Pharmacy & Therapeutics Committee Meeting
Private Dining Room
February 14, 2013 7:00 a.m.

Agenda Items	Individual Responsible
1. Call to Order	Richard Pesce, MD
2. Approval of December, 2013 Minutes	Richard Pesce, MD
3. Therapeutic Interchanges and Formulary Decisions	Page
A. Exparel® (liposomal bupivacaine)	Patrick Ellis, Pharm.D……..4-6
B. Eliquis® (apixaban)	7-10
C. Linzess® (linaclotide)	Karen Babb, Pharm.D…..11-12
D. Kyprolis® (carfilzomib)…….	……..13-14
E. Proton Pump Inhibitor (PPI) Formulary	Patrick Ellis, Pharm.D……15
F. Azithromycin 5 Day Automatic Stop Proposal	16
4. Medication Safety	
A. APAP content–combination prescription products..	Patrick Ellis, Pharm.D……..17
B. Promethazine IV – infusion site reactions	18-19
5. MUE	
A. Levemir® (insulin detemir)	Patrick Ellis, Pharm.D....20-21
B. Vancomycin induced nephrotoxicity	John Jantz, Pharm.D.…22-23
6. Policy, Procedure & Protocols	
A. Alcohol Withdrawal Management Protocol….	Patrick Ellis, Pharm.D....24-26
B. Med Administration–Timeliness of Scheduled Medications	……27-31
C. TPN Protocol–pharmacist ordering of sliding scale insulin	Karen Babb, Pharm.D...32-33
7. Pharmacy Clinical Dashboard…….	34
8. Nutrition Support Team	
A. TBD……	Brian Jones, RD ……...24-26
9. Adjournment	

Next Meeting will be April 11, 2013 at 7:00am in the Private Dining Room

CATHOLIC HEALTH INITIATIVES
Memorial Health Care System

PHARMACY AND THERAPEUTICS COMMITTEE

DATE: December 13, 2012 CALLED TO ORDER: 7:00 A.M.
LOCATION: Private Dining Room ADJOURNED: 7:56 A.M.

Members Present:		**Members Absent**:		**Guest**:
Richard Pesce, M.D.	Karen Babb, Pharm.D. Jackie Jackson, RN, COO	John L. Gwin, Jr., M.D.	Scott Madaris, RN	John Jantz, Pharm.D.
Mark Anderson, M.D.	Diona Brown, RN, C.N.O. Jane Rawlston, RN	Tareck Kadrie, M.D	Deb Moore, RN, SVP	
Samuel Currin, M.D.	Vickie Burger, Lab Sandy Vredeveld, DPh	Robert Mynatt, M.D.	Nan Payne, RN	
David Dodson, M.D.	Patrick Ellis, Pharm.D. Beverly Slate, Supply Chain	William Oellerich, M.D.	Melissa Roden, RN	
Nathan Chamberlain, M.D.	Rodney Elliott, CPT	Gwen Davis, RN	Hannah Walker, RN	
Michael Stipanov, M.D	Lila Heet, Pharm.D.	Patrick Hagan, Finance	Elvie Smith, RN	
		Brian Jones, RD	Don Jones, DPh	

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 October 11, 2012 minutes were approved as submitted.		Complete
Therapeutic Interchanges and Formulary Decisions	The following medications were reviewed: 1. **Remicade® (Infliximab)** – New policy to be enacted to no longer accept NEW orders unless prior treatment with Humira® or other TNF-antagonist agents has been made and it has been documented that the patient does not tolerate the alternate agents. This change in procedure will not impact any patients currently treated in the infusion center. 2. **Exparel® (Bupivacaine Liposomal)** – Liposomal formulation indicated for post-surgical analgesia in bunionectomy and hemorrhoidectomy. Dr. Headrick now requesting this for nerve block s/p thoracic surgery. Due to a lack of data in this area the committee felt they could not formally recommend adding to formulary at this time. Due to the high cost of this medication and probable future requests a financial analysis will be performed and presented to the Value Analysis Steering Committee for final evaluation. 3. **Zioptan® (Tafluprost)** – Topical eye drop used for open-angle glaucoma or ocular hypertension. Recommended to not add to formulary and add to existing therapeutic interchange utilizing latanoprost. 4. **Myrbetriq® (Mirabegron)** – Used in the treatment of overactive bladder. Recommended to add to formulary due to the drug's unique mechanism of action and no similar drugs currently on formulary. 5. **Nplate ® (Romiplostim)** – Used in the treatment of refractory thrombocytopenia in patients with ITP. Recommended to add to formulary with use restricted to Hematology service. 6. **Stadol NS ® (Butorphanol nasal spray)** – Recommended to remove from formulary. 7. **Pre-Pen (Penicilloyl polylysine) -** Skin test reagent used to identify patients with immune mediated penicillin hypersensitivity in patients with vague or unclear history of penicillin allergy. Recommended to add to formulary with restriction to ID. Protocol/Policy will be developed prior to utilizing this product.	1. Approved 2. To be discussed at Value Analysis Steering Committee 3. Not Approved for formulary addition. 4. Approved 5. Approved 6. Remove from formulary 7. Approved	Complete Pending Complete Complete Complete Complete Complete
Medication Safety	1. **Xarelto® -** The new indications for this product were reviewed. Pharmacy will be	1. Information	Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	providing education to the Hospitalists and reviewing all orders for rivaroxaban for appropriateness to ensure safe use of this medication. Patient education will also be provided by the pharmacists for all patients newly started on rivaroxaban. 2. **ADR Summary Q1FY13** – ADR summary was reviewed. (1) category 3 ADR was reported this quarter and will be reported to the FDA MedWatch program. An increased trend in antibiotic adverse reactions was observed. 3. **Toradol® (Ketorolac) Dose Limits** – Recommended to institute automatic stop date for total duration of therapy not to exceed 5 total days if no duration of therapy already indicated by the prescriber. This is due to the increased risk of severe adverse effects that can result from prolonged courses of therapy.	2. Trend will be monitored closely 3. Approved	Complete Complete
Medication Use Evaluation	**Samsca® (Tolvaptan)** - An MUE was conducted to identify the types of prescribers with highest utilization, provide information about expenditures, and determine the usual indications surrounding its use. The findings revealed that the use in CHF patients was often accompanied with the highest beginning serum sodium levels at the time of therapy initiation. These findings will be discussed with the prescribers of highest utilization to determine possible opportunities for improved tolvaptan utilization.	Information	Pending
Policy and Procedure	• **Look – Alike/Sound – Alike Medications Policy –** This policy was reviewed and updated based and updated based on review of previous year's errors. • **Anaphylaxis Reaction Protocol –** Anaphylaxis protocol was developed to assist in the rapid treatment of patients with severe, life-threatening reactions to medications. • **Medication Orders – Pharmacist Review Policy –** This policy was amended to include a statement allowing pharmacists to order necessary laboratory tests in consideration of patient safety and improved patient care when clinically necessary/appropriate. The laboratory tests that may be ordered are pursuant to P&T committee approval or previous committee approvals.	1-3. Approved	Complete
Pharmacy Clinical Dashboard	Committee reviewed.	Information	Complete

There being no further business, the meeting was adjourned at 7:56 A.M. The next P&T meeting is February 14, 2012.

Respectfully submitted,

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

Approved by,

Richard Pesce, M.D. Chairman

FORMULARY REVIEW

GENERIC NAME: Bupivacaine Liposomal

PROPRIETARY NAME: Exparel (Pacira)

INDICATIONS: Exparel is a liposome injection of bupivicaine, an amide local anesthetic, indicated for single-dose tissue infiltration into the surgical site to produce postsurgical analgesia.

CLINICAL PHARMACOLOGY: Local anesthetics block the generation and the conduction of nerve impulses presumably by increasing the threshold for electrical excitation in the nerve, by slowing the propagation of the nerve impulse, and by reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers.

PHARMACOKINETICS: Local infiltration of EXPAREL results in significant systemic plasma levels of bupivacaine which can persist for 96 hours. The rate of systemic absorption of bupivacaine is dependent upon the total dose of drug administered, the route of administration, and the vascularity of the administration site. Systemic plasma levels of bupivacaine following administration are not correlated with local efficacy. The difference in pain intensity when compared to placebo occurred only during the first 24 hours following study drug administration. Between 24 and 72 hours after study drug administration, there was minimal to no difference between liposomal bupivacaine and placebo on mean pain intensity.

ADVERSE REACTIONS: Nausea, Constipation, and Vomiting were reported in greater than or equal to 10% of the patients.

DRUG INTERACTIONS: Do not admix with lidocaine or other non-bupivacaine-based local anestheics.

DOSING: Is intended for single-dose administration only. The recommended dose is based on the surgical site and the volume required to cover that area:

Surgery	Dose of EXPAREL	Volume of EXPAREL
Bunionectomy	106 mg	8 mL
Hemorrhoidectomy	266 mg	20 mL

PRODUCT AVAILABILITY and STORAGE: This medication was approved by the U.S. FDA on October 28, 2011. It is available in 20ml single use vials at 13.3mg/ml. The vials should be stored in the refrigerator (2-8 degrees C) in the original carton to protect from light. The vials may be held at a controlled room temperature of 20-25 degrees C for up to one month in sealed, unopened vials. Vials should not be re-refrigerated. Do not freeze.

CONTRAINDICATIONS: Do not use in obstetrical paracervical block anesthesia.

WARNINGS AND PRECAUTIONS: Monitoring of cardiovascular and neurological status, as well as vital signs should be performed during and after injection. It is metabolized by the liver, so use with caution in patients with hepatic disease. It is substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Other formulations of bupivacaine should not be administered within 96 hours following administration of Exparel.

STUDY RESULTS: One hundred eighty-nine patients were randomly assigned and treated; 186 completed the study. Pain intensity scores were significantly lower in the bupivacaine extended-release group in comparison with the group receiving placebo (141.8 vs 202.5, *P*< 0001). More patients in the bupivacaine extended-release group remained opioid free from 12 hours (59%) to 72 hours (28%) after surgery compared with patients receiving placebo (14% and 10%; *P*<.0008 through 72 h). The mean total amount of opioids consumed through 72 hours was 22.3 mg and 29.1 mg in the bupivacaine extended-release and placebo groups (*P*<.0006). The median time to first opioid use was 14.3 hours in the

bupivacaine extended release group vs 1.2 hours in the placebo group (P<.0001). A greater proportion of patients in the bupivacaine extended-release group were satisfied with their postsurgical analgesia (95% vs 73%, P<.0007) than in the placebo group.

It is important to note that for both the FDA approved indications (bunionectomy & hemmorhoidectomy) that liposomal bupivacaine demonstrated a significant reduction in pain intensity compared to placebo for up to 24 hours. The difference in mean pain intensity between treatment groups occurred only during the first 24 hours following study drug administration. Between 24 and 72 hours after study drug administration, there was minimal to no difference between liposomal bupivacaine and placebo treatments on mean pain intensity.

COMPARISON TO CONVENTIONAL BUPIVACAINE: The FDA approval for liposomal bupivacaine was based on a comparison to placebo therapy for determining superiority based on the primary efficacy endpoint of the area under the curve (AUC) of the numerical rating scale pain scores as compared to placebo. The formal FDA review does however also have unpublished information related to the comparison of conventional bupivacaine to the liposomal formulation. It is important to note that for both soft tissue infiltration following bunionectomy and hemorrhoidectomy that the liposomal formulation failed to demonstrate superiority when actively compared to the conventional buipivacaine formulation and actually performed worse than conventional bupivacaine for hemorrhoidectomy.

CONCLUSION & RECOMMENDATION: Based on the study results above, Exparel demonstrated a statistically significant reduction in pain through 72 hours, decreased opioid requirements, delayed time to first opioid use, and improved patient satisfaction compared with placebo after hemorrhoidectomy when compared to placebo. Although, the primary efficacy end point of pain intensity scores through 72 hours did show superiority as compared to placebo, the difference in pain intensity compared to placebo was only observed during the first 24 hours following drug administration. Between 24 and 72 hours after study drug administration, there was minimal to no difference between liposomal bupivacaine and placebo treatments on mean pain intensity. Based on the pharmacokinetics of liposomal bupivacaine, local infiltration results in significant systemic plasma levels of bupivacaine which can persist for 96 hours. Based on the trial results, the systemic plasma levels of bupivacaine are clearly not correlated with local efficacy as indicated by no difference being observed between 24 and 72 hours after drug administration when compared to placebo. Additionally, when compared to conventional bupivacaine for soft tissue infiltration no difference in pain intensity scores were observed.

Based on the available data, it is recommended to designate liposomal bupivacaine non-formulary for soft tissue infiltration use following surgical procedures. Use for other indications (nerve blocks, etc.) will need to be assessed by the committee on a case by case basis when requested. No data is currently available for the use as post surgical nerve blocks (intercostal nerve blocks, etc.).

COST: $285/20 ml

Failure Mode and Effects Analysis
Medication: bupivicaine liposomal (Exparel)

Medication Management Step	Identified Risk	Steps for Prevention
Selection & Procurement		
• Therapeutic interchange?	No	
• Special Ordering Requirements?	No	
Storage		
• LASA* – separation of stock?	Yes- bupivicaine standard formulation, propofol	Separation of stock
• Special storage – refrigeration, protect from light, controlled substance, etc.?	Yes – refrigerate, protect from light	
• Pharmacist/Technician Education?	Yes	Education on use and difference b/w standard bupivicaine.
Ordering & Prescribing		
• Restriction to particular specialty, indication, or particular patient population?	Yes (if approved)	
• Dosing Issues – i.e. renal, hepatic dosage adjustment, max dose warnings	No	
• Drug Interactions?	No	
• Pregnancy?	Category C	
• Absolute Contraindications?	No	
• Requires Order Set, Protocol, concomitant therapy with another drug?	No	
• LASA* – nomenclature issues?	Yes	
• Prescriber education?	Yes	
Processing, Preparing, & Dispensing		
• High-risk Drug double check?	No	
• Drug Interaction check in place?	Yes	
• LASA* – computer warnings?	Yes	
• Administration Notes for MAR – handling precautions, surrounding food or other drugs, etc.?	No	
•		
• Packaging/Labeling – i.e. prepacking, etc.?	No	
• Dispensing – auxiliary labeling, light protection, refrigeration, etc.?	Yes – refrigerate, protect from light	
• Pharmacist/Technician Education?	Yes	
Administration		
• Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, etc.?	Yes – closely resembles propofol in syringe	
• Special delivery system – i.e. pump, etc.?	No	
• Documentation required? (i.e. double check, etc.)	No	
• Nurse education?	No	
Monitoring		
• Interactions, adverse effects, efficacy, changes in renal function, etc.?	Ye	
• Follow-up laboratory tests?	Yes, pain scores.	
• Education?	No	

- LASA=Look-alike, sound-alike

FORMULARY REVIEW

GENERIC NAME: APIXABAN

PROPRIETARY NAME: ELIQUIS (Bristol Myers Squibb / Pfizer)

INDICATIONS: Apixaban is indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.

Comparison of the FDA-Approved Indications for similar agents.			
Indication	**Apixaban**	**Dabigatran**	**Rivaroxaban**
Prevention of VTE in patients undergoing hip or knee replacement			X
Acute treatment of VTE			X
Long-term prophylaxis of secondary VTE			X
Stroke prevention in patients with atrial fibrillation	X	X	X

CLINICAL PHARMACOLOGY: Apixaban is a direct-acting, reversible oral inhibitor of factor Xa, which is responsible for the conversion of prothrombin (factor II) to thrombin (factor IIa), ultimately leading to thrombus formation and clotting. Apixaban is selective for factor Xa; therefore, thrombin and other downstream clotting factors (eg, IIa, fibrin) are inhibited without affecting factors XIIa, XIa, IXa, or VIIa.

PHARMACOKINETICS: Apixaban is readily absorbed, reaching peak plasma concentrations (C_{max}) within 1 to 3 hours after administration. After oral administration, apixaban is absorbed in the stomach and small intestine, with an absolute bioavailability of approximately 66%. After administration of multiple doses of apixaban for 7 days, dose-proportional increases in C_{max} and area under the curve were observed with only mild accumulation. Approximately 25% of an orally administered dose is recovered in the urine and feces as metabolites. The half-life of apixaban is approximately 5 hours; however, the apparent half-life after oral administration is about 12 hours due to prolonged absorption.

ADVERSE REACTIONS: The most common adverse reactions reported in the clinical trials were various types of bleeding, nausea, vomiting, and constipation.

COMPARATIVE SAFETY & EFFICACY: In the double-blind phase III ARISTOTLE trial, apixaban was compared with dose adjusted warfarin in patients with non-valvular AF and a CHADS2 score $\geq$ 1. Primary efficacy and safety endpoints were the composite of stroke and systemic embolism, and major bleeding events. Rates of primary endpoint events in the apixaban and warfarin groups were 1.3% and 1.6% per year ($p = 0.01$ for superiority). Compared with patients who received warfarin, patients who received apixaban had significantly lower rates of major bleeding events (2.1% vs. 3.1% per year; $p < 0.001$), intracranial hemorrhage (0.3% vs. 0.8% per year; $p < 0.001$), and mortality (3.5% vs. 3.9% per year; $p = 0.047$).

Because of differences in trial design and patient enrollement, efficacy and safety data for rivaroxaban, apixaban and dabigatran cannot be directly compared for the indication of stroke prevention in non-valvular atrial fibrillation. Dabigatran and apixaban both demonstrated superiority over warfarin in their respective trials whereas rivaroxaban showed non-inferiority to warfarin for prevention of stroke in non-valvular atrial fibrillation. However, patients enrolled in the rivaroxaban clinical trial (ROCKET-AF) had a higher mean CHADS2 stroke risk score (3.5) than those enrolled in either of the pivotal trials examining the use of apixaban or dabigatran (2.1) which reflects higher proportions of patients with a history of heart disease, prior stroke, or other co-morbidities in the rivaroxaban trial. Patients with multiple risk factors for stroke also increase the risk of bleeding, which may have contributed to the higher bleeding event rates observed in the rivaroxaban trial as compared to the dabigatran and apixaban trials.

All three drugs showed a reduction in ICH when compared to warfarin although apixaban appears to offer

the lowest rate of major bleeding when compared to conventional warfarin therapy (30% reduction). The major bleeding rates of dabigatran and rivaroxaban were similar when compared to warfarin with no significant difference in major bleeding observed. However, apixaban did demonstrate a statistically significant reduction in major bleeding as compared to warfarin (2.1% vs. 3.1%). Again, the definitions of major bleeding and the differences in the patient population enrolled in each trial do make direct comparisons somewhat difficult.

Although all three of the novel anticoagulants that are approved for stroke prevention rely on renal elimination, each drug does have some differences related to their degree of renal elimination (dabigatran – 80%, rivaroxaban – 33%, apixaban – 40%). These differences may be significant in patients who present with acute bleeding complications particularly in patients with impaired renal function as this may delay the return of hemostasis in this patient population.

CONTRAINDICATIONS: Apixaban is contraindicated in patients with active pathological bleeding and in patients with a severe hypersensitivity reaction to apixaban.

BLACK BOX WARNING: Discontinuing apixaban in patients without adequate continuous anticoagulation increases the risk of stroke. An increased rate of stroke was observed following discontinuation of apixaban in clinical trials in patients with non-valvular atrial fibrillation. If anticoagulation with apixaban must be discontinued for a reason other than pathological bleeding, coverage with another anticoagulant should be strongly considered.

ADVERSE REACTIONS: The most common adverse reactions reported in the clinical trials were various types of bleeding, nausea, vomiting, and constipation.

DRUG INTERACTIONS: Apixaban metabolism is inhibited when co-administered with strong CYP3A4 and P-gp inhibitors such as ketoconazole, itraconazole, ritonavir, or clarithromycin. If co-administration of one of these drugs is unavoidable, it is recommended that the dose be lowered to 2.5 mg twice daily. Additionally, concomitant use of metabolism inducers (e.g., rifampin, carbamazepine, phenytoin, St. John's wort, etc.) should be avoided. Co-administration of antiplatelet agents, fibrinolytics, heparin, aspirin and chronic NSAID use increases the risk of bleeding.

MONITORING: No specific laboratory tests are recommended for patients on apixaban therapy. In major clinical trials, laboratory monitoring of aPTT, PT/INR, and factor Xa levels was not required. However, modified PT and Heptest appear to be 10- to 20-fold more sensitive than aPTT or PT for monitoring the anticoagulant effect of apixaban.

DOSING:
Normal Dose: 5 mg twice daily
Dose adjustment: 2.5 mg twice daily – for patients with any 2 of the following characteristics

- Age $\geq$ 80 years
- Body weight $\leq$ 60 kg
- Serum creatinine $\geq$ 1.5 mg/dl

DISCONTINUATION FOR SURGERY & OTHER INTERVENTIONS: Should be discontinued at least 48 hours prior to elective surgery or invasive procedures with a moderate or high risk of unacceptable or clinically significant bleeding. Apixaban should be discontinued 24 hours prior to elective surgery or invasive procedures with a low risk of bleeding or where the bleeding would be non-critical in location and easily controlled.

CONVERTING TO/FROM OTHER ANTICOAGULANTS:

- Switching from warfarin to apixaban: warfarin should be discontinued and apixaban started when the INR is below 2.
- Switching from apixaban to warfarin: apixaban affects INR, so that INR measurements during co-administration with warfarin will be difficult to interpret and may not be useful. If continuous anticoagulation is necessary, discontinue apixaban and begin both a parenteral anticoagulant and warfarin at the time the next dose of apixaban would have been taken.
- Switching b/w apixaban and anticoagulants other than warfarin: discontinue one being taken and

begin the other at the next scheduled dose.

COST & COMPARISON TO SIMILAR AGENTS – *atrial fibrillation stroke prevention indication*
Apixaban – 5 mg twice daily: $8 per day
Rivaroxaban – 20 mg once daily: $6.58 per day
Dabigatran – 150 mg twice daily: $7.20 per day

CONCLUSION: Apixaban is an oral agent that appears to offer similar efficacy to the other two novel oral anticoagulants that are currently available for prevention of stroke in patients with non-valvular atrial fibrillation. Like dabigatran, the only currently FDA approved indication for apixaban is for the prevention of stroke in patients with non-valvular atrial fibrillation whereas rivaroxaban is also approved for VTE prevention in orthopedic surgery (knee/hip arthroplasty) and for acute treatment and maintenance therapy of VTE (DVT or PE). As indicated above, apixaban may have a slight safety benefit in regard to the rates of major bleeding as compared to dabigatran and rivaroxaban although differences in study design makes direct comparisons difficult.

It is recommended at this time to add apixaban to formulary without restrictions. Post marketing safety and efficacy data will be monitored closely and the formulary status of these new agents will be re-evaluated if and when new data or new FDA approved indications emerge.

Failure Mode and Effects Analysis

Medication: apixaban (Eliquis)

Medication Management Step	**Identified Risk**	**Steps for Prevention**
Selection & Procurement		
• Therapeutic interchange?	No	
• Special Ordering Requirements?	No	
Storage		
• LASA* – separation of stock?	No	
• Special storage – refrigeration, protect from light, controlled substance, etc.?	No	
• Pharmacist/Technician Education?	Yes	Education on appropriate dosing, etc.
Ordering & Prescribing		
• Restriction to particular specialty, indication, or particular patient population?	No	
• Dosing Issues – i.e. renal, hepatic dosage adjustment, max dose warnings	No	
• Drug Interactions?	No	
• Pregnancy?	Category B	
• Absolute Contraindications?	No	
• Requires Order Set, Protocol, concomitant therapy with another drug?	No	
• LASA* – nomenclature issues?	Yes (abacavir)	Meditech alert
• Prescriber education?	Yes	Education on appropriate dosing , etc.
Processing, Preparing, & Dispensing		
• High-risk Drug double check?	No	
• LASA* – computer warnings?	Yes	
• Administration Notes for MAR – handling precautions, surrounding food or other drugs, etc.?	No	
• Packaging/Labeling – i.e. prepacking, etc.?	No	
• Dispensing – auxiliary labeling, light protection, refrigeration, etc.?	No	
• Documentation required? (i.e. double check, worksheet, etc.)	No	
• Pharmacist/Technician Education?	No	

FORMULARY REVIEW

GENERIC NAME: LINACLOTIDE

PROPRIETARY NAME: Linzess (Forest Labs)

INDICATIONS: Linaclotide is approved for the treatment of irritable bowel syndrome with constipation (IBS-C) and the treatment of chronic idiopathic constipation.

CLINICAL PHARMACOLOGY: Linaclotide is a guanylate cyclase-C (GC-C) agonist. Both linaclotide and its active metabolite bind to GC-C and act locally on the luminal surface of the intestinal epithelium. Activation of GC-C results in an increase in both intracellular and extracellular concentrations of cyclic guanosine monophosphate (cGMP). Elevation in intracellular cGMP stimulates secretion of chloride and bicarbonate into the intestinal lumen. This action results in increased intestinal fluid and accelerated gastrointestinal (GI) transit. In animal models, linaclotide has been shown to both accelerate GI transit and reduce intestinal pain. The linaclotide induced reduction in visceral pain in animals is thought to be mediated by increased extracellular cGMP, which was shown to decrease the activity of pain-sensing nerves.

PHARMACOKINETICS: Systematic absorption of linaclotide from the GI tract is minimal following oral administration. The concentration of linaclotide and its active metabolite in plasma is below the limit of quantification after the 145 and 290 mcg doses; therefore, standard pharmacokinetic parameters cannot be calculated. Food had no effect on the absorption of linaclotide, but administration with a high-fat breakfast was associated with a higher incidence of loose stools and stool frequency.

ADVERSE REACTIONS: The most common adverse reactions associated with the use of linaclotide in the treatment of IBS-C were diarrhea, abdominal pain, flatulence, and abdominal distension. The diarrhea generally started within the first 2 weeks of therapy. The most common adverse reactions associated with the use of linaclotide in the treatment of chronic idiopathic constipation were diarrhea (16% vs 5%), abdominal pain, flatulence, abdominal distension, upper respiratory tract infection, and sinusitis.

BLACK BOX WARNING: Linaclotide is contraindicated in pediatric patients up to 6 years of age. Avoid use in pediatric patients 6 through 17 years of age. Linaclotide caused deaths in young juvenile mice.

DRUG INTERACTIONS: No drug-drug interaction studies were conducted with linaclotide. However, linaclotide does not affect cytochrome P450 or P-glycoprotein and should have no effect on drugs eliminated through either of these pathways.

DOSING:

- Chronic idiopathic constipation (CIC): 145 mcg once daily (30 mins prior to first meal of the day)
- Irritable bowel syndrome with constipation (IBS-C): 290 mcg once daily (30 mins prior to first meal of the day)

COST: 145 mcg & 290 mcg - $6.80 per day

CONCLUSION & RECOMMENDATION: Linaclotide is a new drug for the treatment of IBS-C and idiopathic chronic constipation. Its mechanism of action is different from the current and previously approved agents for the treatment of IBS and constipation. Linaclotide 290 mcg once daily was better than placebo at improving spontaneous bowel movements, abdominal pain, and quality of life in patients with IBS-C. Linaclotide 145 mcg once daily was better than placebo at decreasing the signs and symptoms of constipation and improving spontaneous bowel movements in patients with idiopathic chronic constipation. The most common adverse reaction in both medical conditions was diarrhea. The long-term efficacy and safety of linaclotide in the treatment of either of these medical conditions remains to be established. The price of linaclotide is comparable to other products with similar indications such as Amitiza (lubiprostone).

Due to linaclotide's unique mechanism of action it is recommended to add linaclotide to formulary without restrictions. This has been discussed with two different gastrointestinal specialists and they both agreed that this medication offers a unique mechanism of action and should be added to formulary.

Failure Mode and Effects Analysis

linaclotide (Linzess)

Medication Management Step	Identified Risk	Steps for Prevention
Selection & Procurement		
• Therapeutic interchange?	No	
• Special Ordering Requirements?	No	
Storage		
• LASA* – separation of stock?	No	
• Special storage – refrigeration, protect from light, controlled substance, etc.?	No	
Ordering & Prescribing		
• Restriction to particular specialty, indication, or particular patient population?	No	
• Are calculations required to obtain the dose?	No	
• Will the drug be limited to the critical care units?	No	
• Dosing Issues – i.e. renal, hepatic dosage adjustment, max dose warnings	No	
• Significant drug interactions?	No	
• Significant side effect profile?	No	
• Pregnancy?	Category C	
• Black box warning?	No	
• Requires Order Set, Protocol, concomitant therapy with another drug?	No	
• LASA* – nomenclature issues?	No	
• Prescriber education?	No	
Processing, Preparing, & Dispensing		
• High-risk Drug double check?	No	
• Drug Interaction check in place?	No	
• LASA* – labeling/packaging?	No	
• Administration Notes for MAR – handling precautions, surrounding food or other drugs, etc.?	No	
• Dispensing – auxiliary labeling, light protection, refrigeration, etc.?	No	
• Documentation required? (i.e. double check, worksheet, etc.)	No	
• Pharmacist/Technician Education?	No	
Administration		
• Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, etc.?	No	
• Does the physician need to be present to administer the drug or monitor the patients	No	
• Special delivery system – i.e. pump, etc.?	No	
• Documentation required? (i.e. double check, etc.)	No	
• Nurse education?	No	
Monitoring		
• Interactions, adverse effects, efficacy, changes in renal function, etc.?	No	
• Narrow therapeutic index?	No	
• Follow-up laboratory tests?	No	
• Education?	No	

* LASA=Look-alike, sound-alike

FORMULARY REVIEW

GENERIC NAME: CARFILZOMIB

PROPRIETARY NAME: *Kyprolis* (Onyx Pharmaceuticals)

INDICATIONS: Carfilzomib is indicated for the treatment of patients with multiple myeloma who have received at least 2 prior therapies (including bortezomib and an immunomodulatory agent) and have demonstrated disease progression on or within 60 days of completion of the last therapy. Accelerated approval for this indication was granted on the basis of the response rate; clinical benefit, such as improvement in survival or symptoms.

CLINICAL PHARMACOLOGY: Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to the N-terminal threonine-containing active sites of the 20S proteasome, the proteolytic core particle within the 26S proteasome. Carfilzomib exhibited antiproliferative and proapoptotic activity in solid and hematologic tumor cells *in vitro*. Additionally, carfilzomib demonstrated blood and tissue proteasome activity and delayed tumor growth in multiple myeloma models in animals. Carfilzomib differs from bortezomib in that it is an irreversible proteasome inhibitor and may be more selective for the chymotrypsin protease. Therefore, carfilzomib may lead to more sustained and selective proteasome activity and has a lower affinity to bind off-target enzymes (e.g., serine proteases). Carfilzomib has minimal cross reactivity with other protease classes and has demonstrated activity in bortezomib-resistant cell lines.

PHARMACOKINETICS: Carfilzomib levels rapidly decline following intravenous (IV) administration. Its terminal half-life is less than 1 hour. Proteasome inhibition is maintained for at least 48 hours following the first dose of carfilzomib for each week of dosing. Carfilzomib is primarily eliminated via extrahepatic metabolism through peptidase cleavage and epoxide hydrolysis, followed by biliary and renal excretion of the inactive metabolites. Renal function appears to have no effect on carfilzomib's pharmacokinetic parameters. The pharmacokinetics of carfilzomib have not been assessed in patients with baseline hepatic impairment.

ADVERSE REACTIONS: The most common serious adverse reactions were pneumonia, acute renal failure, pyrexia, and congestive heart failure. Herpes zoster reactivation was reported in 2% of patients; antiviral prophylaxis should be considered for patients with a history of herpes zoster infection. Dose-limiting toxicities included febrile neutropenia, thrombocytopenia, and hypoxia.

DRUG INTERACTIONS: Carfilzomib is not expected to be affected by co-administration of CYP-450 or P-glycoprotein inhibitors or inducers and is not expected to influence exposure of other drugs.

DOSING: Carfilzomib is administered as an IV infusion over 2 to 10 minutes on 2 consecutive days, each week for 3 weeks (days 1, 2, 8, 9, 15, and 16), followed by a 12-day rest period (days 17 to 28). Each 28-day period is considered 1 treatment cycle. During the first cycle the recommended dose is 20 mg/m^2. If tolerated during the first cycle, the dose should be escalated to 27 mg/m^2 beginning in cycle 2 and continued at that dose in subsequent cycles. Treatment may be continued until disease progression or until unacceptable toxicity occurs.

PRODUCT AVAILABILITY: It is supplied in individually cartoned, single-use, preservative-free vials containing carfilzomib 60 mg as a lyophilized powder.

CONCLUSION: Carfilzomib is a proteasome inhibitor that appears to offer enhanced efficacy and a favorable side effect profile relative to bortezomib in the treatment of patients with relapsed and refractory multiple myeloma.

Failure Mode and Effects Analysis

carfilzomib (Kyprolis)

Medication Management Step	Identified Risk	Steps for Prevention
Selection & Procurement		
• Therapeutic interchange?	No	
• Special Ordering Requirements?	No	
Storage		
• LASA* – separation of stock?	Certolizumab, bortezomib	
• Special storage – refrigeration, protect from light, controlled substance, etc.?	Yes - refrigeration	
Ordering & Prescribing		
• Restriction to particular specialty, indication, or particular patient population?	No	
• Are calculations required to obtain the dose?	No	
• Will the drug be limited to the critical care units?	No	
• Dosing Issues – i.e. renal, hepatic dosage adjustment, max dose warnings	No	
• Significant drug interactions?	No	
• Significant side effect profile?	No	
• Pregnancy?	Category D	
• Black box warning?	No	
• Requires Order Set, Protocol, concomitant therapy with another drug?	No	
• LASA* – nomenclature issues?	No	
• Prescriber education?	No	
Processing, Preparing, & Dispensing		
• High-risk Drug double check?	Yes	Standard double check process for chemo
• Drug Interaction check in place?	Yes	
• LASA* – labeling/packaging?	Yes	Meditech alerts
• Administration Notes for MAR – handling precautions, surrounding food or other drugs, etc.?	Yes	Standard chemo precautions
• Dispensing – auxiliary labeling, light protection, refrigeration, etc.?	Yes - refrigeration	
• Documentation required? (i.e. double check, worksheet, etc.)	Yes	
• Pharmacist/Technician Education?	No	Orders reviewed by 2 pharmacists
Administration		
• Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, etc.?	Yes	Standard chemo precautions
• Does the physician need to be present to administer the drug or monitor the patients	No	
• Special delivery system – i.e. pump, etc.?	No	
• Documentation required? (i.e. double check, etc.)	No	
• Nurse education?	No	
Monitoring		
• Interactions, adverse effects, efficacy, changes in renal function, etc.?	No	
• Narrow therapeutic index?	No	
• Follow-up laboratory tests?	No	
• Education?	No	

* LASA=Look-alike, sound-alike

FORMULARY REVIEW
PROTON PUMP INHIBITORS

BACKGROUND: Since 2010 the only proton pump inhibitor (PPI) on formulary has been pantoprazole. During previous discussions at the Pharmacy and Therapeutics committee meetings these agents were considered to be therapeutically equivalent and acquisition cost has driven the choice of formulary agent. Pantoprazole is currently the most cost effective PPI although wide generic availability of multiple other PPI's has resulted in similar pricing for many of the agents.

Recently it has been suggested by Gastroenterology to add an additional agent to formulary for patients who may be intolerant of our current formulary agent pantoprazole. Periodically, "do not substitute" orders are received for other proton pump inhibitors and these have been dispensed on a case by case basis as a non-formulary request.

Additionally, some cardiologists have requested an alternate PPI for patients needing concomitant therapy with clopidogrel due to the possible drug interaction associated with clopidogrel-PPI combination therapy. Recent retrospective cohort studies have not shown any difference concerning adverse cardiovascular events when concomitant PPI + clopidogrel therapy is utilized. However, pharmacodynamic studies investigating a potential interaction found a significant decrease in clopidogrel effect for PPI's with more pronounced CYP2C19 inhibitors such as omeprazole. Historically, pantoprazole was considered one of the "safest" options for use with clopidogrel but now a recent study has also shown potential interaction with this agent as well. Overall, the evidence is inconclusive regarding the optimal PPI for use along with clopidogrel although less potent inhibitors of CYP2C19 are likely preferred (lansoprazole, pantoprazole).

PROPOSAL: It is recommended based on Gastroenterology's suggestion to add an additional PPI to formulary for patients intolerant of pantoprazole. Pantoprazole will continue to be utilized as the "work horse" agent with lansoprazole to be added for situations when an alternative is necessary. Lansoprazole offers similar pricing and is also a weak inhibitor of CYP2C19 with minimal risk of clinically significant drug interactions with medications such as clopidogrel.

AZITHROMYCIN – 5 DAY AUTOMATIC STOP – *PROPOSAL*

BACKGROUND: Azithromycin is a macrolide antimicrobial that is frequently given in conjunction with a beta-lactam (ceftriaxone) for the inpatient treatment of community acquired pneumonia. Azithromycin possesses an extremely long half-life (68 hours) which is explained by its extensive tissue uptake and slow release from the tissues. A number of studies comparing azithromycin with various control agents have shown that a shorter duration of treatment is possible using azithromycin. Due to the long half-life, a course of 3-5 days of azithromycin is arguably the equivalent of a course of several days' duration for any other drug because of its uniquely prolonged half-life that distinguishes it from virtually all other antibiotics. Traditionally, a 500 mg daily dose is utilized for treatment of community acquired pneumonia. Based on the long half-life, a 5 day course of azithromycin 500 mg daily will provide a therapeutic effect for 8-10 days. Studies have demonstrated therapeutic success with short course therapy with azithromycin for treatment of acute respiratory disorders. NOTE: infections due to *Legionella* do require a longer duration of treatment (10-14 days).

PROPOSAL: Based on the above information, it is recommended to institute a 5 day automatic stop for azithromycin when used for treatment of acute respiratory infection. This recommendation has been discussed with multiple physicians (Hospitalists, Pulmonologists/Intensivists) and all have been supportive of this proposed initiative. Prescribers will be alerted of this change via written communication (progress note notice) and this automatic stop can be overridden via written order.

The following exceptions will apply:

- Patients on long term preventative therapy (250 mg daily) for prevention of COPD exacerbations.
- Patient with suspected or confirmed *Legionella* infection.

ACETAMINOPHEN CONTAINING PRESCRIPTION PRODUCTS
LIMIT OF 325 MG PER DOSAGE UNIT

BACKGROUND: In Januray 2011 the FDA issued a recommendation to the manufacturers of combination prescription products containing acetaminophen (e.g., hydrocodone/APAP – Lortab, Vicodin, etc.) that the maximum amount of acetaminophen in a prescription tablet, capsule, or other dosage unit will be limited to 325 mg. However, the total number of tablets or capsules that may be prescribed and the time intervals at which they may be prescribed will not change as a result of the lower amount of acetaminophen. OTC products containing acetaminophen were not affected by this action. These actions were taken to help reduce the risk of severe liver injury associated with acetaminophen. Across various studies, patients were found to have taken more than the recommended dose when using prescription combination products often due to accidental overdose with many resulting in cases of documented acute liver injury.

This mandated change by the FDA was originally scheduled to be phased in by requiring manufacturers to comply with this change by 2014. When this recommendation was issued in 2011 few manufacturers produced combination products with 325 mg of acetaminophen per dosage unit. Due to the limited supply at that time the pricing for the 325 mg acetaminophen containing products were considerably higher than the more readily available 500 mg products. An analysis of Memorial Health Care System's usage of hydrocodone containing products revealed in 2011 that a conversion to 325 mg containing products would result in excess of $20,000 in additional annual cost. Now that multiple manufacturers are now producing products containing 325 mg of acetaminophen a conversion would only cost approximately ~$3,000 in additional annual cost.

RECOMMENDATION: Recent in hospital reviews have shown that patients are at times receiving an excess of 4 grams of acetaminophen per day due to receiving multiple doses of acetaminophen containing products. Due to the increased risk of exceeding recommended daily maximum doses of acetaminophen and increasing the risk of acute liver injury, it is recommended to now only dispense hydrocodone and other acetaminophen combination products containing 325 mg of acetaminophen per dosage unit. All order sets and physician orders will be adjusted to reflect this change and orders for 500 mg containing products will be converted to the comparable 325 mg acetaminophen product (example: hydrocodone 5/500 → hydrocodone 5/325).

FDA Drug Safety Communication - Intravenous Promethazine and Severe Tissue Injury, Including Gangrene

Safety Announcement

[09/16/2009] FDA is requiring a Boxed Warning for promethazine hydrochloride injection, USP products to better communicate the risks of severe tissue injury associated with administration of this drug. Perivascular extravasation, unintentional intra-arterial injection and intraneuronal or perineuronal infiltration of the drug may result in irritation and tissue damage, including gangrene. The Boxed Warning will remind practitioners that due to the risks of intravenous injection, the preferred route of administration is deep intramuscular injection and that subcutaneous injection is contraindicated.

This action is based on FDA's analysis of post-marketing reports of severe tissue injury, including gangrene, requiring amputation following intravenous administration of promethazine as well as FDA's review of the current prescribing information for these products. FDA has determined that the presentation, organization, and content of the prescribing information should be revised to more effectively communicate the risk of severe tissue injury following intravenous administration.

In addition to the Boxed Warning, FDA is requiring a revision to the ***Dosage and Administration*** section to increase the visibility and accessibility of specific recommendations for the maximum concentration (25 mg per mL) and rate of administration (25 mg per minute) when intravenous administration of promethazine is required.

FDA is requiring the changes to the prescribing information under the authorities granted to FDA by the Food and Drug Administration Amendments Act (FDAAA) of 2007.

Promethazine hydrochloride injection, USP is approved for a variety of uses including allergic reactions, sedation, motion sickness, nausea, and vomiting associated with anesthesia and surgery, and as an adjunct to analgesics for control of postoperative pain.

This information reflects FDA's current analysis of data available to FDA concerning this drug. FDA intends to update this sheet when additional information or analyses become available.

Considerations for Healthcare Professionals:

- Intravenous administration of promethazine can cause severe tissue injury, including gangrene, requiring fasciotomy, skin graft, and/or amputation
- Severe tissue injury can occur from perivascular extravasation, unintentional intra-arterial injection, and intraneuronal or perineuronal infiltration
- Deep intramuscular injection is the preferred way to administer promethazine hydrochloride injection, USP products
- Intra-arterial and subcutaneous administration of promethazine are contraindicated
- Promethazine hydrochloride injection, USP is available in two strengths, 25 mg/mL and 50 mg/mL
- The 50 mg/mL promethazine hydrochloride injection, USP product is for deep intramuscular injection only
- The 25 mg/mL promethazine hydrochloride injection, USP product may be administered by deep intramuscular injection or intravenous injection (see maximum dosage and rate below)
- If intravenous administration of promethazine is required, the maximum recommended concentration is 25 mg per mL and the maximum recommended rate of administration is 25 mg per minute through the tubing of an intravenous infusion set known to be functioning properly
- Be alert for signs and symptoms of potential tissue injury including burning or pain at the site of injection, phlebitis, swelling, and blistering
- Injections should be stopped immediately if a patient complains of pain during injection

- Inform patients that side effects may occur immediately while receiving the injection or may develop hours to days after an injection
- Refer to the prescribing information for additional information on warnings, contraindications, adverse events, and dosage and administration of promethazine hydrochloride injection, USP products
- Promethazine should not be used in patients less than 2 years of age due to the risk of fatal respiratory depression

Background and Data Summary:
FDA has been aware of the risks of perivascular extravasation and inadvertent intra-arterial administration causing severe tissue injury that are associated with intravenous administration of promethazine, and communicated these risks to healthcare professionals and consumers in the December 2006 and February 2008 FDA Patient Safety News (see links to previous communications below). Furthermore, the current prescribing information for promethazine hydrochloride injection, USP products contains information regarding the risk of intra-arterial injection and severe tissue injury, including gangrene. Despite the previous safety communications and the current prescribing information, cases of severe tissue injury following intravenous administration of promethazine continue to be reported to FDA.

FDA reviewed the published literature and post-marketing adverse event reports submitted to FDA's Adverse Event Reporting System (AERS) from 1969 to 2009 and identified cases of gangrene requiring amputation associated with intravenous administration of promethazine. The most common amputations involved the fingers and hands. Numerous other cases of injection reactions such as injection site pain, redness, phlebitis, cyanosis, swelling, blistering, necrosis, and nerve damage were also found.

Additionally, FDA's review of the current prescribing information for these products found that the warnings for gangrene and intra-arterial injection were present, but their organization and presentation in the labeling could be improved to better convey the risk information. Therefore, based on the above case reports and conclusions from the prescribing information review, FDA is requiring manufacturers of these products to revise the labeling for promethazine, including addition of a Boxed Warning describing the risk of severe tissue injury, including gangrene, requiring amputation following intravenous administration of promethazine.

Lantus vs. Levemir Drug Use Evaluation
Memorial Hospital
December 2012

In December of 2012, a medication use evaluation was conducted to determine how the formulary change from Lantus (insulin glargine) to Levemir (insulin detemir) impacted blood glucose control at Memorial Hospital.

Methods:

The Lantus group was comprised of 20 patients admitted during April 2012 with a home medication of Lantus that were continued on Lantus during their admission.

The Levemir group was comprised of 20 patients admitted during July 2012 with a home medication of Lantus that were switched to Levemir during their admission.

Patients were excluded from this evaluation if they did not receive the basal insulin throughout their entire admission, and patients with an extremely elevated blood glucose (BG) upon admission (BG > 450)

Table 1: Baseline characteristics

	Lantus group (n=20)	**Levemir group** (n=20)
Avg. Length of admission	7 days (3 – 18 days)	8.15 days (3 – 19 days)
Avg. Lantus home dose	44.95 units (8 – 100 units)	37.65 units (5 – 170 units)
Number of pts with systemic steroid home med	3/20 (15%)	0/20 (0%)
Avg. Admission BG	199.6 mg/dL (94 – 375 mg/dL)	211.85 mg/dL (50 – 430 mg/dL)

Results:

Table 2: Endpoints and confounding variables

	Lantus group	**Levemir group**
Number of days with BG >180	41	41
Number of days with BG <60	6	3
Number of pts with systemic steroid during admission	3/20 (15%)	5/20 (25%)
Number of pts that received an insulin drip during admission	1/20 (5%)	1/20 (5%)
Avg. Discharge BG	142.95 mg/dL	150.05 mg/dL
Dose Variance from home dose (%)	**45.7%**	**19.85%**

Discussion:

There has been some controversy over the conversion of patients from Lantus to Levemir and whether they have equipotent dosing and equivalent blood glucose control. Therefore, the focus of this evaluation was to compare the dose variance from home dose, while also considering adequate glycemic control. While this is a small sample size (n=40), the two study groups had similar baseline characteristics, see Table 1. The results show that the groups had an identical number of days of BG greater than 180 (41 days). Both the Lantus and Levemir groups had similar BG upon discharge, despite more patients in the Levemir group receiving systemic corticosteroids during the admission. The most surprising finding from this evaluation

was the disparity between the dose variance from home dose between the Lantus and Levemir groups (45.7% and 19.85% respectively).

Conclusion:

Levemir is an appropriate formulary substitution for Lantus. In the patients evaluated, Levemir had similar glucose control to Lantus with much less variance from the patient's home Lantus dose to achieve the glucose control.

(Order Set: 2234) Revised: (1/31/2013)

WEIGHT:
HEIGHT:

DATE/TIME ORDERED

ALCOHOL WITHDRAWAL MANAGEMENT PROTOCOL

Medications:

Alpha-2 Agonists

Clonidine (Catapres): 0.1mg orally every 6 hours PRN for adrenergic symptoms of sweating, itching, nausea or tremors; HOLD for HR < 55/min, systolic BP < 90mmHg

Beta Blockers

Metoprolol tartrate (Lopressor): 25mg orally every 6 hours PRN for HR > 110/min, systolic BP > 150mmHg

Vitamins

Thiamine: 100mg (IV/IM) once a day x 1 day; then switch to thiamine 100mg PO once a day x 2 days
Folic Acid: 1mg (PO/IV) once a day x 3 days
Multivitamin: 1 tablet PO once a day

Other Medications

Famotidine (Pepcid): 20 mg PO every 12 hours

Nicotine Patch: apply one daily

Ativan Protocol

- Lorazepam (Ativan) is to be given PO unless patient is NPO or unable to tolerate PO
- Assess CIWA score 15-30 minutes after each IV lorazepam (Ativan) dose
- Assess CIWA score 30-60 minutes after each PO lorazepam (Ativan) dose
- If patient develops any of the following signs of oversedation, **HOLD lorazepam (Ativan) and contact physician:**
  - HR less than 50 bpm
  - Systolic BP less than 90 mmHg
  - Respiratory rate less than 10/min
  - Sustained oxygen saturation less than 90%
  - Not arousable, ataxia, or slurred speech
- **Contact physician if maximum daily dose of lorazepam (Ativan) is reached and symptoms are not well controlled:**
  - Regimen A and B = 20mg total daily dose
  - Regimen C = 40mg total daily dose
  - Regimen D = Max infusion rate of 10mg/hr

WEIGHT:
HEIGHT:

DATE/TIME ORDERED

ALCOHOL WITHDRAWAL MANAGEMENT PROTOCOL

CIWA Score	Regimen	Lorazepam (Ativan) Dosing	Notes
8-14	Moderate Alcohol Withdrawal (A)	1 mg PO/IV every 1 hr THEN 1 mg PO/IV every 4 hrs THEN Once CIWA score < 8 for 24 hrs Begin LOW taper	If CIWA score increases by 2 or more, go immediately to Regimen (B) If IV lorazepam (Ativan) is initiated, begin cardiac monitoring with continuous pulse oximetry
15-20 or Failed (A)	Progressive Alcohol Withdrawal (B)	2 mg PO/IV every 1 hr x 2 doses THEN 2 mg PO/IV every 2 hrs THEN Once CIWA score < 8 for 24 hrs Begin HIGH taper	If CIWA score increases by 2 or more or if any score > 20 go immediately to Regimen (C) If IV lorazepam (Ativan) is initiated, begin cardiac monitoring with continuous pulse oximetry
21-30 or Failed (B)	Transfer to ICU (C)	3 mg IV STAT AND 3 mg IV every 30 mins THEN Once CIWA score < 8 for 24 hrs Begin Regimen (B)	If CIWA score increases by 2 or more or if any score > 30 go immediately to Regimen (D)
Any CIWA Score > 30 or Failed (C)	(D)	IV Infusion 1 mg/hr continuous IV infusion; to target RASS score of 0 on day shift and negative 2 on night shift. Continue for 24 hr duration then attempt to wean infusion and begin monitoring CIWA THEN Once CIWA score < 30 for 24 hrs Begin above regimen based on CIWA score [i.e. if CIWA score is 17 begin Regimen (B)]	CIWA and RASS monitoring If lorazepam (Ativan) MAX rate of 10 mg/hr achieved AND If CIWA score remains > 30 ADD Dexmedetomidine (Precedex): 0.2 mcg/kg/hr continuous IV infusion; titrate in increments of 0.2 mcg/kg/hr to target RASS score of 0 on day shift and negative 2 on night shift; max rate of 1.5mcg/kg/hr; to be started in ICU.

CATHOLIC HEALTH INITIATIVES
Memorial Health Care System
2525 deSales Avenue Chattanooga, TN 37404
2051 Hamill Road Hixson, TN 37343

(Order Set: 2234) Revised: (1/31/2013)

WEIGHT:
HEIGHT:

DATE/TIME ORDERED

ALCOHOL WITHDRAWAL MANAGEMENT PROTOCOL

Ativan Taper protocol

	Lorazepam (Ativan) Dosing	Notes
LOW TAPER Previously on Regimen (A)	1 mg PO every 4 hours x 6 doses THEN 1 mg PO every 8 hours x 3 doses THEN 1 mg PO every 12 hours x 2 doses THEN STOP	If CIWA score increases to 8 or greater during taper return to Regimen (A)
HIGH TAPER Previously on Regimen (B)	2 mg PO every 4 hours x 6 doses THEN 2 mg PO every 8 hours x 3 doses THEN 2 mg PO every 12 hours x 2 doses THEN	If CIWA score increases to 8 or greater during taper return to Regimen (B)
DISCONTINUE ALCOHOL WITHDRAWAL REGIMEN WHEN TAPER COMPLETE		

Physician Signature:_____ Date:_____ Time:_____

Title: MEDICATION ADMINISTRATION – TIMELINESS OF SCHEDULED MEDICATIONS		
	Page 1 of 6	
Policy Number: MM-	*Date Last reviewed/Revised:* 1/13	*Valid Until:* 1/16
Department(s) Affected: All Clinical Areas	*Review Period:* every 3 years	

OUTCOME:

Timely administration of patient medication to support the delivery of scheduled medications in a timely manner to provide safe and effective patient care, and to maintain therapeutic blood levels over a period of time.

POLICY:

Centers for Medicare & Medicaid Services (CMS) and the Institute for Safe Medication Practices (ISMP) support the timely administration of patient medication in order to optimize pharmacotherapy.
The purpose of this policy is to:

a. Group medications according to time-critical dosing
b. Offer time based dosing guidelines

Medications Not Eligible for Scheduled Dosing Times

I. Definition: Medications which are not eligible for scheduled dosing times are medications which require exact or precise timing of administration, based on diagnosis type, treatment requirements, or therapeutic goals. These medications are NOT administered according to a standard repeated cycle of frequency.
II. Examples
    a. Stat and Now doses (immediate)
    b. First time or loading doses
    c. One-time doses
    d. Doses specifically timed for procedures
    e. On-call doses
    f. Time-sequenced doses or concomitant medications (chemotherapy and rescue agents, n-acetylcysteine and iodinated contrast media)
    g. Doses timed for serum drug levels (medications administered at specific times to ensure accurate peak/trough/serum drug levels)
    h. Investigational medications (administration time defined by the clinical research)
    i. PRN medications
III. Procedure: Medications not eligible for scheduled dosing times should be administered in a timely manner, considering reasonable preparation and delivery times. This applies to administration of these medications hospital-wide.

Medications Eligible for Scheduled Dosing Times (Scheduled Medications)

I. Definition: Scheduled medications include medications where maintenance doses are administered according to a standard, repeated cycle of frequency. Surgical and intra-procedural areas are not subject to following scheduled dosing times.

II. Examples: Daily, BID, TID, q4h, q12h, weekly, etc.

III. **Time-Critical Scheduled Medications**

A. Definition: Time-critical scheduled medications are those where early or delayed administration of greater than 30 minutes from the scheduled administration time may cause harm or have a significant, negative impact on the intended therapeutic or pharmacological effect.

B. Examples of scheduled medications that are always time-critical, hospital-wide:

i. Antibiotics
ii. Anticoagulants
iii. Anticonvulsants
iv. Medications with a dosing schedule more frequent than every 4 hours
v. Scheduled (not PRN) opioids used for chronic pain or palliative care (fluctuations in the dosing interval may result in unnecessary breakthrough pain)
vi. Immunosuppressive agents used for the prevention of solid-organ transplant rejection or to treat myasthenia gravis
vii. Medications prescribed for administration within a specified period of time of the medication order
viii. Medications that must be administered apart from other medications (e.g. antacids and fluoroquinolones)
ix. Certain medications that require administration within a specified period of time before, after, or with meals
    1. Example: rapid-, short-, or ultra-short-acting insulins, certain oral antidiabetic agents (e.g. acarbose, nateglinide, repaglinide, glimepiride), and pancrelipase.
    2. Medications administered around mealtimes require nursing judgment regarding the actual time of administration, which may fluctuate based on meal delivery time, actual consumption of the meal, and the patient's condition
x. Time-critical medications may differ among patients based on diagnosis, clinical situation, various risk factors, or therapeutic intent. Some scheduled medications can be time-critical for certain patients given their diagnoses and/or indication. Nursing judgment should be used to determine if a medication should be treated as time-critical.
xi. Prescribers, pharmacists, or nurses may declare any scheduled medication to be time-critical by including this designation with the medication order and/or electronic medication administration record (eMAR) entry.

C. Procedure:

i. Time-critical scheduled medications will be designated on the eMAR with the label comment, "Time-Critical Med".
ii. Medication administration times will be highlighted in green on the eMAR once the time of day is within the administration time window of 30 minutes before to 30 minutes after the scheduled administration time.
iii. Time-critical scheduled medications will be administered:
    1. At the exact time indicated when necessary, or

2. Within 30 minutes before or 30 minutes after the scheduled administration time, for a total administration time window of 1 hour

IV. **Non-Time-Critical Scheduled Medications**

A. Definition: Non-time-critical scheduled medications are those where early or delayed administration within a range of 1 hour from the scheduled administration time should not cause harm or have a significant, negative impact on the intended therapeutic or pharmacological effect.

B. Examples:

i. Medications not included in the Time-Critical Scheduled Medications list (above)

ii. Medications with a dosing schedule frequency of every 4 hours or less (e.g. q4h, TID, q12h, BID)

C. Procedure:

i. Medication administration times will be highlighted in green on the eMAR once the time of day is within the administration time window of 60 minutes before to 60 minutes after the scheduled administration time.

ii. Non-time-critical scheduled medications will be administered within 60 minutes before or 60 minutes after the scheduled administration time, for a total administration time window of 2 hours.

V. Standard Scheduled Administration Times

A. Standard administration schedules will be adhered to based on the prescribed dosing frequency whenever possible. See Standard Scheduled Administration Times chart below.

B. First Doses

i. New medication orders will be scheduled according to standard scheduled administration times. If the order entry time falls between standard scheduled administration times, pharmacy will back-time the medication order to include a past administration time. (An order is received at 1400 for a medication with a q6h schedule. Pharmacy will back-time the medication order, so that a 1200 dose is available on the eMAR).

ii. Nursing judgment should be used to determine whether to administer or hold the back-timed medication dose.

1. If the current time is closer to the back-timed dose than the future scheduled dose, the first dose should be administered now and documented as “given” with a reason code of “First Dose”.
2. If the current time is closer to the future scheduled dose than the back-timed dose, the back-timed dose should be held and the first dose should be administered at the future scheduled administration time.
3. Example: The time is now 1400. A new medication has been ordered with a q6h schedule, and has been placed on the eMAR according to the q6h standard scheduled administration times of 1200, 1800, 0000, and 0600. Since 1400 is closer to 1200 (back-timed dose) than 1800 (future scheduled dose), a medication dose should be given now.

C. Subsequent doses should be given according to standard scheduled administration time guidelines.

D. Exceptions
    i. Exceptions to the standard scheduled administration times will be allowed if the physician orders the medication to be given at a specific time, or in a unique patient situation
    ii. Exceptions to standard scheduled administration times may be appropriate to stagger numerous IV piggyback medications, or to keep a time-critical chronic medication on the same schedule used prior to admission.
    iii. Nursing may request changes to standard scheduled administration times if:
        1. Schedule adjustments are needed for IV cardiac medications
        2. Schedule adjustments are needed for IV antibiotics
        3.

Standard Scheduled Administration Times

Daily	0900
ACB	0600
WB	0800
ACS	1730
WS	1800
HS	2100
BID, q12	0900, 2100
ACBS	0600, 1730
ACBSI (Insulin)	0730, 1730
WBS	0800, 1800
TID	0900, 1300, 1800
ACI (Insulin)	0730, 1130, 1730
WM	0800, 1200, 1800
q8	0600, 1400, 2200
Four times a day	0900, 1300, 1800, 2100
AC&HSI (Insulin)	0730, 1130, 1730, 2100
q6	0000, 0600, 1200, 1800
q6R (Respiratory)	0200, 0800, 1400, 2000
q4WA	0800, 1200, 1600, 2000
q4	0000, 0400, 0800, 1200, 1600, 2000
q3	0000, 0300, 0600, 0900, 1200, 1500, etc.
q2	0000, 0200, 0400, 0600, 0800, 1000, etc.
q1	0000, 0100, 0200, 0300, 0400, 0500, etc.

VI. Early/Late/Missed Administrations

A. Time-critical and non-time-critical medications may be given early or late, or may be omitted in some clinical situations. Notify physician if medication is withheld due to a change in patient status.
B. Staff administering medications should always reference past administration times on the eMAR. This helps to avoid early administration of a medication that was previously administered late, resulting in a dosing interval that is too short.
C. Overdue medications will show in red in the nursing status board “Next Due” column, and will be highlighted red on the eMAR until documented as “given” or “not given”.
D. Early/Late Administration
    i. Any early or late medication administration is to be documented at the time the medication was actually given.
    ii. The reason for administering the medication early or late must be documented with a reason code from the drop-down menu or in the free

text box on the eMAR documentation screen (i.e. IV Access Unavailable, Last Dose Late, NPO, Patient Off Unit, etc.).

E. Missed Administrations
    i. Any missed medication dose is to be documented as “not given”.
    ii. The reason for the missed dose must be documented with a reason code from the drop-down menu or in the free text box on the eMAR documentation screen (i.e. NPO, Patient Off Unit, Patient Refused, etc.).

F. Schedule Adjustment
    i. If a medication dose has been late/missed for any reason, the nurse (in collaboration with the pharmacist and/or physician) will decide whether the late/missed dose should be rescheduled. This decision will be based on the type of medication that is involved, how it is being used, and the patient’s condition.
        1. If the late/missed medication is a non-time-critical medication, the nurse may use his/her own judgment regarding rescheduling of doses
        2. If the late/missed medication is a time-critical medication, the nurse must notify the pharmacist and/or physician regarding rescheduling of doses
    ii. Adherence to standard scheduled administration times is recommended whenever possible when rescheduling a medication dose.
    iii. The rescheduled dose may be documented as a “non-scheduled” dose on the eMAR.

G. Adverse Outcomes
    i. When an adverse outcome is anticipated or has occurred due to a late/missed medication dose, the following will be completed:
        1. Provider notification
        2. Patient notification
        3. Occurrence report
    ii. Data from occurrence reports should be used to identify the causes of early/late/missed medication administration, to revise the list of time-critical drugs as appropriate, and to make system-based changes to facilitate timely order review, dispensing, and administration of medications.
    iii. A non-punitive policy and just culture algorithms should be used to evaluate cases of late/missed medication administration. The goal is to remedy the processes and environmental conditions that contributed to untimely administration

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Approved/Reviewed by: Sandy Vredeveld, Director of Pharmacy, Pharmacy & Therapeutics
Joint Commission Standard: Medication Management (MM)
References: Centers for Medicare & Medicaid Services (CMS) and the Institute for Safe Medication Practices (ISMP)
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Pharmacy & Therapeutics Committee
Pharmacy Dashboard
November-December
FY13

		May-June	July-Aug	Sept-Oct	Nov-Dec	%Chg Mo.
Documented Clinical Interventions		8,747	8,960	8,751	8,858	1.2%
Major ADE's Prevented		12	31	27	24	-11.1%
Pharmacokinetic Service						
# Patients		498	523	512	580	13.3%
# Doses		2,162	2,395	2,367	2,799	18.3%
TPN Utilization						
# Patients		44	59	62	36	-41.9%
#Pts./1,000 Adj.Pt.days		1.1	1.6	1.7	1.02	-40.0%
# Doses		352	503	411	311	-24.3%
# Doses/1,000 Adj.Pt.days		9.25	14.08	11.4	8.8	-22.8%
Average # days of TPN		8	8.5	6.6	8.6	30.3%
Central line bloodstream infections pts on TPN		0	1	0	0	0.0%
Coumadin Dosing by Pharmacy						
# Patients		63	68	59	72	22.0%
# Doses		261	311	359	354	-1.4%
Antimicrobial Stewardship Clinical Interventions		267	297	279	290	3.9%
Chemotherapy Doses		322	304	337	226	-32.9%