Pharmacy & Therapeutics Committee Meeting
Private Dining Room
June 12, 2014 7:00 a.m.

Agenda Items — Individual Responsible

1. Call to Order — Richard Pesce, MD

2. Approval of April, 2014 Minutes — Richard Pesce, MD

3. Therapeutic Interchanges and Formulary Decisions — Page
   A. Exparel® (liposomal bupivacaine) ..Mark Brzezienski, MD……...5-6
   B. Ultiva® (remifentanil)……Nathan Schatzman, MD..…...7-8
   C. Zontivity® (vorapaxar) ….Rachel Kile, Pharm.D.……..9-10
   D Anoro Ellipta® (umeclidinium/vilanterol) .....Patrick Ellis, Pharm.D..……...11
   E. Outpatient IV iron formulary…….……...12
   F. Namenda XR – Formulary Interchange…….……...13

4. MUE
   A. Tranexamic Acid – Total Joint Replacement.....Rachel Kile, Pharm.D.....14-15

5. Medication Safety
   A. ADR Review ..Patrick Ellis, Pharm.D…...16-17
   B. Anti-XA assay - LMWH.....……

6. Policy, Procedure & Protocols
   A. Fentanyl IVP…. .....Patrick Ellis, Pharm.D…….....18

7. Nutrition Support Team
   A. Vital High Protein …. .....Brian Jones, RD……19-20
   B. PEPuP Protocol – Quality Improvement Trial …….....……

8. Adjournment

Next Meeting will be August 14, 2014 at 7:00am in the Private Dining Room

CATHOLIC HEALTH INITIATIVES
Memorial Health Care System

PHARMACY AND THERAPEUTICS COMMITTEE

DATE: April 10, 2014 CALLED TO ORDER: 7:00 A.M.
LOCATION: Private Dining Room ADJOURNED: 7:35 A.M.

Members Present:			**Members Absent**:		**Guests**:
Richard Pesce, M.D.	Karen Babb, Pharm.D.	Brian Jones, RD, LDN	Allen Atchley, M.D.	Don Jones, RPh	Darrin Majors, Pharm D Resident
Mark Anderson, M.D.	Michelle Denham, RN	Keith Lockwitz, RN	Nathan Chamberlain, M.D.	Vickie Burger, Lab	Rachel Kile, Pharm D Resident
David Dodson, M.D.	Patrick Ellis, Pharm.D.	Nan Payne, RN	Samuel Currin, M.D.	Deb Moore, RN	Karen Garner, RN
	Rodney Elliott, CPT	Melissa Roden, RN	Kevin Lewis, M.D.	Beverly Slate, Supply Chain	
	Patrick Hagan, Finance	Hannah Walker, RN	Nathan Schatzman, M.D.	Elvie Smith, RN	
	Lila Heet, Pharm.D.		Michael Stipanov, M.D	Danine Watson, RN	
	Sandy Vredeveld, DPh		William Oellerich, M.D.		

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 27, 2014 minutes were approved as submitted.		Complete
Therapeutic Interchanges and Formulary Decisions	The following medications were reviewed:		
	1. **Farxiga ® (dapagliflozin) –** New oral medication indicated for the treatment of type 2 diabetes utilizing a mechanism of action unique from other available agents (increases urinary glucose excretion). Dr. Dodson recommended not adding to formulary at this time due to concern of adverse reactions in elderly and patients with impaired renal function.	1. Not approved.	Complete
	2. **Gazyva® (obinutuzumab)** – New anti-CD20 monoclonal antibody indicated for treatment of CLL. New data suggests this agent may have some benefits over Rituxan® and it was recommended by Dr. Stipanov to add to formulary.	2. Approved.	Complete
	3. **Cleviprex® (clevidipine)** – Injectable dihydropyridine calcium channel antagonist similar to nicardipine although with a much shorter terminal half life. Dr. Schatzman requested this be added to formulary in order to have a primary arterial vasodilator available that can be used both introperatively and perioperatively as an alternative to Nitroglycerin and Sodium Nitroprusside. Dr. Pesce discussed this agent with Dr. Atchley and he agreed that this would be a desirable option to have available for patients due to its short half life and rapid onset of action. Dr. Pesce recommended that clevidipine be added to formulary but restricted to anesthesiology, cardiology, and intensivists for a maximum duration of 24 hours. Patrick discussed the potential for look-a-like errors with propofol since they are both available as 50 & 100 ml bottles and are both lipid emulsions. He suggested that smart pump entries and education be completed for ICU and OR staff prior to clevidipine being used.	3. Approved with 24 hr use restriction and prescribing limited to Cardiology, Anesthesiology, and Intensivists	Pending
	4. **Pancrelipase Formulary Interchange –** It was recommended to add Creon 24 t o the formulary to help ease the pill burden for patients requiring doses of ≥ 20,000 lipase units	4. Approved	Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	per dose. 5. **Omega-3 Fatty Acid Supplements –** Vascepa® and Lovaza® were reviewed. A generic fish oil supplement (Promega®) is currently the only omega-3 supplement carried by the pharmacy. Dr. Pesce discussed this class of drugs with Dr. Atchley and he was in favor of not adding these newer agents to formulary and automatically substituting the currently stocked drug on a milligram per milligram basis. 6. ***Clostridium difficile* - Therapeutic Review –** The appropriate dose of oral Vancomycin was discussed by Dr. Anderson. New data has shown that the 125 mg Q 6 hr regimen has equivalent clinical response with no difference in mortality or recurrence rates as compared to a 250 mg Q 6 hr regimen. This confirms what is currently recommended by the IDSA and ACG guidelines for patients with mild, moderate or severe *C. difficile* infection (CDI). Dr. Anderson recommended that pharmacy automatically substitute the 125 mg Q 6 hr dose for any orders written for the higher dose of 250 mg Q 6 hr (excluding patients in the ICU with life threatening disease complicated by ileus or mega colon). The use of bile acid binders (cholestyramine, etc.) and anti-motility agents (loperamine, diphenoxylate, etc.) were also discussed for patients with CDI. Dr. Anderson recommended that pharmacy automatically discontinue orders for these agents in patients with CDI.	5. Formulary Interchange Approved. 6. Approved	Complete Complete
Medication Use Evaluation	• **Relistor® (methylnaltrexone)** – MUE evaluating 25 patients receiving Relistor® was completed to evaluate the use of this agent. The evaluation demonstrated that much of the drug's use was for the off-label indication of post-op ileus. The evaluation also demonstrated that 66% of doses dispensed were continued following return of bowel function (documented bowel movement). Pharmacy estimated that approximately $10,000 in annual savings could be realized if the medication is discontinued upon return of bowel function. It was recommended to automatically stop scheduled orders for Relistor® following 24 hours of return of bowel function (documented bowel movement).	Approved automatic stop.	Complete
Policy, Procedure & Protocols	• **Surgical Prophylaxis – Antimicrobial Dosing –** New IDSA surgical prophylaxis dosing recommendations were discussed for cefazolin, vancomycin, gentamicin, cefoxitin and clindamycin. It was recommended to adopt the new weight based dosing for these perioperative antimicrobials on all surgical standing orders. Dr. Anderson will present this at the next Med Exec committee meeting for final approval. • **Pharmacist Ordering of Lab Values –** Discussed editing the *Medication Orders-Pharmacist Review* policy to add the following: Aminoglycoside levels and Procalcitonin assays. • **VTE Prevention Policy –** A draft version of a new VTE Prevention Policy was discussed. CHI is requiring all facilities to adopt standardized evidence based practices for the prevention of VTE. The only element of the policy that has required a change in	Approved Approved Approved	Pending Complete Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	practice is the frequency of the nursing VTE risk assessment which will now be done daily. It is hoped that this will help identify patients that may need mechanical and/or pharmacological VTE prophylaxis as well as improve VTE core measure performance.		
Nutrition Support Team	• **Diet Orders Policy –** Wound team workgroup recommended adding an additional guideline where patients with a Braden score of 13 will have a medically appropriate oral nutrition supplement added to their diet.	Approved	Complete

There being no further business, the meeting was adjourned at 7:35 A.M. The next P&T meeting is June 12, 2014.

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)

Requested for use by Dr. Brzezienski for use in breast surgery

INDICATIONS: Exparel is a liposome injection of bupivicaine, an amide local anesthetic, indicated for single-dose 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. For the FDA approved indications 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

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.

Bupivacaine liposome injectable suspension must NOT be mixed with or come in direct contact with non-bupivacaine-based local anesthetics, including lidocaine. These products may cause an immediate release of bupivacaine from the liposomes. Bupivacaine hydrochloride products if injected immediately before bupivacaine liposome injectable suspension may alter the pharmacokinetic and/or physicochemical properties of the drugs if the dose of bupivacaine hydrochloride solution exceeds 50% of the bupivacaine liposome injectable suspension (Exparel) dose.

MAMMAPLASTY STUDY RESULTS:
To date only one clinical trial has been published outlining the use of Exparel for patients undergoing breast surgery. The trial was a double-blind, randomized trial in which patients were randomized to receive either a single dose of Exparel 300 mg or bupivacaine 200 mg into each implant pocket at the conclusion of surgery. The study was terminated early due to "administrative reasons" and was thus underpowered to detect statistically significant differences in treatment groups. Assessments of cumulative pain score and opioid usage trended in favor of Exparel, however neither reached a *P* value of less than .05. Numerically lower pain intensity scores were observed for Exparel at 8 hrs and 12 hrs, however the scores were not significantly different at the other timed assessments. Overall, due to the early termination of this trial it is difficult to draw accurate comparisons between treatments.

COST: $299/20 ml

FORMULARY REVIEW

GENERIC NAME: REMIFENTANIL

PROPRIETARY NAME: *ULTIVA® (Mylan)*

INDICATIONS:

- As an analgesic agent for use during the induction and maintenance of general anesthesia for inpatient and outpatient procedures.
- For continuation as an analgesic into the immediate postoperative period in adult patients under the direct supervision of an anesthesia practitioner in a postoperative anesthesia care unit or intensive care setting.
- As an analgesic component of monitored anesthesia care in adult patients.

CLINICAL PHARMACOLOGY: Remifentanil is a potent μ-opiate receptor agonist. The analgesic effect of remifentanil is rapid in onset and offset. The effects and side effects to remifentanil are dose dependent and similar to other opioids.

PHARMACOKINETICS: Remifentanil is rapidly hydrolyzed by plasma esterases. Its clearance is not dependent on organ (kidney or liver) function. Peak effect occurs within 3-5 minutes and duration of action is approximately 5-10 minutes. Remifentanil has no significant accumulation in adipose tissue which allows for ideal body weight dosing in obese patients.

CONTRAINDICATIONS: Remifentanil is contraindicated for use in epidural or intrathecal administration due to the presence of glycine in the formulation. It also should not be used in patients with hypersensitivity to fentanyl or to fentanyl analogs.

WARNINGS & PRECAUTIONS: Due to an increased risk of apnea and respiratory depression, remifentanil should be administered only by providers trained in the management of respiratory effects of potent opioids, including cardiopulmonary resuscitation. Continuous oxygen saturation monitoring is recommended.

Skeletal muscle rigidity has been reported after single doses of 1 mcg/kg or at infusion rates >0.1 mcg/kg/min and is related to both dose and speed of infusion. Rigidity can be managed in nonintubated patients by stopping or slowing the infusion, as the rigidity will self-resolve within minutes, due to the short half-life of the drug. Life-threatening rigidity should be managed with administration of a neuromuscular blocker or opioid antagonist.

The package insert for remifentanil recommends that IV bolus administration should be used only during maintenance of general anesthesia, and should be given over 30-60 seconds in nonintubated patients.

Rapid offset of action: within 5-10 minutes after the discontinuation of remifentanil, no residual analgesic activity will be present. Additionally, remifentanil should not be used as a sole agent for induction of anesthesia because loss of consciousness cannot be assured and because of a high incidence of apnea, muscle rigidity, and tachycardia.

ADVERSE REACTIONS: Common adverse reactions associated with administration of remifentanil and other mu-opioids include respiratory depression (3%), bradycardia (4%), hypotension (4%), and skeletal muscle rigidity (3%). Due to the short half-life of the drug, these effects dissipate quickly after dose decrease or drug discontinuation. Other adverse effects as reported in ≥5% of adult patients in clinical trials of remifentanil as an anesthetic agent included nausea (44%), vomiting (22%), pruritis (18%), headache (18%), sweating (6%), shivering (5%), and dizziness (5%).

DRUG INTERACTIONS: Use of additional opioids or other respiratory depressants such as alcohol are likely to increase the depressant effects of remifentanil. There are no known drug interactions with regard to metabolism.

DOSING: Remifentanil should be dosed based on total body weight in patients who are not obese but should be dosed based on IDEAL BODY WEIGHT in patients greater than 30% over their IBW.

Due to the fast onset and short duration of action, remifentanil may be titrated upward in 25-100% increments in adult patients during maintenance of anesthesia.

General anesthesia and continuing as an analgesic into the PACU or ICU

Phase	Continuous IV Infusion of ULTIVA (mcg/kg/min)	Infusion Dose Range of ULTIVA (mcg/kg/min)	Supplemental IV Bolus Dose of ULTIVA (mcg/kg)
Induction of Anesthesia (through intubation)	0.5 - 1*		
Maintenance of anesthesia with:			
Nitrous oxide (66%)	0.4	0.1 - 2	1
Isoflurane (0.4 to 1.5 MAC)	0.25	0.05 - 2	1
Propofol (100 to 200 mcg/kg/min)	0.25	0.05 - 2	1
Continuation as an analgesic into the immediate postoperative period	0.1	0.025 - 0.2	not recommended

Analgesic component of monitored anesthesia care

Method	Timing	ULTIVA Alone	ULTIVA + 2 mg Midazolam
Single IV Dose	Given 90 seconds before local anesthetic	1 mcg/kg over 30 to 60 seconds	0.5 mcg/kg over 30 to 60 seconds
Continuous IV Infusion	Beginning 5 minutes before local anesthetic	0.1 mcg/kg/min	0.05 mcg/kg/min
	After local anesthetic	0.05 mcg/kg/min (Range: 0.025 - 0.2 mcg/kg/min)	0.025 mcg/kg/min (Range: 0.025 - 0.2 mcg/kg/min)

COST & AVAILABILITY:
Available as 1, 2, & 5 mg vials (stable 24 hrs once reconstituted)
$42.48 per 1 mg

Cost analysis of 1 hour surgery (based on 80 kg patient)
0.2 mcg/kg/min → 0.96 mg/hr ($42.48)
0.25 mcg/kg/min → 1.2 mg/hr ($84.96)
0.5 mcg/kg/min → 2.4 mg/hr ($127.44)

Cost analysis of 2 hour surgery (based on 80 kg patient)
0.2 mcg/kg/min → 0.96 mg/hr ($84.96)
0.25 mcg/kg/min → 1.2 mg/hr ($127.44)
0.5 mcg/kg/min → 2.4 mg/hr ($212.40)

Comparative Cost of Precedex® (dose of 0.2-1 mcg/kg/hr)
(1) 50 ml bottle of Precedex® (4 mcg/ml) would be sufficient for a 2 hour case → $64.72

CONCLUSION:
Due to remifentanil's rapid metabolism by plasma esterases it does offer the advantage of rapid onset and short duration of action which may be beneficial in cases in which it is beneficial for the patients to be awake or under lighter sedation/analgesia during the surgery. The brief duration of action allows for potent analgesia without residual respiratory depression post-operatively. It appears to be best suited in settings where a potent, short acting opioid is required and there is little associated post-procedure pain. However, due to the high cost it will likely be important to limit the use to shorter duration procedures.

FORMULARY REVIEW

GENERIC NAME: VORAPAXAR

PROPRIETARY NAME: *Zontivity* (Merck)

INDICATIONS: Vorapaxar is indicated for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction (MI) or with peripheral arterial disease (PAD). Vorapaxar has been shown to reduce the rate of a combined endpoint of cardiovascular death, MI, stroke, and urgent coronary revascularization (UCR).

CLINICAL PHARMACOLOGY: The role thrombin plays in the formation of an arterial thrombus is assisted by protease-activated receptors (PARs) 1. PAR-1 is found on platelets, smooth muscle cells, and endothelial cells. Vorapaxar is as a competitive, selective, and reversible inhibitor of PAR-1. Through PAR-1 inhibition, vorapaxar interferes with thrombin-receptor activating peptide-induced platelet activation. Selectivity for PAR-1 facilitates vorapaxar's absence of effect on alternative platelet aggregation and adhesion pathways of normal hemostasis. It also appears to have an absence of effect on the anticoagulation parameters of prothrombin time, thrombin time, activated partial thromboplastin time, ecarin clotting time, and activated clotting time.

PHARMACOKINETICS: The elimination half-life of vorapaxar is 7 to 11 days (173 to 269 hours). Vorapaxar is a substrate of CYP450, primarily CYP3A4 (see drug interactions below). Vorapaxar should be avoided in patients with active hepatobiliary disease.

ADVERSE REACTIONS: Increased incidence of clinically significant moderate or severe bleeding.
See primary safety end point data below.

WARNINGS/PRECAUTIONS: The benefits versus risks of bleeding should be considered prior to initiating therapy. A post-hoc analysis demonstrated that patients experiencing a lower rate of adverse events might include those younger than 75 years of age with no history of stroke or TIA and weight greater than 60 kg. No reported recommendations exist for peri-operative/procedure holding parameters.

Black Box Warning(s): Do not use vorapaxar in patients with a history of stroke, transient ischemic attack (TIA), intracranial hemorrhage (ICH) or active pathological bleeding. Antiplatelet agents, including vorapaxar, increase the risk of bleeding, including ICH and fatal bleeding**.**

DRUG INTERACTIONS: Strong CYP3A4 inhibitors increase and inducers decrease vorapaxar exposure. Avoid concomitant use of vorapaxar with strong CYP3A4 inhibitors or inducers

DOSING: The dosage is 2.08 mg once daily. Vorapaxar should not be used as monotherapy; there is no experience with use of vorapaxar alone as the only administered antiplatelet agent. Vorapaxar has been studied only as an addition to aspirin and/or clopidogrel.

CONTRAINDICATIONS: Vorapaxar is contraindicated in patients with a history of stroke, TIA, or ICH because of an increased risk of ICH in this population. Discontinue in patients who experience a stroke, TIA, or ICH. Vorapaxar is contraindicated in patients with active pathological bleeding such as ICH or peptic ulcer.

PRODUCT AVAILABILITY and COST: Will be available third quarter 2014.

Cost per tablet (dose): $8.48

PERTINENT CLINCAL TRIAL RESULTS:
<u>TRA 2P-TIMI 50 Trial: Vorapaxar in the Secondary Prevention of Atherothrombotic Events</u>

- Primary efficacy end point: Composite of cardiovascular death, MI, or stroke
    - Vorapaxar demonstrates efficacy > placebo (9.3% vs. 10.5%; p <0.0001)
- Secondary efficacy end point: Composite of cardiovascular death, MI, stroke, or urgent coronary revascularization
    - Vorapaxar demonstrates efficacy > placebo (11.2% vs. 12.4%; p = 0.001)

- Primary safety endpoint: GUSTO moderate or severe bleeding
    - Vorapaxar demonstrates increased bleeding risk vs. placebo (4.2% vs. 2.5%; p <0.001)
    - *Vorapaxar was discontinued in all patients with history of stroke upon recommendation of the data safety and monitoring board's report of excess intracranial hemorrhage in patients receiving vorapaxar

94% concurrently received aspirin; 24% received thienopyridine (primarily clopidogrel)

Coronary artery bypass graft (CABG)-related major bleeding: The difference in CABG-related major bleeding, according to TIMI criteria, was not statistically significant between vorapaxar and placebo. Study investigators were encouraged not to discontinue treatment with study drug prior to surgery. Approximately 12.3% of patients discontinued vorapaxar more than 30 days prior to CABG.

TRA 2P-TIMI 50 Trial: Subgroup Analysis of Patients with previous MI

- Primary efficacy end point: Composite of cardiovascular death, MI, or stroke
    - Vorapaxar demonstrates efficacy > placebo (8.1% vs. 9.7%; p <0.001)
- Secondary efficacy end point: Composite of cardiovascular death, MI, stroke, or urgent coronary revascularization
    - Vorapaxar demonstrates efficacy > placebo (10.5% vs. 12.1%; p = 0.001)
- Primary safety endpoint: GUSTO moderate or severe bleeding
    - Vorapaxar demonstrates increased bleeding risk vs. placebo (3.4% vs. 2.1%; p <0.001)
- Efficacy of vorapaxar was maintained regardless of timing of MI relative to study randomization

98% concurrently received aspirin; 78% received thienopyridine (primarily clopidogrel)

Coronary artery bypass graft (CABG)-related major bleeding: The difference in CABG-related major bleeding, according to TIMI criteria, was not statistically significant between vorapaxar and placebo.

Post-Hoc Analysis (84% of patients): < 75 years of age; no history of TIA or stroke; ≥ 60 kg

- Cardiovascular death, MI, or stroke was less common with vorapaxar vs. placebo
- Net clinical outcome: cardiovascular death, MI, stroke, urgent coronary revascularization, or GUSTO moderate or severe bleeding less common with vorapaxar vs. placebo

TRA 2P-TIMI 50 Trial: Subgroup Analysis of Patients with PAD

- Primary efficacy end point: Composite of cardiovascular death, MI, or stroke
    - Vorapaxar did not reduce composite end point vs. placebo (11.3% vs. 11.9%; p = 0.53)
- Secondary efficacy end point: Composite of cardiovascular death, MI, stroke, or hospitalization for urgent coronary revascularization
    - Vorapaxar did not reduce composite end point vs. placebo 12.7% vs. 13.4%; p = 0.57)
- Primary safety endpoint: GUSTO moderate or severe bleeding
    - Vorapaxar demonstrates increased bleeding risk vs. placebo (7.4% vs. 4.5%; p = 0.001)
- Peripheral vascular end points: acute limb ischemia, peripheral revascularization (urgent and elective), and urgent hospitalization for vascular cause of an ischemic nature
    - Vorapaxar demonstrates efficacy > placebo for all endpoints

88% concurrently received aspirin; 37% received thienopyridine (primarily clopidogrel)

CONCLUSIONS: Vorapaxar is a novel PAR-1 antagonist that is effective for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction or with peripheral arterial disease, in combination with aspirin and/or clopidogrel. Vorapaxar is associated with clinically significant moderate to severe bleeding and the benefits and risks of use should be evaluated for individual patients.

FORMULARY REVIEW

GENERIC NAME: UMECLIDINIUM BROMIDE AND VILANTEROL TRIFENATATE

PROPRIETARY NAME: *Anoro Ellipta* (GlaxoSmithKline)

INDICATIONS: Umeclidinium bromide/vilanterol trifenatate inhalation powder is indicated for the long-term, once-daily maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.

CLINICAL PHARMACOLOGY: Umeclidinium is a long-acting muscarinic antagonist (similar to tiotropium), also referred to as an antimuscarinic. Umeclidinium has affinity for M1 through M5 receptors, with greater affinity for M3 than M2 receptors and similar receptor affinities to tiotropium. Vilanterol is a highly selective long-acting beta agonist (LABA) that activates beta-2 adrenoreceptors on airway smooth muscle, causing bronchodilation and has demonstrated 24-hour activity; in vitro tests have shown similar functional selectivity to salmeterol.

PHARMACOKINETICS: Following inhalation of umeclidinium and/or vilanterol, time to maximum concentration (T_{max}) occurred at a median of 5 to 15 minutes. There was no difference in vilanterol T_{max} when delivered as monotherapy or in combination. In vitro studies show that umeclidinium is metabolized by cytochrome P450 (CYP-450) 2D6 and is a substrate for P-glycoprotein transport. In vitro studies show that vilanterol is metabolized by CYP3A4 and is a substrate for P-glycoprotein transport.

ADVERSE REACTIONS: In 2 placebo-controlled and 2 active-controlled trials, adverse reactions occurring at a rate of at least 1% and more frequently than with placebo included pharyngitis (2% vs less than 1%), sinusitis (1% vs less than 1%), lower respiratory tract infection (1% vs less than 1%), constipation (1% vs less than 1%), diarrhea (2% vs 1%), pain in extremity (2% vs 1%), muscle spasm (1% vs less than 1%), neck pain (1% vs less than 1%), and chest pain (1% vs less than 1%).

DRUG INTERACTIONS: Vilanterol is a substrate of CYP3A4. Coadministration of ketoconazole, a potent CYP3A4 inhibitor, increases systemic exposure to vilanterol. Use caution when administering vilanterol to patients being treated with monoamine oxidase inhibitors, tricyclic antidepressants, or drugs known to prolong the QTc interval, or within 2 weeks of discontinuation of such agents. Beta-blockers may block the pulmonary effects of respiratory beta agonists, such as vilanterol, and may also produce severe bronchospasm in patients with COPD.

DOSING: The recommended dose is umeclidinium 62.5 mcg/vilanterol 25 mcg as a single oral inhalation taken once daily. The dose should be given at the same time every day. The maximum daily dose is 1 inhalation once daily. No dosage adjustment is required for elderly patients, patients with renal impairment, or patients with moderate hepatic impairment.

PRODUCT AVAILABILITY & COST: *Anoro Ellipta* was approved for marketing in the United States on December 18, 2013. Umeclidinium bromide/vilanterol trifenatate inhalation powder is available as a disposable, light-grey and red plastic inhaler containing 2 double-foil blister strips containing both medications with 7 (institutional pack only) or 30 blisters each.

COST - $60.03 (7 day institutional pack)

CONCLUSION: Umeclidinium/vilanterol is the first fixed-dose combination of a LAMA and LABA. Vilanterol is already approved in combination with fluticasone furoate for the treatment of COPD. Current guidelines state that combining bronchodilators with different mechanisms of action increases the magnitude of bronchodilation for equivalent or less side effects. Spiriva (tiotropium) is currently the only LAMA agent carried on formulary, however it is currently not available as a combination LAMA-LABA formulation. **Additionally, the price of the single tiotropium product ($56.28) is comparable to the price of the combination product Anoro Ellipta and carrying this new agent will be more cost effective than utilizing Spiriva plus a separate LABA medication. Therefore, it is recommended to add this drug to formulary in order to maintain continuity of care for patients already stabilized on this medication at admission. This product line will be further evaluated as new LABA-LAMA combination agents are FDA approved.**

FORMULARY REVIEW

Outpatient IV Iron Formulary

BACKGROUND:
Currently all IV iron products are available for outpatient use at MHCS. This includes the following products: Nulecit® (sodium ferric gluconate complex), Venofer® (iron sucrose), Infed® (iron dextran), and Feraheme® (ferumoxytol). Historically each of these medications has been individually reimbursable in addition to the corresponding administration charge when administered in the outpatient setting. Due to recent coding changes now only Infed® and Feraheme® are eligible for drug specific outpatient reimbursement.

DOSING SUMMARY:

	Dosing	Administration	Max Infusion Rate	Special Instructions
Sodium Ferric Gluconate	125 mg at each dialysis session until target monitoring parameters achieved, then minimum dose required to maintain target parameters	May be given undiluted as slow IV injection or diluted in 100 ml 0.9% sodium chloride (NS) and infused over 1 hr	125 mg over 10 minutes	Use immediately after dilution in saline
Iron Sucrose	Hemodialysis-dependent CKD: 100 mg at each dialysis session for total cumulative dose of 1000 mg	Hemodialysis-dependent CKD: given by slow IV injection over 2-5 minutes, or diluted in a maximum of 100 ml NS given over at least 15 min	100 mg of undiluted solution over 2 minutes	Continue therapy at lowest dose necessary to maintain monitoring parameter targets
	Non-dialysis dependent CKD: 200 mg on 5 different occasions within 14 day period	Non-dialysis dependent CKD: given by slow IV injection over 2-5 minutes, or by IV infusion over at least 15 minutes		
	Peritoneal dialysis-dependent CKD: 2 doses of 300 mg given 14 days apart, 400 mg 14 days after second dose	Peritoneal dialysis-dependent CKD: diluted in a maximum of 250 mL NS & given by slow IV infusion over 1.5 hours		
Ferumoxytol	510 mg followed by 510 mg 3-8 days later	Given by rapid IV injection (at least 17 seconds) In hemodialysis, wait at least one hour into dialysis session & until blood pressure stable to administer	30 mg (1 ml) per second	Monitor for hypotension, signs & symptoms of hypersensitivity reactions for 1 hour post-dose

RECOMMENDATION:
Due to the above mentioned reimbursement changes, corporate CHI is requesting that each market stop using Venofer® and Nulecit® and only utilize Feraheme® and Infed® as outpatient iron therapies. Although the cost per treatment of Feraheme® is significantly higher than that of the other treatments, the outpatient reimbursement for this product makes this the most cost effective outpatient non-dextran iron therapy. Based on this information and the recommendation from CHI, it is recommended to remove sodium ferric gluconate and iron sucrose from the outpatient formulary and only allow the use of iron dextran and ferumoxytol for outpatient use. Sodium ferric gluconate and iron dextran will still be on formulary for inpatient use.

FORMULARY REVIEW

GENERIC NAME: MEMANTINE EXTENDED RELEASE

PROPRIETARY NAME: *Namenda XR* (Forest)

Namenda immediate release was previously the only product on the U.S. market until Forest pharmaceuticals began making an extended release formulation of memantine. Forest is planning to discontinue manufacturing the immediate release formulation in August of this year in advance of the upcoming patent expiration of the immediate release formulation of their product in April of 2015. The intent of this strategy is to force all patients to convert to the XR formulation prior to the subsequent generic release of immediate release memantine.

It should be noted that there are no data on the comparative efficacy of these two regimens. However, Forest Pharmaceuticals does have detailed information available in their package inserts detailing how to convert between the two formulations.

DOSING & COST:

Immediate Release	Extended Release
5 mg PO Daily ($4.57/day)	7 mg PO Daily ($8.60/day)
5 mg PO BID ($9.14/day)	14 mg PO Daily ($8.60/day)
10 mg PO BID ($9.14/day)	28 mg PO Daily ($8.60/day)

DOSE CONVERSION BETWEEN PRODUCTS:

Immediate Release		Extended Release
5 mg PO Daily	→	7 mg PO Daily
5 mg PO BID	→	14 mg PO Daily
10 mg PO BID	→	28 mg PO Daily

CONCLUSION & RECOMMENDATION:

Currently the extended release formulation of memantine offers a modest savings of $0.54 per day of therapy as compared to the immediate release formulation. However, in order to temporarily convert our inpatient memantine use to the extended release formulation would require a significant inventory expense in order to acquire the XR product with the likely need to convert back to the IR product next spring when the generic product will be available. It is likely that the generic product will offer a significant cost savings as compared to the XR formulation and will be much more cost effective for institutional use once this is available. **Therefore it is recommended to NOT add Namenda XR to formulary and to institute an automatic therapeutic substitution to the IR product for all Namenda XR orders.**

MEDICATION USE EVALUATION

Tranexamic Acid in Total Joint Arthroplasty

Introduction/Purpose
Tranexamic acid (TXA), an antifibrinolytic agent, is known to reduce peri-operative blood loss and subsequent blood transfusions surrounding total joint replacement surgery.

The purpose of this study was to evaluate TXA for reducing peri-operative blood loss and associated costs in patients undergoing total hip or knee replacement surgery.

- *TXA efficacy evaluation* for reducing peri-operative blood loss
- *Cost savings analysis*: decreased utilization of blood transfusions and blood conservation systems (drains)

Methods
TXA use was evaluated from November 2013 through April 2014.

	No. of Patients	TXA Administered? (Y/N)
Control group	92	N
Study group	39	Y

TXA Dosing Regimen

- TXA 1 gram IV administered in operating room as a 10 minute infusion
- TXA 1 gram topically administered throughout surgery*

Study Inclusion Criteria:

- Age $\geq$ 18 years of age
- Total hip or knee arthroplasty
- Tranexamic acid administered peri-operatively
- Arthroplasty performed by single, pre-identified surgeon

TXA Contraindications (Study Exclusion Criteria):

- History of venous thromboembolism (DVT or PE)
- History of coronary stenting within 6 months
- History of arterial thromboembolism

Results

TXA Efficacy Analysis

Variable	Mean or Frequency (%)	
	Control Group	Study Group
Age (years)	65.4	66.4
Arthroplasty		
Knee	54 (58.7%)	20 (51.3%)
Hip	38 (41.3%)	19 (48.7%)
Pre-op Hgb (g/dL)	13.7	13.8
Post-op Hbg drop (g/dL)	3.7	2.8
Estimated blood loss (mL)	144	148
# Blood transfusions (units per patient)	0.18	0.13
Blood conservation system utilization	**86 (93.4%)**	**0**

Cost Savings Analysis

Control group expense (blood conservation system)	$101.99/pp
Study group expense (TXA medication cost)	-$40.12/pp
Total Cost Savings with TXA use	**$61.88/pp**

Discussion

Multiple TXA dosing regimens have been described in the literature and we chose to evaluate a 1 gm IV pre-operative dose regimen in our patient population. It was felt by the surgeon that this regimen did not achieve adequate hemostasis; therefore, an additional 1 gm dose, administered topically throughout surgery, was added to the regimen.

No numerical differences were identified between the control and study groups for all measures of TXA efficacy, with the exception of blood transfusions, use of blood conservation systems, and post op hemoglobin drop.

- The difference between groups for number of blood transfusions per patient is *not* considered clinically significant.

Limitations:

- Retrospective chart review
- Small sample size
- Incomplete documentation of TXA administration
- Two administration regimens throughout the study period (*cost analysis accounts for this modification)

Conclusion

Given the large number of total joint replacement surgeries performed annually at Memorial, use of TXA may be a source of cost savings when the use of a drain is eliminated or reduced. The elimination of drain placement with TXA administration in this study was driven by surgeon choice, and may not reflect actual efficacy of TXA for reducing the need for the drain. However, elimination of the drain when TXA is administered does create cost savings of approximately $62.00 per patient.

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).

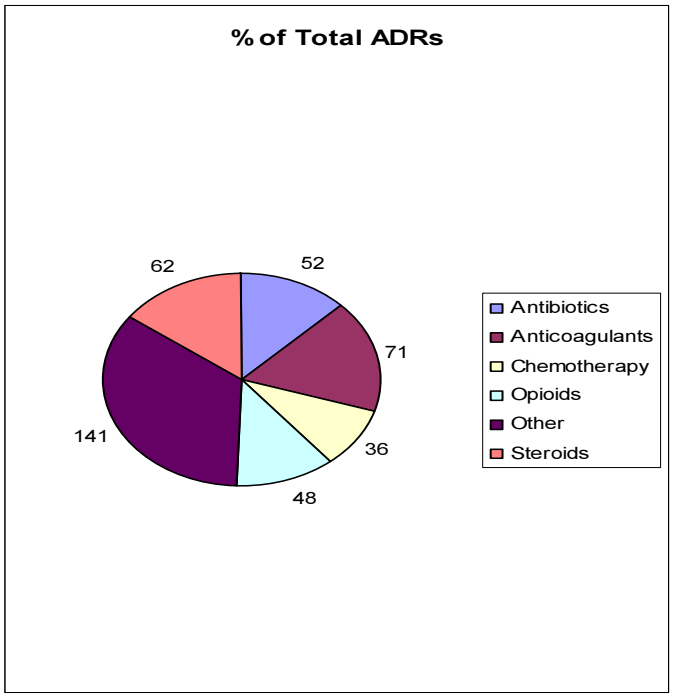
Inpatient: 124 (30%)
Prior to hospitalization: 286 (70%)
Total: 410

Category 1: 284
Category 2: 124
Category 3: 1

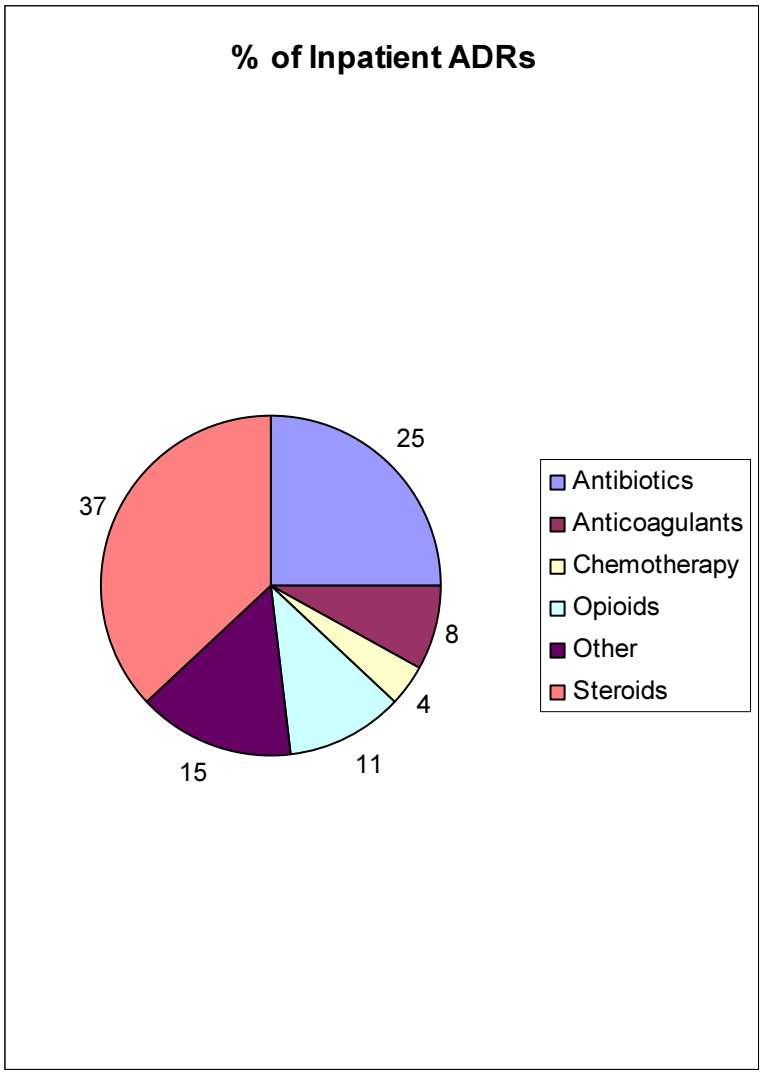
ADRs to be discussed:

0038656864—Patient was admitted for fairly alarming set of lab work with the thought that dialysis would be needed. Patient was taking Lithium. After a lengthy stay, one of her diagnoses was medication-induced extrapyramidal side effects and nephrogenic diabetes insipidus requiring DDAVP and vasopressin.

Total ADRs



Inpatient ADRs:



Antibiotics: 6 (26%) Acute kidney injury with Vancomycin
7 (30%) Rash/itching was most common reaction with this class

Anticoagulants: 3 (25%) Epistasis with Coumadin
4 (33%) HIT with Heparin
1 (8%) GI bleed with Lovenox/Coumadin combo

Opioids: 4 (26%) Over sedation
5 (33%) Constipation

Steroids: 39 (79%) Hyperglycemia
11 (22%) leucocytosis

FENTANYL – IV PUSH for PRN pain relief

BACKGROUND:
Fentanyl IVP is currently restricted to the following patient care areas: ED, OR/procedural areas, PACU, CSSU, and ICU's. Dr. Mull has requested that the committee review this restriction and consider allowing fentanyl to be used as an intermittent pain medication on the patient care areas outside of those listed above. Currently, only two existing medication management policies address the use of IV fentanyl but these policies only address this medication when used via PCA and no existing policy mentions the PRN use of IVP fentanyl.

The below information regarding comparative efficacy and side effects is provided to aid in the committee's discussion of fentanyl as mentioned above.

COMPARATIVE EFFIFACY & SIDE EFFECTS:

Incidence of Side Effects (Medication summary data from RCT's)

Adverse Event	Fentanyl (%)	Hydromorphone (%)	Morphine (%)
Respiratory	3.1	3.7	3.5
Pruritis	16.9	39.9	18.5
Gastrointestinal	31.6	37.3	37.7
Urinary retention	11	12.1	32.3
CNS	804	42.7	30

J Pain. 2002 Jun;3(3):159-80. Adverse events associated with postoperative opioid analgesia: a systematic review. Wheeler M, Oderda GM, et al.

Comparative Efficacy, Onset of action, etc.

Medication	Onset of action	Duration of action	Usual dosing interval	Equi-analgesic Dosing
Fentanyl	Immediate	30-60 mins	1-2 hrs	100 mcg
Hydromorphone	15 mins	4-6 hrs	3-6 hrs	1.5 mg
Morphine	5-10 mins	3-6 hrs	3-6 hrs	10 mg

Summary Review of Vital HP

Low fat & high protein peptide-based formula for patients with malabsorption, impaired GI function and/or feeding intolerance

Proprietary Name: Vital High Protein
Abbott Laboratories Nutrition
Product of USA

Indications/Use:

- Provides 1.0 Cal/mL— keeping osmilality lower despite very high protein
- Very high protein (87.5 g/L, 35% of calories) to support protein synthesis, tissue repair and wound healing.
- Immune support:
  - 23.2g/L fat, a balanced blend of MCT/LCT, 20% total calories
  - 3.6g/L EPA+DHA from fish oil
  - Fortified with Vitamin D3 (1000 IU/L)
- Tolerance:
  - Advanced blend of hydrolyzed protein and structured lipid promote absorption and tolerance.
  - Hydrolyzed, peptide-based protein system.
  - MCT/fish oil structured lipid, a well-tolerated and absorbed next generation fat to promote absorption of fatty acids.
- Meets or exceeds 100% of the RDI for 24 vitamins and minerals in 1422 cal (1422 mL).
- Halal.
- Gluten free.
- Suitable for lactose intolerance.

Pricing: Vital HP is $11.39 per liter (1000 kcal). For the average patient receiving 1800 kcal daily this would be $20.00 daily to feed. (See price comparison)

Conclusion:
Vital HP would be unique to our formulary as it would provide a very-high-protein, hydrolyzed, peptide-based enteral formula for use with critically ill patients. It is specifically useful with patients who are obese and or on high amounts of propofol as it is the highest protein per calorie formula available from Abbott.

Recommendations:
It is recommended by the Nutrition Support Team to implement use of this product as an enteral source of complete nutrition for patients who require a very high protein elemental enteral feedings.

Product Comparison:

67 year old female on mechanical ventilation.
Height: 5'4, Weight: 280#, BMI: 48
Diprovan @ 25ml/hr = 660kcal from lipid

Estimated caloric needs using the Modified Penn State Equation: ~1779kcal
Estimated protein needs using Critical Care guidelines for Obesity: 2.5g/kg ideal body weight (1.1g/kg actual body weight or 30.5% of ttl kcal): 136g
Estimated fluid needs adjusted for obesity: ~2180ml daily

Using Existing Formulary Item: Vital 1.5	Using Proposed Item: Vital High Protein
Diprovan @ 25ml/hr = 660kcal from Fat	Diprovan @ 25ml/hr = 660kcal from Fat
7 Packs Pro-Source = 420kcal & 105g Protein	3 Packs Pro-Source = 180kcal & 45g Protein
Vital 1.5@25ml/hr=825kcal, 37g Pro, 31g Fat	Vital HP@48ml/hr=1056kcal, 92g Pro, 23g Fat
600ml of required fluid flushes	360ml of required fluid flushes
Total Nutrients and Cost: 1905kcal, 142g protein, 97g fat&1020ml free H20. (45% kcal from fat) Pt. meeting 55% of RDIs for micronutrients. $12.43 Total Daily Cost	Total Nutrients and Cost: 1896kcal, 137g Protein, 89g fat&1215ml free H20 (42% kcal from fat) Pt. meeting 66% of RDIs for micronutrients. $15.00 Total Daily Cost
w/o Diprovan	w/o Diprovan
Vital 1.5 @ 47ml/hr w/ 4 Packs of Pro Source = ~$14.30	Vital HN @ 80ml/hr = ~$20.06