Pharmacy & Therapeutics Committee Meeting
Private Dining Room
October 10, 2013 7:00 a.m.

Agenda Items — Individual Responsible

1. Call to Order — Richard Pesce, MD

2. Approval of February, 2013 Minutes — Richard Pesce, MD

3. Therapeutic Interchanges and Formulary Decisions — Page
   A. Nesina® (alogliptin).....Patrick Ellis, Pharm.D…….....5
   B. Tivicay® (dolutegravir) 6
   C. Simponi Aria® (golimumab)…. .....…….Karen Babb, Pharm.D……...7
   D. Alpha-1 proteinase inhibitors (Prolastin®, Aralast®)…. .....……...8
   E. Kadcyla® (Ado-trastuzumab) .....Patrick Ellis, Pharm.D……...9
   F. Biosimilar medications - review.....10
   G. Tbo-Filgrastim ..... Darrin Majors, Pharm.D...11-12

4. Medication Safety
   A. ADR review ..... Patrick Ellis, Pharm.D.…13-14
   B. Antiemetic orders .....…15

5. MUE
   A. Argatroban .....Rachel Kile, Pharm.D.....16-17

6. Policy, Procedure & Protocols
   A. Argatroban, Bivalirudin – addition to existing policies…...Patrick Ellis, Pharm.D…….....
   B. Heparin therapeutic range – edits to weight based protocol…. 18
   C. Penicillin Allergy – surgery antibiotic administration .....……19
   D. IV to PO – policy updates…. .....Karen Babb, Pharm.D…..…20

7. Adjournment

Next Meeting will be December 12, 2013 at 7:00am in the Private Dining Room

CATHOLIC HEALTH INITIATIVES
Memorial Health Care System

PHARMACY AND THERAPEUTICS COMMITTEE

DATE: August 8, 2013 CALLED TO ORDER: 7:00 A.M.
LOCATION: Private Dining Room ADJOURNED: 7:45 A.M.

Members Present:			**Members Absent**:		**Guests**:
Richard Pesce, M.D.	Karen Babb, Pharm.D.	Keith Lockwitz, RN	David Dodson, M.D.	Brian Jones, RD, LDN	Rhonda Hanley, Student
Mark Anderson, M.D.	Diona Brown, RN,C.N.O.	Patrick Ellis, Pharm.D.	Nathan Chamberlain, M.D.	Don Jones, RPh	Rachel Kyle, Pharm D Resident
Allen Atchley, M.D.	Nan Payne, RN	Melissa Roden, RN	William Oellerich, M.D.	Beverly Slate, Supply Chain	Darrin Majors, Pharm D Resident
Samuel Currin, M.D.	Rodney Elliott, CPT	Sandy Vredeveld, DPh	Nathan Schatzman, M.D.		Sarah Smith, Pharm D Resident
Michael Stipanov, M.D	Patrick Hagan, Finance	Hannah Walker, RN	Elvie Smith, RN		Dori Neufeld, RD
	Lila Heet, Pharm.D.		Vickie Burger, Lab		
	John Jantz, Pharm.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 June 13, 2013 minutes were approved as submitted.		Complete
Therapeutic Interchanges and Formulary Decisions	The following medications were reviewed:		
	1. **Injectable Iron (non-dextran) Formulary Review** – The following products were reviewed: sodium ferric gluconate complex (Ferrlecit®), iron sucrose (Venofer®), and ferumoxytol (Feraheme®). All three products exhibit similar clinical efficacy and safety. Due to recent contract and pricing changes it was recommended to only utilize sodium ferric gluconate complex for inpatient use. Inpatient orders for all other non-dextran iron products will be automatically interchanged to a therapeutically equivalent dose of sodium ferric gluconate complex. All three products will remain on formulary for outpatient use at this time.	1. Approved	Complete
	2. **Rh(D) Immune Globulin Formulary Review: WinPho® SDF vs. Rhophylac®** – A review of the available Rh(D) Immune Globulin products indicates similar therapeutic efficacy and safety and both products have indications for both ITP and suppression of Rh isoimmunization during pregnancy. Rhophylac® offers a significant pricing advantage and due to similar efficacy it was recommended to remove WinRho® from formulary and stock only Rhophylac® for patients needing Rh(D) immune globulin therapy.	2. Approved	Complete
	3. **Adcirca® (tadalafil) –** Oral phosphodiesterase inhibitor indicated for the treatment of pulmonary arterial hypertension. Tadalafil exhibits similar efficacy to Revatio® (sildenafil) although it is significantly more expensive per day of therapy than tadalafil. It was recommended to not add tadalafil to formulary and sildenafil will be substituted via a therapeutic interchange when tadalafil is ordered.	3. Therapeutic interchange approved	Complete
	4. **Edarbi® (azilsartan) –** Angiotensin receptor blocker indicated for the treatment of hypertension. It was recommended to add azilsartan to formulary to provide continuity of care for patients admitted to the hospital who take this medication as a home therapy. The angiotensin receptor blocker class of medications will be reviewed again as more medications become generically available for the possibility of utilizing a formulary interchange in the future.	4. Approved	Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	5. **Cinryze® (C1 inhibitor) –** Injectable medication indicated for routine prophylaxis against angioedema attacks in patients with hereditary angioedema. Annual cost of ~$600,000 annually per patient. Due to the extreme cost, it is recommended to designate this agent non-formulary for inpatient use and for use as an outpatient therapy on a case by case basis ONLY pursuant to insurance pre-approval and finance review to ensure reimbursement available.	5. Approved for outpatient use on a case-by-case basis only.	Complete
	6. **Rapaflo ® (silodosin) –** Alpha antagonist indicated for treatment of signs/symptoms of BPH. Demonstrates similar efficacy and safety to current formulary agent Flomax® (tamsulosin) although significantly more expensive per day of therapy as compared to tamsulosin. It was recommended to not add tamsulosin to formulary and substitute a therapeutically equivalent dose of tamsulosin via a therapeutic interchange when silodosin is ordered.	6. Therapeutic interchange approved	Complete
	7. **Exparel® (bupivacaine iposomal)** – Trial still ongoing evaluating this therapy for use as an intercostal nerve block s/p thoracic surgery with trial results expected by the October meeting. Committee reiterated to not allow any additional use of Exparel® at this time and future requests will be evaluated on a case by case basis as requested.	7. Review on case-by-case basis. All requests to go through P & T committee for approval.	Pending
Medication Safety	• **Promethzaine IV –** Work still ongoing to further standardize antiemetic orders on standing orders to help minimize the risk of tissue injury/phlebitis in patients requiring extended therapy with IV promethazine.	Information	Pending
	• **Medication Error Review –** 6 month summary. ◦ 332 Errors reported ◦ 187 Reached Patient ◦ 1 Serious Safety Event ◦ 74% did not cause harm or additional monitoring ◦ Top 3 medication errors: Insulin, Heparin and Vancomycin ◦ Top therapeutic classes: Anticoagulants, Opiate Agonists, Antimicrobials, Insulins ◦ Action Plans and Improvements were reviewed.	Information	Complete
	• **Ketoconazole FDA Warning –** A recent FDA warning was issued advising against the use of ketoconazole if at all possible due to risk of liver injury, adrenal insufficiency and serious drug interactions. Ketoconazole is rarely used at MHCS as an antifungal but it is sporadically used off label as treatment for patients with advanced prostate cancer due to its ability to reduce androgen production. Dr. Currin felt that a limited supply of Ketoconazole should be kept on formulary for patients needing this medication as an adjunct therapy for prostate cancer. The committee agreed and recommended to designate Ketoconazole as non-formulary for all other indications.	Formulary restrictions approved	Complete
Medication Use Evaluation	• **Monurol® (Fosfomycin) –** An evaluation was performed to examine the use of fosfomycin as an alternative antimicrobial agent for the treatment of ESBL cystitis. The data suggests that when used to treat patients with complicated ESBL cystitis it is a viable oral alternative to conventional therapies such as carbapenems with comparable success rate.	Information	Complete
Policy and Procedure	• **Bivalirudin Weight Based Protocol (HIT) –** A draft protocol was presented to allow the use of bivalirudin as an alternative to argatroban in patients with HIT or other intolerance to heparin with indications for full anticoagulation. Recent data has demonstrated that bivalirudin can safely and effectively be used for the treatment of HIT and it is only partially eliminated by the kidneys (20%) which can allow it to be safely used in patients with hepatic or renal failure. The protocol will be a	Approved	Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	nurse driven sliding scale nomogram that will function similarly to the existing Argatroban protocol (goal PTT: 55-75). Pharmacy will monitor the efficacy and safety of the protocol once implemented. The draft protocol was approved and no additions/edits were suggested. • **Antimicrobial Surgical Prophylaxis Guidelines –** The Infectious Disease Society of America recently published updated antimicrobial surgical prophylaxis guidelines. The most significant of these changes involves a larger emphasis on weight based dosing than previous recommendations with cefazolin doses up to 3 gm and weight based dosing for vancomycin and gentamicin. Dr. Anderson and the Antimicrobial Stewardship Committee are developing a standardized document with the recommended changes to the hospital's current standards of practice while also utilizing the hospital's antibiogram data. These recommendations will be reviewed with the various medical specialties prior to changes being made to current practices. • **Look-Alike, Sound-Alike Medications Policy –** It was recommended to add Ketamine - Keppra to the policy in response to recent errors involving these medications. Action plan and added safety measures will be implemented and these were discussed and reviewed.	Information Approved	Pending Complete
Nutrition Support Team	**Diet Order Policy –** Dori presented an update to the Diet Orders Policy related to dietician management of tube feedings. An order for dietician to "manage", "TF per dietician", etc. will now be interpreted as an order to manage and/or change the formula, strength or rate of the tube feeding without further physician order. If a practitioner orders tube feeding goal per dietician, the dietician will write the order for the tube feeding goal, but not take over continued management of the feeding unless otherwise ordered.	Approved	Complete

There being no further business, the meeting was adjourned at 7:45 A.M. The next P&T meeting is October 10, 2013.

Respectfully submitted,

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

Approved by,

Richard Pesce, M.D. Chairman

SUMMARY REVIEW

GENERIC NAME: ALOGLIPTIN

PROPRIETARY NAME: *Nesina* (Takeda)

INDICATIONS: Alogliptin is indicated for use as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It can be used as monotherapy or in combination with other antidiabetic medications, including metformin, sulfonylureas, thiazolidinediones, or insulin.

CLINICAL PHARMACOLOGY: Alogliptin is a selective dipeptidyl peptidase-4 (DPP-4) inhibitor. DPP-4 inhibitors lower blood glucose by preventing the breakdown of glucagonlike peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, thus prolonging the activity of these peptides.

PHARMACOKINETICS: Following oral administration, peak plasma concentrations are reached within 1 to 2 hours. Oral bioavailability is approximately 100%. Alogliptin is primarily excreted renally. Approximately 60% to 80% of the administered dose is excreted unchanged in the urine within 24 to 72 hours. The pharmacokinetic parameters of alogliptin are altered in patients with renal impairment and drug concentrations are increased in patients with mild, moderate, and severe renal impairment.

ADVERSE REACTIONS: Adverse reactions that occurred in at least 4% of patients treated with alogliptin and with more frequency with alogliptin than placebo were nasopharyngitis, headache, and upper respiratory tract infection.

DRUG INTERACTIONS: Alogliptin is primarily renally excreted, and cytochrome P450 (CYP-450)–related metabolism is negligible.

DOSING: The recommended dosage of alogliptin is 25 mg once daily with or without food.
CrCl > 60 ml/min – no adjustment necessary
CrCl 30-59 ml/min – 12.5 mg ONCE daily
CrCl < 30 ml/min or dialysis – 6.25 mg ONCE daily

PRODUCT AVAILABILITY: Alogliptin received Food and Drug Administration approval on January 25, 2013. It is available as 6.25, 12.5, and 25 mg tablets.

CONCLUSION: Alogliptin is an addition to the DPP-4 inhibitor class of drugs for the treatment of patients with type 2 diabetes. It is intended to be used as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. It can be used as monotherapy or in combination with other antidiabetic agents, including metformin, pioglitazone, sulfonylureas, and insulin; it was approved simultaneously for use as a single-agent product and in combination dosage forms with metformin and pioglitazone. All of the DPP-4 inhibitors are effective in lowering blood glucose levels and improving the hemoglobin A_{1c}, and all can be given once daily without regard to meals. The acquisition cost for each of the available agents is also very comparable with no significant cost difference currently exists.

Currently a therapeutic interchange is in place for the other available DPP-4 inhibitors (sitagliptin, linagliptin, saxagliptin) in which the other DPP-4 inhibitors are converted to a therapeutically equivalent dose of sitagliptin. It is recommended to add alogliptin to the exiting therapeutic interchange as indicated below.

ORDERED	SUBSTITUTION
Linagliptin (Tradgenta®) 5 mg DAILY	Sitagliptin (Januvia®) CrCl > 50 ml/min → 100 mg DAILY CrCl 30-50 ml/min → 50 mg DAILY CrCl < 30 ml/min → 25 mg DAILY
Saxagliptin (Onglyza®) 5 mg DAILY	Sitagliptin (Januvia®) 100 mg DAILY
Saxagliptin (Onglyza®) 2.5 mg DAILY	Sitagliptin (Januvia®) CrCl 30-50 ml/min → 50 mg DAILY CrCl < 30 ml/min → 25 mg DAILY
Alogliptin (Nesina®) 25 mg DAILY	Sitagliptin (Januvia®) 100 mg DAILY
Alogliptin (Nesina®) 12.5 mg DAILY	Sitagliptin (Januvia®) 50 mg DAILY
Alogliptin (Nesina®) 6.25 mg DAILY	Sitagliptin (Januvia®) 25 mg DAILY

SUMMARY REVIEW

GENERIC NAME: DOLUTEGRAVIR

PROPRIETARY NAME: Tivicay (ViiV Healthcare)

INDICATIONS: Treatment of HIV infection, in combination with other antiretroviral agents, in adults and adolescents.

CLINICAL PHARMACOLOGY: Dolutegravir is an HIV-1 integrase strand transferase inhibitor and is the second drug of this class to be approved by the FDA with the other agent being Isentress (raltegravir). Dolutegravir has exhibited binding differences that enable it to form strengthened interactions with viral DNA compared with raltegravir, as well as an ability to adjust its position and conformation in response to structural changes in the active sites of raltegravir-resistant integrase. In addition, it has displayed slower dissociation from wild-type and integrase-inhibitor resistant integrase-DNA complexes than raltegravir and elvitegravir.

PHARMACOKINETICS: Dolutegravir excretion is primarily in the feces (approximately 64% of the dose) and to a lesser extent in the urine (approximately 32% of the dose). Less than 1% of the dose is excreted unchanged in the urine. Metabolism is predominantly related to glucuronidation and thus dosing adjustments are not necessary for patients with mild to moderate hepatic or renal impairment.

ADVERSE REACTIONS: Adverse events reported most frequently in clinical trials were nausea, diarrhea, headache, fatigue, asthenia, nasopharyngitis, insomnia, dizziness, abnormal dreams, pyrexia, and depression.

DRUG INTERACTIONS: No significant drug interactions although dolutegravir should be taken 2 hours before or 6 hours after taking cation containing antacids or laxatives, sucralafate, oral iron supplements, oral calcium supplements, or buffered medications.

DOSING: 50 mg ONCE daily*
** dose adjustment to 50 mg TWICE daily for patients also taking potent inducers of dolutegravir metabolism (efavirenz, fosamprenavir/ritonavir, rifampin, etc.) and for patients with confirmed or suspected drug resistance.*

PRODUCT AVAILABILITY & COST: FDA approved – August 2013; Cost: $37.56 per day of therapy

CONCLUSION: Dolutegravir is the second integrase inhibitor approved for treatment of HIV infection that offers the advantage of ONCE daily dosing as compared to raltegravir.

It is recommended to add dolutegravir to the hospital formulary in order to provide continuity of care for patients who take this medication as a home therapy.

SUMMARY REVIEW

GENERIC NAME: GOLIMUMAB INJECTION

PROPRIETARY NAME: *Simponi Aria* (Centocor)

INDICATIONS: Golimumab is indicated for use in combination with methotrexate in the treatment of adults with moderately to severely active rheumatoid arthritis.

Simponi Aria is an IV formulation of golimumab that was recently (July 2013) approved by the FDA. The subcutaneous administration formulation (Simponi) has been FDA approved since 2009. The new IV formulation is only indicated for treatment of RA whereas the SQ formulation is also indicated for other indications as well (ankylosing spondylitis, psoriatic arthritis, ulcerative colitis).

CLINICAL PHARMACOLOGY: Golimumab is a monoclonal antibody with human-derived antibody variable and constant regions against tumor necrosis factor (TNF) alpha. It neutralizes the biological activity of TNF alpha by binding to it and blocking its interaction with cell surface TNF receptors thereby decreasing TNF associated inflammation and immune responses. Simponi Aria is an IV formulation of golimumab that was recently (July 2013) approved by the FDA. The subcutaneous administration formulation (Simponi) has been FDA approved since 2009.

PHARMACOKINETICS: No direct pharmacokinetic data are available comparing 2 mg/kg (IV administration) and the 50 mg subcutaneous administration of the conventional Simponi® formulation. No dosage adjustments are required for patients with hepatic or renal disease.

ADVERSE REACTIONS: The most common adverse reactions, occurring in more than 5% of golimumab-treated patients, included upper respiratory tract infection, nasopharyngitis, and injection-site reactions. Less frequently reported adverse reactions included liver enzyme elevations and new-onset or worsening psoriasis.

DRUG INTERACTIONS: Live vaccines should not be given to patients receiving golimumab therapy.

DOSING: 2 mg/kg IV infusion over 30 minutes at weeks 0 and 4, then every 8 weeks.

COST:
$1102.51 per 50 mg vial; Average annual cost (80 kg patient) - $36,366 per year

SUMMARY: Simponi Aria was requested to be considered for formulary addition by Dr. Richard Brackett as he feels that this medication would be a beneficial treatment option for some patients with RA.

The IV formulation of golimumab offers an alternative route of administration although the cost (depending on patient weight) can be significantly greater than that of the SQ formulation when annual average expense per patient is taken into consideration.

Since this medication has just recently been added to the market, there is currently not a specific HCPCS “J” code to be utilized for outpatient reimbursement. After discussing this with representatives from our finance department it is their preference to not add this or other non-chemotherapy outpatient therapies to formulary until a medication specific “J” code is available in order to guarantee reimbursement. Therefore it is recommended to not add this agent to the outpatient formulary until a drug specific HCPCS code is assigned by CMS.

Alpha-1 Proteinase Inhibitor (Aralast®, Prolastin®)
Formulary Review

Background:
Aralast® and Prolastin® are both IV preparations used to inhibit serine proteases such as neutrophil elastase, which is capable of degrading protein components of the alveolar walls and which is chronically present in the lung. Patients with alph-1 proteinase inhibitor deficiency have an imbalance in the anti-neutrophil elastase protection. This imbalance allows unopposed destruction of the connective tissue framework of the lung parenchyma.

Both products are indicated for maintenance therapy in adults with emphysema due to alpha-1 proteinase inhibitor deficiency. These products are dosed ONCE weekly via IV administration.

Product Availability:
Aralast® and Prolastin® are both distributed through a direct distribution process on a patient specific basis. Once insurance authorization is obtained by the drug company the medication is then shipped to the patient's home, doctor's office, local infusion center, or any other location chosen by the patient.

Neither product is available for direct purchase through any of the pharmacy's medication distributors and thus the hospital is unable to bill for the drug if administered in the hospital's infusion center.

Conclusion & Recommendation:
In the past we have treated 2-3 patients (some long term) in our outpatient infusion center that required this therapy and requested to have their infusions at our infusion center with the last patient being treated in 2008. Recently we had a new request from a patient to have their Prolastin® administered at our outpatient infusion center. Due to the inability to bill for the medication and the issues related to purchasing the medication as explained above, it was decided to not accept this patient for Prolastin® administration at our facility.

It is the recommendation to the committee to consider removing these agents from formulary and no longer accept future patients requesting the administration of these therapies at MHCS infusion centers.

SUMMARY REVIEW

GENERIC NAME: ADO-TRASTUZUMAB EMTANSINE (Trastuzumab-DM1)

PROPRIETARY NAME: *Kadcyla* (Genentech)

INDICATIONS: Ado-trastuzumab emtansine is approved for treatment of patients with human epidermal growth factor receptor 2 (HER2)–positive, metastatic breast cancer who have received prior treatment with Herceptin® (trastuzumab) and a taxane, separately or in combination.

CLINICAL PHARMACOLOGY: Ado-trastuzumab emtansine is an antibody drug conjugate. The trastuzumab is linked to DM1, a small molecule microtubule inhibitort, using a stable linker. The stable linker is designed to keep DM1 attached to trastuzumab until taken up by a HER2 positive cell. Its pharmacologic effects are the result of 2 strategies: the anti-HER2 activity from trastuzumab and the intracellular activity of DM1. The antibody drug conjugate remains intact until it is transported into the cytoplasm through endocytosis. Once inside, it is designed to destroy the cell by releasing the DM1 inside the cell.

PHARMACOKINETICS: Ado-trastuzumab emtansine is a prodrug and its metabolism is predominantly secondary to hepatic clearance (CYP3A4) although no clinically meaningful effect on medication exposure was observed in patients with hepatic impairment.

ADVERSE REACTIONS: The most common adverse reactions (frequency greater than 25%) were fatigue, nausea, musculoskeletal pain, thrombocytopenia, headache, increased transaminases, and constipation. Serious reactions: hepatotoxicity (possibly fatal), pulmonary toxicity (pneumonitis), infusion related hypersensitivity reactions, and neurotoxicity.

BLACK BOX WARNINGS (hepatotoxicity, cardiac toxicity, emryo-fetal toxicity):

- Do not substitute ado-trastuzumab for or with trastuzumab
- Hepatotoxicity, liver failure and death have occurred in Kadcyla® treated patients. Monitor hepatic function prior to initiation and prior to each dose. Institute dose modifications or permanently discontinue as appropriate.
- Reduction in LVEF may develop during treatment and LVEF should be assessed prior to initiation of therapy.
- Can cause fetal harm and should be avoided in pregnancy.

DRUG INTERACTIONS: No formal drug-drug interaction studies have been conducted although concomitant administration with strong 3A4 inhibitors should be avoided (ketoconazole, clarithromycin, etc.).

DOSING: 3.6 mg/kg given as an IV infusion every 3 weeks (21 day cycle) until disease progression or unacceptable toxicity.

COST:
$2773.57 per 100 mg vial; Average cost per treatment (80 kg patient) - $8320

CONCLUSION: Ado-trastuzumab was requested to be added to formulary by Dr. Darryl Johnson. Ado-trastuzumab emtansine is currently one of two antibody drug conjugate medications that is currently on market in the U.S. The phase 3 results have shown improved progression-free survival and 1-year survival in patients treated with ado-trastuzumab emtansine compared with those treated with lapatinib plus capecitabine therapy in patients previously treated with trastuzumab and a taxane chemotherapy (median progression free survival: 9.6 months vs. 6.4 months). A more recent study has also shown that Ado-trastuzumab also showed longer delay in disease progression in comparison to patients treated with a combination of Herceptin (trastuzumab) and other chemotherapy drugs (median progression free survival: 6.2 months vs. 3.3 months).

It is recommended to add this agent to formulary for the above described clinical indications.

Biosimilars

What is a biosimilar?

Biologic medications are medicines whose active ingredients are or are derived from proteins (such as growth hormone, insulin, antibodies) and other substances, and are produced by living organisms (such as cells, yeast and bacteria), rather than by chemical reactions. They are larger and more complex than chemically-synthesized smaller molecule medicines. This complexity makes the full characterization of biotherapeutic medicines particularly difficult.

The Biologics Price Competition and Innovation Act (BPCI) defines biosimilar or biosimilarity as "a highly similar biological product to the originator's biopharmaceutical notwithstanding minor differences in clinically inactive components and where there are no clinically meaningful differences between the biological product and the originator's product in terms of safety, purity and potency."

The BPCI Act states that the biological product must be proven to be biosimilar to a reference product based on data derived from analytical, animal, and clinical studies.
Additionally, the biosimilar product and reference product must utilize the same mechanism or mechanisms of action for the condition or conditions of use prescribed, recommended, or suggested in the proposed labeling, but only to the extent the mechanism or mechanisms of action are known for the reference product; and the proposed biosimilar product have the same route of administration, dosage form, and strength as the reference product.

Biosimilars are 'similar' but not identical versions of their innovative biological medicine of reference whose patents have expired.

Because biologics are complex products produced by living systems, they will inherently exhibit some physiochemical differences in addition to the varying production processes that will also modify the products (e.g., purification methods), and therefore biosimilars can be close or "similar" to the innovator products but will not be identical.

Minor differences are allowed in clinically inactive components as long as no clinically meaningful differences exist between the proposed biosimilar and the reference product with regard to safety, purity, and potency (presumably pharmacokinetics, pharmacodynamics, clinical safety, and efficacy).

Generic small-molecule drugs can be replicated in an exact way so that they are atomically identical to their reference drug. They are derived from structurally simple chemical compounds with smaller molecular weight compared to biological medications. Therefore, because generic versions of small-molecule drugs are completely identical, they can be manufactured, marketed, and used in clinical practice with relative ease compared with biosimilar products.

Regulatory Background

The BPCI Act establishes an abbreviated approval pathway for an applicant to demonstrate their drug's biosimilarity to and/or interchangeability with an FDA approved innovator's reference biologic medication. However, a legislative pathway for biosimilars is still being defined.

TBO-filgrastim is not a biosimilar but rather a "competitive biologic" and unlike our common generic drugs, it is not an interchangeable product. It was approved by the FDA through a biologics license application (like Neupogen), on the basis of comparison with placebo. Safety and efficacy studies demonstrated both superiority over placebo (i.e., as a new molecular entity) and comparability to Neupogen.

Europe has a legislative pathway for biosimilars and tbo-filgrastim (marketed as tevagrastim) was approved as a biosimilar of Neupogen.

SUMMARY REVIEW

GENERIC NAME: TBO-FILGRASTIM

PROPRIETARY NAME: Granix (Teva)

INDICATIONS:
TBO-filgrastim is FDA approved for the reduction in the duration of severe neutropenia in patients with non-myeloid malignancies receiving anti-cancer agents associated with a clinically significant incidence of febrile neutropenia.

CLINICAL PHARMACOLOGY:
TBO-filgrastim is a human granulocyte colony-stimulating factor (G-CSF) produced by recombinant DNA technology using the bacterium strain E. coli K802. TBO-filgrastim binds to G-CSF receptors and stimulates proliferation of neutrophils.

PHARMACOKINETICS:
In healthy subjects, the absolute bioavailability of 5 mcg/kg subcutaneous tbo-filgrastim was 33%. The median time to maximum concentration was between 4 to 6 hours and the median elimination half-life was between 3.2 to 3.8 hours.

COMPARATIVE EFFICACY:
The efficacy of tbo-filgrastim at increasing the ANC in neutropenic patients following chemotherapy has been established previously. Subsequent studies were predicated on establishing bioequivalence between filgrastim and tbo-filgrastim.

A randomized crossover study, conducted in healthy volunteers, compared tbo-filgrastim with filgrastim at two doses (5 mcg/kg/day and 10 mcg/kg/day). Serum G-CSF levels were measured by ELISA for 48 hours following injection, and the ANC was measured 96 hours after injection. The bioequivalence threshold was met and side effects were comparable for the two drugs.

A randomized study conducted with 92 patients being treated for non-Hodgkin's lymphoma, compared 5 mcg/kg of either tbo-filgrastim or filgrastim daily for 5 to 14 days. No statistical differences were found in the mean duration of severe neutropenia (0.5 days in the tbo-filgrastim group and 0.9 days in the filgrastim group) or the incidence of febrile neutropenia (11.1% in the tbo-filgrastim group and 20.7% in the filgrastim group). Side effects were comparable between the groups.

A randomized, controlled trial of tbo-filgrastim was conducted in 348 patients being treated with docetaxel/doxorubicin chemotherapy for breast cancer. Patients received 5 mcg/kg of tbo-filgrastim, filgrastim, or placebo daily for 5 to 14 days. Found no statistical difference in mean duration of severe neutropenia between tbo-filgrastim and filgrastim (1.1 days in each group). Found statistical difference mean duration of severe neutropenia between tbo-filgrastim and placebo (1.1 days vs. 3.9 days, respectively). Mean ANC nadir was 0.7 109/L for both tbo-filgrastim and filgrastim and 0.2 109/L in the placebo group. Mean time to ANC recovery was 8 days in the tbo-filgrastim group, 7.8 days in the filgrastim group and 14 days in the placebo group. Incidence of febrile neutropenia was 12.1% in the tbo-filgrastim group, 12.5% in the filgrastim group, and 36.1% in the placebo group. Side effects were comparable between tbo-filgrastim and filgrastim.

A randomized study, conducted in 240 patients with either small cell or non-small cell lung cancer being treated with platinum-based chemotherapy, compared 5 mcg/kg of either tbo-filgrastim or filgrastim for 5 to 14 days. Mean duration of severe neutropenia was 0.5 days in the tbo-filgrastim group and 0.3 days in the filgrastim group and thus demonstrated equivalence. The incidence of febrile neutropenia was not significantly different between the two groups and the side effects profiles were comparable.

ADVERSE REACTIONS:
Most subject complaints with regard to the side effects of tbo-filgrastim involve musculoskeletal pain.

CONTRAINDICATIONS:
No published contraindications with the use of tbo-filgrastim.

WARNINGS AND PRECAUTIONS:
Same as innovative biological medicine of reference.

DRUG INTERACTIONS:
No formal drug interaction studies with tbo-filgrastim have been performed.

However, the following DDI have been documented with Neupogen and thus monitored when given concurrently with tbo-filgrastim:
Vincristine - severe peripheral neuropathy. Severity: Major
Topotecan - prolonged duration of neutropenia. Severity: Major
Lithium – greater than expected increase in WBC count. Severity: Moderate

DOSING:
The recommended dose of tbo-filgrastim is 5 mcg/kg per day administered as a subcutaneous injection. The first dose of tbo-filgrastim should not be administered within 24 hours before or after myelosuppressive chemotherapy.

PRODUCT AVAILABILITY:
TBO-filgrastim was approved in an original biologic license application (BLA). It is not a biosimilar but a "competitive biologic." It is a non-originator biologic that is molecularly similar to the originator biologic, Neupogen.

Projected launch date is November 10th, 2013 with availability in December 2013.

Dosage Forms and Strengths:
300 mcg/0.5 mL in single-use prefilled syringe
480 mcg/0.8 mL in single-use prefilled syringe

Projected savings based on previous FY usage:
20% savings - $20,753.56
30% savings - $31,130.34

RECOMMENDATIONS:
In discussion with a few of Memorial's oncologists, it is reasonable to substitute tbo-filgrastim for filgrastim as a cost savings initiative as long as there is similar bioequivalence, side effects, and neutrophil recovery (particularly in hematologic malignancies). The data discussed above was in support of all three of these stipulations.

Recommend adding tbo-filgrastim to the formulary as soon as it becomes commercially available in the United States. There have been adequate, well-designed studies to determine that the therapeutic effect of tbo-filgrastim is equivalent to the therapeutic effect of the same dose of filgrastim. Additionally, the drug has been used successfully in Europe since 2009. Current projections indicate that tbo-filgastrim is likely to enter the market with a price 30% below the cost of Neupogen. Switching to tbo-filgrastim would lead to significant savings for the health system while maintaining our standard of patient care.

Adverse Drug Reaction Summary
4th Quarter (FY13) April-June 2013

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.

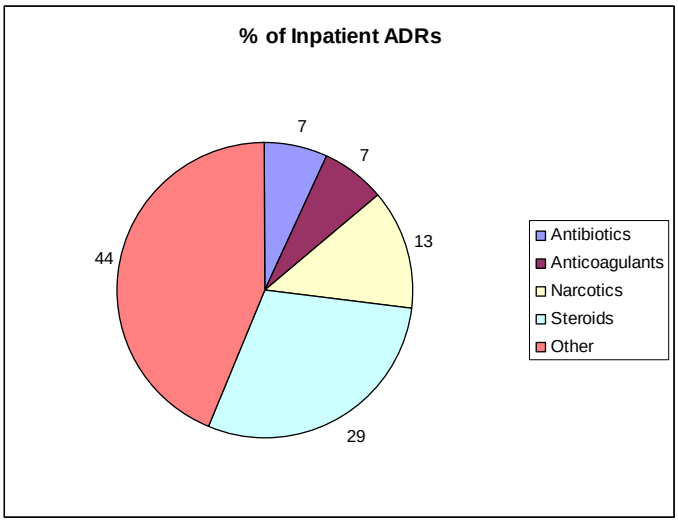
Category 3: A serious or rare ADR which has abnormal characteristics compared with published reports of the reaction (e.g. heparin induced platelet aggregation resulting in limb amputation). ADR's from this category should be reported to the manufacturer and/or the FDA (MedWatch or the Vaccine Adverse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

Inpatient: 192 (47%)
Prior to hospitalization: 221 (53%)
Total: 413

Category 1: 307
Category 2: 105
Category 3: 1

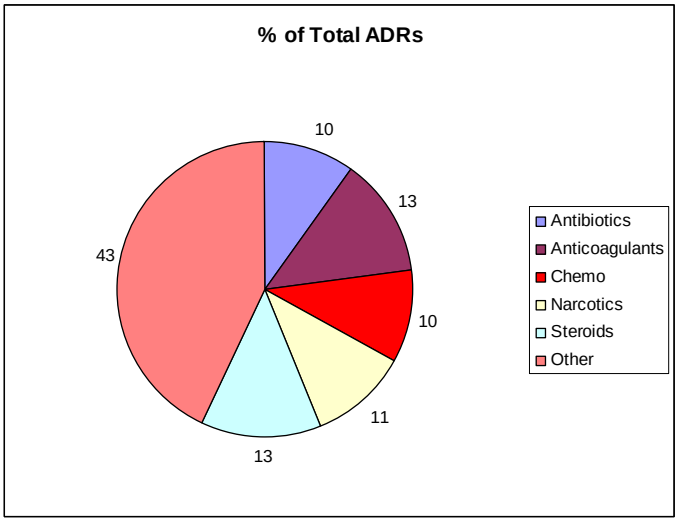
Category 3 to be discussed:
62 year old patient who developed acute kidney injury 48 hours following initiation of Colistin therapy for multi-drug resistant *Pseudomonas*. Following the kidney injury the patient also developed a decline in mental status with subsequent seizures and progressively labored respirations which ultimately required hemodialysis to assist with the removal of the cefepime. Due to minimal recovery the patient was eventually transitioned to comfort measures and eventually passed away.

Inpatient ADRs:



Antibiotics: 7% with Bactrim® contributing to 3%. Reactions included nausea, vomiting, rash, and CNS issues.
Anticoagulants: 7% with warfarin contributing to 60%. Reactions included hematoma, GI bleed, and hematuria.
Narcotics: 13%. Reactions included over sedation, hallucinations, confusion, nausea, constipation, and itching.
Steroids: 29%. Most common reaction was hyperglycemia.

Total ADRs:



Antibiotics: 10% with 23% of those being Bactrim®
Anticoagulants: 13% with 69% being Warfarin
Chemo: 10%
Narcotics: 11%
Steroids: 13%

Antiemetic Orders

Examples of Existing Antiemetic Orders:

Nausea:
☑ Ondansetron (Zofran) 4mg IV q 4 hr prn nausea and 30 minutes to 1 hour prior to meals as needed.
If nausea persists or vomitting occurs, Promethazine (Phenergan) 6.25mg IV Q 4 hrs PRN.

NAUSEA AND VOMITING:
☐ Ondansetron (Zofran) 4 mg oral dissolving tablet SL Q 4 hrs PRN - mild
☐ Ondansetron (Zofran) 4 mg IV Q 4 hrs PRN - moderate
☐ Ondansetron (Zofran) 8 mg IV Q 4 hrs PRN - severe
If nausea continues or vomiting occurs, give Promethazine (Phenergan) 6.25 mg IV Q 4hrs PRN. May repeat x 1 in 30 minutes if necessary.

Proposed Standard Antiemetic Orders:

- Ondansetron (Zofran) 4 mg oral dissolving tablet SL Q 4 hrs PRN – MILD
  Ondansetron (Zofran) 4 mg IV Q 4 hrs PRN – MODERATE
- MODERATE to SEVERE
  Promethazine (Phenergan) 6.25 mg IV Q 4 hrs PRN. May repeat x 1 in 30 minutes if necessary. IV Phenergan to not exceed 48 hrs unless administered via central line. Prochlorperazine (Compazine) 5 mg IV Q 4 hrs PRN if IV therapy still needed beyond 48 hrs.

Argatroban Use Evaluation
Memorial Health Care System
October 2013

Data from patients receiving argatroban for prophylaxis and treatment of thrombosis associated with heparin-induced thrombocytopenia (HIT) was evaluated to determine if initial infusion rates of 2 mcg/kg/min were consistently leading to supratherapeutic PTT values.

Methods

All patients receiving argatroban from September 2012 through August 2013 were included in this evaluation (28 patients).

Data collected: argatroban start date/time, argatroban stop dates, initial infusion rate, baseline and subsequent PTT values while on argatroban, accuracy of PTT draws according to current protocol, timing and accuracy of argatroban rate changes according to current protocol, hours and number of rate adjustments to achieve therapeutic PTT.

Results

	Mean value
Initial infusion rate	1.2 mcg/kg/min
# Hours to therapeutic PTT value	**34.1** hours
% Total therapeutic PTT values	51%
% Rate adjustment errors	**56%**

*Therapeutic PTT defined as 2 consecutive PTT readings within goal range 55-75 seconds

- Average length of therapy was 6 days.
- Initial infusion rate was unknown in 4 patients.
- Ten patients were initiated on 2 mcg/kg/min argatroban.
- Documentation of infusion rates was missing or incomplete for multiple patients.

Conclusions

- Proper execution of the argatroban dosing protocol is lacking.
- Inconclusive data does not allow a conclusion of elevated PTT values secondary to initial infusion rate of 2 mcg/kg/min.
- Number of hours to therapeutic PTT is above the accepted timeframe of 24 hours.
- Fifty-six percent rate of error with infusion rate adjustments necessitates modification of the current argatroban dosing protocol (see proposed updated protocol attached).
- Proposed protocol clearly defines “critically ill” as patients with heart failure, multiple organ dysfunction, severe anasarca, or postcardiac surgery.
    - Two patients initiated on 2 mcg/kg/min with consistently elevated PTT values met the new criteria for critically ill; one patient met the current criteria for critically ill.
- Proposed protocol simplifies criteria for use, clarifies laboratory monitoring of PTT, streamlines selection of initial infusion rate and subsequent rate adjustments, and clarifies guidelines for administration with warfarin.
- eMAR will only display rate adjustments specific to the argatroban initial rate protocol selected per prescriber.
- Similar to heparin infusion rate adjustments, argatroban infusion rate adjustments will require RN co-signature.

ARGATROBAN ORDERS AND DOSING PROTOCOL

1. **Criteria for Use**
   - Should be used for suspected or confirmed heparin-induced thrombocytopenia (HIT) or other intolerance to heparin
   - This dosing protocol is not intended for use in PCI or other invasive procedures (vascular surgery, cardiac surgery, etc.)

2. **Baseline Labs:** PTT, PT/INR, platelet count, HIT assay (if not already done), liver panel

3. **Available Concentration:** 1 mg/mL (1000 mcg/mL)

4. **Laboratory Monitoring**
   - Check PTT 3 hours after start of infusion and adjust rate (see chart below)
   - Check PTT 3 hours after each rate adjustment
   - After two consecutive PTT values in therapeutic range (55-75), check PTT daily
   - CBC daily
   - INR daily (if on warfarin)

5. **Initial Rate and Rate Adjustments (Goal PTT 55-75 seconds)**

PHYSICIAN MUST SPECIFY INITIAL RATE

	☐ Normal Hepatic Function **Initial Rate: 2 mcg/kg/min**	☐ Hepatic Impairment/Critically Ill***** **Initial Rate: 0.5 mcg/kg/min**
PTT (sec)	Dosage adjustment **FROM CURRENT RATE**:	
<36	Increase rate by 1 mcg/kg/min	Increase rate by 0.2 mcg/kg/min
36-54	Increase rate by 0.5 mcg/kg/min	Increase rate by 0.1 mcg/kg/min
55-75	**NO CHANGE *Goal PTT***	
76-100	Decrease rate by 0.5 mcg/kg/min	Decrease rate by 0.1 mcg/kg/min
>100	**Stop** infusion for 1 hour, then decrease rate by 1 mcg/kg/min and restart infusion	**Stop** infusion for 1 hour, then decrease rate by 0.2 mcg/kg/min and restart infusion

   - ***Critically ill** defined as patients with heart failure, multiple organ dysfunction, severe anasarca, or postcardiac surgery
   - Do not exceed doses of 10 mcg/kg/min
   - If PTT not at goal within 24 hours, pharmacist may make adjustments to protocol

6. Guidelines for Administration with warfarin (Physician must order)
   - Argatroban and warfarin should be overlapped for a **minimum** of 5 days
   - Do not start warfarin until platelet count is at least 150,000
   - Starting warfarin dose should be no greater than 5 mg per day. No loading dose recommended.
   - Discontinue argatroban when INR is greater than 4. An INR should be drawn 4-6 hours after the infusion is stopped to confirm that INR is within desired therapeutic range. Notify Physician.
   - If repeat INR is less than desired therapeutic range, the most recent infusion rate should be restarted, INR drawn in 24 hours, and this process repeated until INR is within desired therapeutic range. Discontinue argatroban if repeat INR within desired therapeutic range.

Heparin Therapeutic Range
Changes to Weight Based Protocol

Due to a forthcoming change in the laboratory's PTT testing reagent, the heparin weight based protocol PTT target ranges for both of the protocols (VTE and Cardiac) will need to be adjusted. Any time new reagents are utilized for determining the PTT the laboratory must recalibrate the PTT target range. The upcoming change will result in a significant change in the sensitivity of the PTT assay which will necessitate the below changes. The new ranges have been validated and calculated by the hospital's laboratory department and this analysis has demonstrated that a new heparin therapeutic range should be established.

The current protocols will be adjusted to reflect this change. The dosing for both indication specific protocols will not change nor will the goal PTT ranges for the bivalirudin and argatroban protocols.

Goal PTT Ranges - *current*:

- Cardiovascular Protocol
  - 60-89 seconds (0.3-0.6 anti-Xa units/ml)

- DVT/PE Protocol
  - 60-96 seconds (0.3-0.7 anti-Xa units/ml)

Goal PTT Ranges - *future*:

- Cardiovascular Protocol
  - 71-98 seconds (0.3-0.6 anti-Xa units/ml)

- DVT/PE Protocol
  - 71-108 seconds (0.3-0.7 anti-Xa units/ml)

POLICY

Title: ANTIBIOTIC ADMINISTRATION TO PATIENTS WITH HISTORY OF PENICILLIN ALLERGY WITHIN THE SURGERY DEPARTMENT		
	Page 1 of 1	
Policy Number: SUR-7513	*Date Last reviewed/Revised:* 2/13	*Valid Until:* 2/16
Department(s) Affected: Surgery	*Review Period:* every 3 years	

OUTCOME:

Appropriate administration of anti-microbial prophylaxis to patients with history of a penicillin allergy, will occur within the surgical department.

POLICY:

1. Each patient will be assessed for potential drug allergies.
2. Patients stating a history of penicillin allergy will be interviewed further as to the type of reaction, specific signs and symptoms, along with any type of required treatment. This information will be documented on the patient home medication admission assessment in EMR.
3. The following definition will be used to determine the presence of an anaphylactic reaction: "**Immediate life threatening systemic reaction following exposure to a particular substance. Reactions include: laryngeal edema, bronco spasm, wheezing, hypotension, periorbital edema, seizures, or severe skin reactions such as Stevens-Johnson syndrome or toxic epidermal necrolysis."**
4. In the event of a documented anaphylactic reaction to penicillin, or any reaction/allergy to Ancef (cefazolin), Vancomycin will be administered instead of Ancef.

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Key Contact: Lisa Fitzsimmons, RN Executive Director of Surgical Services
Approved/Reviewed by: OR Executive Committee, Teresa Denham
Reference(s): AMA
Date First Effective & Revision/Review dates: 4/99 & (12/09) (2/13)
Distribution: MHCS Intranet

Title: INTRAVENOUS TO ORAL THERAPY		
	Page 1 of 1	
Policy Number: PHRM-POL-0535	***Date Last Reviewed/ Revised:*** 9/12	***Valid Until:*** 9/15
Department(s) Affected: Pharmacy	***Review Period:*** every 3 years	
Signature(s):	Medical Staff Signature if applicable	
	VP/Chief Nurse Executive Signature:	

OUTCOME: Transition patients who meet clinical criteria from intravenous (IV) to Oral Therapy.

POLICY: A Pharmacist may use established criteria to evaluate targeted IV antibiotic and antifungal therapies, proton pump inhibitors (PPIs) and histamine 2 receptor antagonists (H2 blockers) for potential conversion to oral (PO) therapy.

CRITERIA:

- Able to tolerate oral medications either by mouth or through a feeding tube
- Afebrile for at least 24 hours (T < 100.4)
- WBC that is normalizing (< 15K)
- Functioning GI tract (eating full liquids or better)
- Absence of severe nausea, vomiting, or diarrhea
- Absence of an active GI bleed
- Non ICU setting

A pharmacist will initiate an order for patients who meet the criteria and place in the progress notes section of the chart to inform the physician. Orders written by the pharmacist will be considered execution of the IV to PO protocol and will not require co-signature by the physician.

MEDICATIONS PERTAINING TO THIS POLICY:
Antibiotics: azithromycin, ciprofloxacin, clindamycin, doxycycline, fluconazole, levofloxacin, linezolid, metronidazole
Gastrointestinal agents: famotidine, pantoprazole
Miscellaneous agents: levetiracetam, folic acid, multivitamin, thiamine

PROPOSED CHANGES

CRITERIA FOR INCLUSION:

- *Taking oral medications either by mouth or through a feeding tube*
- *Afebrile for at least 24 hours (T <100.4)*
- *WBC that is normalizing (<15K), or known, non-infectious reason can be identified for white blood cell count (i.e., steroids) – antibiotics*
- *Functioning GI tract (eating full liquids or better)*
- *Non ICU setting*

CRITERIA FOR EXCLUSION:

- *ICU*
- *NPO*
- *Meningitis/central nervous system infections, endocarditis, osteomyelitis, septicemia, toxic megacolon, febrile neutropenia – antibiotics*
- *Active GI bleed*
- *Severe diarrhea, vomiting, short bowel syndrome, GI obstruction*
- *Inability to swallow*