID consult for further criteria and review by Antimicrobial Stewardship Team.

ACTION: A motion was made and seconded to assign Formulary, Restricted status to ertapenem (Invanz®) according to the recommended restrictions and criteria for use.

Voting: FOR: 22
AGAINST:
ABSENT: 2

EXCEPTION OR APPEAL DECISIONS SUMMARY

A. Exception Request (SBAR) for use of liposomal bupivacaine (Exparel®) at CHI Health

Summary
In March 2016, the CHI Medication Use and Evaluation Committee determined that liposomal bupivacaine (Exparel®) would be non-formulary status.
On April 29, 2016, CHI Health Division submitted an exception request to allow use of liposomal bupivacaine (Exparel®) for total knee procedures only within CHI Health facilities.

MUE COMMITTEE DECISION
The decision is to table the request from CHI Health.

ACTION: A motion was made and seconded to table the request from CHI Health. The decision was made to extend the implementation of the MUE decision for CHI Health with a suitable time period to be determined based upon further discussion.

Voting: FOR: 22
AGAINST:
ABSENT: 2

Date: June 23, 2016

Members Present: see attached Attendance Roster

Committee Meeting Packet with references posted in CHI MUE SharePoint:
CHI MUE Committee Compiled Packet 06 21 2016 Final

MEDICATION USE AND EVALUATION COMMITTEE DECISION SUMMARY

A. alvimopan (Entereg®)

Drug Summary
Alvimopan (Entereg®) is a selective, high affinity mu opioid receptor antagonist with peripheral activity. The Food and Drug Administration (FDA) approved the drug for accelerating time to upper and lower gastrointestinal (GI) recovery following bowel resection surgeries with primary anastomosis. Alvimopan is activated by intestinal microflora and acts on gastrointestinal mu opioid receptors. The drug's zwitterion structure keeps it from crossing the blood-brain barrier. Clinical trials were designed to compare time to GI recovery measured by time to toleration of solid food, first noted bowel movement or flatus, or a composite of these factors, as well as various measures of length of stay (LOS). The trials utilized alvimopan 6 or 12 mg once preoperatively followed by twice daily postoperatively for up to seven days. These trials have shown modest reductions in hospital LOS and time to GI recovery ranging from 14 to 29 hours and 8 to 41 hours respectively. Postoperative ileus (POI) prevention has not been demonstrated. However, LOS for patients experiencing postoperative ileus was reduced by 2.2 days with the use of alvimopan. Adverse events were comparable to placebo and included dyspnea and GI effects; nausea, vomiting, flatus, constipation, hypokalemia, back pain, urinary retention, and fever. Majority of published data includes alvimopan as a component of enhanced recovery after surgery (ERAS) protocols. It is unclear if the total benefit to LOS reduction is due to the drug or these fast track protocols. Published data indicates hospitals may realize cost savings with the addition of alvimopan in accelerated care pathway for patients with appropriate indications.

Within CHI alvimopan use and incorporation of fast track surgical recovery programs is variable. When the LOS is compared across CHI in procedures with and without alvimopan, the patients who receive alvimopan for open hemicolectomy, or laparoscopic or open sigmoidectomy surgeries appear to have a reduced average LOS (~0.7-1.9 days) compared to patients who did not receive alvimopan. There may be a modest LOS reduction (~0.5 day) in patients receiving alvimopan for laparoscopic hemicolectomy and radical cystectomy. There did not appear to be any LOS reduction in patients who received alvimopan for prostatectomy. These data should be interpreted cautiously as they are cumulative averages. Facilities have variable practices and protocols across the organization and it is unlikely that alvimopan is the sole reason for changes in LOS.

MUE COMMITTEE DECISION
The decision is to classify alvimopan as Formulary, Restricted.
Restrictions:

- Restricted to use for upper and lower gastrointestinal recovery following bowel resection surgeries with primary anastomosis and recommended with enhanced recovery after surgery (ERAS) protocols
- Facilities where alvimopan is used should have automatic stop orders in place to limit to maximum of 15 doses
- Facilities where alvimopan is used should have protocols in place to automatically discontinue alvimopan once bowel function returns

ACTION: **A motion was made and seconded to accept the recommendation for alvimopan to have Formulary, Restricted status with the recommended restrictions (above) and for MUE to review the data (including LOS) in 12 months.**

Voting: FOR: 15
AGAINST: 6
ABSENT: 3

B. Discussion Topics

Biosimilars

This educational presentation was provided to prepare the MUE committee to evaluate biosimilars since several new products are anticipated soon. No formal voting was conducted for this agenda item as it was for educational purposes only.

MUE Metrics

Beginning with August MUE decisions, each decision will include an implementation timeline. Markets will be held accountable for implementing the MUE decisions within the specified time frame. The timelines will vary depending on complexity (i.e., requires electronic health record (EHR) build changes, clinician education, etc.).

- Metrics representing Process, Compliance and Cost will be shared with the MUE Committee and the Clinical Leadership Council (CLC), which reports directly to the CHI National Presidents Council.
- An example process metric was shared; the 10 drugs reviewed during the March, April and May MUE meetings are distributed into three formulary categories:
  - CHI Formulary Approved, Restricted: 50%
  - CHI Formulary Approved, Unrestricted: 10%
  - CHI Non-Formulary: 40%

RESPIRATORY FORMULARY INTERCHANGE- *product updates August 2016*

Beta-agonists	
ORDERED	**SUBSTITUTION**
Levalbuterol (Xopenex®)	Albuterol
Indacaterol (Arcapta® Neohaler) 1 inhalation (75 mcg) once daily	Arformoterol (Brovana®) 15 mcg via neb twice daily
Olodaterol (Striverdi Respimat®) 2 inhalations (5 mcg) once daily	Arformoterol (Brovana®) 15 mcg via neb twice daily
Formoterol (Perforomist®)	Arformoterol (Brovana®) 15 mcg via neb twice daily
Salmeterol (Serevent Diskus®) 1 inhalation (50 mcg) twice daily	Arformoterol (Brovana®) 15 mcg via neb twice daily
Inhaled Antimuscarinics & Antimuscarininc/Beta-agonist combination products	
ORDERED	**SUBSTITUTION**
Ipratropium (Atrovent MDI®) 2 sprays inhaled 2-4 times daily	Iptratropium nebulizer solution 0.5 mg via neb at same frequency
Iptratropium/albuterol (Combivent Respimat®) 2 inhalations 4 times daily SCH or PRN	Ipratropium/albuterol (Duoneb®) 1 nebulization 4 times daily SCH or PRN
Aclidinium (Tudorza®) 400 mcg twice daily via oral inhalation	Tiotropium (Spiriva Handihaler®) 18 mcg (1 cap) once daily via oral inhalation
Tiotropium (Spiriva Respimat®) 5 mcg (2 puffs) via oral inhalation once daily	Tiotropium (Spiriva Handihaler®) 18 mcg (1 cap) once daily via oral inhalation
Umeclidinium (Incruse Ellipta®) 62.5 mcg (1 puff) via oral inhalation once daily	Tiotropium (Spiriva Handihaler®) 18 mcg (1 cap) once daily via oral inhalation
Tiotropium/Olodaterol (Stiolto Respimat®) 5 mcg/5 mcg (2 puffs) via oral inhalation once daily	Umeclidinium/Vilanterol (Anoro Ellipta®) 62.5 mcg/25 mcg (1 puff) via oral inhalation once daily
Note: When tiotropium (Spiriva®) is ordered for a patient currently on ipratropium (Atrovent®), the Atrovent® will automatically be discontinued per protocol.	

Theophylline Product Change & Updated Therapeutic Interchange:
As of June 2016 only one extended release formulation of theophylline is available – Theo-24 (24 hour formulation)

Updated Interchange:
Theophylline ER BID (non-24 hour formulations) → Theo-24 (total daily dose or ER product administered ONCE DAILY)
Examples: Theophylline ER 200 mg BID → Theo-24 400 mg DAILY
Theophylline ER 300 mg BID → Theo-24 600 mg DAILY
*** Note: Orders for Theo-24 **BID** will be continued on a TWICE DAILY schedule if this is how they take this product at home per home med sheet.*

DRUG CLASS REVIEW

ANTIMUSCARINIC MEDICATIONS FOR OVERACTIVE BLADDER

CURRENT FORMULARY AGENTS:
Ditropan XL® (oxybutynin) & Detrol LA® (toleterodine) – all other agents interchanged via approved therapeutic interchange (2009)

PROPOSED FORMULARY AGENT:
Sanctura® (trospium) – all other agents interchanged via approved therapeutic interchange (see below)

BACKGROUND & SUMMARY:
Symptoms of overactive bladder (OAB), also termed urge urinary incontinence, occur because the detrusor muscle is overactive and contracts inappropriately during the filling phase. The symptoms of OAB include urinary frequency, urgency, and urge incontinence. Anticholinergic/antispasmodic drugs are the first choice for OAB, as they have been proven to be the most effective agents in suppressing premature detrusor contractions, enhancing bladder storage, and relieving symptoms. Anticholinergic and antispasmodic agents act by antagonizing cholinergic muscarinic receptors, through which different parasympathetic nerve impulses evoke detrusor contraction. In 1970, flavoxate was the first drug in this class to be approved by the Food and Drug Administration (FDA) to treat OAB. Then, in 1975, oxybutynin became the mainstay of treatment for OAB, as it was shown to be more efficacious than flavoxate. The next agent introduced in the class was tolterodine in 1996. Lastly, in 2004, three newer agents—darifenacin, solifenacin, and trospium—challenged older compounds by having a less frequent dosing schedule and a more favorable side effect profile.

PHARMACOLOGY & PHARMACOKINETICS:
Of the five known muscarinic subtypes (M_1 through M_5), M_3 appears to be the most clinically relevant in the human bladder. M_2 muscarinic receptors are the predominant subtype (comprising about 80% of all muscarinic receptors); however, contraction of smooth muscle, including muscles in the urinary bladder, is mediated mainly by M_3 receptors. M_3 receptors are also involved in contraction of the gastrointestinal smooth muscle, saliva production, and iris sphincter function. Inhibition of the muscarinic receptors in the urinary bladder results in decreased urinary bladder contraction, increased residual urine volume, and decreased detrusor muscle pressure.

Oxybutynin, tolterodine, darifenacin, solifenacin, and trospium antagonize the effects of acetylcholine at muscarinic receptors on the detrusor muscle and are known as antimuscarinic agents. These agents potently and selectively bind to the M_3 receptor subtype more than other muscarinic receptor subtypes, with the exception of tolterodine, which has demonstrated no specificity for any subtype. All of the antimuscarinic agents exhibit functional selectivity for urinary bladder over secretory glands (e.g., salivary) and have little or no affinity for nicotinic receptors compared with muscarinic receptors. The newer agents (i.e., darifenacin, solifenacin, and trospium) have demonstrated greater tissue selectivity for inhibition of detrusor contraction over salivation, offering an advantage over other agents by reducing adverse effects and improving compliance. Trospium, a quaternary ammonium antimuscarinic, is hydrophilic and theoretically should not cross the blood-brain barrier like lipophilic anticholinergic agents (e.g., oxybutynin, tolterodine); therefore, adverse central nervous system (CNS) effects (e.g., dizziness) should be minimal.

Parameter	Darifenacin	Flavoxate	Oxybutynin	Solifenacin	Tolterodine	Trospium
Oral bioavailability	15%–25%	N/A	6%	90%	77%	9.6%
Affected by food	No	No	Yes (increased serum concentrations ~25%)	No	No	Yes (70%–80% reduced absorption with high-fat meal)
Time to peak concentration (hours)	7	2	1 (IR) 3–6 (ER) 24–48 (patch)	3–8	1–2 (IR) 2–6 (ER)	4–6
Half-life (hours)	13–19	N/A	1.1–2.3 (IR) 12–16 (ER)	40–68	1.9–3.7 (EM) 9.6 (PM)	20
Excretion: feces	40%	N/A	N/A	23%	17%	85%
Excretion: renal	60%	57%	<0.1%	3%–6%	77%	6%
Metabolism	Liver by CYP3A4 and 2D6 to inactive metabolites	Mechanism unknown to active metabolite	Liver by CYP3A4 to active metabolite (desethyloxy-butynin)	Liver by CYP3A4 to active metabolite (4R-hydroxy-solifenacin)	Liver by CYP2D6 to active metabolite (5-hydroxyethyl-tolterodine)	Liver, not CYP to inactive metabolites

COMPARATIVE EFFICACY (Trospium vs Oxybutynin or Tolterodine):

Trospium chloride has been compared to both tolterodine and oxybutynin in three randomized, controlled trials. Trospium was found to be equally efficacious in reducing micturation frequency and bladder volume to both agents. Additionally, there was no difference in adverse events between trospium and tolterodine but patients taking trospium had fewer side effects and were less likely to discontinue the medication compared to oxybutynin.

CONTRAINDICATIONS AND PRECAUTIONS:

Darifenacin, oxybutynin, solifenacin, tolterodine, and trospium are contraindicated in patients at risk of or with known urinary or gastric retention or uncontrolled angle-closure glaucoma. Tolterodine and trospium are also contraindicated in myasthenia gravis. Because of the risk of urinary retention, darifenacin, oxybutynin, solifenacin, tolterodine, and trospium should be used with caution in patients with clinically important bladder outflow obstruction. The antimuscarinic agents oxybutynin, tolterodine, trospium, solifenacin, and darifenacin may decrease gastrointestinal motility. Caution should be used in patients with severe constipation, intestinal atony, ulcerative colitis, or myasthenia gravis.

COMPARATIVE DOSING:

Drug name	Initial dose	Maximum dose	Adjust for renal or hepatic dysfunction	Geriatric dosing	Adjustment for CYP3A4 interactions
Darifenacin (Enablex)	7.5 mg daily	15 mg daily	7.5 mg daily for moderate hepatic impairment	N/A	7.5 mg daily
Flavoxate (Urispas)	100–200 mg 3–4 times daily	200 mg 4 times daily	No	N/A	N/A
Oxybutynin IR (Ditropan)	5 mg 2–3 times daily	5 mg 4 times daily	No	Initial dose: 2.5 mg 2–3 times daily	N/A
Oxybutynin ER (Ditropan XL)	5–10 mg daily	30 mg daily	No	N/A	N/A
Oxybutynin patch (Oxytrol)	1 patch (36 mg) twice weekly		No	N/A	N/A
Solifenacin (Vesicare)	5 mg daily	10 mg daily	Maximum 5 mg daily for severe renal and moderate hepatic impairment	N/A	5 mg daily
Tolterodine IR (Detrol)	1 mg twice daily	2 mg twice daily	Maximum 1 mg twice daily for severe renal impairment Avoid use in severe hepatic impairment	N/A	1 mg twice daily
Tolterodine ER (Detrol LA)	2 mg daily	4 mg daily	Maximum 2 mg daily for severe renal impairment Avoid use in severe hepatic impairment	N/A	2 mg daily
Trospium (Sanctura)	20 mg daily	20 mg twice daily	Maximum 20 mg daily for severe renal impairment Avoid use in severe hepatic impairment	20 mg daily	N/A

ADVERSE EFFECTS – PRODUCT COMPARISON:

Adverse event	Darifenacin	Flavoxate*	Oxybutynin†	Solifenacin	Tolterodine	Trospium
Dry mouth	20.2%–35.3%	*	29%–61%	10.9%–27.6%	23%	20.1%
Constipation	14.8%–21.3%	*	7%–13%	5.4%–13.4%	6%	9.6%
Upper abdominal pain	2.4%–3.9%	No report	<5	1.2%–1.9%	4%	1.5%
Dyspepsia	2.7%–8.4%	*	5%–7%	1.4%–3.9%	3%	1.2%
Nausea	1.5%–2.7%	*	2%–9%	1.7%–3.3%	*	>0.5%
Diarrhea	0.9%–2.1%	*	7%–9%	No report	*	No report
Urinary retention	No report	*	<5%	1.4%	No report	1.2%
Urinary tract infection	4.5%–4.7%	No report	5%	2.8%–4.8%	1%	1.2%
Vertigo	1.3%–2.1%	*	4%–6%	1.9%	2%	No report
Blurred vision	>1%	*	1%–8%	3.8%–4.8%	1%	>0.5%
Drowsiness	0.9%–2.1%	*	2%–12%	1.0%–2.1%	3%	1.9%
Headache	No report	*	6%–10%	No report	6%	4.2%
Dry eyes	1.5%–2.1%	*	3%–6%	0.3%–1.6%	3%	No report

PHARMACOECONOMICS:

Drug	Cost Per day of therapy
Trospium	$1.14 for 20mg
Solifenacin	$9.16 for 5mg, 10mg
Darifenacin	$7.79 for 7.5mg, 15mg
Oxybutynin Long Acting	$1.75 for 5mg, $3.50 for 15mg
Tolterodine Long Acting	$5 for 2mg, 4mg

SUMMARY:

Darifenacin, oxybutynin, solifenacin, tolterodine, and trospium suppress premature detrusor contractions and allow enhanced bladder storage and relief of symptoms of OAB. Oxybutynin and flavoxate also have antispasmodic effects and more side effects than the other agents. Tolterodine and oxybutynin appear to be equally effective in relieving the symptoms of OAB, although tolterodine is much better tolerated than oxybutynin in comparative studies. The three newest agents in the class, darifenacin, solifenacin, and trospium, have the lowest incidence of adverse events and exhibit efficacy rates comparable to those of tolterodine and oxybutynin.

RECOMMENDATION:

Trospium is now the most cost-effective agent within this class of medications. It is recommended to modify the current interchange to now utilize trospium as the sole formulary agent within this class and automatically interchange all other meds ordered to a therapeutically equivalent dose of trospium as outlined in the below table.

Bladder Antispasmodics	
ORDERED	**SUBSTITUTION**
Ditropan XL 5 mg daily	Trospium (Sanctura®) 20 mg daily
Ditropan XL 10 mg daily	Trospium (Sanctura®) 20 mg BID
Ditropan XL 15 mg daily	Trospium (Sanctura®) 20 mg BID
Darifenacin (Enablex®) 7.5 mg daily	Trospium (Sanctura®) 20 mg daily
Darifenacin (Enablex®) 15 mg daily	Trospium (Sanctura®) 20 mg BID
Oxybutynin (Oxytrol® Patch) 3.9 mg/day	Trospium (Sanctura®) 20 mg daily
Tolteridine (Detrol®) 1 mg BID	Trospium (Sanctura®) 20 mg daily
Tolteridine (Detrol®) 2 mg BID	Trospium (Sanctura®) 20 mg BID
Tolteridine (Detrol LA®) 2 mg daily	Trospium (Sanctura®) 20 mg daily
Tolteridine (Detrol LA®) 4 mg daily	Trospium (Sanctura®) 20 mg BID
Solifenacin (Vesicare®) 5 mg daily	Trospium (Sanctura®) 20 mg daily
Solifenacin (Vesicare®) 10 mg daily	Trospium (Sanctura®) 20 mg BID
Trospium (Sanctura XR®) 60 mg daily	Trospium (Sanctura®) 20 mg BID
Fesoterodine (Toviaz®) 4 mg daily	Trospium (Sanctura®) 20 mg daily
Fesoterodine (Toviaz®) 8 mg daily	Trospium (Sanctura®) 20 mg BID

FORMULARY CLASS REVIEW

THERAPEUTIC CLASS: Proton Pump Inhibitors – SUSPENSION PRODUCTS

CURRENT FORMULARY AGENT: For patients unable to take oral PPI (tablet) → Nexium® (esomeprazole) delayed release powder for suspension. Protonix® (pantoprazole) delayed release oral suspension was formerly the formulary agent of choice within this class but all use was transitioned (Nov 2013) to Nexium® suspension due to reports of clogged tubes when pantoprazole suspension was administered via tube.

COMPARISON:

PPI	INSTRUCTIONS FOR TUBE ADMINISTRATION	SMALLEST FRENCH SIZE TUBING USED	COST
Nexium® suspension	1. Add 15 mL of water to a catheter-tipped syringe. 2. Empty contents of packet into syringe (10, 20, or 40 mg). 3. Shake syringe; allow 2–3 minutes for suspension to thicken. 4. Shake syringe again and administer. 5. Draw 15 mL of water into syringe; shake and flush tube. 6. Administer in a French size 6 tube or larger.	6 fr	$7.95 per 40 mg packet
Protonix® suspension	1. Remove plunger from 60-mL catheter-tipped syringe; attach syringe to tube. 2. Empty packet contents into syringe. 3. Add 10 mL of apple juice. 4. Gently shake syringe to empty contents into tube. 5. Flush syringe and tubing with 10 mL of apple juice. 6. Repeat flush at least two additional times or until no granules remain in syringe. 7. Administer in a French size 16 tube or larger.	16 fr	$2.68 per 40 mg packet
Omeprazole compounded suspension	1. Only PPI studied successfully in J-tubes, and most studied PPI per tube overall 2. Studied in smallest tube sizes 3. Not commercially available and must be compounded by pharmacy in sodium bicarbonate. 4. 30 day shelf life refrigerated	6 fr	$2 per 20 mg dose
Protonix IV	Potential alternative for patients unable to take traditional oral formulations	N/A	$2.95

CHI NATIONAL RECOMMENDATION: CHI is recommending that all facilities transition to the pantoprazole suspension or other alternative (compounded omeprazole suspension) due to national cost savings opportunity and increased cost of non-pantoprazole suspension formulations.

Annual usage: 2950 Nexium suspension packets per year
Potential cost savings if Protonix suspension or Protonix IV used as alternative: $15,000

RECOMMENDATION:

Patients unable to take conventional oral Protonix formulation

1. Transition to Protonix suspension as formulary agent for patients unable to take oral Protonix – feeding tubes 16 fr and larger.
    a. Educate nursing on appropriate dilution when administered via appropriate tube size
2. If tube size is not appropriate (< 16 fr) and PPI still needed, IV pantoprazole may be used as an alternative.
    a. If no IV access available pharmacy will compound omeprazole suspension for tube administration
        i. Limit omeprazole suspension to this population only.

FORMULARY INTERCHANGE

Nucynta® ER → Nucynta® IR

CURRENT FORMULARY PRODUCT**:** Nucynta® (tapentadol) 50 mg immediate release

FORMULATION COMPARISON:

Nucynta® IR
- Normal dose: 50-100 mg PO Q 4-6 hours
- Time to Cmax: 1.25 hours
- Terminal half-life: approximately 4 hours

Nucynta® ER
- Normal dose: 50-250 mg PO Q 12 hours
- Time to Cmax: 3-6 hours
- Terminal half-life: approximately 5 hours

PROPOSED FORMULARY INTERCHANGE:

Nucynta® ER			**Nucynta® IR**
50 mg	BID	→	25 mg Q 6 hours
100 mg	BID	→	50 mg Q 6 hours
150 mg	BID	→	50 mg Q 4 hours
200 mg	BID	→	100 mg Q 6 hours
250 mg	BID	→	125 mg Q 6 hours

RECOMMENDATION:
It is recommended to automatically interchange any orders for Nucynta® ER to a therapeutically equivalent dose of Nucynta® IR as outlined in the above proposed interchange.

BASAL INSULIN CONVERSION INITIATIVE

Background

Lantus® (insulin glargine U-100), Toujeo® (insulin glargine U-300) and Levemir® (insulin detemir) are all long-acting human insulin analogues approved for subcutaneous injection in diabetes mellitus types 1 and 2. They are absorbed slowly with a stable plateau effect that lasts most of the day. Consequently, they are used to control blood sugar overnight, while fasting and between meals. Lantus® and Toujeo® are FDA approved for once daily dosing; Levemir® is FDA approved for once and twice daily dosing.

There are no head to head inpatient trials comparing the two long-acting insulins (glargine vs detemir). A systematic review of 187 literature citations concluded there were no significant differences in efficacy or safety with the long acting insulins.

These basal insulin agents have comparable safety, efficacy, pharmacokinetic and pharmacodynamic considerations, thus they are therapeutically interchangeable at a 1:1 ratio. In addition, the unit-to-unit dose conversion is supported in the insulin detemir package insert. Therefore, the basal insulins should be interchangeable to the most cost-effective agent.

Tresiba® (insulin degludec) is a long-acting insulin analogue for use as basal insulin in the treatment of patients with type 1 and type 2 diabetes mellitus. It has a duration of action exceeding 24 hours, and may have a lower pharmacodynamic variation than insulin glargine. In comparative studies with insulin glargine, insulin degludec has exhibited comparable reductions in HbA_{1c}, with lower insulin doses and less confirmed nocturnal hypoglycemia.

Proposal

Levemir® (insulin detemir) is the preferred basal insulin agent across CHI.

Lantus® (glargine – U-100) or Toujeo® (glargine U-300) should not be the preferred basal insulin. It is recommended that each facility establish formulary status and evidence-based criteria around the conversion of insulin glargine to insulin detemir.

A pharmacist-driven automatic, substitution from insulin glargine to insulin detemir using:

- Conversion of 1 unit insulin glargine to 1 unit of insulin detemir
- Continuation of order frequency

Prepare patient-specific doses in the IV clean room where appropriate.

Therapeutic Substitution Recommendation

Drug/Dose Written	Drug/Dose Interchanged

Insulin glargine U-100 (Lantus®)
• units ordered daily
  ○ (for example: 40 units daily ordered)
• units ordered twice daily
  ○ (for example: 30 units twice daily ordered)
OR
• For total daily doses less than 10 units, SQ daily-twice daily
• For total daily doses greater or equal to 10 units SQ daily-twice daily
	Insulin detemir (Levemir®) 100 units/ml
	• Half of total daily Lantus units ordered twice daily
	  ○ (20 units twice daily is the interchange)
	• Unit per unit of Lantus ordered twice daily
	  ○ (30 units twice daily is the interchange)
	• Unit per unit of Lantus with the same frequency for twice daily dosing (daily dosing will be divided evenly into 2 doses given twice daily)
	• Unit per unit with the same frequency

Drug/Dose Written	Drug/Dose Interchanged

Insulin glargine U-300 (Toujeo®) 300 units/ml
• units ordered daily
  ○ (for example: 40 units daily ordered)
• units ordered twice daily
  ○ (for example: 30 units twice daily ordered)
	Insulin detemir (Levemir®) 100 units/ml
	• Half of total daily Toujeo units ordered twice daily
	  ○ (20 units twice daily is the interchange)
	• Unit per unit of Toujeo ordered twice daily
	  ○ (30 units twice daily is the interchange)

Drug/Dose Written	Drug/Dose Interchanged

Insulin degludec (Tresiba®)
• units ordered daily
  ○ (for example: 40 units daily ordered)
	Insulin detemir (Levemir®) 100 units/ml
	• Half of total daily Tresiba units ordered twice daily
	  ○ Start 24hrs after patient had received their last Tresiba dose
	(for example: 20 units twice daily is the interchange)

Pharmacokinetics								
	Onset of Action	**Peak Effect**	**Time to Peak, Plasma**	**Duration**	**Excretion**	**Distribution**	**Bioavailability**	**Half-life Elimination**
Long Acting Basal Insulin								
Glargine (Lantus, Lantus Solostar)	3-4 hrs	No pronounced effect	5hrs	≥ 24 hrs Reported range: 10.8 to ≥ 24 hrs	Urine			
Glargine (Toujeo Solostar) U-300	3-4hrs	No pronounced effect	5hrs	≥ 24 hrs Reported range: 10.8 to ≥ 24 hrs	Urine			
Detemir (Levemir, Levemir Flex Pen)	3-4 hrs	3-9 hrs	6-8 hrs	5.7-23 hrs (dose dependent	Urine	Vd: 0.1 L/kg	60%	5-7 hrs (dose dependent)
Ultra Long Acting Basal Insulin								
Degledec (Tresiba Tresiba FlexTouch) U-100; U-200	1-3hrs	No pronounced effect	12hrs	25-42hrs	Urine			

Detemir/Glargine to Deguldec Comparison Literature[8]			
Objective	**Design**	**Results Efficacy**	**Conclusion**
To compare changes of basal insulin dose and blood glucose profile in basal-bolus therapy of type I diabetes mellitus at the switching of basal insulin from insulin glargine or detemir to insulin degludec	N = 16 **Ten Type I DM** patients treated with insulin glargine or detemir twice daily were switched to insulin degludec with 80-90% of the prior insulin dose. **Six patients** treated with insulin glargine once daily were switched to insulin degludec without down titration. The changes of daily insulin dose and glycated hemoglobin were examined for 12 weeks after switching	In patients switched from twice daily basal insulin, no significant difference was found between before and after switching in the blood glucose profle. In the once-daily group, blood glucose levels showed a tendency to decrease after switching to the degludec treatment. In both groups, the HA1c changes were in significant.	The author s concluded it is possible to achieve similar glycemi control with once-daily injections and lower doses of insulin degludec in patients with Type I DM who have been treated with insulin glargine or detemir.

Recommendations:

There are currently four basal or long acting insulins approved by the FDA for treatment of Type I and Type II diabetes. The most recent two approved by the FDA are insulin degludec (Tresiba) which is available as U-100 and U-200 and insulin glargine U-300. Insulin glargine and insulin detemir are interchangeable in a 1:1 ratio. The current recommendation is to therapeutically substitute insulin glargine (U-100 and U-300) to insulin detemir while the patient is hospitalized. Across the CHI organization, endocrinologists have recommended a few variations in the appropriate manner to convert patient dosing and this will be left to the discretion of the local market in conjunction with their providers. Included, is also a proposed recommendation for converting insulin degludec to insulin determir for patients being hospitalized who currently use insulin degludec.

FORMULARY REVIEW

GENERIC NAME: BRIVARACETAM

PROPRIETARY NAME: *Briviact* (UCB Pharma)

THERAPEUTIC CLASS: Anticonvulsant

SIMILAR DRUGS: Keppra® (levetiracetam)

INDICATIONS: Brivaracetam is a 2-pyrrolidine derivative and levetiracetam analog approved for partial onset seizures as add-on treatment to other medications in patients aged 16 years and older.

CLINICAL PHARMACOLOGY: Brivaracetam is a high-affinity ligand of synaptic vesicle protein 2A (SV2A) in the brain. Similarly to levetiracetam (Keppra®), the antiepileptic effect of brivaracetam most likely occurs as it binds to SV2A which is located in presynaptic membranes and regulates the calcium-dependent exocytosis of neurotransmitters into the synaptic gap. Brivaracetam has a 15 to 30 fold higher affinity for SV2A compared to levetiracetam.

PHARMACOKINETICS:
Absorption: The time to peak concentration (T_{max}) after oral administration of brivaracetam tablets without food is 1 hour. Administration with a high-fat meal results in slower absorption, but does not change the extent of absorption; T_{max} is delayed by 3 hours and peak plasma levels are decreased by 37%, while the area under the curve (AUC) is unaffected.

Distribution: The volume of distribution is 0.5 L/kg. Brivaracetam is weakly bound (20% or less) to plasma proteins.

Metabolism/Elimination: The primary route of metabolism is via hydrolysis. Secondary metabolism is via hydroxylation (cytochrome P450 [CYP-450] 2C19). All metabolites are inactive. The terminal plasma half-life of brivaracetam is 9 hours. However, patients who are poor CYP2C19 metabolizers or who are receiving CYP2C19 inhibitors may require a brivaracetam dose reduction because of delayed clearance of the brivaracetam molecule. The majority (95%) of brivaracetam and its metabolites are excreted in the urine within 72 hours. Fecal excretion is less than 1% and urine excretion in less than 10%.

SPECIAL POPULATIONS:
Hepatic Impairment: Brivaracetam exposure is increased with hepatic impairment. When compared to matched healthy controls, subjects with hepatic cirrhosis with Child-Pugh scores A, B, and C had increases in brivaracetam exposure of 50%, 57%, and 59%, respectively. Patients with hepatic impairment should receive a lower dosage.

Renal Impairment: The plasma AUC of brivaracetam increased by 21% in subjects with severe renal impairment (creatinine clearance less than 30 mL/minute/1.73 m2) compared to healthy controls. Brivaracetam has not been studied in patients undergoing hemodialysis.

CLINICAL STUDIES:
In three phase III studies (N01252, N01253, N01358), brivaracetam (BRV) as adjunctive therapy demonstrated decreased rates of partial onset seizures per set period of time compared to placebo in patients 16 years and older with focal epilepsy. Most patients included in these trials were on 1-2 other AEDs and all three studies determined that brivaracetam was effective at demonstrating a dose dependent reduction in uncontrolled focal seizures when used in combination with other concomitant AEDs. Two studies (N01252 and N01253) included patients on concomitant leviteracetam (LEV). Post-hoc analysis of concomitant LEV/BRV therapy demonstrated reduced BRV effect. These results suggest that concomitant use of LEV/BRV is less effective than using either agent alone as adjunctive therapy. No direct comparator trials with BRV and LEV have been completed.

One small phase IIIb study (N01395) looked at an immediate switch from therapeutic doses of LEV to therapeutic doses of BRV in patients who were experiencing behavioral adverse events (BAEs) while on LEV. In this population of 29 patients, BRV showed equivalent antiseizure effect while reducing overall BAEs. These results suggest that patients experiencing BAEs resulting in discontinuation of LEV may be transitioned to BRV without any titration period and see equivalent efficacy and reduced BAEs.

CONTRAINDICATIONS:
Brivaracetam is contraindicated in patients with known hypersensitivity reactions to brivaracetam or any of the inactive ingredients. Bronchospasm and angioedema have occurred in patients taking brivaracetam.

WARNINGS AND PRECAUTIONS:
Suicidal ideation effects: Like all AEDs, brivaracetam may increase the risk of suicidal thoughts or behavior. Patients should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.

Psychiatric effects: Psychiatric-type adverse reactions (eg, irritability, anxiety, nervousness, aggression, belligerence, anger, agitation, restlessness, depression, depressed mood, tearfulness, apathy, altered mood, mood swings, affect lability, psychomotor hyperactivity, abnormal behavior, adjustment disorder, psychotic disorder along with hallucination, paranoia, acute psychosis, psychotic behavior) have been reported and may require discontinuation of therapy.

CNS Effects: Brivaracetam can cause somnolence, fatigue, dizziness, and disturbances of coordination. Patients should be advised not to drive or operate machinery until they know how the medication will affect them. Brivaracetam can cause adverse reactions related to dizziness and disturbance of gait and coordination (eg, dizziness, vertigo, balance disorder, ataxia, nystagmus, gait disturbance, abnormal coordination). The risk of these type of adverse events is greatest early in treatment, but could occur at any time. Brivaracetam is associated with dose-dependent increases in somnolence and fatigue-related adverse events (eg, fatigue, asthenia, malaise, hypersomnia, sedation, lethargy). The risk of these type of adverse events is greatest early in treatment, but can occur at any time.

Hypersensitivity: Hypersensitivity-type reactions (eg, bronchospasm, angioedema) may occur. If these types of reactions occur, brivaracetam should be discontinued.

Withdrawal seizures: Gradual withdrawal of AEDs is recommended, when possible, to reduce the risk of increased seizure frequency and status epilepticus.

The warnings and precautions associated with brivaracetam and levetiracetam are similar, with the exception of differences in pediatric use. Levetiracetam is approved for use in younger patients than brivaracetam.

ADVERSE REACTIONS:
Neurological adverse reactions were frequently reported with brivaracetam during clinical trials. Among patients who received brivaracetam, drowsiness and sedation (16%), dizziness (12%), and fatigue (9%) were observed. A total of 3% of patients had cerebellar coordination and balance disturbances (i.e., ataxia, balance disorder, abnormal coordination, and nystagmus). Somnolence and fatigue-related reactions (i.e., fatigue, asthenia, malaise, hypersomnia, sedation, and lethargy) are dose dependent and the risk of occurrence is greatest early in treatment.

Psychiatric adverse reactions were observed in 13% of patients who received brivaracetam (50 mg/day or more) compared to 8% of patients who received placebo. Irritability with brivaracetam was reported in 3% of patients. Other non-psychotic reactions included anxiety, nervousness, aggression, belligerence, anger, agitation, restlessness, depression, depressed mood, tearfulness, apathy, altered mood, mood swings, emotional lability, psychomotor hyperactivity, abnormal behavior (unspecified), and adjustment disorder. Psychotic reactions observed were psychotic disorder along with hallucinations, paranoia, acute psychosis, and psychotic behavior. Euphoria (>= 3%) and feeling drunk (>= 3%) have been reported with the use of brivaracetam injection.

DRUG INTERACTIONS:
Brivaracetam does not inhibit CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, or 3A4. Brivaracetam weakly inhibited CYP2C19 in vitro. Brivaracetam is not a substrate of P-gp, MRP1, or MRP2 and does not inhibit transporters such as BCRP, BSEP, MATE1, MATE2/K, MRP2, OAT1, OAT3, OCT1, OCT2, OATP1B1, OATP1B3, or P-gp.

CYP-450 inhibitors or transporter inhibitors are not expected to affect brivaracetam exposure.

Coadministration of brivaracetam with carbamazepine resulted in increased exposure to carbamazepine's active metabolite, carbamazepine-epoxide. No adverse safety issues were reported because of this change in carbamazepine-epoxide exposure.

Brivaracetam can increase the plasma levels of phenytoin. Patients receiving concurrent therapy with brivaracetam and phenytoin should be monitored for changes in phenytoin levels when brivaracetam is added or discontinued.

Rifampin can substantially decrease brivaracetam plasma levels. The dose of brivaracetam should be increased by up to 100% (ie, double the dosage) in patients requiring concomitant treatment with rifampin and brivaracetam.

DOSING AND ADMINISTRATION:
Adult Dosing: When initiating treatment, gradual dose escalation is not required. The recommended starting dose is brivaracetam 50 mg orally twice daily (100 mg per day), with or without food. The dosage may be adjusted down to 25 mg twice daily (50 mg per day) or adjusted up to 100 mg twice daily (200 mg per day), depending on patient tolerability and response. For patients with any stage of hepatic impairment, the recommended starting dosage is 25 mg twice daily (50 mg per day) and the recommended maximum dosage is 75 mg twice daily (150 mg/day).

Abrupt discontinuation of brivaracetam therapy should be avoided in order to minimize the risk of increased seizure frequency and status epilepticus.

The injectable formulation is intended for temporary use only when oral administration is not feasible; brivaracetam injection should be administered at the same dosage and frequency as the oral dose forms. In clinical trials, use of the injectable formulation was limited to 4 consecutive days of treatment. Long-term safety of this formulation is not known.

DOSING ADJUSTMENTS:
Hepatic impairment: For patients with any stage of hepatic impairment, the recommended starting dosage is 25 mg twice daily (50 mg per day) and the recommended maximum dosage is 75 mg twice daily (150 mg/day).

Renal impairment: No dosage adjustment required

PHARMACOECONOMICS/COST

Tablet Strength/Formulation	Cost per unit	Cost per Dose
Briviact (brivaracetam) 10mg tablets	$866.05/#60	$14.43
Briviact (brivaracetam) 25mg tablets	$866.05/#60	$14.43
Briviact (brivaracetam) 50mg tablets	$866.05/#60	$14.43
Briviact (brivaracetam) 75mg tablets	$866.05/#60	$14.43
Briviact (brivaracetam) 100mg tablets	$866.05/#60	$14.43
Briviact (brivaracetam) 10mg/ml (300 ml) oral solution	$866.05/30ml	Dose dependent
Briviact (brivaracetam) 50mg/5ml injection	$371.17/#10	$37.11

MEDICATION ERROR POTENTIAL:
There is no REMS required for brivaracetam

BLACK BOX WARNINGS
There are no black box warnings for brivaracetam

CONCLUSIONS:
Brivaracetam (Briviact®) is a 2-pyrrolidine derivative and levetiracetam analog indicated for partial onset seizures as add-on treatment to other medications in patients ages 16 years and older.

The phase III three studies determined that brivaracetam was effective at demonstrating a dose dependent reduction in uncontrolled focal seizures when used in combination with other concomitant anti-epileptic drugs (AEDs). Overall, the phase III studies demonstrate that brivaracetam is effective for its labeled indication although trials directly comparing it to levetiracetam are lacking at this time. Despite the similarities to levetiracetam, the lack of studies directly comparing brivaracetam to levetiracetam creates difficulties in accurately determining its place in therapy although it may have a role for some patients with refractory focal seizures who have failed multiple other therapies.

RECOMMENDATION:
Formulary: New inpatient starts restricted to neurology for patients with refractory seizures.

FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)

Medication Management Step	Identified Risk	Steps for Prevention
Selection & Procurement		
Therapeutic interchange?	N/A	N/A
Special Ordering Requirements?	N/A	N/A
Storage		
LASA* separation of stock?	LASA – levetiracetam	Separate stock, educate pharmacy staff.
Special storage (e.g. refrigeration, protect from light, controlled substance)?		
Pharmacist/Technician Education?		
Ordering & Prescribing		
Restriction to particular specialty, indication, or particular patient population?	Restriction to neurology (if approved)	Physician education on approved restrictions
Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)?	• Renal: No dose adjustments required for renal impairment; no data in patients with ESRD/dialysis; use not recommended in these patients • Hepatic: 50% dose reduction recommended for all stages of hepatic impairment.	Nurse, provider, and pharmacist education on dosing.
Drug Interactions?	See monograph	
Pregnancy?	Pregnancy Category C	
Absolute Contraindications?	N/A	
Processing, Preparing, & Dispensing		
High-risk drug double check?	N/A	Nurse, provider, and pharmacist education on drug-drug interactions
Drug Interaction check in place?	Drug interaction checks in EMR.	
LASA* computer warnings?	N/A	
Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)?	N/A	
Packaging/Labeling (e.g. prepacking)?	N/A	
Dispensing (e.g. auxiliary labeling, light protection, refrigeration)?	Refrigeration not required	
Documentation required (e.g. double check, worksheet)?	N/A	
Administration		
Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information?	N/A	N/A
Special delivery system (e.g. pump)?		
Documentation required? (e.g.double check)		
Nurse education?		
Monitoring		
Interactions, adverse effects, efficacy, changes in renal function, or similar?	Monitor interactions and hepatic function for need for possible adjustments.	Nurse, provider, and pharmacist education on interactions and appropriate patient populations.
Follow-up laboratory tests?	N/A	N/A
Education?	N/A	N/A

FORMULARY REVIEW

GENERIC NAME: DARATUMUMAB

PROPRIETARY NAME: *Darzalex* (Janssen)

THERAPEUTIC CLASS: Anti-CD38 monoclonal antibody; antineoplastic agent

SIMILAR DRUGS: NONE

INDICATIONS: Treatment of multiple myeloma in patients 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. On July 26, 2016 the FDA also has granted breakthrough status for treatment of multiple myeloma in combination with standard of care regimens for patients with previously treated multiple myeloma.

CLINICAL PHARMACOLOGY: Daratumumab is an IgG1κ human monoclonal antibody directed against CD38. CD38 is a cell surface glycoprotein which is highly expressed on myeloma cells, yet is expressed at low levels on normal lymphoid and myeloid cells. By binding to CD38, daratumumab inhibits the growth of CD38 expressing tumor cells through a variety of mechanisms inducing 1) apoptosis directly through Fc mediated cross linking, 2) immune-mediated tumor cell lysis through complement dependent cytotoxicity, 3) antibody dependent cell mediated cytotoxicity, and 4) antibody dependent cellular phagocytosis.

PHARMACOKINETICS: In a population pharmacokinetic analysis of daratumumab in 223 patients with multiple myeloma, the mean central volume of distribution was 4.7 L (standard deviation +/- 1.3L), the mean linear clearance was 171.4 mL/day (SD +/- 95.3 mL/day), and the mean estimated terminal half-life was about 18 days (SD +/- 9 days). Daratumumab clearance decreased with increasing dose and repeated dosing. Central volume of distribution and clearance both increase with body weight increases, supporting the body weight-based dosing regimen as suggested by the manufacturer.

Daratumumab is expected to be bio-transformed similarly to other endogenous IgG through degradation into small peptides and amino acids via intracellular catabolic pathways following receptor mediated endocytosis. Renal excretion and hepatic enzyme mediated metabolism of daratumumab are not likely to represent major elimination routes.

SPECIAL POPULATIONS:
Hepatic Impairment: No dosage adjustment necessary

Renal Impairment: No dosage recommended but has not been studied

CLINICAL STUDIES:

<table>
<tr><td colspan="3">MMY2002</td></tr>
<tr><td>Trial design</td><td colspan="2">Open-label, international, multicenter, phase 2 study</td></tr>
<tr><td>Intervention</td><td colspan="2">Daratumumab monotherapy at various doses, 16 mg/kg reported in abstract
Dosing schedule follows package insert recommendations
Pre- and postmedications administered as indicated in package insert
Treatment continued until disease progression or unacceptable toxicity</td></tr>
<tr><td>Inclusion</td><td colspan="2">Relapsed or refractory multiple myeloma who met the following restrictions:
1) received at least 3 prior lines of therapy including a PI and an immunomodulatory agent
2) who were double-refractory to a proteasome inhibitor and an immunomodulatory agent</td></tr>
<tr><td>Demographics</td><td colspan="2">Median time since diagnosis: 4.8 years
Median number of prior treatment lines: 5
96% refractory to last line of therapy
95% refractory to both PI and immunomodulary agent
80% prior autologous transplant</td></tr>
<tr><td rowspan="3">Results
N = 106</td><td>Outcome</td><td>Result</td></tr>
<tr><td>Median time to response</td><td>1 month (range: 0.9 to 5.6 months)</td></tr>
<tr><td>Median duration of response</td><td>7.4 months (range: 1.2 to 13.1+ months)</td></tr>
</table>

	Overall response rate (ORR)* N (%) [95% CI] Stringent complete response (sCR) Complete response (CR) Very good partial response (VGPR) Partial response (PR)	 31 (29.2%) [20.8 – 38.9] 3 (2.8%) 0 10 (9.4%) 18 (17%)
Adverse effects	Fatigue (39.6%), anemia (33.0%), nausea (29.2%), thrombocytopenia (25.5%), back pain (22.6%), neutropenia (22.6%), cough (20.8%)	
	Infusion reactions (42.5%): grade 3: 4.7%, no grade 4 No patients quit therapy due to infusion reactions	

*ORR= sCR + CR + VGPR + PR, CI = confidence interval

Lockhorst et al

Trial design:

- Open-label dose escalation trial
- Daratumumab monotherapy in 42 patients with relapsed or refractory multiple myeloma who had received at least 2 different cytoreductive therapies
- Daratumumab 16 mg/kg administered with pre- and post-infusion medications
- Treatment continued until unacceptable toxicity or disease progression

Patients:

- Median of 4 prior treatment lines
- 79% refractory to last treatment
- 64% refractory to both PI and immunomodulary therapy
- 76% prior autologous transplant

Results:

- Overall response rate was 36% (95% CI: 21.6, 52.0%) with 1 CR and 3 VGPR
- Median time to response was 1 month (range: 0.5 to 3.2 months)
- Median duration of response was not estimable (range: 2.2 to 13.1+ months)
- 71% had infusion reactions, 1% grade 3

CONTRAINDICATIONS:

No contraindications currently listed in package insert.

WARNINGS AND PRECAUTIONS:

- Infusion reactions:
    - Daratumumab can cause severe infusion reactions.
        - Most grade 1-2 in clinical trials
        - 46% with 1st infusion, 5% 2nd infusion, 4% subsequent infusions
    - Most reactions occur within 1.5 hours of beginning infusion to 4 hours post infusion
        - Can occur up to 48 hours post infusion
        - Patients must take pre and post medications
    - Interrupt daratumumab infusion for infusion reactions of any severity
    - Permanently discontinue the infusion in case of life-threatening infusion reactions
- Interference with cross-matching and red blood cell antibody screening:
    - Type and screen patients prior to starting treatment.
    - Inform blood banks that a patient has received daratumumab.
        - Daratumumab binds to CD38 on red blood cells and results in a positive Indirect Antiglobulin Test (Coombs test). This positive result may persist for 6 months after therapy.
        - Daratumumab bound to RBCs masks detection of antibodies to minor antigens in the patient's serum.
    - If an emergency transfusion is required, non-cross-matched ABO/RhD-compatible RBCs can be given per local blood bank practices.
- Interference with determination of complete response
    - Daratumumab is a human IgG monoclonal antibody

        - Drug can be detected on serum protein electophoresis (SPE) and immunofixation (IFE) which are used to monitor M-protein
        - Since most patients have IgG monoclonal subtype of multiple myeloma, this interaction can affect response monitoring
    - Patients will likely need bone marrow to accurately assess response and disease progression

ADVERSE REACTIONS:

Infusion reactions	All grades (48%), grade 3 (3%), grade 4 (0%)
Cardiovascular	Hypertension (10%)
Central Nervous System	Fatigue (39%), headache (12%), chills (10%)
Gastrointestinal	Nausea (27%), diarrhea (16%), constipation (15%), decreased appetite (15%), vomiting (14%)
Hematologic and Oncologic	Lymphocytopenia (72%; grade 3: 30%; grade 4: 10%), neutropenia (60%; grade 3: 17%; grade 4: 3%), thrombocytopenia (48%; grade 3: 10%, grade 4: 8%), anemia (45%; grade 3 19%, grade 4: 0%)
Infection	Herpes zoster (3%)
Neuromuscular & skeletal	Back pain (23%), arthralgia (17%), leg pain (15%), musculoskeletal chest pain (12%)
Respiratory	Cough (21%), upper respiratory (20%), nasal congestion (17%), dyspnea (15%), nasopharyngitis (15%), pneumonia (6% to 11%)

DRUG INTERACTIONS:
No known significant interactions

DOSING AND ADMINISTRATION:

- Must be administered through in-line, sterile, nonpyrogenic, low protein-binding polythersulfone (PES) filter
    - Pore size 0.22 or 0.2 micrometer
    - Polyurthane (PU), polybutadiene (PBD), PVE, PP, or PE administration sets can be used
- Dosing
    - Week 1 to 8: 16 mg/kg IV once weekly
    - Week 9 to 24: 16 mg/kg IV once every 2 weeks
    - Week 25 and beyond: 16 mg/kg IV once every 4 weeks until disease progression
- Premedications:
    - Corticosteroid: Methylprednisolone 100 mg IV or equivalent intermediate- or long-acting corticosteroid; following the second infusion, the dose may be decreased (eg, methylprednisolone 60 mg or equivalent) plus
    - Antipyretic: Acetaminophen 650 mg to 1000 mg PO plus
    - Antihistamine: Diphenhydramine 25 to 50 mg IV/PO or equivalent
- Post-infusion medication:
    - Administer an oral corticosteroid (eg, methylprednisolone 20 mg or equivalent) on the first and second day after all infusions.
    - In patients with a history of obstructive pulmonary disorder, consider short and long-acting bronchodilators and inhaled corticosteroids post-infusion.
    - If no major infusion reactions occur during the first 4 infusions, these additional inhaled post-infusion medications may be discontinued.
- Prophylaxis for Herpes Zoster Reactivation should be started within 1 week of starting daratumumab and continue for 3 months following treatment.

- Infusion Rates

	Dilution Volume	Initial Rate (first hour)	Rate Increment	Maximum Rate
First Infusion	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second Infusion[a]	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent Infusions[b]	500 mL	100 mL/hour	50 mL/hour every hour	200 /hour

Note: Infusion must be completed within 15 hours once started

[a] Escalate only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion.

[b] Escalate only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of ≥100 mL/hr in the first two infusions

- Interruption and dose adjustments for infusion reactions: must stop infusion for all reactions
  - Grade 1-2 (mild-moderate): Once symptoms resolve, resume infusion at half rate. Can reescalate if no other symptoms occur.
  - Grade 3 (severe):
    - If symptoms decrease to grade 2 or lower, can resume infusion at half rate. Can reescalate if no other symptoms occur.

If recurrence of grade 3 symptoms, repeat as indicated above

DOSING ADJUSTMENTS:
Renal Impairment – No dose adjustment needed.

Hepatic impairment
Mild impairment (total bilirubin 1 to 1.5 times ULN or AST >ULN): No dosage adjustment necessary.
Moderate to severe impairment (total bilirubin >1.5 times ULN and any AST): There are no dosage adjustments provided in the manufacturer's labeling (has not been studied)

PHARMACOECONOMICS/COST

Drug and Strength	Price per vial	NDC
Daratumumab 100 mg/5 mL vial	$450.00	57894-502-05
Daratumumab 400 mg/20 mL vial	$1800.00	57894-502-20

Annual expense (12 months of therapy – 90 kg): $155,250

MEDICATION ERROR POTENTIAL:
Drug Safety/Risk Evaluation and Mitigation
There is no REMS required for daratumumab

BLACK BOX WARNINGS
There are no black box warnings for daratumumab

CONCLUSIONS: Daratumumab is the first human anti-CD38 monoclonal antibody approved in the United States and is the first monoclonal antibody to be approved for the treatment of multiple myeloma. From the available data, daratumumab has been shown to be a safe and effective medication for use in the treatment of multiple myeloma. The safety and efficacy of daratumumab was demonstrated in two open-label studies. 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. In the second study of 42 participants, 36% had a complete or partial reduction in tumor burden.

RECOMMENDATION:
Daratumumab should be added to the formulary, but restricted to use in the outpatient infusion clinics by oncologists for the treatment of patients with multiple myeloma for the FDA approved indications. Daratumumab will be added to the Hazardous Drug List at a facility level as a Biotherapy/Non-Hazardous medication.

Failure, Mode and Effects Analysis

Medication Management Step	**Identified Risk**	**Steps for Prevention**
Selection & Procurement • Therapeutic interchange? • Special Ordering Requirements?	• No therapeutic interchange	
Storage • LASA* – separation of stock? • Special storage – refrigeration, protect from light, controlled substance, etc.? • Pharmacist/Technician Education?	• Storage: refrigerate at 2°C - 8°C. • Protect from light	• Once product is received it should be protected from light and only prepared once the patient is present • Nurse, provider, pharmacist, and technician education regarding storage.
Ordering & Prescribing • Restriction to particular specialty, indication, or particular patient population? • Dosing Issues – i.e. renal, hepatic dosage adjustment, max dose warnings • Drug Interactions? • Pregnancy? • Absolute Contraindications? • Requires Order Set, Protocol, concomitant therapy with another drug? • LASA* – nomenclature issues? • Prescriber education?	• No renal or hepatic dosage adjustments • No drug interactions noted • Pregnancy and lactation: Based on its mechanism, may cause fetal myeloid or lymphoid-cell depletion and decreased bone density. To avoid exposure to fetus, women of reproductive potential should use effective contraception during treatment and for 3 months after cessation of treatment. • Contraindications: none listed in package insert • Must be given with appropriate premedications, postmedications, and antiviral prophylaxis	• Nurse, provider, and pharmacist education on dosing and population in which drug is indicated for • Ensure co-medications are added to ordersets Nurse, provider, and pharmacist education on proper comedications
Processing, Preparing, & Dispensing • High-risk Drug double check? • Drug Interaction check in place? • LASA* – computer warnings? • Administration Notes for MAR – handling precautions, surrounding food or other drugs, etc.? • Packaging/Labeling – i.e. prepacking, etc.? • Dispensing – auxiliary labeling, light protection, refrigeration, etc.? • Documentation required? (i.e. double check, worksheet, etc.) • Pharmacist/Technician Education?	• Protect from light • Multiple different volumes based on dose/infusion	• Nurse, provider, pharmacist, and technician education on dosing and population in which drug is indicated for • Pharmacist and technician education on applying protect from light auxilliary labels on packaging • Nurse, provider, pharmacist, and technician education on volumes and rate differences for each dose
Administration • Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, etc.? • Special delivery system – i.e. pump, etc.? • Documentation required? (i.e. double check, etc.) • Nurse education?	• Biotherapy medication • Infusion must be complete within 15 hours • Many rate adjustments based on tolerability and infusion reactions	• Nursing flow sheet to monitor infusion reactions and allow for rate titration • Nurse, provider, pharmacist, and technician education on management of infusion reactions as indicated in package insert
Monitoring • Interactions, adverse effects, efficacy, changes in renal function, etc.? • Follow-up laboratory tests? • Education?	Obtain blood type prior to start of therapy ▪ RBCs masks detection of antibodies to minor antigens in the patient's serum.	• Nurse, provider, and pharmacist education on ordering type and screen prior to beginning therapy • Nurse, provider, and pharmacist education on interference with SPE and IFE for monitoring response in patients with IgG subtype. Will likely require bone marrow.

Adverse Drug Reaction (ADR) Summary
February through April 2016

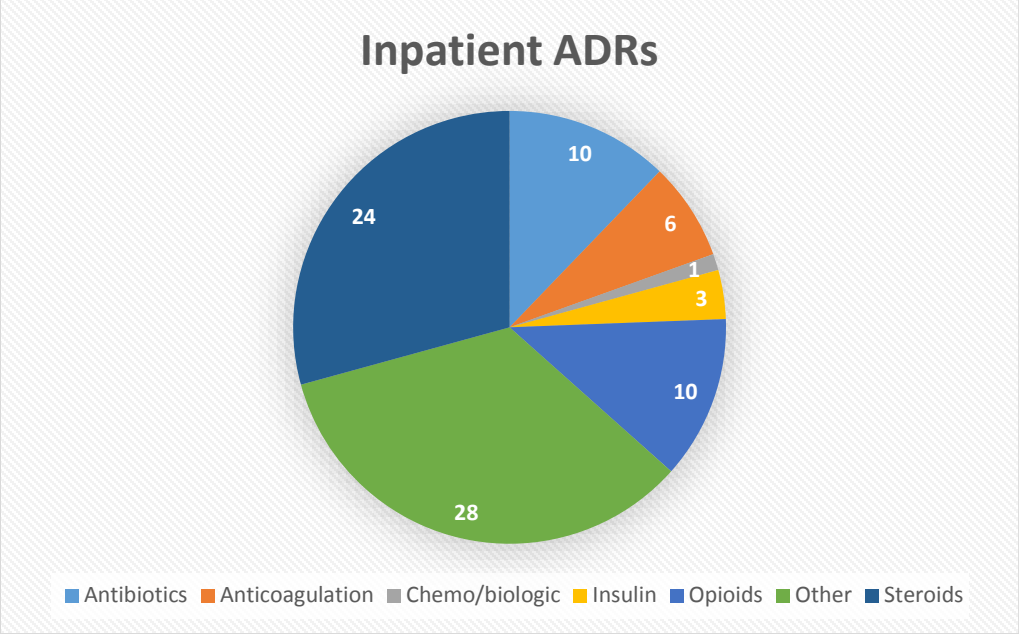
Category 1: Commonly recognized ADR's which are expected and do not result in serious medical consequences or extended hospitalization (e.g. antibiotic rash, nausea, mild hypokalemia).

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

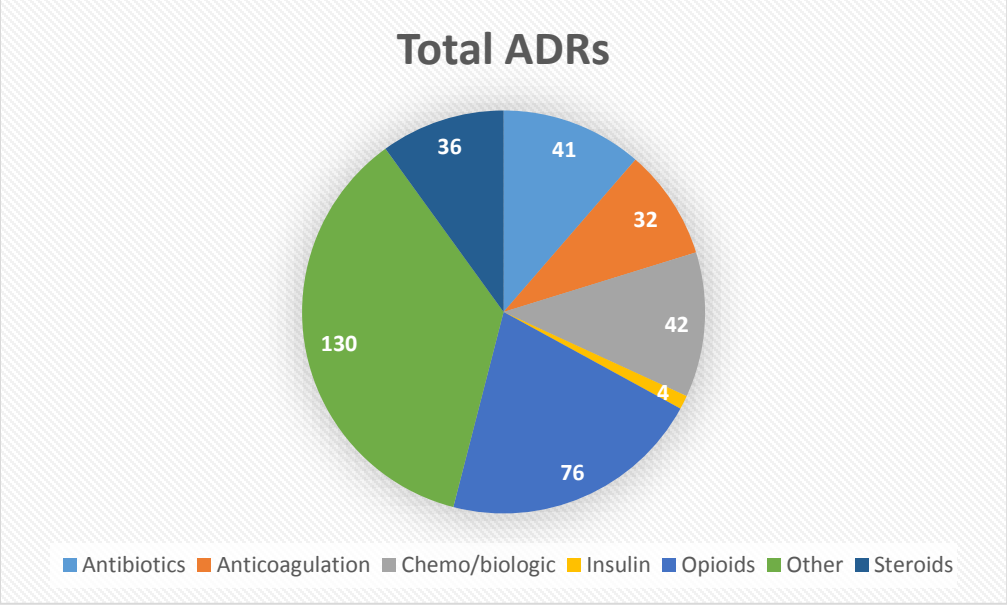
Category 3: A serious or rare ADR which has abnormal characteristics compared with published reports of the reaction (e.g. heparin induced platelet aggregation resulting in limb amputation). ADR's from this category should be reported to the manufacturer and/or the FDA (MedWatch or the Vaccine Adverse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

Inpatient: 81 (27%)
Prior to hospitalization: 221 (74%)
Total: 302

Category 1: 205
Category 2: 97
Category 3: 0



Antibiotics: Rocephin most common (2) – rash, vancomycin (1) – AKI, Bactrim (1) – swelling, Levaquin (1) – acute decompensation
Anticoagulants: Plavix+Coumadin (hematochezia), Xarelto (epistaxis), alteplase (angioedema)
Narcotics: Reactions included AMS (5), nausea, constipation, and respiratory distress (2)
Steroids: Hyperglycemia
Other: Mostly blood pressure or arrhythmia related (14), angioedema (1), EPS (1)



Antibiotics: Multiple medications – Macrobid (rash), Cipro (AKI), Amoxicillin (diarrhea, rash)
Anticoagulants: Coumadin, Plavix, Xarelto, Eliquis, Arixtra—various bleeds
Antineoplastics: Fever, rash, pancytopenia, anemia, syncope
Narcotics: AMS, constipation, metabolic encephalopathy, respiratory depression
Steroids: Hyperglycemia and leukocytosis

Antithrombotic Reversal & Surgical Management Recommendations* 12/15

Drug Class	*Non-Urgent*	*Urgent - Bleeding or immediate surgery necessary*	*Comments*
Anti-platelet Agents	Hold 5 days prior to procedure* o Plavix® (clopidogrel) o Brilinta® (ticagrelor) Hold 7 days prior to proc.* o Effient® (prasugrel) o Aggrenox® (ASA/dyprid.)	• Consider platelet transfusion	• Caution advised in patients with cardiac stents • Abrupt discontinuation can increase risk of acute stent thrombosis
Unfractionated Heparin	• Infusion: Stop infusion 2 – 6 hours prior to procedure • SQ doses: Hold the evening dose prior to the procedure	• Protamine sulfate: 1 mg for every 100 units of heparin given in previous 3 hrs (max dose: 50 mg single dose or 100 mg in 2 hr period)	• aPTT can be utilized to determine degree of anticoagulation
Low Molecular Weight Heparins	• The last dose should be given 24 hours before the procedure. i.*e., enoxaparin at a dose of 1 mg/kg ONCE 24 hrs prior to surgery if dose was 1 mg/kg BID.*	• Wait 24 hours if possible • Consider protamine sulfate if delay not possible for high bleed risk procedure (only partially reverses LMWH) • Protamine sulfate (based on last dose): LMWH administered ≤ 8 hrs: 1 mg protamine per 1 mg LMWH LMWH administered > 8 hrs: 0.5 mg protamine per 1 mg LMWH	• Elimination can be further delayed in patients with acute or chronic kidney disease • Anti Xa assay can be used to assess degree of anticoagulation
Indirect Factor Xa Inhibitor			
Arixtra® (fondaparinux)	• Hold 36-48 hours prior to procedure	• No specific antidote • rVIIa – limited data available *consider low dose (1-2 mg) and assess response*	• Elimination can be further delayed in patients with acute or chronic kidney disease
Vitamin K Antagonist			
Warfarin	• Stop 5 days prior to procedure • Check INR 1-2 days prior, and if INR greater than 1.5, give Vitamin K 1-2 mg PO • May consider bridge therapy with LMWH in high risk patients	• If procedure can be delayed 6-24 hours, Vitamin K 5-10 mg PO/IV • If procedure cannot be delayed or <u>life threatening bleeding (ICH, etc.)</u>, give FFP or PCC prior to procedure. If PCC used give Vitamin K 5-10 mg IV to sustain anticoagulation reversal	• PCC dosing: *life threatening bleeding (ICH, etc.)* Dose based on INR: 2 – 3.9 → 25 units/kg (max dose: 2500) 4 – 5.9 → 35 units/kg (max dose: 3500) ≥ 6 → 50 units/kg (max dose: 5000) *Caution: Risk of thrombosis when PCC used, particularly in patients with history of thrombosis.*

***This is intended to provide the clinician with possible strategies for patient management and does not establish a fixed set of guidelines that preempt physician judgment. Consider risk of thrombosis when reversal agents utilized.**

Antithrombotic Reversal & Surgical Management Recommendations* 12/15

Drug Class	*Non-Urgent*	*Urgent - Bleeding or immediate surgery necessary*	*Comments*
Thrombin Inhibitor			
Pradaxa® (Dabigatran)	• Hold for 1-2 days prior to procedure for CrCl greater than 50 ml/min • Hold for 3-5 days prior to procedure for CrCl less than 50 ml/min	• Idarucizumab (Praxbind®): 5 grams IV x 1 dose Limited data to repeat 5gm dose 12-24 hrs after first dose IF bleeding persists in combination with elevated coagulation parameters • Hemodialysis	• Thrombin Time (preferred) or aPTT can be used to rule out substantial residual effect
Factor Xa Inhibitors			
Xarelto® (Rivaroxaban)	• Hold for <u>at least</u> 24 hours prior to procedure with normal renal function (>90 ml/min). Consider holding 2-3 days for patients with CrCl 30-90 ml/min.	• No specific antidote/Not dialyzable • PCC – 25 units/kg and assess response. - Consider 50 units/kg if life-threatening bleed (limited clinical data) – max dose: 5000 units - May consider repeat dose if clinically indicated • Vitamin K not effective if given	• PT can be used to rule out substantial residual effect. Normal value may rule out clinically relevant residual anticoagulant effect. PT not intended to be used for dosage adjustment.
Eliquis® (Apixaban)	• Hold for at least 48 hrs prior to procedures with high risk of bleeding; 24 hrs prior to procedures with low risk of bleeding. Consider holding 2-3 days if CrCl < 60 ml/min regardless of procedure type or 3 or more days if CrCl < 50 ml/min.	• No specific antidote/ Not dialyzable • PCC – 25 units/kg and assess response. - Consider 50 units/kg if life-threatening bleed (limited clinical data) – max dose: 5000 units - May consider repeat dose if clinically indicated • Vitamin K not effective if given	• PT can be used to rule out substantial residual effect. Normal value may rule out clinically relevant residual anticoagulant effect. PT not intended to be used for dosage adjustment.
Savaysa® (Edoxaban)	• Hold for at least 48 hrs prior to procedures with high risk of bleeding; 24 hrs prior to procedures with low risk of bleeding. Consider holding 1-2 days for CrCl > 50 ml/min and 3 or more days if CrCl ≤ 50 ml/min.	• No specific antidote/ Not dialyzable • PCC – 25 units/kg and assess response. - Consider 50 units/kg if life-threatening bleed (limited clinical data) – max dose: 5000 units - May consider repeat dose if clinically indicated • Vitamin K not effective if given	• PT can be used to rule out substantial residual effect. Normal value may rule out clinically relevant residual anticoagulant effect. PT not intended to be used for dosage adjustment.
Coagulopathies Not Associated with Anticoagulants			
To achieve hemostasis post-operatively or liver coagulopathy (not on anticoagulant)	• Vitamin K • FFP	• PCC – 25units/kg and assess response (max dose: 2500) - Use standard dose – Do not base PCC dose on INR. May repeat dose if clinically necessary • Vitamin K – consider in addition to PCC	PT can be used to rule out substantial residual effect. Normal value may rule out clinically relevant residual anticoagulant effect. PT not intended to be used for dosage adjustment.

***This is intended to provide the clinician with possible strategies for patient management and does not establish a fixed set of guidelines that preempt physician judgment. Consider risk of thrombosis when reversal agents utilized**

Medication Use Evaluation: Hypnotic and Sedative-Related Falls
CHI Memorial & CHI Memorial Hixson

The purpose of this evaluation was to evaluate causes and contributing factors to falls in patients who received hypnotics or other non-opioid sedation medications.

Background:

Falls are a constant area for concern and prevention in any healthcare setting. While falls are often nothing less than multifactorial, the possibility for medication or polypharmacy-related falls is likely, especially in cases of the elderly. A 2013 Journal of Hopistal Medicine study by Kolla et al published a retrospective cohort study on zolpidem-related falls in non-ICU inpatients at a tertiary care center, finding that the use of zolpidem was a strong and independent risk factor for inpatient falls.[1] In the setting of other sedating medications such as benzodiazepines, and sedating medications such as trazodone, tramadol and gabapentin, the risk for a fall is further compounded when a sedative or other hypnotic is prescribed.

Data Analysis/Methods:

Risk management provided a set of data over a period of six months related to falls as reported through the IRIS system. Those falls were then reviewed to determine if there was a recently given sedative or medication that is known to otherwise cause sedation. All falls reported by the IRIS system occurring at CHI-Memorial Glenwood and CHI-Memorial Hixson between June 2015 and January 2016 were collected. Opioids were excluded from the analysis in order to best focus on the medications in the Sedatives/Hypnotics for Sleep Policy (MM – 05410). A Medication Fall Risk Score was calculated on patients for whom enough data was provided. Any score greater than or equal to six is classified as high risk for fall, and recommends an evaluation of the patient. Drugs preceding the time of the fall incidence were recorded and assessed for their prescribing origin (e.g. continuation of home med, order set, or a handwritten order by MD).

Results:

Hypnotic Medications Associated with Falls

Among the hypnotic agents ordered for sleep management (Ambien, Benadryl, Melatonin, Restoril), the most commonly implicated agent among this group of medications was Melatonin (8 total patients), followed by Ambien (6 total patients). Also pertinent to note is that 12/16 (75%) of the falls potentially related to the use of hypnotic agents were ordered as scheduled medications as opposed to as needed therapies (PRN). The origin of the medication order was equally distributed among handwritten orders and continuation of home medication therapies.

For the patients receiving Ambien with an inpatient fall, three of the patients were > 65 years of age but these were all continuation of home medication regimens which complies with the current policy restrictions for the ordering of Ambien in this patient population. The remaining patients that had a fall potentially related to Ambien use were all < 65 years of age and the dosing was appropriate or limited to 5 mg as per the current Sedative/Hypnotics for Sleep policy.

All of the patients who experienced an inpatient fall while on melatonin were receiving scheduled doses of melatonin (3 or 6 mg QHS) with 6/8 of these being ordered via handwritten order by the physician (not home medications). It is important to note that 5 of these patients were also receiving multiple other sedating medications that may have contributed to the patient fall (benzodiazepines, gabapentin, trazodone, antipsychotics, etc.).

Non-hypnotic Medications Associated with Falls

Approximately two-thirds of all non-hypnotic medications related to falls (n = 60) were continued or restarted home medications. The most common non-hypnotic drugs were Ativan (11 scheduled, 6 PRN), Neurontin (13 scheduled), Xanax (4 scheduled, 4 PRN), Seroquel (7 scheduled), Valium (2 scheduled, 2 PRN), Klonopin (3 scheduled, 1 PRN), and Desyrel (6 scheduled). <10% were from order sets, and the remainder were handwritten orders. Benzodiazepines were involved in 33 (55%) of the falls associated with medications that were not related to administration of a hypnotic for sleep.

Medications Potentially Associated with Patient Falls

Medication Class	Count	Percentage of total falls (306 total)	Average Age (years)
Hypnotics (Ambien, Benadryl, Melatonin, Restoril)	16	5%	72
Non-hypnotic sedating medications	60	19.6%	67
All medications	76	24.8%	68

Falls After a Hypnotic (16)

Drug	Scheduled	PRN	Avg Age	Prescribing Origin
Ambien 5 mg	3	3	63	• 4 home med • 2 substitution per policy
Benadryl 25 mg	1	0	54	• 1 home med
Melatonin 3 or 6 mg	8	0	84	• 2 home med • 6 handwritten
Restoril 15 mg	0	1	58	• 1 substitution from home med per policy
	12	**4**	72	

Summary & Conclusion:

This review has affirmed that the current *Sedative/Hypnotics for Sleep* policy appears to be effective in minimizing the utilization of sedative-hypnotic medications in elderly patients as evidenced by the small number of patients receiving these medications experiencing an inpatient fall. The medications specifically controlled by this policy (Ambien, Benadryl, Restoril) were only implicated in 5 total falls (1.6% of all falls). For the purpose of this evaluation any medication that was specifically ordered for the purpose of assisting with sleep was included (including melatonin) although the utilization of melatonin is not controlled by the previously mentioned policy. However, the patients receiving melatonin were noted to be of greater age and more often receiving other concomitant sedating medications which may have collectively contributed to the patient becoming over sedated and experiencing a fall. Regardless, the higher association of melatonin with inpatient falls was surprising although as previously mentioned, polypharmacy and the more advanced age of the patients receiving melatonin likely explains this observed higher association with falls. The higher association of scheduled medication orders among the use of sedative-hypnotics implicated in falls (12/16 orders) could potentially suggest the need for re-evaluating if all sedative-hypnotics should be ordered as PRN medications instead of scheduled orders.

Not surprisingly, among the non-hypnotic medications most commonly associated with falls were predominantly due to the use of benzodiazepines (BZDs) – (33/60 patients). The average age of patients experiencing falls in this category was 67 years of age and the use of anxiolytics such as benzodiazepines is discouraged as outlined in the 2015 Beers list due to the implications of their contribution to falls. Many of the patients receiving BZDs were receiving their scheduled home medication regimens in addition to other sedating medications as ordered during their hospitalization. This finding may suggest that patients with scheduled orders for BZDs may need to be considered at higher risk of falls and extra precautions taken to minimize the risk of falls.

References:

Kolla BP, et al. Zolpidem is Independently Associated with Increased Risk of Inpatient Falls. Journal of Hospital Medicine. 2013 Jan;8(1):1-6.

WEIGHT:
HEIGHT:

DATE/TIME ORDERED

PNEUMONIA ADMISSION ORDERS

1. ☐ Monitored ☐ Non-Monitored
2. Diagnosis: _____
3. Allergies: _____
4. Code Status: DNR or limited code orders must be documented on POST Form.
5. If severely ill or neutropenic consider ☐ Pulmonary Consult
   ☐ Infectious Disease Consult

   ☐ Emergent / Urgent - See patient ASAP; physician to physician communication required
   ☐ Same Day - See patient on next rounds, but no later than end of the day; consults after 3 pm require physician to physician communication.
   ☐ Routine - See patient on next day rounds
   ☐ Courtesy - Notification only
6. Influenza Vaccine screening (Oct-Mar) per Patient Admssion Assessment.
7. Activity: _____
8. Vital Signs Q 4 hrs x 24 hrs then 4 times a day.
9. Respiratory:
   ☐ O2 Sat Q shift x 48 hrs - **if < 90% call physician.** Then PRN if stable and not on O2.

   ☐ O2 per _____ ☐ Bronchodilator Protocol
10. Sputum C&S (If not done in ER).
11. Diet: _____
12. Lab: CBC, Blood Cultures x 2 different sites (if not done in ED or physician office.
    ADMINISTER ANTIBIOTIC FIRST DOSE STAT AFTER BLOOD CULTURES OBTAINED.
    ☐ Basic Metabolic Panel
    ☐ Comprehensive Metabolic Panel
    ■ Streptococcus Pneumoniae Urinary Antigen
    ■ Legionella Urinary Antigen
    ■ Procalcitonin
13. Chest x-ray (if not done in ED or physician office).

DATE/TIME ORDERED

PNEUMONIA ADMISSION ORDERS

MEDICATION / IV

On Admission, see Home Medication list for home meds to be given during hospitalization.

COMMUNITY ACQUIRED PNEUMINIA (CAP)

Non-ICU Treatment

☐ Levofloxacin 750 mg IV Q 24 hrs

OR

☐ Ceftriaxone 2 gm IV Q 24 hrs (1 gm if < 80 kg) **PLUS**
Azithromycin 500 mg IV Q 24 hrs for 5 days

ICU Treatment

☐ Ceftriaxone 2 gm IV Q 24 hrs (1 gm if < 80 kg) **PLUS**
Azithromycin 500mg IV q 24 hrs for 5 days

If suspicious for CA-MRSA (prior influenza, presence of cavitary disease on chest imaging)

☐ Vancomycin 1 gm IV now then Pharmacy to dose

ICU Treatment (Anaphylaxis to PCN and/or Severe Cephalosporin allergy)

☐ Levofloxacin 750 mg IV Q 24 hrs

If suspicious for CA-MRSA (prior influenza, presence of cavitary disease on chest imaging)

☐ Vancomycin 1 gm IV now then Pharmacy to dose

HEALTHCARE ASSOCIATED/HOSPITAL ACQUIRED/VENTILATOR ASSOCIATED PNEUMONIA (HCAP/HAP/VAP)

Non-ICU Treatment

Preferred regimen

☐ Cefepime 1g IV q 6 hrs **PLUS**
Vancomycin 1 gm IV now then Pharmacy to dose

Alternate regimen (Anaphylaxis to PCN and/or Severe Cephalosporin allergy)

☐ Aztreonam 2 gm IV Q 8 hrs **PLUS**
Vancomycin 1 gm IV now then Pharmacy to dose

ICU Treatment

Preferred regimen

☐ Cefepime 1g IV Q 6 hrs **PLUS**
Tobramycin 7mg/kg IV now then Pharmacy to dose **PLUS**
Vancomycin 1 gm IV now then Pharmacy to dose

Alternate regimen (Anaphylaxis to PCN and/or Severe Cephalosporin allergy)

☐ Aztreonam 2 gm IV Q 8 hrs **PLUS**
Tobramycin 7mg/kg IV now then Pharmacy to dose **PLUS**
Vancomycin 1 gm IV now then Pharmacy to dose

Suspected Aspiration

(check box below to add metronidazole to any of above orders)

☐ Metronidazole 500 mg IV Q 8 hours

PHARMACY AUTOMATIC RENAL ADJUSTMENTS

AUGUST 2016 - UPDATES

Cefepime (Maxipime®)			
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		1 gm Q 12 hrs
≤ 10 or HD	1 gm Q PM (give after dialysis)		

Aztreonam (Azactam®)		
CrCl (ml/min)	**UTI**	**Systemic infection**
≥ 30	1 g IV q8h	2 gm IV Q 8 hrs (q6h is OK in life threatening infections)
10-30	1g IV q12h	2g IV q12h
< 10	1g IV q24h	1 g IV q12h
Hemodialysis	1 g IV x 1 dose, then 1 g IV Qpm	
CRRT	2g IV q12h	

Ampicillin		
CrCl (ml/min)	**Uncomplicated Infection**	**Meningitis or Endovascular infection**
> 50	2g IV q6h	2g IV q4h
10-50	1g IV q6h	2g IV q6h
<10	1g IV q12h	1g IV q8h
HD	1-2g IV q12h	
CRRT	1-2g IV q6h	

Ampicillin/Sulbactam (Unasyn®)	
CrCl (ml/min)	**Renal Adjustment**
> 50	3g IV q6h
10-50	1.5g IV q6h
<10	1.5g IV q12h
HD	1.5-3g IV q12h
CRRT	1.5-3g IV q6h

Ceftaroline (Teflaro®)		
CrCl (ml/min)	**Uncomplicated Infection**	**Pneumonia, Severe Infections**
> 50	600 mg IV q12h	600 mg IV q8h
30-50	400 mg IV q12h	600 mg IV q12h
15-29	300 mg IV q12h	400 mg IV q12h
<15 or HD	200-300mg IV q12h	
CRRT	400-600 mg IV q12h	

Ceftazidime/Avibactam (Avycaz®)	
CrCl (ml/min)	**Renal Adjustment**
> 50	2.5 g IV q8h
31-50	1.25 g IV q8h
16-30	0.94 g IV q12h
6-15	0.94 g IV q24h
≤ 5 or HD	0.94 g IV q48h

Ceftolozane/Tazobactam (Zerbaxa®)		
CrCl (ml/min)	**Uncomplicated Infection**	**Pneumonia, Severe Infections**
> 50	1.5g IV q8h	3g IV q8h
30-50	750 mg IV q8h	1.5g IV q8h
15-29	375 mg IV q8h	750 mg IV q8h
HD	750 mg IV x 1 dose, then 150mg IV q8h	

CHI Memorial
Imagine better health.℠

POLICY

Title: **24 HOUR STOP ON ROUTINE PERI-OPERATIVE ANTIBIOTIC PROPHYLAXIS**		
	Page 1 of 1	
Policy Number: MM-05433	Date Last Reviewed/Revised: 9/13	Valid Until: 9/16
Department(s) Affected: All Clinical Areas	Review Period: every 3 years	

OUTCOME:

Ensure adherence to evidence-based practice regarding management of routine, peri-operative antibiotic prophylaxis in patients with uneventful clinical course.

POLICY:

Routine, peri-operative prophylactic antibiotics will be automatically stopped after 24 hours for patients whose clinical course does not suggest infection. *The 24 hour time frame will include the first documented peri-operative dose given by Surgery.*

For exceptions to this policy,

A. The physician must write an order to continue antibiotic therapy.

B. Medical record documentation by the physician must state indication for continuation of antibiotics beyond the automatic 24 hour stop time. Indications might include but are not limited to: abscess, sepsis, surgical site or wound infection, or osteomyelitis.

If it is unclear whether antibiotics are for routine prophylaxis or for treatment of infection, the pharmacist will contact the surgeon for clarification before any changes are made.

Key Contact: Patrick Ellis, Pharmacy Review Team
Approved/Reviewed by: Sandy Vredeveld, Director of Pharmacy; Diona Brown, Chief Nurse Executive
Approved by Pharmacy & Therapeutics Committee: 10-11-08, 12-9-10
Approved by Medical Executive Committee: 10-28-08
Approved by Nursing Professional Practice Council: 01/04/2011
Reference(s): SCIP Guidelines
Date First Effective/Revisions: 10/08, (12/10) (9/13)
Distribution: MHCS Intranet

CATHOLIC HEALTH INITIATIVES

Memorial Health Care System

POLICY

Title: INTRAVENOUS TO ORAL THERAPY - PHARMACY		
	Page 1 of 1	
Policy Number: PHRM-0535	Date Last Reviewed/ Revised: 3/14	Valid Until: 3/17
Department(s) Affected: Pharmacy	Review Period: every 3 years	

OUTCOME:

Transition patients who meet clinical criteria from IV to Oral Therapy.

POLICY:

A pharmacist may use established criteria to evaluate targeted IV antibiotic and antifungal therapies, proton pump inhibitors (PPIs), histamine 2 receptor antagonists (H2 blockers) and other Pharmacy and Therapeutics committee approved medications for potential conversion to oral (PO) therapy.

CRITERIA FOR INCLUSIOIN:

- Taking other oral medications by mouth
- Afebrile for at least 24 hours (T<100.4)
- WBC that is normalizing (<15K), or a known, non-infectious reason can be identified for WBC count (i.e., steroids) – *applies to antibiotics & antifungals only*
- Functioning GI tract (eating full liquids or better)
- Non ICU setting

CRITERIA FOR EXCLUSION:

- Patient has not yet received at least 24 hour duration of IV therapy
- ICU
- NPO
- Active GI bleed – *applies to PPI's and H2 blockers only*
- Febrile neutropenia – *applies to antibiotics & antifungals only*
- Patient with recent nausea or vomiting (antiemetic use within the last 24 hours)
- GI obstruction or non-functioning GI tract
- Inability to swallow

MEDICATIONS PERTAINING TO THIS POLICY:

Antibiotics: azithromycin, ciprofloxacin, clindamycin, doxycycline, fluconazole, levofloxacin, linezolid, metronidazole
Gastrointestinal agents: famotidine, pantoprazole
Miscellaneous agents: levetiracetam, folic acid, multivitamin, thiamine, levothyroxine

---

Key Contact: Patrick Ellis, Pharmacy Review Team
Approved/Reviewed by: Sandy Vredeveld, Director Pharmacy; Lila Heet, Manager Pharmacy
Date First Effective/Revisions: 12/20/88, 5/07, 12/07 **Revised:** 1/10 (1/13) (3/14)
Distribution: MHCS Intranet