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

Agenda Items	Individual Responsible
1. Call to Order	Richard Pesce, MD
2. Approval of November, 2015 Minutes	Richard Pesce, MD
3. Therapeutic Interchanges and Formulary Decisions	Page
A. Keytruda® (pembrolizumab)	Whitney Williams, PharmD…...6-7
B. Blincyto® (blinatumomab).....	……...8-9
C. Voraxaze® (glucarpidase)……..	Patrick Ellis, PharmD……..10
D. Nucala® (mepolizumab)	…….Camellia Davis, PharmD…….11-12
E. Cresemba® (isavuconazole)	…….Linda Johnson, PharmD…….13-14
F. Exparel® (liposomal bupivacaine)….	…...Eric Nelson, MD……15-17
4. CHI Medication Use and Evaluation (MUE) Committee.....	18
5. Medication Safety/Quality	
A. Opioid Safety Work Group – *update*	Patrick Ellis, PharmD…….....
6. Policy, Procedure & Protocols	
A. Antimicrobial Stewardship Policy….	Linda Johnson, PharmD.....19-21
B. Sedative/Hypnotics for Sleep….	..Patrick Ellis, PharmD.....22-23
C. Medication Administration – Timeliness of Meds	…Michelle Denham, RN…24-28
7. Nutrition Support Team……	Susan Fuchs, RD……
8. Adjournment	

Next Meeting will be April 14, 2016 at 7:00 AM in the Private Dining Room

PHARMACY AND THERAPEUTICS COMMITTEE
Minutes of Meeting

DATE: November 12, 2015 CALLED TO ORDER: 7:00 A.M.
LOCATION: Private Dining Room ADJOURNED: 8:00 A.M.

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

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 August 13, 2015 minutes were approved as submitted.		Complete
Therapeutic Interchanges and Formulary Decisions	The following medications were reviewed: 1. **Orbactiv®** – New long acting glycopeptide antibiotic indicated for the treatment of ABSSI caused by susceptible gram positive organisms. Patrick reviewed that the available data is primarily limited to the treatment of skin infections where this agent is not a cost-effective treatment. It was recommended by Patrick and Dr. Anderson to not add to formulary but that as new data emerges this might be an attractive option for special situations in which long term, daily IV therapy may not be possible of feasible. 2. **Nexavar®** – An oral oncology agent (multi-kinase inhibitor) that has shown recent promise for a subset of patients with AML in addition to standard induction therapies. Due to this being a "specialty pharmaceutical" the distribution system is different and these medications are typically dispensed as patient specific prescriptions direct to the patients from specialty pharmacy distributors. Patrick described a process and order set for Nexavar that has been created which can be initiated to help obtain Nexavar when needed for a hospital inpatient and once obtained dispensed to the patient as their "own medication" via specialty pharmacy distribution channels. This has been discussed with the oncologists and the expectation is that the medication can be obtained or ordered within 72 hours once ordered. They were agreeable to this proposed process.	1. Not approved for formulary addition 2. Patient own use whenever possible	Complete Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	3. **Specialty Pharmacy Medications** – Patrick recommended that a similar process be utilized for other "specialty medications" when ordered and to utilize case management and outpatient pharmacy to arrange for the medication order to be filled as a direct to patient order when possible rather than these medications being ordered and dispensed directly from the inpatient pharmacy.	3. Approved	Complete
	4. **Cimzia®** – Outpatient monoclonal antibody indicated for the treatment of Crohn's disease, rheumatoid arthritis, ankylosing spondylitis, and active psoriatic arthritis. Patrick explained that this was reviewed by the Formulary Business Committee and it was recommended by this sub-committee to not approve due to this predominantly being a self-administered medication. The review of the clinical data also does not demonstrate any superiority over other formulary agents within this same class of medications. It was recommended by Dr. Pesce to not approve to formulary.	4. Not approved for formulary addition	Complete
	5. **Praxbind®** – Monoclonal antibody designed for the specific reversal of dabigatran. Patrick reviewed the clinical data which suggests that it is highly effective in reversing the anticoagulant effects of dabigatran. Patrick recommended that a single dose be stocked at each Memorial campus for patients with severe/life-threatening bleeding or patients needing urgent reversal prior to surgery.	5. Approved for formulary addition	Complete
	6. **Antithrombotic Reversal & Surgical Management** – Pocket cards have been updated to include Praxbind and non-anticoagulant associated coagulopathies. These cards will be distributed to all medical staff.	6. Approved	Complete
	7. High Dose Influenza Vaccine – The use of the high dose flu vaccine was discussed for patients $\geq$ 65 years of age. Although the CDC currently doesn't specifically recommend this vaccine some of the available data appears to indicate a benefit (lower hospitalizations, reduced incidence of influenza) although a more recent study failed to demonstrate a benefit except in patients $\geq$ 85 years of age. Patrick explained that there is a mechanism in place to receive additional inpatient payment for Medicare patients receiving inpatient flu vaccines which could help offset the additional cost. Based on this information the committee recommended that this be added to hospital formulary and vaccination protocols for next flu season.	7. Approved for 2016-2017 flu season	Pending
	8. **Fentanyl IV Use Restrictions** – A request to allow the use of IV fentanyl (outside of ICU and procedural areas) for patients receiving palliative care/end of life care was discussed. Dr. Goldman has requested this for some patients and the committee felt that this was a reasonable request for patients being seen by his service. However, the committee felt that this should be restricted to certain patient care areas to assure nursing competency with administering IV fentanyl. Patrick suggested that this aspect be discussed with Rhonda Poulson to engage her input. Dr. Schatzman made the	8. Approved for palliative care use – as IV push on any patient care unit. PCA usage will be allowed once appropriate policies have been edited.	Pending

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	recommendation that use of fentanyl via PCA may be the most optimal option for these patients instead of intermittent IVP.		
	9. **Statin Class Review** – A class review of all the available statins was discussed for the possibility of a therapeutic interchange for Crestor due to a cost savings opportunity. Dr. Atchley supported the conversion of Crestor orders to a therapeutically equivalent dose of Lipitor and suggested that the conversion be modified slightly to utilize Lipitor 80 mg for only Crestor 40 mg dosages.	9. Formulary interchange approved for Crestor	Complete
	10. **Entresto CHI guidelines for appropriate use** – Patrick reviewed the CHI guidelines with the committee and stated that pharmacy will develop processes to ensure that GFR, K+, allergies, and ACE/ARB washout times are appropriately observed when clinically appropriate. Dr. Atchley supported this process and also brought to the committee's attention that although the clinical trials for Entresto showed a clinical benefit that due to issues related to study design and tolerability issues observed in the clinical trials this may result in lower utilization of this agent than what was initially thought. Patrick offered to share the full CHI guidelines with the hospitalist physicians.	10. Monitoring criteria approved	Complete
	11. **Phosphate Binder Class Review** – A new class of iron based phosphate binders was discussed (Velphoro®, Auryxia®). Clinical trials have not shown these to be superior to other formulary agents such as sevelamer. However, Dr. Chamberlain stated that some patients are able to tolerate these agents better than other drugs within this class. For this reason his recommendation was to not utilize a formulary interchange but to declare these non-formulary and have patients utilize their own supply while hospitalized.	11. New agents not approved for formulary addition – patients will be allowed to take their home medication supply	Complete
Medication Safety/Quality	**ADR Review** – Tabled until next meeting.	Information Only	Tabled
Policy, Procedure & Protocols	1**. Pharmacy Formulary Business Review Committee –** Patrick reviewed a new policy that was created to govern the activities of this P&T sub-committee to evaluate outpatient medication therapies. The policy outlines sub-committee membership and mechanisms for reviewing medications via a standard or expedited review process.	1. Approved	Complete
	2. **Ketamine IV Infusion for Pain** – Patrick and Dr. Schatzman reviewed the benefit of utilizing sub-anesthetic doses of ketamine for post-surgical patients with acute on chronic post-operative pain. The policy outlines usual dosing and restricts the use of continuous infusion ketamine to PACU/PACU extended stay and the intensive care units and prescribing limited to anesthesiologists and intensivists. Dr. Schatzman requested that extra measures be taken to prevent the possibility of diversion and recommended to dispense ketamine as a PCA to further limit access to ketamine infusions.	2. Approved with restrictions as noted	Complete
	3**. Chemotherapy and Biologic Dose Rounding –** A new policy outlining the rounding of both cytotoxic and biologic medications intended for infusion was discussed. The policy	3. Approved	Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	would allow pharmacists the authority to round doses of designated biologics within 10% of the ordered dose (to the nearest vial size when possible) and within 5% of the ordered dose for cytotoxic medications. The policy outlines the medications applicable to this policy. 4. **TID Schedule Modification –** Patrick reviewed a recommendation to modify the current "TID" (three times daily) medication administration schedule to 0900-1500-2100 (formerly 0900-1300-1800) to more closely mimic the schedule in which patients take "TID" medications at home. Pertinent policies would be modified to reflect this modification.	4. Approved	Complete

There being no further business, the meeting was adjourned at 8:00 A.M. The next P&T meeting is **February 11, 2016 at 7:00 a.m.**

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

Approved by,
Richard Pesce, M.D. Chairman

FORMULARY REVIEW

GENERIC NAME: PEMBROLIZUMA**B**

PROPRIETARY NAME: *Keytruda (Merck)*

INDICATIONS: Pembrolizumab is approved for the treatment of un-resectable and/or metastatic melanoma following the use of ipilimumab and, if the tumor is BRAF V600 mutation positive, a BRAF inhibitor. Pembrolizumab is also approved in the treatment of PD-L1 positive metastatic non-small cell lunch cancer with disease progression on or after platinum containing chemotherapy and after progression on an EGFR or ALK targeted therapy.

CLINICAL PHARMACOLOGY: Pembrolizumab, a humanized immunoglobulin G4 (chain kappa) monoclonal antibody, binds to the programmed cell death protein 1 (PD-1) receptor found on T cells and blocks its interaction with PD-1 ligand 1 (PD-L1) and PD-L2, allowing T-cell proliferation and cytokine production. Up-regulation of the PD-1 ligands by some tumors, including some melanomas, inhibits the active regulation by T cells and may induce a state of unregulated tumor growth.

PHARMACOKINETICS: Clearance of pembrolizumab was not impacted by age, gender, renal or mild hepatic impairment, or overall tumor burden. The peak and trough concentrations and area under the curve (AUC) at steady state increased proportionally when the dosage was increased from 2 to 10 mg/kg every 3 weeks.

Patients with mild (estimated glomerular filtration rate [eGFR] 60 to 89 mL/min/1.73 m^2), moderate (eGFR 30 to 59 mL/min/1.73 m^2), or severe (eGFR 15 to 29 mL/min/1.73 m^2) renal impartment had no clinically important changes in the clearance of pembrolizumab when compared with those patients with normal renal function.

Clearance	0.22 L/day
Steady State	After 18 weeks
Half-life	26 days

ADVERSE REACTIONS: Pembrolizumab was evaluated in studies involving 411 patients.
- 9% of the patients discontinued due to an adverse reaction
- Those adverse reactions that occurred in at least 2 patients and led to pembrolizumab discontinuation:
    - Pneumonitis, renal failure and pain
- Renal failure, dyspnea, pneumonia and cellulitis were the most commonly reported serious adverse reactions during the clinical trials.

DRUG INTERACTIONS: No pharmacokinetic drug interaction studies have been conducted with pembrolizumab, nor have any potential drug interactions been identified.

DOSING: Based on the finding with the previously reported randomized clinical trial data, no difference in efficacy between the 10 mg/kg every 3 weeks and 2 mg/kg every 3 weeks dosages was found; the recommended pembrolizumab dose and schedule is 2 mg/kg every 3 weeks via IV infusion.

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS): No REMS program is required for pembrolizumab.

COMPARISON TO NIVOLUMAB:
-No nivolumab vs pembrolizumab trials
-Current trial data and indications suggest similar uses.
-No evidence clearly indicates niche or advantage for pembrolizumab.

<table>
<tr><td></td><td colspan="4">Nivolumab</td><td colspan="3">Pembrolizumab</td></tr>
<tr><td>Indication</td><td colspan="4">Melanoma, NSCLC, Renal cell cancer</td><td colspan="3">Melanoma, NSCLC</td></tr>
<tr><td>Administration</td><td colspan="4">60 min</td><td colspan="3">30 min</td></tr>
<tr><td>MOA</td><td colspan="4">Nivolumab is a fully human immunoglobulin G4 (IgG4) monoclonal antibody that selectively inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor to block the ligands PD-L1 and PD-L2 from binding.</td><td colspan="3">Highly selective anti-PD-1 humanized monoclonal antibody which inhibits programmed cell death-1 (PD-1) activity by binding to the PD-1 receptor on T-cells to block PD-1 ligands (PD-L1 and PD-L2) from binding.</td></tr>
<tr><td rowspan="4">Advanced Melanoma</td><td colspan="4">Phase III- Larkin et al. 2015</td><td colspan="3">Phase III- Robert et al. 2015</td></tr>
<tr><td></td><td>Ipilimumab</td><td>Nivolumab</td><td>Nivolumab + Ipilimumab</td><td></td><td>Pembrolizumab</td><td>Ipilimumab</td></tr>
<tr><td>Median PFS</td><td>2.9 months</td><td>6.9 months</td><td>11.5 months</td><td>6 month PFS</td><td>47.3 %</td><td>26.5 %</td></tr>
<tr><td>Median PFS with PD-L1 (+) tumors</td><td>3.9 months</td><td>14 months</td><td>14 months</td><td>Response Rate</td><td>33.7 %</td><td>11.9 %</td></tr>
<tr><td colspan="4"></td><td colspan="3">** Less adverse effects with pembrolizumab compared to ipilimumab</td></tr>
<tr><td rowspan="4">NSCLC</td><td colspan="3">Phase III- Brahmer et al. 2015</td><td colspan="3">Garon et al. 2015</td></tr>
<tr><td></td><td>Nivolumab</td><td>Docetaxel</td><td></td><td colspan="2">Pembrolizumab</td></tr>
<tr><td>Median Overall Survival</td><td>12.2 months</td><td>9.4 months</td><td>Median duration of overall survival</td><td colspan="2">12 months</td></tr>
<tr><td></td><td colspan="2">HR 0.73 96% CI [0.59-0.89] p = 0.002</td><td>Median duration of progression free survival</td><td colspan="2">3.7 months</td></tr>
</table>

COST: 100 mg/4 mL (4 mL): $5179.20 50 mg (1): $2589.60

CONCLUSION: Pembrolizumab appears to be a safe and effective option for the treatment of unresectable or metastatic melanoma in patients in whom ipilimumab, and possibly a BRAF inhibitor, has failed. Lack of an active control group and analysis against historic values made study results difficult to compare. Pembrolizumab was approved under the accelerated approval process based on tumor response rate and durability of response.

FORMULARY REVIEW

BLINCYTO (BLINATUMOMAB)

INDICATIONS: Treatment of Philadelphia chromosome–negative (Ph−) relapsed or refractory B-cell acute lymphoblastic leukemia (ALL).

CLINICAL PHARMACOLOGY: Blinatumomab is a novel biospecific antibody T cell–engager with dual specificity for CD19 and CD3. It creates a temporary cytolytic synapse between cytotoxic T cells, which express CD3 receptors, and targeted cancerous and non-cancerous B cells that express CD19 surface antigens. This allows the direct fusion of cytotoxic granules that contain granzymes and perforin, leading to the lysis of tumor B cells. Thus, blinatumomab activates cytotoxic T cells by binding CD3 on receptors of T cells and brings cancerous B cells to close proximity by binding CD19 on surfaces of B cells.

PHARMACOKINETICS: Blinatumomab exhibits linear pharmacokinetics from doses of 5 to 90 mcg/m^2/day (about 9 to 162 mcg/day).

Average steady-state plasma concentration during continuous IV infusion:
9 mcg/day: 211 pg/mL
28 mcg/day: 621 pg/mL

Vd	4.52 L (poor distribution in tissue)
Clearance	2.92 L/hr
Excretion	Urine (negligible)
Steady State	Within 1 day
Half-life	2.11 hr

TRIAL DATA:

Topp MS, et al, 2014.	
Study Design:	Open-label, single-arm, 3-stage, multicenter study
Patient population	189 patients with Ph− B-cell ALL primary refractory -OR- relapsed within 12 months of first remission -OR- relapsed within 12 months of having allogeneic HSCT -OR- refractory to/relapsed after 1 or more rounds of salvage therapy.
Intervention	-2 cycles of blinatumomab therapy, blinatumomab 28 mcg/day IV for 4 weeks followed by 2 weeks of no treatment. **first treatment cycle increased in a stepwise manner
Primary Endpoint	Complete or partial hematologic recovery within 2 treatment cycles was 43% (95% CI, 36% to 50%). 63 patients achieved complete hematologic recovery 18 patients achieved partial hematologic recovery
Secondary Endpoints	Median relapse-free survival was 5.9 months (95% CI, 4.8 to 8.3) 6.9 months (95% CI, 4.2 to 10.1) for patients who achieved complete hematologic recovery 5 months (95% CI, 1.4 to 6.2) for patients who achieved partial hematologic recovery Median overall survival was 6.1 months (95% CI, 4.2 to 7.5), with a median follow up of 9.8 months
Other Endpoints	Discontinuation occured because of reasons such as death (115 patients), loss to follow up (1 patient), or withdrawal of consent (1 patient). Of the 115 patients who died, 23 patients died because of fatal adverse reactions (only 3 were considered to be related to drug exposure). Dose reductions (19 patients) and treatment discontinuations (34 patients) occurred because of adverse reactions.

**2 other similar small phase two studies in Germany

ADVERSE REACTIONS:

Common adverse reactions (>20%): pyrexia, headache, peripheral edema, febrile neutropenia, nausea, hypokalemia, and constipation

Serious adverse events: (65% of patients enrolled in the clinical studies)

-Cytokine Release Syndrome: pyrexia, headache, nausea, asthenia, hypotension, increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), increased total bilirubin (TBili), disseminated intravascular coagulation (DIC), capillary leak syndrome (CLS), and hemophagocytic lymphohistiocytosis/ macrophage activation syndrome (HLH/MAS)

-Neurological Toxicities: encephalopathy, convulsions, speech disorders, disturbances in consciousness, confusion and disorientation, and coordination and balance disorders

Median time to onset: 7 days

Approximately 50% of patients receiving Blincyto in clinical trials experienced neurological toxicities

MANAGEMENT OF ADVERSE REACTIONS:

Toxicity	Grade	Action
Cytokine Release Syndrome	Grade 3	Withhold Blincyto until resolved, then restart Blincyto at 9 mcg/day. Escalate to 28 mcg/day after 7 days if toxicity does not recur.
	Grade 4	Discontinue Blincyto permanently.
Neurological Toxicity	Seizure	Discontinue Blincyto permanently if more than one seizure occurs.
	Grade 3	Withhold Blincyto until no more than Grade 1 (mild) and for at least 3 days, then restart Blincyto at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity does not recur. If the toxicity occurred at 9 mcg/day, or if the toxicity takes more than 7 days to resolve, discontinue Blincyto permanently.
	Grade 4	Discontinue Blincyto Permanently.
Other Clinically Relevant Adverse Effects	Grade 3	Withhold Blincyto until no more than Grade 1 (mild), then restart Blincyto at 9 mcg/day. Escalate to 28 mcg/day after 7 days if the toxicity dose not recur. If the toxicity takes more than 14 days to resolve, discontinue Blincyto permanently.
	Grade 4	Consider discontinuing Blincyto permanently.

DRUG INTERACTIONS: Blinatumomab has not been formally studied for drug interactions.

DOSING: Induction phase of up to 2 cycles followed by consolidation phase of up to 3 additional cycles.

Cycle 1: patients ≥ 45 kg

Week 1: blinatumomab 9 mcg/day Weeks 2-4: blinatumomab 28 mcg/day

Weeks 5&6: no treatment

Subsequent Cycles: blinatumomab 28 mcg/day for all 4 weeks followed by 2 weeks of no treatment

**Hospitalization for the first 9 days of the first cycle and first 2 days of the second cycle is recommended.

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS): The *Blincyto* REMS program was created because of the increased risk of cytokine release syndrome, neurological toxicities, and errors related to preparation and administration. Amgen, is required to send REMS letters and REMS fact sheets to health care providers and REMS letters to hospital and home health care pharmacists.

COST: 35 mcg (1): $3814.28

CONCLUSION: Blinatumomab is a novel drug for the treatment of patients with Ph− relapsed or refractory B-cell A

FORMULARY REVIEW

GENERIC NAME: GLUCARPIDASE

PROPRIETARY NAME: *Voraxaze* (BTG International, Inc.)

INDICATIONS: Glucarpidase is indicated for the treatment of toxic plasma methotrexate concentrations (greater than 1 mcmol/L) in patients with impaired renal function resulting in delayed clearance of methotrexate. Patients with normal or mild renal dysfunction are not classified as appropriate candidates for therapy due to the risk of potential sub-therapeutic exposure to methotrexate.

CLINICAL PHARMACOLOGY: Methotrexate is normally excreted unchanged in the urine. However, in patients with impaired renal function, elevated plasma methotrexate concentrations may occur. Leucovorin is used to diminish cytotoxicity from exposure to high concentrations of methotrexate; however, it does not reduce methotrexate levels and is of limited value in patients who cannot adequately clear methotrexate. Glucarpidase provides an alternative, non-renal route of methotrexate elimination in patients with impaired renal function who are receiving high-dose methotrexate therapy. All patients with a baseline methotrexate concentration of > 50 micromol/L had a > 95% rapid reduction in methotrexate concentration that was maintained up to 8 days after glucarpidase receipt. Glucarpidase is not indicated for use in patients who exhibit the expected clearance of methotrexate or in patients with normal or mildly impaired renal function.

PHARMACOKINETICS: Following intravenous (IV) administration of glucarpidase 50 units/kg over 5 minutes in healthy subjects, the mean peak plasma concentration (C_{max}) was 3.3 mcg/mL and the mean exposure (area under the curve $[AUC]_{0-\infty}$) was 23.3 mcg•h/mL. Systemic clearance of glucarpidase was 7.5 mL/min, with an elimination half-life of 5.6 hours. The manufacturer notes a prolonged glucarpidase enzymatic activity half-life of 8.2 hours in renally compromised patients versus 5.64 hours in patients with normal renal function. However, in pharmacokinetic enzyme-linked immunosorbent assay analysis, a significant time difference between the 2 patient groups and the mean half-life was not observed.

ADVERSE REACTIONS: The most common adverse reactions reported in relation to glucarpidase therapy, with an incidence of greater than 1%, include paresthesias, flushing, nausea and/or vomiting, hypotension, and headache.

DRUG INTERACTIONS: Leucovorin is a substrate for glucarpidase. Cancer patients treated with high-dose methotrexate (1 g/m^2 or more) and leucovorin rescue therapy followed by glucarpidase 2 hours prior to leucovorin had a reduction in (6S)-leucovorin AUC_{0-3h} of 33% and a reduction in C_{max} of 52%. Additionally, the active metabolite (6S)-5-methyltetrahydrofolate AUC_{0-3h} was reduced by 92% and the C_{max} was reduced by 93%. Therefore, it is recommended that leucovorin not be administered 2 hours before or after a dose of glucarpidase.

DOSING: Glucarpidase is approved for a single 50 unit/kg bolus dose that is administered by IV injection over 5 minutes. Adjustment of dose for patients with renal or hepatic impairment is not necessary. The benefits of a second dose is questionable; based on the experience with 7 patients, the Food and Drug Administration–approved labeling states a "lack of efficacy with a second dose."

PRODUCT AVAILABILITY: Glucarpidase was approved on January 17, 2012. Glucarpidase is available as a single-use, sterile, preservative-free lyophilized powder in an individually packaged glass vial. Each vial contains 1,000 units of glucarpidase.

COST: price per 1,000 unit vial = $26,045; average cost of single dose per patient (85 kg patient) = $104,180

CONCLUSION: Glucarpidase has been shown to rapidly reduce plasma methotrexate levels after IV administration and is currently the only available therapy to rapidly reduce methotrexate serum levels in patients with acute kidney injury with methotrexate toxicity.

FORMULARY REVIEW

GENERIC NAME: MEPOLIZUMAB

PROPRIETARY NAME: *Nucala (GlaxoSmithKline)*

INDICATION:
Add-on maintenance treatment of severe asthma in adults and children 12 years and older with an eosinophilic phenotype.

- Severe asthma: high dose ICS + LABA + oral corticosteroids
- Eosinophilic phenotype: Blood Eosinophil > 150 cell/µl in patients on recommended treatment, Blood Eosinophil > 300 cell/µl in naïve patients.

CLINICAL PHARMACOLOGY

- Mepolizumab is an interleukin-5 antagonist (IgG1 kappa). IL-5 is the major cytokine responsible for the growth and differentiation, recruitment, activations, and survival of eosinophils (a cell type associated with inflammation and an important component of the pathogenesis of asthma).
- This contrasts from Omalizumab (Xolair), in which the primary mechanism of action is targeting circulating IgE inflammatory markers.

BACKGROUND: While the majority of asthmatic patients can be controlled using the step-wise management approach, a subset of patients still exist with severe, un-controlled asthma despite optimized therapy (i.e. high dose ICS + additional controller medications). For these patients, it is important to identify other biological markers for treatment. Once thought of as a single disorder, asthma is now recognized as a collection of phenotypically different respiratory diseases; therefore, targeted therapy to the particular subtype is important. Eosinophilic asthma is thought to be associated with allergic sensitization and T-helper type 2–related inflammation that can occur due to specific interleukins, such as IL-5, IL-13, and IL-4. A treatment review for this particular asthma phenotype (ie, eosinophilic) recommends use of inhaled corticosteroids and beta-2 agonists, while steroid-refractory patients should be treated with more specific agents such as omalizumab, mepolizumab, or other experimental agents. Mepolizumab (Nucala) is a humanized anti-Interleukin-5 monoclonal antibody developed for use as an add-on therapy for severe asthmatic patients with an eosinophilic phenotype. This can be defined as a blood eosinophil level >150 cells/µl while on appropriate therapy. Another agent, Omalizumab (Xolair), is an IgG1 monoclonal antibody that targets circulating IgE to inhibit the pro-inflammatory cascade.

A recent report of patients with severe asthma found that after applying National Institute for Health and Care Excellence (NICE) guidelines, only 6.2% of patients with severe asthma qualified for Omalizumab use (Xolair). When the omalizumab label criteria were applied to the severe eosinophilic asthma population, there was an approximately 30% overlap with the mepolizumab target population. Severe, allergic asthma is a complicated disease state defined by multiple inflammatory cascades. There may be some overlap between Omalizumab and Mepolizumab, as defined areas for use have not been determined.

LITERATURE REVIEW:

DREAM	**Phase 2**	Change from baseline in Blood Eosinophil levels at Week 12	• Mepolizumab reduced the rate of clinically significant asthma exacerbations • No consistent improvements in symptoms or lung function (FEV1)
MENSA	**Phase 3**	Mepolizumab administered either IV or SC significantly reduced asthma exacerbations and was associated with improvements in markers of asthma control	• exacerbation rate decreased to 1.75 exacerbations per year with placebo treatment • 0.93 per year with the 75-mg IV dose of mepolizumab • 0.81 per year with the 100-mg SC dose of mepolizumab • **50% reduction in placebo group indicates baseline non-adherence**
Eosinophilic Airway Inflammation and Mepolizumab	**Active**	The primary endpoint of the study is the percent of BAL EOS after SBP, before and after mepolizumab administration	• 87% dose reduction of glucocorticoids • 100% patients experienced a dose reduction
Mepolizumab Steroid-Sparing Study in Subjects with Severe Refractory Asthma	**Phase 3**	Percent reduction of oral corticosteroid (OCS) dose during weeks 20 to 24 compared with the Baseline dose, while maintaining asthma control	• mean percentage reduction in the dose of glucocorticoids (50%) • proportion of patients who had this reduction (54%) • results lower than reductions that have been reported for higher doses of the drug (750 mg) administered intravenously in patients with sputum eosinophilia

MEMORY study	*Not yet recruiting*	The primary outcome is the mean change from baseline in pre- and post-bronchodilator residual volume (RV) at visit 10 (week 24) and at time of response	

DOSING:
Mepolizumab 100mg SC Q 4 weeks

COST:
Mepolizumab: $2,500/ 100ml vial
Omalizumab: $909/ 150ml vial

- Dosing titrated using IgE Levels
- Cost ranges from $909 per month – $2,272.50 per 2 weeks

PHARMACOKINETICS:
Distribution: Vd ~3.6 L
Metabolism: Undergoes proteolytic degradation via enzymes that are widely distributed in the body and not restricted to hepatic tissue
Bioavailability: 80%
Half-life elimination: 16-22 days
Excretion: non-renal

ADVERSE REACTIONS:

- Central nervous system: Headache (19%), fatigue (5%)
- Local: Injection site reaction (8%; includes pain, erythema, swelling, pruritus, or burning sensation)
- Hypersensitivity reactions: Hypersensitivity reactions (eg, angioedema, bronchospasm, hypotension, urticarial, rash) may occur, typically within hours of administration. Delayed hypersensitivity reactions, occurring days after administration, have also been reported. Discontinue use in patients who experience a hypersensitivity reaction. Systemic/allergic/hypersensitivity reactions were reported by 2% of subjects in the placebo group and 1% of subjects in the group receiving Nucala. The most commonly reported manifestations of systemic allergic/hypersensitivity reactions reported in the group receiving Nucala included rash, pruritis, headache, and myalgia. Systemic non-allergic reactions were reported by 2% of patients in the group receiving Nucala and 3% of subjects in the placebo group. The most commonly reported manifestations of systemic non-allergic reactions in the Nucala group included rash, flushing, and myalgia.
    - No cases of anaphylactic reactions have been documented in any clinical trials for Mepolizumab
    - Trials for Omalizumab reported 3 cases of anaphylaxis (0.1%). Two reactions occurred within 2 hours of first injection, and one occurred after the 4^{th} injection.
- Long term safety: Herpes zoster infections have occurred in patients receiving Nucala. Varicella vaccination may be considered, if medically appropriate, prior to starting therapy.

CONCLUSION:

- Mepolizumab has shown benefit in a niche group of severe asthmatic patients with a hyper-eosinophilic phenotype.
- Mepolizumab reduces the rate of clinically significant asthma exacerbations by 50%; although, this has shown only marginal improvement in lung function (FEV1)
- Trials have also shown a statistically significant reduction in asthma exacerbations in placebo groups. This indicates a fundamental issue of baseline non-adherence to standard asthmatic therapy within the treatment population.
- Use of Mepolizumab was associated with a mean 50% reduction in oral glucocorticoids in 54% of patients receiving therapy.
- Mepolizumab has a unique mechanism of action compared to Omalizumab (Xolair); and therefore offers an alternative treatment option for patients with severe eosinophilic asthma.
- Long term safety monitoring is needed to assess risk for hypersensitivity reactions. In Omalizumab (Xolair), most anaphylactic reactions occurred after the first or second dose with a time onset of $\leq$ 60 minutes. However, some instances of anaphylactic reaction were reported after > 1 year of therapy. Close monitoring of Mepolizumab will be required until post-marketing data can determine the rate of hypersensitivity reactions to this therapy in the general population.

FORMULARY REVIEW

GENERIC NAME: ISAVUCONAZONIUM SULFAGE

PROPRIETARY NAME: *Cresemba* (Astellas)

FDA Approved Indications:
Isavuconazole: Invasive aspergillosis, Invasive mucormycosis

Dosage and Administration:

Isavuconazole (IV/PO)	Loading dose: 372 mg q8h x 6 doses
	Maintenance dose: 372mg daily

Renal Impairment: No dosage adjustments recommended for isacuconazole
Hepatic impairment: No dosage adjustments in mild to moderate impairment; No data in severe impairment.

Therapeutic monitoring:
Isavuconazole: no recommendations

Microbiology:

- Spectrum: Candida, Aspergillus, Mucorales, Cryptococcus, Blastomyces, Histoplasma, Coccidioides
- Holes in Coverage: Fusarium spp; Scedosporium spp (MIC_{90} > 8mcg/mL)

Pharmacology: Azole - Inhibits cytochrome P450 dependent 14α-lanosterol demethylation (essential for ergosterol synthesis)

Pharmacokinetics:

	Isavuconazole
Cmax (ng/mL)	7,499
Tmax (hr)	3
AUC_{0-24} (h*ng/mL)	121,402
Protein Binding	99%
Metabolism	CYP3A4, 3A5, UGT
Excretion	Primarily via feces <1% of active metabolite in urine

*Similar to voriconazole, isavuconazole metabolism map be affected by race; Chinese subjects have lower clearance and higher AUCs as compared to healthy white subjects (No dosage adjustments recommended thus far)

Adverse Effects:

Isavuconazole
N/V/D
Headache
Rash
QTc shortening Avoid in patients with familial short QT syndrome
Elevation of liver enzymes
Infusion reactions Use an in-line filter for IV infusion

Contraindications: Known hypersensitivity to any azoles

Drug Interactions:

Isavuconazole
3A4 substrate • Inhibitors increase levels • Inducers decrease levels
Moderate 3A4 inhibitor (Much less compared to voriconazole) • Significant effects on tacrolimus, sirolimus, cyclosporine • Mild effects on statins, midazolam Weak P-gp inhibitor • Higher digoxin levels Mild/no effect on warfarin

Cost:

	Price per dose	**Cost for 10 days**	**Cost for 42 days**
Isavuconazole	$133.16 (2 caps)	$1,864.24	$6,125.36
	$276.00	$3,864	$12,696

Clinical Trials for isavuconazole:

1) Randomized, double blind, non-inferiority clinical trial: isavuconazole vs. voriconazole for invasive aspergillosis
    a. N=516, adult pts w/ proven, probable, or possible invasive fungal disease, randomized 1:1
        i. Proven or probable aspergillus N=231; 16% proven and 84% probable
    b. Primary end point – all cause mortality at day 42
        i. 18.6% for isavuconazole and 20.2% for voriconazole
    c. Clinical success (measured by EORTC/MSG criteria)
        i. 35% for isavuconazole and 36.4% voricaonazole

2) Open-label, non-comparative trial – evaluating isavuconazole for the treatment of invasive fungal infections
    a. N=149, 37 patients had proven (86%) or probable (14%) invasive mucormycosis.
    b. 21 had no prior antifungal therapy, 11 had refractory disease, and 5 did not tolerate prior Tx
    c. Primary endpoint – all cause mortality at day 42
        i. Patients with primary mucormycosis – 33.3% (refractory and pt.'s who did not tolerate Tx ↑ mortality
    d. Matched case control analysis done with 21 patients w/ primary mucormycosis with 33 patients treated with amphotericin B from global Fungiscope registry
        i. Similar 42 day mortality 33.3% (isavuconazole) vs 41.3% (amphotericin B)
            1. Consistent with historical mortality rates w/ ampho therapy (35-45%)

Recommendation:

- Add to formulary (limited stock)
    - Aspergillus: Patients who are intolerant of voriconazole or who are on concomitant drugs with severe DDIs with voriconazole prohibiting its use
    - Mucormycosis: Patients who are intolerant of amphotericin B or who need salvage therapy
- Restricted to Infectious Diseases service

FORMULARY REVIEW

GENERIC NAME: Bupivacaine Liposomal

PROPRIETARY NAME: Exparel (Pacira)

Requested by Dr. Eric Nelson – use as a TAP block for colorectal procedures

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.

DURATION OF 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.

The FDA approved Exparel after a review of 22 studies including three phase 3 studies which focused on hemorrhoidectomy and buinionectomy procedures. Two phase 3 studies demonstrated a significant effect over **placebo** for the primary outcome of cumulative pain scores over a period limited to less than 24 hours. In the bunionectomy and hemorrhoidectomy studies the FDA concluded that "… Exparel 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 Exparel and placebo treatments on mean pain intensity." The studies also used a cumulative outcomes analysis for their efficacy outcome for opioid rescue medication consumption. The FDA analysis determined that a difference was only detectable (compared to placebo) for the 0-12 hr time point. The differences at each time point after that were not statistically significant nor were they clinically releveant from the 12-72 hour time points. Similarly to the pain intensity outcomes the difference in opioid consumption was only realized (compared to placebo) for the first 12 hours post drug administration.

The official FDA review further summarized the effect of Exparel in the following statements regarding the phase 3 study for hemorrhoidectomy. "In the placebo controlled studies, Exparel was significantly better than placebo for reducing pain intensity during the first 12 hours following administration. This effect diminished over the next 12 hours such that by 24 hours after administration there was no clinically relevant difference in pain experienced by subjects treated with Exparel compared to those treated by normal saline." Similarly in the phase 3 bunionectomy study, the FDA review states "by 8 hours after study drug administration, both treatment groups have mean scores that are indicative of moderate levels of pain, and are indistinguishable from each other and by 12 hours the pain scores in the Exparel group are as if they had not received any treatment at all."

The pharmacokinetic onset of action of Exparel was evaluated in clinical trials that assessed pain intensity and other outcomes. These studies demonstrated that the onset of action for Exparel was less than 2 minutes, and was similar to conventional bupivacaine. In the clinical trials described in the medical review, the duration of Exparel's analgesic effect appears to be no more than 24 hours and not longer than that of un-encapsulated bupicaine HCL."

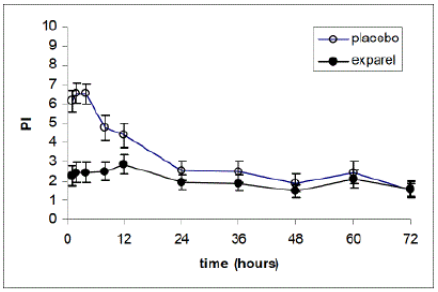

Figure 1: Mean Pain Intensity versus Time plot for hemorrhoidectomy study (C-316) *FDA Amended Clinical Review, Center for Drug Evaluation and Research, October 2011

CLINICAL EFFICACY:

Active Comparison Trials – Bupivacaine (data submitted to FDA)

In a 3rd phase 3 study submitted to the FDA as part of the new drug application, an active control study versus bupivacaine (204 patients) was evaluated for hemorrhoidectomy. None of the 60 endpoints reviewed illustrated a beneficial effect of a single injection of conventional bupivacaine and in fact was outperformed in the trial by the plain bupivacaine arm in regard to mean integrated numerical rating scale at rest (NRS-R) pain intensity score and supplemental opioid consumption at 84 hours. This study has never been published outside of the medical review by the FDA.

Additionally, there are several earlier phase 2 studies of Exparel in comparison to bupivacaine + epinephrine. These study populations included those undergoing inguinal hernia repair (2), knee arthroplasty (2), hemorrhoidectomy (2), and breast augmentation (1). In these 7 studies, there were a total of 17 different treatment arms with varying dosages of each medication. There was no difference in the proportion of patients avoiding opioid rescue in any of the treatment arms. Some of the treatment arms utilized Exparel doses that exceeded the FDA approved maximum dose and others utilized doses of conventional bupivacaine that are not considered to be therapeutically equivalent to comparable doses of Exparel so accurate comparisons for all endpoints cannot be made in regard to pain intensity scores.

Transversus abdomins plane Blocks (TAP blocks)

Definition: The transversus abdomins plane (TAP) local anesthetic block is an analgesic technique that has become increasingly popular over the last decade and involves the infiltration of local anesthetic in the plane between the internal oblique and transversus abdominis muscles.

TAP blocks utilizing conventional local anesthetics

Several studies have been published that have evaluated the use of conventional (un-encapsulated) local anesthetics via TAP blocks for various abdominal surgeries.

- Elective total abdominal hysterectomy: Carney and colleagues (RCT) evaluated 55 patients (ropivacaine 1.5 mg/kg TAP vs. placebo) and demonstrated reduced total morphine requirements in the first 48 post-operative hours as well as reduced post-operative visual analog scale (VAS) pain scores compared to placebo ($p < 0.001$).
- Major GYN or abdominal surgery: Sharma and colleagues evaluated (RCT) evaluated 60 patients (bupivacaine 75 mg TAP vs. standard care) and demonstrated reduced analgesic requirement in 24 hours ($P < 0.01$) and 48 hours post-operatively.
- Laparoscopic colorectal resections: Conaghan and colleagues evaluated 74 patients (levobupivacaine 100 mg TAP plus morphine PCA vs. morphine PCA) and demonstrated that patients receiving TAP blocks had a significant reduction in overall IV opiate use ($P = 0.03$; 31.3 mg vs. 51.8 mg) and showed a trend toward a shorter hospital stay (3 vs. 4 days; $P = 0.17$).
- Elective Laparoscopic Colorectal Surgery: Favuzza and colleagues evaluated 100 consecutive patients utilizing a laparoscopic guided TAP block (0.5 mg/kg bupivacaine) to evaluate LOS impact in conjunction with an enhanced recovery plan (ERP). The evaluation revealed that the overall median hospital stay was 2 days and the mean length of stay was 2.9 days. The authors concluded that the addition of a TAP block to an established ERP can reproducibly reduce length of stay to less than 3 days.
- Laparoscopic colorectal surgery: Keller and colleagues evaluated 200 patients (bupivacaine 75 mg TAP vs. standard care) and demonstrated a shorter LOS (2.6 days) than that demonstrated in 2 separate consecutive series of 1,000 laparoscopic colon procedures with a standardized enhanced recovery plan (3.7, 4.1 days) – performed at the same institution.
    - Keller et al, in a follow up randomized, double-blind controlled trial (79 patients) further evaluated the use of bupivacaine TAP block (0.5 ml/kg of bupivacaine 0.5% (max 30 ml) vs. 0.5 ml/kg of 0.9% normal saline (max 30 ml)) versus a placebo TAP block to evaluate post-operative pain and nausea/vomiting scores in post anesthesia care unit, opioid use, length of stay, and 30 day readmission rates. In the PACU, the TAP block group had significantly lower pain scores ($P < 0.01$) and used fewer opioids ($P < 0.01$) than the control group and post-op N/V scores were comparable ($P = 0.99$). Additionally, the TAP block group had significantly lower pain scores on post-op day 1 and throughout the study period ($P < 0.01$). No significant difference in post-op opioid use however were observed ($P = 0.65$). Although not statistically significant, patients treated with TAP block trended toward a reduced LOS (median 2 days vs. median 3 days; $P = 0.50$).

Additionally, a 2012 meta-analysis of 9 studies evaluating TAP blocks in adults undergoing abdominal surgery was published and evaluated the effect of TAP block on morphine requirements 24 hours after surgery. Secondary outcomes included the effect of TAP block on morphine use 48 hours after surgery, incidence of post-op nausea and vomiting (PONV) and impact on reported pain scores. A total of 413 patients were included (205 TAP block vs. 208 placebo). Cumulative morphine utilization was significantly reduced at 24 hours ($P = 0.002$; WMD = 23.71 mg) and 48 hours ($P < 0.0001$; WMD = 38.08 mg) in patients who received a TAP block. Additionally, the incidence of PONV was significantly reduced ($P = 0.003$; OR = 0.41). Due to differences in how the visual analog scores were reported between the studies a difference in pain scores did not reach statistical significance ($P = 0.2$) although a trend toward lower scores was observed in the TAP block treated patients.

TAP blocks utilizing Exparel

Only two manuscripts have been published regarding the use of Exparel for TAP blocks and both were only observational cohort studies which are summarized below.

- Elective laparoscopic colorectal resection: Keller and colleagues evaluated 25 experimental (Exparel) and 25 controls (standard care with no TAP block) to evaluate post-op pain and narcotic use, length of stay, and PACU pain scores. Patients receiving Exparel received significantly less intraoperative fentanyl ($P < 0.01$), lower initial ($P < 0.01$) and final PACU pain scores ($P = 0.04$), and shorter LOS (3 vs 4.1 days; $P = 0.04$). However, patients treated with Exparel TAP blocks did not result in lower opioid use or daily pain scores as compared to the standard care treatment group.
- Open abdominal hernia repair: Feierman and colleagues, conducted a 13 patient observational study (no comparator group) to evaluate pain scores and patient satisfaction. Mean VAS scores remained below ≤ 2.3 through 120 hours after infiltration. Ten patients required supplemental analgesia and median time to first use was 11 hours. At discharge and day 10, 54% and 62% of patients were "extremely satisfied" with postsurgical analgesia.

SUMMARY:

Overall, the data supporting the extended duration of effect for liposomal bupivacaine is based on placebo controlled trials utilized as a surgical site infiltration for treatment of bunionectomy and hemorrhoidectomy. Although Exparel was evaluated in comparison to placebo for up to 72 hours, the benefit (pain scores, opioid utilization) were only clinically relevant for the first 12 hours following administration. This data when critically analyzed draws into question the true extended duration of this therapy when compared to placebo or other comparative therapies. Furthermore, in the unpublished active control study outlined above (Exparel vs. un-encapsulated bupivacaine) demonstrated inferior performance of the liposomal bupivacaine formulation as compared to conventional bupivacaine. This all draws into question the true clinical benefit of Exparel and questions the manufacturer's claims of prolonged effects up to 72 hours.

Additionally, as demonstrated above, the utilization of local anesthetic TAP blocks (conventional local anesthetics) has shown to be a promising therapy for reducing post-operative opioid requirements, improved pain scores, and a trend toward reduced length of hospital stay. However, only two published manuscripts have evaluated the use of Exparel when utilized as a TAP block and both in a very limited number of patients. There is currently a lack of published evidence to suggest that Exparel provides superior efficacy over the utilization of conventional local anesthetics for TAP blocks.

More multi-centered trials with larger patient groups are needed to evaluate its efficacy. Until then, the advantage of liposomal bupivacaine over conventional local anesthetics is speculative.

COMPARATIVE COST:

Exparel	$315 per vial
Bupivacaine 0.5% (30 ml)	$1.19 per vial
Bupivacaine 0.25% (30 ml)	$1.14 per vial
Ropivacaine 0.5% (30 ml)	$5.96 per vial

Catholic Health Initiatives

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Introduction: CHI Medication Use and Evaluation (MUE) Committee

CHI MUE Purpose Statement

To engage a multidisciplinary group of national and market-based content experts to evaluate, approve, and promote medication therapies for use within "in-scope" care areas of CHI facilities (hospital-based services and locations). The committee will approve medications and criteria for use to achieve optimal effectiveness and value, considering efficacy, patient outcomes, patient safety, and total cost when approving medications.

Voting Members (24 Total)

- Co-chairs (2): Division CMO and National VP, Pharmacy Services
- Physicians (12 + Co-Chair=13 Total):
  - Pharmacy & Therapeutics (P&T) Physicians (8) – 1/Division (Exception: SE division has 2; 1 from Arkansas and 1 from Tennessee
  - National Service Line Physicians (4) – 1/Service Line (Orthopedics, Hospitalist, Oncology, Cardiovascular)
- Nursing (2 Total) - 1 Advance Practice Clinician and 1 Division CNO
- Pharmacy (8 + Co-Chair=9 Total):
  - 7 Division Directors (1/Division) and 1 Clinical Pharmacist

AdHoc Membership (Non-Voting)

Additional members will be engaged from areas such as Analytics, CNO or CMO (National), Communications, Finance, Informatics, ITS, Missions, National Pharmacy Informatics/Operations, and Supply Chain as needed.

Medication Formulary Categories

- MUE will assign each drug entity to one of the following categories
  - Formulary, unrestricted
  - Formulary, restricted
    - Restricted to certain clinicians
    - Restricted to certain diagnoses or conditions
    - Use subject to institutional approval process
    - Restricted by patient location of service (e.g. outpatient, critical care, etc.)
  - Non-formulary
- Market/Local P&T Committees may be more restrictive but not less

MUE Product Review Process Entry Pathways (same review process regardless of entry)

- Clinician Request
  - Market clinician submits request
- Proactive Product Selection for Review
  - Service Line, Pharmacy Clinical Council, MUE members
  - Review of existing formularies in organization to identify consistency and variance to prioritize opportunities

Local P&T Meetings

- Decisions from CHI MUE are presented to local P&T Committee by member of local P&T
- Local P&T possible actions:
  - Approve with no changes
  - Approve with more restrictions
  - Appeal the MUE decision
- Request an Exception to the MUE decision

Additional details are available in supporting CHI MUE Documents: CHI MUE (Current Documents)

CHI Memorial
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POLICY

Title: ANTIMICROBIAL STEWARDSHIP POLICY			
		Page 1 of 2	
Policy Number:		Date Last reviewed/Revised: 1/15	Valid Until: 1/18
Department(s) Affected:		Review Period: every 3 years	

PURPOSE:

The CHI Memorial Antimicrobial Stewardship Program (ASP) monitors appropriate use of antimicrobial agents and develops interventions to improve antimicrobial use across Glenwood and Hixson campuses. The goals of the ASP are to improve clinical outcomes while reducing unintended consequences of antimicrobial use for both individual patients and the broader clinical population of the Health System. This policy describes the structure, responsibilities and essential activities of the ASP.

PERSONNEL:

The core personnel include:

1. A Medical Director with expertise in infectious diseases. The Medical Director is responsible for co-direction of the ASP with the Clinical Pharmacist, development of antimicrobial stewardship policy and procedures, reporting antimicrobial utilization and other outcomes to quality committees and clinicians, identifying target areas for intervention, developing interventions to improve antimicrobial use, and interacting with clinicians to provide education and implement stewardship interventions.

2. A Clinical Pharmacist with expertise in infectious diseases and training in antimicrobial stewardship from a recognized professional organization. The Clinical Pharmacist is responsible for co-direction of the ASP with the Medical Director, developing guidelines for antimicrobial use, monitoring antimicrobial utilization, and conducting prospective audit and feedback of antimicrobial orders and making recommendations to prescribers to improve appropriateness of therapy.

Additional personnel include pharmacy clinical coordinator, clinical microbiologist, infection control member(s) and additional ASP pharmacists.

POLICY:

The ASP prioritizes collaboration with stakeholders, use of evidence-based best practices, and data tracking to promote appropriate antimicrobial use. Appropriate antimicrobial use includes timely therapy with the right agent, at the right dose, for the right duration, and avoidance of unnecessary therapy.

PROCEDURE:

A. Responsibilities:

In order to achieve the goals of the program, the ASP Medical Director, affiliated ASP Pharmacists, and other qualified ASP program staff have the following responsibilities with regard to oversight of antimicrobial therapy:

1. Identification and review of medical records for patients on antimicrobial therapy, and patients with positive microbiology findings in whom antimicrobial therapy may be indicated, but has not been initiated.

2. Provision of feedback to providers regarding antimicrobial therapy choices.

3. Documentation of antimicrobial therapy recommendations in the medical record in the form of clinical interventions.

4. Approval of restricted anti-infective agents.

5. Access to data reports on institutional antimicrobial use and ability to report these data to regulatory organizations and/or external benchmarking systems.

B. Core Activities:

The Medical Director, Clinical Pharmacist, Infection Control, and Microbiology collaborate with each other as well as seek stakeholder input to develop specific interventions and procedures according to the needs of the clinical populations served. Specific procedures are developed and updated on an ongoing basis. The following is an overview of the core activities of the ASP. The ASP may also initiate special projects that align with institutional goals.

1. Prospective Audit and Feedback:

Inpatient antimicrobial use is monitored prospectively to identify opportunities to improve therapy with regard to agent selection, dose, frequency, or duration. Feedback is given to prescribers with education and recommendations to modify therapy. Infectious Diseases consultation may also be recommended if the problem is deemed to be too complex for a focused recommendation. The frequency of audit and procedures for feedback to providers are determined by the ASP Medical Directors and Clinical Pharmacists.

2. Monitoring Antimicrobial Utilization:

The ASP monitors overall antimicrobial utilization and utilization of specific targeted antimicrobial agents using standard metrics. Utilization data are used for internal and external benchmarking, to identify target areas for intervention. Quality improvement activities, policies and interventions are implemented in a scientific/evidence-based manner towards the goal of improving antimicrobial utilization for inpatients.

3. Formulary Review, Restriction and Pre-Authorization:

The ASP Medical Director and ASP Pharmacists serve on the Antimicrobial Subcommittee. In this capacity, they participate in management of the antimicrobial formulary, including review of new agents for inclusion, review of dosing references, and modifications based on emerging evidence and/or institutional resistance patterns. They develop the annual institutional antibiogram and distribute it to clinicians with accompanying education. ASP personnel oversee implementation of Pharmacy and Therapeutics Policies regarding antimicrobial use, including oversight of restricted antimicrobial agents.

4. Guideline Development:

ASP personnel develop evidence-based guidelines, clinical pathways, and order sets for appropriate use of antimicrobial therapy for common infectious syndromes, oversee approval of guidelines and distribute guidelines to clinicians with accompanying education.

5. Education:

ASP personnel provide education to clinicians regarding trends in antimicrobial use and resistance, appropriate antimicrobial use, and management of common infectious syndromes. Education may take many forms including, but not limited to: presentations, distribution of written materials, and focused consultation on antimicrobial selection.

6. Regimen Optimization and Therapeutic Drug Monitoring:

ASP personnel collaborate with Prescribers and Pharmacy staff to implement dose optimization and therapeutic drug monitoring strategies for special circumstances, such as drug resistant infections, narrow therapeutic index antimicrobials, and/or patients receiving long term antimicrobial therapy.

C. Reporting:

The CHI Memorial ASP reports directly to the Pharmacy and Therapeutics Committee. Informational reports will also be provided to additional interested groups.

Key Contact: First Last, Title, Dept or Committee
Approved/Reviewed by: **List applicable** Councils, and leaders that have reviewed and/or signed in the approval process
Reference(s): **list as applicable**
Attachment(s): None or Attachment Title (if applicable) Note: forms can be hyperlinked rather than attached if available in Policy Manager.
Related Forms: Use Hyperlink (if applicable)
Date First Effective & (Revision/Review dates): 2/01 (7/06)
Distribution: MHCS Intranet

POLICY

Title: SEDATIVES/HYPNOTICS FOR SLEEP		Page 1 of 2
Policy Number: MM - 05410	Date Last Revised: 4/13	Valid Until: 4/16
Department(s) Affected: All Clinical Areas	Review Period: every 3 years	

OUTCOME:

Sedatives/hypnotics for sleep in hospitalized patients will be used safely and in an effort to reduce the risk of fall and injury, especially in the elderly population of patients.

POLICY:

1. No sedative/hypnotic will be administered for sleep to any patient 65 or greater. **Exceptions are limited to the following:**
    a. Receiving as a home medication (note item 5.b, 6)
2. **Physicians will not be called after office hours to request an order regarding sleep meds.**
3. All sleep medications must have a written order by physician.
4. All sleep medication included on physician standing order sets must have a check box (□) for physician to individually designate appropriateness for medication.
5. Zolpidem (Ambien®)
    a. The **maximum** Zolpidem (Ambien ®) dose is **5 mg** for any patient. This dose may not be repeated.
    b. Patients currently receiving as a home medication any dose greater than 5mg will only be provided 5mg maximum dosage.
6. Diphenhydramine (Benadryl®)
    a. **Only** patients currently receiving diphenhydramine as a home medication may continue to receive this medication as a sedative/hypnotic. Patients who do not take diphenhydramine as a home sedative/hypnotic will not be allowed to receive this medication as a sedative/hypnotic.
    b. The maximum Diphenhydramine (Benadry®) dose is 25 mg for any patient. This dose may not be repeated. Patients currently receiving as a home medication any dose greater than 25 mg will only be provided 25 mg maximum dosage.
7. Approved formulary therapeutic substitutions are listed below. A pharmacist will automatically interchange any non-formulary drug/dose to the formulary agent.

Drug/ Dose Written	Therapeutic Interchange
Ramelteon (Rozerem®) 8 mg	Melatonin ® 3 mg
Zaleplon (Sonata®) 5 mg	Zolpidem (Ambien®) 5 mg
Zaleplon (Sonata®) 10 mg	Zolpidem (Ambien®) 5 mg
Triazolam (Halcion®) 0.25 mg	Zolpidem (Ambien®) 5 mg
Eszopiclone (Lunesta ®) 1 mg	Zolpidem (Ambien®) 2.5 mg
Eszopiclone (Lunesta®) 2 mg	Zolpidem (Ambien®) 5 mg
Eszopiclone (Lunesta®) 3 mg	Zolpidem (Ambien®) 5 mg
Flurazepam (Dalmane®) 15 mg or 30 mg	Zolpidem (Ambien®) 5 mg
Estazolam (Prosom®) 1 mg or 2 mg	Temazepam (Restoril®) 15 mg

POLICY

Title:
SEDATIVES/HYPNOTICS FOR SLEEP

Policy Number:
MM - 05410

Temazepam (Restoril®) 7.5 mg	Zolpidem (Ambien®) 5 mg
Temazepam (Restoril®) 15 mg or 30 mg	Temazepam (Restoril®) 15 mg
Zolpidem CR (Ambien CR®) 6.25 mg or 12.5	Zolpidem (Ambien®) 5 mg

Key Contact: Patrick Ellis, Pharmacy
Reviewed by: Pharmacy & Therapeutics Committee, Nursing Professional Practice Council, Medical Executive Council
Reference(s):

1. Young, Julie, S., Bourgeois, James, A., Hilty, Donald, M., & Hardin, Kimberly, A. (2009). Sleep in Hospitalized Medical Patients, Part 2: Behavioral and Pharmacological Management of sleep Disturbances. *Society of Hospital Medicine, 4(1), 50-59*
2. Nagel, Corey, L., Markie, Megan, B., Richards, Kathy, C., & Taylor, Jan, L. (2003). Sleep Promotion in Hospitalized Elders. *MEDSURG Nursing, 12(5), 270-290*

Joint Commission Standard: Medication Management (MM)

Date First Effective/Revisions: 9/10, (12/11), (4/13)

Distribution: MHCS Intranet

Title: **MEDICATION ADMINISTRATION – TIMELINESS OF SCHEDULED MEDICATIONS**		
	Page 1 of 5	
Policy Number: MM-05455	Date Last reviewed/Revised: 1/16	Valid Until: 1/19
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. Investigational medications (administration time defined by the clinical research)
    h. 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:
        a. Antibiotics: Vancomycin, Tobramycin, Gentamicin, and Amikacin
        b. Anticoagulants: Therapeutic doses of oral and injectable anticoagulants. This excludes warfarin and prophylactic doses of injectable anticoagulants (enoxaparin 40 mg, fondaparinux 2.5 mg)
    C. Insulins: Rapid-, short-, or ultra-short-acting insulins are considered time-critical in relation to meal consumption time. Although scheduled dosing times are used for

insulin doses on eMAR, actual administration time should be based on meal delivery time and actual consumption of the meal. **Procedure:**

a. Time-critical scheduled medications will be designated on the eMAR with the label comment, ''Time-Critical Med''.
b. 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.
c. 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. Procedure:

a. 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.
b. 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. Use of Professional Judgment: Staff are expected to use their professional judgment in organizing and prioritizing patient care work-loads to assure that medications are delivered in a safe and timely manner. In exercising such judgment staff must take into account the following:

A. Complex nature and variability among medications; the indications for which they are prescribed; the clinical situations in which they are administered; and the needs of the patients receiving them

B. Prioritization of additional activities that may be required, in the case of particular drugs, such as vital sign assessment or the collection and review of blood work, to ensure safe and timely medication administration.

VI. 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

a. 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).
b. 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

a. 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

b. 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.

c. 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

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, 1500, 2100
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.

VII. 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**

a. Any early or late medication administration is to be documented at the time the medication was actually given.

b. 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**

a. Any missed medication dose is to be documented as ''not given.''

b. 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**

a. 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

b. Adherence to standard scheduled administration times is recommended whenever possible when rescheduling a medication dose.

c. The rescheduled dose may be documented as a ''non-scheduled'' dose on the eMAR.

G. **Adverse Outcomes**

a. 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

b. 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.

c. 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.

Key Contact: Michelle Denham RN, Pharmacy/Nursing Liaison
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)
Date First Effective/Revisions: 3/13 (11/15)
Distribution: MHCS Intranet

CHI MEMORIAL

PHARMACY FINANCIAL PRO FORMA: NUCALA

	Total							Per Case				
Payer	Cases	Mix	Days	Charges	Payments *	Direct Costs	Dir Contribution Margin	ALOS	Charges	Payments *	Direct Costs	Dir Contribution Margin
Commercial / Mgd Care	46	3.8%	0	$836,743	$436,741	$117,009	$319,732	0.0	$18,190	$9,494	$2,544	$6,951
Medicare	1,160	96.2%	0	$14,886,741	$2,865,616	$2,078,136	$787,480	0.0	$12,833	$2,470	$1,791	$679
	1,206	**100.0%**	**0**	**$15,723,484**	**$3,302,356**	**$2,195,144**	**$1,107,212**	**0.0**	**$13,038**	**$2,738**	**$1,820**	**$918**
Based upon the following patient population:						**Baseline per Patient:**			**$13,038**	**$2,738**	**$1,820**	**$918**
- FY15 - Dec FY16 Outpatients												
- Patients used Xolair						**Less:**						
- Charge Markup Factor	*300%*					XOLAIR 150 MG			$12,288		$1,716	
						Adjusted Baseline			**$750**		**$104**	
						Add:						
						NUCALA (MEPOLIZUMAB) 100 MG			$7,500		$2,500	
						Reimbursement remains as the same $ amount:			**$8,250**	**$2,738**	**$2,604**	**$134**