Pharmacy & Therapeutics Committee Meeting
Private Dining Room
November 12, 2015 7:00 a.m.

Agenda Items	Individual Responsible
1. Call to Order	Richard Pesce, MD
2. Approval of August, 2015 Minutes	Richard Pesce, MD
3. Therapeutic Interchanges and Formulary Decisions	Page
A. Orbactiv® (Oritavancin)	Patrick Ellis, PharmD 5
B. Nexavar® (sorafenib)	6-7
C. Speacialty Pharmacy Medications	
D. Cimzia® (certolizumab pegol)	Sean Bergeron, PharmD 8-9
E. Praxbind® (idarucizumab)	Patrick Ellis, PharmD 10-11
F. Antithrombotic Reversal & Surgical Management Recommendations	12
G. High Dose Influenza Vaccine	13
H. Fentanyl IV use restrictions.	14
I. Statin Class Review	15-17
J. Entresto: CHI guidelines for appropriate use	18
K. Phosphate Binder Class Review	Camellia Davis, PharmD 19-20
4. Medication Safety/Quality	
A. ADR Review	Karen Babb, PharmD 21-22
5. Policy, Procedure & Protocols	
A. Pharmacy Formulary Business Review Committee	Patrick Ellis, PharmD 23-24
B. Ketamine – IV infusion for pain	25-26
C. Chemotherapy and Biologic Dose Rounding	27
D. "TID" schedule modification	Michelle Denham, RN 28
6. Adjournment	

Next Meeting will be February 11, 2015 at 7:00 AM in the Private Dining Room

PHARMACY AND THERAPEUTICS COMMITTEE
Minutes of Meeting

DATE: August 13, 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	Rodney Elliott, PhT	Tatum Daniel, Student
David Dodson, M.D.	Patrick Ellis, PharmD	Hannah Walker, RN	William Oellerich, M.D.	Nan Payne, RN	Sean Bergeron, Resident
Samuel Currin, M.D.	Lila Heet, PharmD	Brian Jones, RD	Shannon Harris, RN	Kevin Lewis, CMO	Camellia Davis, Resident
Mark Anderson, MD	Rhonda Poulson, CNO		Michael Stipanov, M.D.	Melissa Roden, RN	Erin Massarrello, Resident
Allen Atchley, M.D	Vickie Burger, Lab		Michelle Denham, RN		Whitney Williams, Resident
Michael Harper, M.D	Scott Harbaugh, Finance		Karen Regal, Supply Chain		

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 25, 2015 minutes were approved as submitted.		Complete
Therapeutic Interchanges and Formulary Decisions	The following medications were reviewed: 1. **Ketamine –** IV infusion for pain 2. **Afrezza® (inhaled insulin) –** A new inhaled insulin formulation was reviewed. Data suggests a 1:1 conversion when converting to Novolog insulin. Due to risk of errors associated with this new insulin formulation it was recommended to convert any home medication orders of Afrezza to an equal dose of Novolog while hospitalized. 3. **Extended Release Morphine Formulary Interchange –** Patrick reviewed a proposed therapeutic interchange for the extended released morphine products. MS Contin is the most utilized extended release morphine by a very wide margin and is proposed to be the only formulary agent on formulary. The proposed interchange would utilize an automatic conversion to MS Contin for any orders for Avinza, Kadian, or Oramorph. In no situation will a substitution result in more than a 10 mg difference in total morphine dose per 24 hours and when this is not possible by utilizing available strengths of MS Contin the prescriber will be contacted for alternative orders or utilization of the patient's home supply will be arranged. 4. **Entresto® (sacubitril/valsartan) –** New heart failure drug utilizing valsartan (ARB) and sacubitril which is a new therapeutic entity known as a neprilysin inhibitor which inhibits the breakdown of endogenous vasoactive and natriuretic peptides. Data indicates a mortality benefit associated with the use of this product and Dr. Atchley recommended this agent be added to formulary. 5. **Kengreal® (cangrelor) –** New procedural antiplatelet agent indicated for use during PCI in patients not receiving oral platelet inhibitors or GP IIb/IIIa inhibitors. Patrick has discussed this with the CHI interventional cardiologists and although they don't feel this will be commonly used they felt it would be useful having this on formulary for patients	1. Tabled until next meeting 2. Not approved for formulary addition 3. Therapeutic Interchange Approved 4. Approved for formulary addition 5. Approved for formulary addition	Pending Complete Complete Complete Pending

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	unable to take oral platelet agents. The cardiologists requested that they have an opportunity to collaborate together to develop appropriate use criteria along with the national cardiovascular service line. It was recommended to conditionally approve cangrelor to formulary pending this being added to the smart pump dictionary and development of appropriate use criteria as recommended by the Invasive Cardiology committee and the national CVSL.		
	6. **Cyramza® (ramucirumab) –** A new monoclonal antibody for the treatment of refractory gastric cancers, NSCLC, and metastatic colorectal cancer. It was recommended by Dr. Stipanov to have this agent available for use on an outpatient basis for treatment of the previously mentioned malignancies.	6. Approved for outpatient formulary addition	Complete
	7. **Panhematin® (Hemin) –** Agent indicated for the treatment of recurrent attacks of acute intermittent porphyria related to the menstrual cycle or other patients with various forms of porphyria. In the event of acute attacks this agent is usually necessary to mitigate the signs/symptoms of acute porphyria attacks. Despite the extreme expense of Panhematin (~ $25,000 per course of treatment) it was recommended to add this drug to formulary in order to provide this therapy for a patient who is routinely being admitted to the Glenwood campus for treatment of acute porphyria. Scott Harbaugh has evaluated the reimbursement associated with Panhematin and unfortunately no separate inpatient reimbursement for this product is available.	7. Approved for formulary addition	Complete
	8. **Dalvance® (dalbavancin) –** New long acting glycopeptide antibiotic indicated for the treatment of ABSSSI 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 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 or feasible.	8. Not approved for formulary addition	Complete
	9. **"GI Cocktail" Formulary Interchange –** A recent cost increase in the price of Donnatal tablets has resulted in the re-evaluation of the clinical effectiveness of this product for treatment of dyspepsia – primarily used in the ED. Patrick reviewed a study that demonstrated that the addition of other agents such as Donnatal to liquid antacids provided no additional benefit compared to monotherapy with a liquid antacid. Drs. Visser and Champion were agreeable to removing Donnatal from "GI Cocktail" based on this data and thus it was recommended to automatically substitute the formulary liquid antacid for all "GI Cocktail" orders.	9. Formulary interchange approved	Complete
	10. **PCSK9 Inhibitors –** Patrick updated the committee that a new class of monoclonal antibodies for hyperlipidemia are beginning to emerge to the market. He explained that these appear to be only distributed via specialty pharmacy and will not be available for purchase or use while hospitalized unless the patient's own supply is utilized. Dr. Atchley agreed that these drugs likely have no utility for hospital management and further data is needed to fully validate their current place in therapy.	10. Information only	Complete
	11. **Combigan Formulary Interchange –** Due to a recent price increase it was recommended to automatically substitute the separate products (bromonidine 0.2% and timolol 0.5%) for any Combigan orders.	11. Formulary interchange approved	Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
Medication Use Evaluation	**Pharmacy Discharge Service:** Patrick reviewed the data associated with a year-long pharmacy project that evaluated the potential impact of utilizing de-centralized pharmacists to provide medication discharge order review and medication counseling to a high risk group of patients. The LACE tool was utilized to identify patients for pharmacy intervention and readmission rates were compared to the same population of patients that did not have pharmacist intervention. The data demonstrated a statistically significant reduction in readmission rates for the patients with pharmacist intervention. Dr. Atchley recommended that this data be presented at the upcoming Clinical Operations Council (MEC subgroup) for further discussion.	Clinical Operations Committee (MEC) for discussion	Pending
Medication Safety/Quality	**Estimated GFR Equations (MDRD, CKD-EPI):** Patrick reviewed a letter that was submitted by Dr. Leonard Hays requesting that the hospital consider utilizing the CKD-EPI equation instead of the MDRD equation due to data suggesting its superiority in estimating a patient's risk of developing acute kidney injury. Vicki Burger explained that she has discussed this with pathology and they have agreed to change the equation used by lab to calculate GFR to the CKD-EPI formula. Patrick explained that the cockcroft gault equation will continue to be utilized by pharmacy since most pharmacokinetic studies utilize this equation for determining renal dosing needs. **Prescription Ear Products:** Patrick updated the committee on a recent FDA decision to remove numerous otic products from the US market including one agent utilized on the hospital formulary – benzocaine/antipyrine otic. This product has now been removed from the hospital formulary.	Information only Information only	Complete Complete
Policy, Procedure & Protocols	**IV Levothyroxine - appropriate use:** Patrick reviewed with the committee that recent price increases associated with IV Levothyroxine will result in annual expenditures exceeding $100,000 per year. In order to minimize the cost impact several possible options were discussed including expanded use of IV to PO conversion or less frequent dosing (every 2-3 days) due to the long half-life of levothyroxine. The majority of our IV levothyroxine usage in the ICU's for patients unable to take oral medications. Drs. Harper and Pesce both recommended that administration of IV levothyroxine every other day would be preferred and this is what was recommended to the committee. Dr. Dodson was also in agreement of this strategy from a hospitalist standpoint.	Approved	Complete
Nutrition Support Team	**ENFit Connector:** Brian Jones updated the committee on work that is ongoing to incorporate the use of ENfit connectors to ensure safe and appropriate use of enteral feedings and enteral medication administration for patients with certain tubes such as G tubes, DHT, etc. A multidisciplinary team will be meeting to help with the transition to the ENFit feeding tubes, connectors, and syringes. **Ensure High Protein:** A new high protein formula that was recommended to be added to formulary and for use with the med pass program previously presented at the June 2015 P&T meeting.	Information only Approved	Pending Complete

There being no further business, the meeting was adjourned at 8:00 A.M. The next P&T meeting is **October, 8, 2015 at 7:00 a.m.**

Respectfully submitted,
Sandy Vredeveld, D.Ph. Director of Pharmacy

Approved by,
Richard Pesce, M.D. Chairman

FORMULARY REVIEW

GENERIC NAME: ORITAVANCIN DIPHOSPHATE

PROPRIETARY NAME: *Orbactiv* (The Medicines Company)

INDICATIONS: Oritavancin is approved for the treatment of adult patients with acute bacterial skin and skin structure infections (SSSIs) caused by or suspected to be caused by susceptible isolates of designated gram-positive microorganisms, including *Staphylococcus aureus* (methicillin susceptible and methicillin resistant), *Streptococcus pyogenes*, *Streptococcus agalactiae*, *Streptococcus dysgalactiae*, *Streptococcus anginosus* group (includes *S. anginosus*, *Streptococcus intermedius*, and *Streptococcus constellatus*), and *Enterococcus faecalis* (vancomycin-susceptible and resistant isolates).

CLINICAL PHARMACOLOGY: All semisynthetic lipoglycopeptide antibacterials share similar mechanisms of action and spectrums of activity. All work by inhibiting the transpeptidase and transglycosylase steps in bacterial cell-wall synthesis of gram-positive bacteria by binding to the terminal D-alanyl-D-alanine of the stem pentapeptide of the nascent peptidoglycan. Differences in binding and anchoring to the cell membrane and dimerization may alter each agent's potency against various bacteria.

PHARMACOKINETICS: The pharmacokinetics of oritavancin are best characterized with a 3-compartment model with linear elimination. Time to maximum plasma concentration is 1 to 1.5 hours. Plasma protein binding is 85% to 90%. Systematic clearance is 0.445 L/hour. Oritavancin is not metabolized but is excreted unchanged in both the urine and feces. The terminal half-life is approximately 350 – 400 hours (> 2 weeks). The long terminal half-life seems to be related to high protein binding and its lipophilic side chain as a volume of distribution of 110 L.

ADVERSE REACTIONS: The most common adverse reactions reported with oritavancin therapy are nausea, headache, diarrhea, and limb and subcutaneous abscesses.

DRUG INTERACTIONS: Coadministration with warfarin may result in increased warfarin levels and increased risk of bleeding due to inhibition of CYP2C9 metabolism. Patients can be treated with the combination but should be monitored for signs of bleeding. Coagulation tests (eg, prothrombin time, international normalized ratio) may be unreliable for up to 24 hours after oritavancin administration; activated partial thromboplastin time may be altered for up to 48 hours, and activated clotting time may be affected. Oritavancin is a nonspecific, weak inhibitor of cytochrome P450 (CYP-450) 2C9 and CYP2C19 and is an inducer of CYP3A4 and CYP2D6. Oritavancin may also inhibit the activity of CYP1A2, CYP2B6, CYP2D6, and CYP3A4, based on in vitro studies. Therefore, caution should be observed if oritavancin is used to treat patients receiving a narrow therapeutic index drug metabolized by these CYP isoforms. Oritavancin is not a substrate nor an inhibitor of the efflux transporter P-glycoprotein.

DOSING: The recommended dose for adults 18 years and older is oritavancin 1,200 mg administered as a single IV infusion over 3 hours. No dosage adjustment is necessary in patients with mild to moderate renal impairment. Patients with severe renal impairment were not evaluated. Oritavancin is not removed from blood by hemodialysis. No dosage adjustment is recommended for patients with mild or moderate hepatic impairment. There are no data available to determine appropriate oritavancin dosing in patients with severe hepatic impairment; therefore, use caution when prescribing oritavancin to these patients.

PRODUCT AVAILABILITY: Oritavancin is supplied in a single-use 50 mL vial containing oritavancin diphosphate 449 mg (equivalent to oritavancin 405 mg) lyophilized powder. The vial contains an extra 5 mg of oritavancin to ensure withdrawal of the recommended 400 mg dose after the lyophilized powder is reconstituted with sterile water for injection.

COST: $2,753 per 1200 mg dose

CONCLUSION: Oritavancin is a semisynthetic lipoglycopeptide antibacterial indicated for acute bacterial SSSIs caused by certain susceptible bacterial strains. Due to the cost and data only available for treatment of cellulitis it is recommended to designate this drug NON-FORMULARY pending new data and/or indications. However, non-formulary use may be considered on a case by case basis for special circumstances for the treatment of off label indications per ID and antimicrobial stewardship approval.

SUMMARY REVIEW

GENERIC NAME: SORAFENIB TOSYLATE

PROPRIETARY NAME: *Nexavar* (Bayer/Onyx)

INDICATIONS: Sorafenib is indicated for the treatment of patients with advanced renal cell carcinoma, hepatocellular carcinoma, and differentiated thyroid cancer. Off-label, sorafenib has shown potential benefit in angiosarcoma, gastrointestinal stromal tumor, and acute myeloid leukemia.

CLINICAL PHARMACOLOGY: Sorafenib is an orally available bisarylurea multi-kinase inhibitor, inhibiting Raf-1 kinase, multiple intracellular (CRAF, BRAF, and mutant BRAF) kinases, and the receptor kinases of vascular endothelial growth factor receptor (VEGFR)-2, VEGFR-3, platelet-derived growth factor receptor-β, c-KIT, FLT-3, and RET, which are involved in proliferation and angiogenesis. In patients with renal cell carcinoma, sorafenib reduced measures of vascular permeability and tumor perfusion.

CLINICAL STUDIES:
Sorafenib has activity in advanced renal cell carcinoma in patients who have failed at least one previous therapy, increasing progression-free survival and possibly prolonging overall survival. It has further proven to show benefit in unresectable hepatocellular carcinoma, differentiated thyroid cancer, angiosarcoma, and gastrointestinal stromal tumors.

Most recently, sorafenib has been discussed with promising results in acute myeloid leukemia (AML). In younger patients with AML (< 60 yrs), Sorafenib (Nexavar) added to chemotherapy improved event-free survival (21 months sorafenib vs. 9 months placebo p=0.013) and relapse-free survival (not reached sorafenib (22% - expected 3 yr) vs. 23 months placebo [40% - expected 3 yr] p=0.017). However, no significant improvement in overall survival has been seen with sorafenib in AML patients. Complete remission was similar between the two groups (60% sorafenib vs. 59% placebo, p=0.764). Of note in FLT3-ITD positive patients, no difference in event-free survival was seen, but these patients trended towards a prolonged relapse free survival and overall survival, which shows to be promising in the acute setting for this unfavorable genetic mutation.

PHARMACOKINETICS: Following oral administration, peak sorafenib concentrations occurred at approximately 3 hours (range, 1.75 to 12.5 hours). Oral bioavailability with the tablets is 38% to 49% compared with an oral solution. Administration with a moderate-fat meal delayed the time-to-peak concentration, but did not affect the extent of absorption. Administration with a high-fat meal reduced bioavailability 29%, compared with administration in the fasted state. Mean peak concentrations and the area under the curve (AUC) increased less than proportionately at dosages greater than 400 mg twice daily. In vitro, plasma protein binding is 99.5%.The mean half-life of sorafenib is 25 to 48 hours. Sorafenib is metabolized in the liver via glucuronidation by the UGT1A9 pathway and oxidative metabolism via the cytochrome P-450 3A4 enzyme system. No dosage adjustments are necessary for age or gender. In patients with mild (Child-Pugh class A) or moderate (Child-Pugh class B) hepatic impairment, systemic exposure to sorafenib was within the range observed in patients with normal hepatic function. Sorafenib pharmacokinetics have not been studied in patients with severe (Child-Pugh class C) hepatic impairment. In patients with normal renal function and patients with mild (creatinine clearance [Ccr] 50 to 80 mL/min) or moderate (Ccr 30 to 50 mL/min) renal impairment, no relationship was observed between renal function and steady-state sorafenib AUC. Sorafenib has not been assessed in patients with severe renal impairment (Ccr less than 30 mL/min) or in patients undergoing dialysis.

ADVERSE REACTIONS: Adverse reactions of sorafenib included rash/desquamation, nausea, diarrhea, stomatitis/pharyngitis, hand-foot skin reaction, alopecia, fatigue, hypertension, pain, neutropenia, increased hepatic transaminases, and increased bilirubin. Adverse reactions in patients treated with sorafenib and interferon alpha have been similar to those observed with the sorafenib regimen alone. Dose-limiting toxicities were diarrhea, fatigue, and skin toxicity.

Skin toxicity, the primary adverse effect, is common, but rarely appears to require discontinuation of therapy.

DRUG INTERACTIONS: See the package insert for full drug interaction data.

DOSING: In all indications, the recommended dosage of sorafenib is 400 mg (two 200 mg tablets) orally twice daily, taken at least 1 hour before or 2 hours after eating. Treatment should continue until the patient is no longer clinically benefitting or until unacceptable toxicity occurs.[1]

PRODUCT AVAILABILITY: Sorafenib received Food and Drug Administration (FDA) approval in December 2005, following submission for FDA approval in July 2005 and a priority review. It is available as red, round, film-coated tablets containing sorafenib tosylate 274 mg, equivalent to sorafenib 200 mg.

COST: $109.86 per tablet ($439.44 per day of therapy)

CONCLUSION: Sorafenib is only available through specialty pharmacy distribution channels. Specialty pharmacy is a newer distribution process that is often utilized for pharmaceutical and biological products that have high acquisition costs, are difficult to manage, and/or present reimbursement challenges. Specialty pharmacy medications such as Nexavar may be purchased by acute care hospitals although it is generally preferred to arrange for the medication to be distributed to the patient directly from the specialty pharmacy as a patient specific prescription due to the high cost and to ensure patient affordability if long term therapy is needed.

Of note, the off label AML indication is the indication that has presented itself for inpatient use. As stated above, in FLT3-ITD positive patients it appears from recent data that sorafenib may be a promising adjunct therapy in the acute setting for patients presenting with this unfavorable genetic mutation.

FORMULARY REVIEW

GENERIC NAME: CERTOLIZUMAB PEGOL

PROPRIETARY NAME: *Cimzia* (UCB)

INDICATIONS: Certolizumab pegol is indicated for reducing signs and symptoms of Crohn disease and maintaining clinical response in adult patients with moderately to severely active disease who have had an inadequate response to conventional therapy. Certolizumab pegol is also approved for use in moderately to severely active rheumatoid arthritis as monotherapy or in combination with non-biological DMARDs. Other indications include ankylosing spondylitis and active psoriatic arthritis.

CLINICAL PHARMACOLOGY: Certolizumab pegol is a polyethylene glycolated Fab fragment of a humanized anti–(tumor necrosis factor) TNF-α monoclonal antibody that neutralizes TNF-α. Certolizumab pegol neutralizes membrane-associated and soluble human TNF-α in a dose-dependent manner. Certolizumab is equally potent as adalimumab and infliximab at neutralizing membrane TNF-α signaling, and exhibited greater potency than adalimumab and infliximab at neutralizing soluble TNF-α. In contrast with adalimumab, etanercept, and infliximab, certolizumab does not mediate increased levels of apoptosis or activate the complement pathway. It is unclear whether these unique aspects incur less immunogenicity than the other agents. Like adalimumab and infliximab, the other TNF-α antagonists with activity in Crohn disease, certolizumab almost completely inhibited lipopolysaccharide-induced interleukin-1β release from monocytes.

PHARMACOKINETICS: A linear dose-dependent relationship has been observed following subcutaneous and intravenous administration for both the maximum serum concentration and the area under the curve (AUC). Age, gender, creatinine clearance, and white blood cell count did not influence the pharmacokinetics of certolizumab pegol. Too few patients with hepatic function impairment were included in studies to determine if hepatic function impairment has any impact on certolizumab pegol pharmacokinetics. Anti-certolizumab pegol antibodies, repeated administration, weight, and immunosuppressant use affected the pharmacokinetics of certolizumab pegol; however, only the presence of antibodies had more than a 30% effect on peak concentration and/or AUC.

ADVERSE REACTIONS: Adverse reactions observed in clinical trials included headache, aggravation of Crohn disease, nausea, nasopharyngitis, dizziness, arthralgia, abdominal pain, fever, cough, urinary tract infection, and upper respiratory tract infection. Reactions occurring in at least 5% of patients and more frequently with certolizumab than placebo were upper respiratory tract infection (20% vs 13%), urinary tract infection (7% vs 6%), and arthralgia (6% vs 4%). Overall, infections occurred in 38% of certolizumab-treated patients compared with 30% of placebo recipients.

DRUG INTERACTIONS: Certolizumab should not be coadministered with anakinra therapy. Combined use of these 2 drugs is associated with an increased risk of serious infections.[1] Live vaccines and attenuated vaccines should not be coadministered with certolizumab therapy. Certolizumab may interfere with activated partial thromboplastin time (aPTT) tests.[1] Erroneously elevated aPTT assay results may occur in patients without coagulation abnormalities.[1]

DOSING: The product labeling states certolizumab should be administered by a health care provider. Cimzia Prefilled Syringes can be self-administered after initial patient education. It is administered subcutaneously in the abdomen or thigh as a 400 mg dose (given as 2 subcutaneous 200 mg injections at separate sites) initially and at weeks 2 and 4. If a response occurs, dosing can be continued with 400 mg subcutaneously every 4 weeks. May consider 200 mg every other week for ankylosing spondylitis, psoriatic arthritis, or rheumatoid arthritis.

PRODUCT AVAILABILITY and STORAGE: Certolizumab received Food and Drug Administration approval in April 2008. It is available as a 200 mg lyophilized powder for reconstitution with 1 mL of sterile water for injection. It is supplied in kits containing 2 glass vials each containing certolizumab pegol 200 mg, two 2 mL glass vials of sterile water for injection, two 3 mL plastic syringes, four 20-gauge needles, two 23-gauge needles, and 8 alcohol swabs. Each single-dose vial provides approximately 200 mg of certolizumab pegol, sucrose 100 mg, lactic acid 0.9 mg, and polysorbate 0.1 mg. Certolizumab pegol is also supplied in a Prefilled Syringe Kit of 200 mg/1 mL SC syringes, which can be self-administered.

PRICING: Cimzia Prefilled Subcutaneous Kit
2 X 200 mg/mL (1): $3651.96
Cimzia Starter Kit Subcutaneous Kit
6 X 200 mg/mL (1): $3651.96
Cimzia Subcutaneous Kit
2 X 200 mg (1): $3651.96

COMPARATIVE EVALUATIONS: No direct comparison studies for safety and efficacy have been performed between certolizumab pegol and any other TNF-α antagonist. The PRECISE2 and WELCOME studies suggest a possible response to certolizumab in patients previously on infliximab, who then lost response or became intolerant to infliximab (64% of patients responded and remission occurred in 39%). More research is needed in order to assess the clinical relevance of these observations.

CONCLUSION: Certolizumab offers an alternative to infliximab and adalimumab for the treatment of Crohn disease and RA although the necessity of adding this agent to formulary in light of other available formulary products should be considered.

CHI MEMORIAL				
OUTPATIENT REIMBURSEMENT ANALYSIS				
HCPCS #J0717 Certolizumab pegol inj 1mg (Cimzia)				
	Allowable Reimbursement		**Cost**	
Payer	**1 mg Dosage**	**200 mg Dosage**	**200 mg Dosage**	**Margin**
Medicare	$6.06	$1,212.00	$1,135.00	**$77.00**
BCBS	$6.73	$1,346.00	$1,135.00	**$211.00**
Cigna	$6.56	$1,312.00	$1,135.00	**$177.00**
United	$5.99	$1,198.00	$1,135.00	**$63.00**
Aetna	$6.56	$1,312.00	$1,135.00	**$177.00**
Humana	70% of Covered Charge			

FORMULARY REVIEW

GENERIC NAME: IDARUCIZUMAB

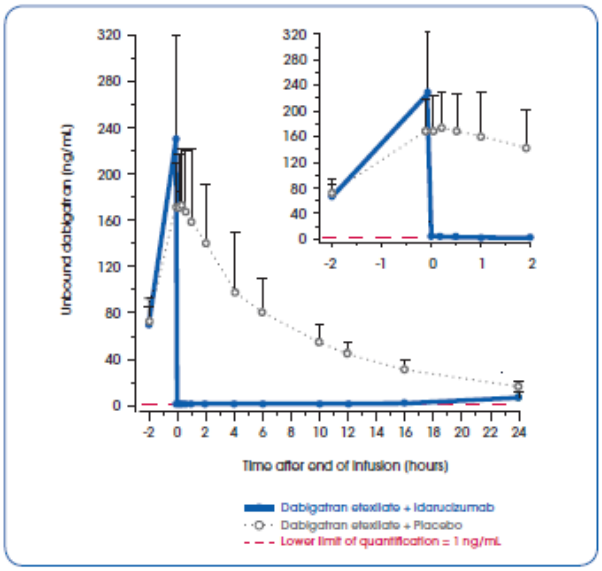
PROPRIETARY NAME: PRAXBIND (Boehringer Ingelheim)

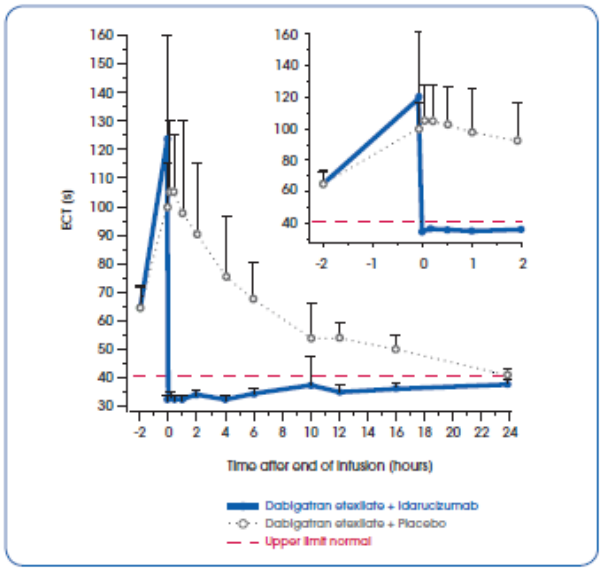
INDICATIONS: For dabigatran reversal during emergency surgery, urgent procedures, or for life-threatening or uncontrolled bleeding.

CLINICAL PHARMACOLOGY: Idarucizumab is a specific reversal agent for dabigatran. It is a humanized monoclonal antibody fragment (Fab) that binds to dabigatran and its acyl glucuronide metabolites with higher affinity than the binding affinity of dabigatran to thrombin, neutralizing their anticoagulant effect. Idarucizumab binds free and thrombin bound dabigatran with an affinity that is 350 times as high as that observed with thrombin.

PHARMACOKINETICS / PHARMACODYNAMICS: In healthy subjects 45 to 64 years, the plasma concentrations of unbound dabigatran were decreased to the lower limit of quantification immediately after administration of idarucizumab 5 gm. The diluted thrombin time, ecarin clotting time, aPTT, thrombin time, and ACT returned to baseline. The reduction in dabigatran plasma concentration was seen over the entire observation period of at least 24 hours. Similar findings were also observed in elderly subjects (65-80 years) as well as subjects with mild and moderate renal impairment. In a limited number of patients, re-distribution of dabigatran from the periphery to plasma led to re-elevation of dTT, ECT, aPTT, and TT.

Idarucizumab is rapidly eliminated with an initial half-life of 47 minutes and a terminal half-life of 10.3 hrs.





CLINICAL STUDIES:
An interim analysis of the ongoing single cohort case series trial included data for 123 patients: 66 patients with serious bleeding (Group A) and 57 requiring an urgent procedure (Group B). Approximately half of the patients in each group were male. The median age was 77 years and the median CrCl was 55 ml/min. Approximately 67% of patients in Group A and 63% of patients in Group B had been treated with dabigatran 110 mg BID. Among the 90 patients with available data, the median maximum reversal of the pharmacodynamics anticoagulant effect of dabigatran as measured by ECT or dTT in the first 4 hours after administration of 5 gm idarucizumab was 100%, with most patients (> 89%) achieving complete reversal. Reversal of the pharmacodynamics effects were evident immediately after administration. Results for Groups A and B were similar. In a limited number of patients, between 12 and 24 hours after administration of a 5 gm dose, elevated coagulation parameters have been observed. Among 35 patients in Group A who could be assessed, hemostasis was reported in 33, and mildly or moderately abnormal hemostasis was reported in 2 patients and 1 patient, respectively. Among 36 patients in Group B who underwent a procedure, normal intraoperative hemostasis was reported in 33, and mildly or moderately abnormal hemostasis was reported in 2 patients and 1 patient, respectively. One thrombotic event occurred within 72 hours after administration in a patient whom received idarucizumab.

ADVERSE REACTIONS, WARNINGS, PRECAUTIONS:

- Common adverse reactions: the most common reactions in ≥ 5% of patients treated were hypokalemia, delirium, constipation, pyrexia, and pneumonia.
- Thromboembolic Risk: Reversing dabigatran therapy exposes patients to the thrombotic risk of their underlying disease. To reduce this risk, resumption of anticoagulant therapy should be considered as soon as medically appropriate. In the interim analysis described above 1 patient had a thrombotic event within 72 hours after administration of idarucizumab.
- Re-elevation of coagulation parameters: If reappearance of clinically relevant bleeding **together with** elevated coagulation assays, administration of an additional 5 gm dose may be considered. Similarly, patients who require a second emergency surgery/urgent procedure and have elevated coagulation assays may receive an additional 5 gm dose.
- Hereditary fructose intolerance due to sorbitol excipient: Patients with the condition of hereditary fructose intolerance who have received parenteral administration of sorbitol, can develop serious adverse reactions. The recommended dose of idarucizumab contains 4 gm of sorbitol as an excipient.

DRUG INTERACTIONS: No significant drug interactions have been observed in clinical trials.

BLACK BOX WARNING: None

DOSING:
The recommended dose is 5 gm, provided as two separate vials each containing 2.5 gm/50 ml idarucizumab.

Repeat dosing: data supporting the administration of an additional 5 gm dose is limited, and the safety and effectiveness of repeat treatment with have not been established. If after administration of 5 gm idarucizumab, reappearance of clinically relevant bleeding in combination with elevated coagulation parameters is observed or a patient requires a second emergency surgery or urgent procedure and has elevated coagulation parameters, then an additional 5 gm dose may be considered.

Re-starting dabigatran therapy: dabigatran therapy may be initiated 24 hours after administration of idarucizumab.

COST:
$3,500 per 5 gm dose

CONCLUSION:
Idarucizumab is the first reversal agent approved for any of the oral novel anticoagulants. Current strategies to reverse the anticoagulant effect of dabigatran are unreliable and involve the replacement of specific clotting factors (PCC, activated factor VII, etc.) and the results can be inconsistent. The FDA approval of idarucizumab will likely prove to be a useful therapy for patients requiring urgent reversal of dabigatran's anticoagulant effects such as those needing urgent surgery or experiencing a severe bleeding episode. It is recommended to add idarucizumab to formulary and maintain inventory of one 5 gram dose on each campus and for its use to be encouraged primarily when urgent reversal is necessary (severe bleeding, urgent surgery).

Antithrombotic Reversal & Surgical Management Recommendations*

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

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

Antithrombotic Reversal & Surgical Management Recommendations*

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

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

Clinical Trials (High-Dose Influenza Vaccine for patients ≥ 65 years of age)

Study	N	Population	Measure	Results	Difference (95% CI)	Conclusion
N Engl J Med 2014;371:635-45 MC, R, DB, AC	HD: 15,991 SD: 15,998	2011-2013 flu seasons	Lab confirmed influenza at least 14 days after vaccination	ITT: 228 (1.4%) in HD vs. 301 (1.9%) in SD	Relative: 24.2% (9.7-36.5)	HD significantly improved protection against laboratory-confirmed influenza illness
Lancet Infect Dis 2015;15:293-300 Retrospective cohort study	HD: 929,730 SD: 1,615,545	Medicare database 2012-2013 flu seasons Patients well matched with regards to age and comorbidities	Influenza related illness defined by a community medical encounter w/ a rapid flu diagnostic test, followed by dispensing of oseltamivir within a 2 day period	1.01 outcomes per 10,000 person wks (HD) vs. 1.30 outcomes per 10,000 person wks (SD)	Absolute: 0.29 (0.19-0.38)	HD flu vaccine was more effective than SD vaccine at prevention of flu-related medical encounters. Similar analyses will be completed in upcoming flu seasons.
			Hospital inpatient admission or ED visit with ICD-9 diagnosis of influenza	0.86 outcomes per 10,000 person wks (HD) vs. 1.10 outcomes per 10,000 person wks (SD)	Absolute: 0.24 (0.17-0.30)	
Clin Infect Dis 2015;61(2):171-6 Retrospective cohort study	HD: 25,714 SD: 139,511	VA Data 2010-2011 flu seasons Patients who received HD vaccine tended to be older, ↑ comorbidities, more likely to have HIV, more likely to have exposure to immunosuppressive drugs	Hospitalization for influenza or pneumonia based on ICD-9 codes (no lab diagnosis of influenza)	0.3% of patients in both groups hospitalized for influenza or pneumonia Subgroup analysis showed that pt.'s aged ≥ 85 had fewer PNA/ influenza related hospitalization after receiving HD as compared to SD – 0.3% vs. 0.66% respectively (RR,0.52; 95% CI, .29-.92)		Did not find that HD vaccine resulted in lower rates of influenza/PNA related hospitalizations, however, found a potential benefit for patients ≥ 85 years of age

MC: Multicenter; R: Randomized; DB: Double blind; AC: Active comparator; HD: High-dose trivalent influenza vaccine; SD: Standard-dose trivalent influenza vaccine; ITT: Intent-to-treat

FENTANYL – IV PUSH for PRN pain relief

BACKGROUND:
Fentanyl IVP is currently restricted to the following patient care areas: ED, OR/procedural areas, PACU, CSSU, and ICU's. Recent situations have raised the request to review this restriction and consider allowing fentanyl to be used as an intermittent pain medication for patients on comfort measures/end of life care outside of those locations listed above. Currently, only two existing medication management policies address the use of IV fentanyl but these policies only address this medication when used via PCA and no existing policy mentions the PRN use of IVP fentanyl.

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

COMPARATIVE EFFIFACY & SIDE EFFECTS:

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

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

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

Comparative Efficacy, Onset of action, etc.

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

PHARMACY AND THERAPEUTICS
CLASS REVIEW
HMG-COA REDUCTASE INHIBITORS (STATINS)

AGENTS IN CLASS: Atorvastatin, Fluvastatin, Lovastatin, Pitavastatin, Pravastatin, Rosuvastatin, Simvastatin

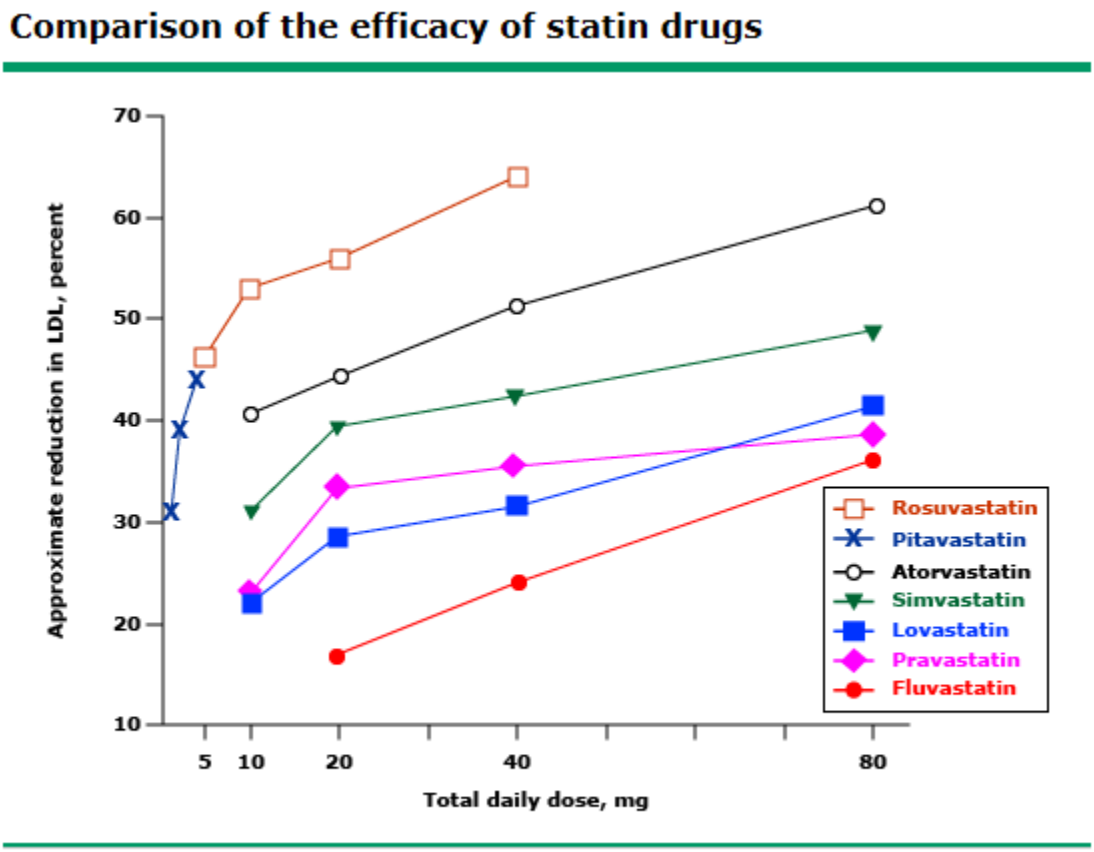
INDICATIONS: Food and Drug Administration (FDA)-approved and non–FDA-approved indications for statins are compared in Table 1. Atorvastatin, simvastatin, rosuvastatin, and pravastatin have the broadest indications, which reflects data from numerous outcome studies demonstrating prevention of cardiovascular (CV) events.

Table 1. Indications of Statins

	Atorvastatin	Fluvastatin	Lovastatin	Pravastatin	Rosuvastatin	Simvastatin
FDA-Approved Indications						
Primary prevention of CV disease in patients with multiple risk factors for CHD, diabetes, peripheral vascular disease, history of stroke, or other cerebrovascular disease to:						
Reduce MI risk	X			X	X	X
Reduce stroke risk	X				X	X
Reduce risk for revascularization procedures and angina	X			X	X	X
Reduce risk of CV mortality	X			X	X	X
Secondary prevention of CV events in patients with clinically evident CHD to:						
Reduce risk of MI	X	X	X	X	X	X
Reduce risk of stroke	X			X	X	X
Reduce risk for revascularization procedures	X	X	X	X	X	X
Reduce risk of hospitalization for CHF	X				X	X
Reduce angina risk	X		X		X	X
Slow progression of coronary atherosclerosis	X	X	X	X	X	
Reduce risk of total mortality by reducing coronary death	X	X		X	X	X
Hypercholesterolemia						
Primary hypercholesterolemia (heterozygous familial and nonfamilial)	X	X	X	X	X	X
Adolescents with heterozygous familial hypercholesterolemia	X	X	X	X	X	X
Homozygous familial hypercholesterolemia	X				X	X
Mixed dyslipidemia (Fredrickson types IIa and IIb)	X	X	X	X	X	X
Hypertriglyceridemia (Fredrickson type IV)	X			X	X	X
Primary dysbetalipoproteinemia (Fredrickson type III)	X			X		X
Non–FDA-approved indications						
Pre- and Post-PCI[a]	X				X	X

CLINICAL PHARMACOLOGY: Statins competitively inhibit the enzyme HMG-CoA reductase. By inhibiting this enzyme, statins greatly reduce plasma concentrations of low density lipoprotein (LDL) and total cholesterol (TC). The rank order for statins, based on LDL-cholesterol (LDL-C)–lowering potencies, is: rosuvastatin > atorvastatin > simvastatin > pravastatin = lovastatin > fluvastatin.

COMPARATIVE EFFICACY: Reductions in LDL of 30% to 40% can often be achieved with the following statin daily doses: rosuvastatin 5 to 10 mg, atorvastatin 10 mg, simvastatin 20 to 40 mg, pravastatin 40 mg, lovastatin 40 mg, and fluvastatin 80 mg. Statin therapy also often produces a 5% to 10% increase in high density lipoprotein (HDL), and a 7% to 30% reduction in triglycerides (TG).



Comparison of the percent reduction in serum low density lipoprotein (LDL)-cholesterol with various statin drugs.

CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS: There is little difference between these agents in warnings and precautions. Active liver disease, hypersensitivity, pregnancy and lactation, myopathy.

ADVERSE REACTIONS: The most common adverse reactions with the statins are the following: headache, rash, GI upset, transient increases in liver function tests, hepatotoxicity, and myopathies. In 2005, the FDA issued a public health advisory on rosuvastatin because of concerns regarding possible increased muscle toxicity and adverse reactions on the kidney compared with other statins on the market.

DRUG INTERACTIONS: The risk of myopathy may be increased by concomitant use of a variety of different medications that carry their own risk of myopathy (eg, niacin, fibrates), as well as medications that inhibit the metabolism of statins. Atorvastatin, lovastatin, and simvastatin are CYP3A4 substrates that carry any increased myopathy risk when administered with CYP3A4 inhibitors. Fluvastatin and rosuvastatin are CYP2C9 substrates with increased levels in the presence of CYP2C9 inhibitors.

DOSING: Patients receiving statin therapy should be placed on a standard cholesterol-lowering diet before receiving statin therapy and should continue on the diet during statin therapy. These agents can be given without regards to meals, with the exception of lovastatin, which should be taken immediately after meals.

Table 2. Dose Comparison Table

Atorvastatin (Lipitor)	Fluvastatin (Lescol)	Lovastatin (Mevacor)	Pitavastatin (Livalo)	Pravastatin (Pravachol)	Rosuvastatin (Crestor)	Simvastatin (Zocor)
5mg (27%)	20mg (22%)	10mg (21%)	1mg (29%)	10mg (22%)		5mg (26%)
10mg (35%)	40mg (25%) 80mg (35%)	20mg (25%) 40mg (30%)	2mg (37%)	20mg (29%) 40mg (34%)		10mg (29%)
20mg (43%)	80mg XL (35%)	80mg (41%)	4mg (44%)	80mg (37%)	5mg (45%)	20mg (38%) 40mg (41%)
40mg (50%)					10mg (48%)	80mg (46%)
80mg (55%)					20mg (54%)	
					40mg (62%)	

% = Average LDL-Lowering

Table 3. Cost per unit & Usage

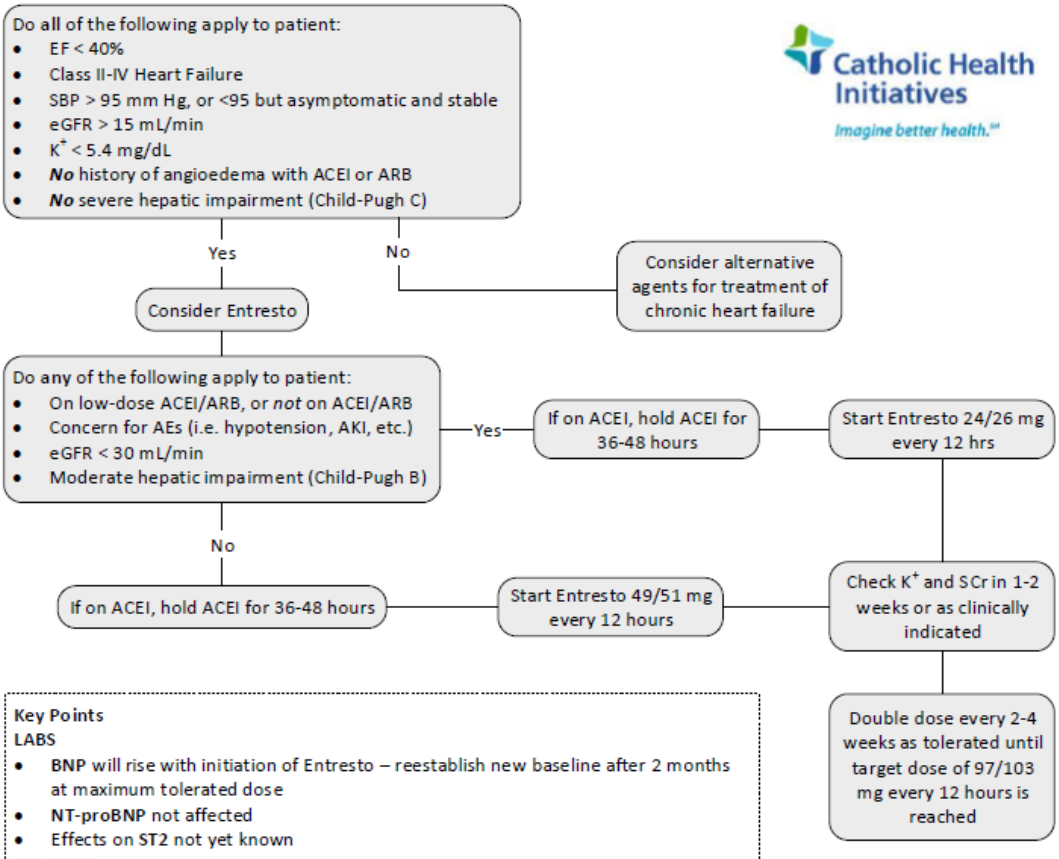
Atorvastatin	Cost per unit	Usage per year
10 mg	$0.22	2732
20 mg	$0.27	4251
40 mg	$0.30	14369
Fluvastatin		
20 mg	$3.81	23
40 mg	$3.42	9
80 mg XL	$7.41	13
Lovastatin		
20 mg	$0.10	1990
Pravastatin		
20 mg	$0.24	3577
40 mg	$0.48	5135
Rosuvastatin		
10 mg	$5.96	2638
20 mg	$5.96	2460
Simvastatin		
10 mg	$0.07	1527
20 mg	$0.08	4398
40 mg	$0.08	5140
Pitavastatin		
2 mg	$6.53	89

POTENTIAL COST SAVINGS: Based on the average per year utilization and cost of each of the available statins a significant cost savings opportunity does still exist despite wide generic availability of most of the available products. Rosuvastatin continues to have a wide utilization and an average cost of approximately $6 per tablet which makes it considerably more expensive per day of therapy. **If all rosuvastatin doses were substituted to a therapeutically equivalent dose of atorvastatin a savings of approximately $30,000 per year could be achieved. A generic version of rosuvastatin may become available in late 2016, however it is realistic to assume that the above mentioned savings amount could be achieved prior to rosuvastatin's generic cost becoming comparable to that of generic atorvastatin.**

CONCLUSION: All statins have been shown to reduce LDL-C levels, although not to the same extent. Patients with higher levels may require more potent agents (eg, rosuvastatin, atorvastatin, simvastatin) to achieve LDL-C goals; less potent agents may effectively reduce LDL-C levels in patients with modestly increased levels. The most extensive outcome data are available for atorvastatin, simvastatin, rosuvastatin, and pravastatin. Pravastatin has the least potential for drug interactions. Some patients may tolerate some statins better than others although it is unclear if a temporary conversion while hospitalized would have a meaningful impact on patient tolerability.

RECOMMENDATIONS: Atorvastatin is now available in generic form. We recommend substituting all rosuvastatin orders to atorvastatin based on the therapeutic interchange above. In addition, due to extremely low utilization of fluvastatin and pitavastatin it would also be recommended to also interchange these to a therapeutically equivalent dose of atorvastatin as outlined above.

Entresto: Guidelines for Appropriate Use



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Key Points

LABS

- **BNP** will rise with initiation of Entresto – reestablish new baseline after 2 months at maximum tolerated dose
- **NT-proBNP** not affected
- Effects on **ST2** not yet known

BENEFITS

- 4.7% absolute risk reduction (ARR) in 1° combined outcome of CV-related death or hospitalization for worsening HF (20% relative risk reduction (RRR))
- 2.8% ARR in all-cause mortality (16% RRR)
- Reduced decline in KCCQ Score at 8 months vs. enalapril (-2.99 vs. -4.63; p=0.001)
- Reduced incidence of SCr > 2.5 mg/dL vs. enalapril (3.3% vs. 4.5%; p=0.007)
- Reduced cough vs. enalapril (11.3% vs. 14.3%; p<0.001)
- Reduced K^+ > 5.5 mEq/L vs. enalapril (16.1% vs. 17.3%; p=0.15)
- Average enalapril dose in comparator group (18.9 mg) was higher than CONSENSUS (16.6 mg) and SOLVD (18.4 mg)

CONCERNS

- Ensure insurance coverage prior to initiation (cash price ~$4,500/yr)
- Increased symptomatic hypotension vs. enalapril (14% vs. 9.2%; p<0.001)
- Increased risk of angioedema (0.45% vs.0.24% ; p=NS)

Memorial Process to ensure appropriate use:

- Pharmacy to review and screen for the following
  - GFR: physician to be notified for new starts if eGFR < 30 ml/min and appropriate dose not started
  - Potassium: all patients will be monitored for potential hyperkalemia while on Entresto and MD to be notified if K+ > 5.4 at any point during therapy
  - ACE/ARB allergies: all patients will be screened for ACE/ARB allergies prior to starting Entresto
  - ACE/ARB washout time: Any patient being transitioned to Entresto must wait at least 36 hours from the time of their last ACE/ARB dose before starting Entresto.

DRUG CLASS REVIEW
Phosphate Binding Agents

Background & Summary:
The ideal phosphate binder (PB) should actively bind dietary phosphate, have minimal systemic side effects, maintain a low pill burden, and be inexpensive. Aluminum PBs have fallen out of favor due to system side effects of encephalopathy, osteomalacia, and anemia. Calcium based PBs then came into favor: first calcium carbonate and then calcium acetate for its greater phosphate binding ability. Long-term use of calcium PB therapy has shown an increased risk for vascular calcification which is linked to cardiovascular morbidity and mortality among hemodialysis patients. The sevelamer products were the first non-calcium phosphate binding agents available without evidence of long term systemic effects. Renagel (sevelamer HCl) has a greater incidence of metabolic acidosis leading to the development of Renvela (sevelamer carbonate). Lanthanum carbonate is another phosphate binder with similar efficacy to calcium-based PB's. Use is limited, however, due to cost and availability.

Two iron-based phosphate binders have recently been approved as a novel therapy choice for management of hyperphosphetemia in CKD patients. Sucroferric oxyhydroxide (Velphoro) and Ferric citrate (Auryxia) have demonstrated to be therapeutically equivalent to sevelamer in clinical trials. Sucroferric oxyhydroxide has also shown to be as effective as Lanthanum carbonate. The side effect profile is similar to current PB agents, with the addition of iron related GI issues such as stool discoloration, constipation, and bloating. These agents may offer an alternative treatment option to CKD patients.

Formulary Agents:

Drug	Initial regimen	Cost per day	Side Effects
Tums (calcium carbonate)**	3 tabs daily	< $10	vascular calcification, may require >17tab/day
PhosLo (calcium acetate)**	1334 mg (2 cap) TID	$3.24	vascular calcification
Renagel (sevelamer HCl)	800-1200mg (1-2 tab) TID	$18.33-$36.66	metabolic acidosis, non-formulary
Renvela (sevelamer carbonate)**	800-1600mg (1-2 tab) TID	$14.67-$29.34	large pill burden (>9 tab/day)
Fosrenol (lanthanum carbonate)**	500-1000 (1-2 tab) TID	$26.67-$53.34	
Velphoro (sucroferric oxyhydroxide)	500-1000(1-2 tab) TID	$25.62-$51.24	Abnormal taste, Fe related GI issues, low pill burden
Auryxia (ferric citrate)	420mg (2tab) TID 8-9 tab/day in trials	$52.44 $69.92-$78.66	Iron overload, theoretical risk of aluminum overload, Fe related GI issues

**Agents currently on formulary

Direct Drug Comparisons:

Ferric citrate (Auryxia)

- 7 trials to assess efficacy, statistically shown to be equivalent to Sevelamer.
- Niche therapy may be a reduced need for Iron infusion and ESA administration. Studies have shown a 25% reduction in ESA usage and a 50% reduction in IV Iron use while on this therapy.
- Cost is significantly more than standard PB therapy.

Sucroferric Oxyhydroxide (Velphoro)

- 4 completed trials, 3 studies pending. Statistically shown to be equivalent to Sevelamer and Lanthanum carbonate.
- Low pill burden, cost is comparable to current therapies.

Recommendations:

Auto-Sub Policy for Novel Phosphate Binders

Novel Agent	Formulary
Velphoro 500 mg TID Velphoro 1000 mg TID	Renvela 800 mg TID Renvela 1600 mg TID
Auryxia 420 mg TID Auryxia 640 mg TID + (Max 12 tabs daily)	Renvela 800 mg TID Renvela 1600 mg TID

Adverse Drug Reaction (ADR) Summary
FY15 MAY-JUNE 2015

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: 52 (25%)
Prior to hospitalization: 156 (75%)
Total: 208

Category 1: 141
Category 2: 66
Category 3: 1

Category 3 to discuss: 84 yo female patient transferred from a physican's office after a sudden cardiac event. EKG showed QT prolongation. Pt had a history of atrial dysrhythmia with sustained rapid heart rates over 120 bpm with episodes of presyncope and syncope. The patient was being treated with Sotalol 80mg PO BID for a likely reentry tachycardia that would be difficult to treat with radiofrequency ablation. Progress notes stated "she seems to have had a reaction to the Sotalol with QT prolongation and torsades, resulting in a sudden death arrhythmia in our offices today." Her hospital stay resulted in placement of a transvenous pacemaker, development of aspiration pneumonia and respiratory failure resulting in intubation, acute kidney injury, refractory cardiogenic shock, and questionable anoxic brain injury vs encephalopathy status post cardiac arrest.

Narcotic Safety – update

As you know, narcotics continue to be a major contributor to inpatient ADRs. Leading reactions include altered mental status changes, nausea, constipation, and respiratory distress. Changes are coming as part of the ESCAPADE campaign, Every Safe Clinician Against Preventable Adverse Drug Events. The first focus of the ESCAPADE committee is preventing opioid-induced oversedation and respiratory depression. Beginning November 3, nurses will be required to do mandatory pain, sedation, and respiratory status assessments for all patients receiving oral or IV opioids. These assessments will automatically be triggered anytime an opioid is documented as being administered. The timing of these assessments will be medication specific and will occur at the time of approximate peak therapeutic efficacy, based on drug and route specific pharmacokinetics.
CHI Memorial will begin using the **POSS Scale (Pasero Opioid-induced Sedation Scale)** for opioid-specific sedation assessments. Nurses have given positive feedback on the POSS Scale because it not only allows them to assess their patient's sedation level, but it also gives direction on actions to take for oversedation.

Pasero Opioid-induced Sedation Scale (POSS)

S = Sleep, easy to arouse
Acceptable; no action necessary; may increase opioid dose if needed

1. Awake and alert
Acceptable; no action necessary; may increase opioid dose if needed

2. Slightly drowsy, easily aroused
Acceptable; no action necessary; may increase opioid dose if needed

3. Frequently drowsy, arousable, drifts off to sleep during conversation
Unacceptable; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory; decrease opioid dose 25% to 50% or notify prescriber or anesthesiologist for orders; consider administering a non-sedating, opioid-sparing nonopioid, such as acetaminophen or an NSAID, if not contraindicated.

4. Somnolent, minimal or no response to verbal or physical stimulation
Unacceptable; stop opioid; consider administering naloxone; notify prescriber or anesthesiologist; monitor respiratory status and sedation level closely until sedation level is stable at less than 3 and respiratory status is satisfactory.

Title:			
PHARMACY FORMULARY BUSINESS REVIEW COMMITTEE			
		Page 1 of 2	
Policy Number: PHRM- 01000		Date Last reviewed/Revised: 11/15	Valid Until: 11/18
Department(s) Affected: All Clinical Areas		Review Period: every 3 years	

OUTCOME: The Pharmacy Formulary Business Review Committee is a sub-committee of the Pharmacy and Therapeutics (P&T) Committee with the purpose of evaluating potential financial and business impact of outpatient medication therapies.

DEFINITIONS & AUTHORITY: The Pharmacy Formulary Business Review Committee is designed to evaluate medication therapy cost and reimbursement. No final formulary decisions are made within this committee, however this sub-committee is designed to conduct a thorough cost and reimbursement analysis for the purpose of evaluating the potential financial and business impact of adding new outpatient therapies to hospital formulary.

Recommendations and analysis from this committee will be discussed at the next scheduled P&T committee meeting for final formulary decision. The P&T committee will utilize the criteria for formulary decisions as outlined in the *Formulary Policy* (MM-05428).

COMMITTEE MEMBERSHIP:

The committee will consist of at a minimum the following individuals:

- Chief Medical Officer (CMO) and/or other hospital administrator*
- P&T Committee Chairman or other designated P&T physician member*
- Financial Representative*
- Director of Pharmacy*
- Pharmacy Clinical Coordinator
- Infusion Center Manager
- Scheduling/Pre-registration Representative
- Ad hoc members: pertinent service line administrators, etc. as deemed appropriate per the committee.

** Indicates sub-committee members who will be involved in the review of any medications requiring an expedited review.*

POLICY:

Meeting Frequency:

The Pharmacy Formulary Business Review Committee will be scheduled to meet on a bi-monthly basis. Scheduled meetings may be cancelled at the sub-committee's discretion if no items are designated for review.

Medication Requests:

I. Standard Review
   A. Medication review requests will be scheduled for the next Formulary Business Review Committee if other similar therapies currently exist on the hospital's formulary.
   B. Medications for review will be communicated to the committee members no later than two weeks prior to the next scheduled meeting.
   C. Recommendations will be forwarded to the P&T committee for ultimate final decision.

II. Expedited Review

   A. If the therapy represents a new or novel therapeutic entity or if a delay could jeopardize a patient's health, an expedited review process may be used.
   B. Director of Pharmacy or designee will gather pertinent information for evaluation by the subset of committee members indicated above.

C. A temporary decision to proceed or deny the medication request will be determined and communicated to the prescriber.
D. Medications that undergo an expedited review will still require final formulary evaluation by the P&T committee as indicated in the *Formulary (MM-05428)* and *Pharmacy and Therapeutics Committee (PHRM-POL-0624)* policies.

Title:			
Ketamine Administration for Pain (Continuous Intravenous Infusions) -Adults			
		Page 1 of 2	
Policy Number: xxx - xxx		Date Last reviewed/Revised: 1/15	Valid Until: 1/18
Department(s) Affected:		Review Period: every 3 years	

OUTCOME: To provide guidance in the care of patients receiving Ketamine as an infusion for treatment of pain.

DEFINITIONS:
Ketamine produces analgesia by binding to receptors in the peripheral and central nervous systems. These receptors are the opioid receptors as well as the N-methyl D-aspartate (NMDA) receptor in the dorsal horn of the spinal cord. NMDA receptors participate in the development and maintenance of what can be called "pathologic pain" after tissue injury which is increased pain perception as a result of pain sensitization. Ketamine inhibits the binding of excitatory amino acids to the NMDA receptors, reducing the impact of painful stimuli. This blocking action is thought to be the mechanism behind its analgesic properties. Ketamine also inhibits the reuptake of dopamine and serotonin and elevates circulating epinephrine and norepinephrine levels. This, increases the heart rate, blood pressure, cardiac output and vascular resistance.

Ketamine is highly lipid soluble and crosses the blood-brain barrier. The onset is quick, within 30 seconds after intravenous administration with full effect within one minute and duration of up to 60 minutes. The half-life is two to three hours. Immediate effects of ketamine include analgesia, sedation, pupil dilation, nystagmus, lacrimation, salivation, and increased muscle tone. There may also be dissociative side effects such as hallucinations. Consideration should be given to decreasing the total opioid dose as ketamine has an opioid effect.

INDICATIONS INCLUDE: postoperative pain, neuropathic pain and acute or chronic pain.

PERSONNEL: Ketamine infusion for pain is approved for administration by competent RNs.

PROCEDURE:

A. Initial Patient Assessment

1. Assess patient according to the *Pain Management* policy (PC-07201)

2. Assess patient for risk of adverse event. Caution is strongly advised in the administration of Ketamine in patients with any of the following:
   a. Cardiovascular or respiratory compromise
   b. Psychosis, post-traumatic stress disorder (PTSD) or schizophrenia
   c. For any concerns, contact prescriber (anesthesia or critical care physician)

B. Initiating Therapy

Review MD Order and prepare for administration. Ordering of Ketamine for pain indication is restricted to anesthesia and/or critical care physicians. Patient must be in PACU extended stay or ICU to receive Ketamine for this indication.

1. Obtain Ketamine infusion from Pharmacy. The standard drip concentration 1 mg per ml (1 mg/ml) 250mg/250ml).

2. Therapy initiation and dose adjustments per anesthesia service or intensivist only.

3. Dosing recommendations may include a one-time infusion (over 30 minutes) or a continuous infusion. Normal doses and maximum doses for each type of dose are listed below. The continuous infusion rate may be titrated up and down based upon clinical response and criteria established by the physician.

- Continuous infusion:
    - Normal dose: 0.1 – 0.35 mg/kg/hr
        - Maximum dose: 0.4 mg/kg/hr
- Intermittent/Bolus dosing (each dose infused over 30 minutes) every 6 hours
    - Normal dose: 0.25 – 0.5 mg/kg
        - Maximum dose: 0.5 mg/kg

4. A benzodiazepine is commonly prescribed and should be considered to reduce the incidence of hallucinations and may be ordered per physician order.

C. Patient Monitoring during Initial Administration and With Dose Change

1. Monitor respiratory rate, oxygenation saturation, heart rate, level of pain and sedation (using RASS) by the frequency below for route of therapy.

    a. IV ketamine: Monitor within 60 minutes of initiation of IV therapy and within 60 minutes of any increase in dose.

D. **Routine Patient Monitoring**

1. Monitor vital signs, pain and sedation score (using RASS) every 2 hours for the first 24 hours then q 4 hours unless an increase in dose, at which time monitor q 2 hours for 24 hours after stable dose is achieved, or more frequently as clinically indicated.

E. Documentation

1. Document the following:
    a. Pain score
    b. Sedation score (RASS)
    c. Oxygenation saturation level
    d. Respiratory rate
    e. Heart rate

F. Reportable Conditions:

Notify ordering MD if any of the following occur:
1. RASS $\leq$-2 or $\geq$ 2.
2. Psychological side effects i.e. hallucinations, vivid dreams, aggressive behavior.
3. Sustained hypertension (>20% increase in blood pressure).
4. Increased pain level or unrelieved pain

Title:			
CHEMOTHERAPY AND BIOLOGIC DOSE ROUNDING POLICY			
			Page 1 of 1
Policy Number: XXX- XXXX		Date Last reviewed/Revised: 11/15	Valid Until: 1/18
Department(s) Affected: Pharmacy		Review Period: every 3 years	

OUTCOME: To minimize waste of high cost and high use medication through dose rounding of biologics and cytotoxic agents typically used for hematology/oncology and autoimmune indications.

DEFINITIONS:

Biologics: Any therapeutic serum, toxin, anti-toxin or analogous microbial product applicable to the prevention, treatment or cure of diseases or injuries; a bioengineered therapeutic agent—e.g., a hormone, antibody, cytokine—produced in bacteria, animals and other organisms.

Cytotoxic Agents: Any therapeutic agent that works by damaging cells, particularly cells that grow at a rapid rate.

POLICY: A pharmacist may use established criteria to round doses of specified biologics within 10 % of the ordered dose to the nearest vial size and specific cytotoxic agents within 5 % of the ordered dose to the nearest vial size.

MEDICATIONS PERTAINING TO THIS POLICY: This list is not all inclusive and medications added to formulary will be considered for addition to this policy per P&T review and approval.

Biologics: ado-trastuzumab, bevacizumab, belimumab, golimumab, nivolumab, panitumumab, pertuzumab, ramucirumab, infliximab, rituximab, tocilizumab, trastuzumab, intravenous immunoglobulin (IVIG), abatacept, brentuximab, cetuximab, ipilimumab

Cytotoxic Agents: arsenic, azacitidine, bendamustine, bleomycin, carboplatin, cisplatin, cladribine, cyclophosphamide, cytarabine, dacarbazine, daunorubicin, decitabine, docetaxel, doxorubicin, eribulin, etoposide, fluorouracil, gemcitabine, idarubicin, ifosfamide, irinotecan, methotrexate, oxaliplatin, paclitaxel, protein-bound paclitaxel, pemetrexed, topotecan, vincristine, vinorelbine

PROCEDURE: Pharmacist will assess original drug order, strength of vials available for the particular drug and calculate if rounding to the nearest vial size may be beneficial within 5-10% of its drug class.

Key Contact: Patrick Ellis, PharmD, Marty Laird, PharmD
Approved/Reviewed by: **List applicable** Councils, and leaders that have reviewed and/or signed in the approval process
Reference(s):

Jenkins P, Wallis R. Dose-rounding of adjuvant chemotherapy for breast cancer: an audit of toxicity. J Oncol Pharm Practice. 2010;16:251-255.

Francis SM, Heyliger A, Miyares MA, Viera M. Potential cost savings associated with dose rounding antineoplastic monoclonal agents. J Oncol Pharm Practice. 2015; 21(4):280-284.

Fasola F, Aita M, Marini L et al. Drug waste minimization and cost-containment in medical oncology: two year results of a feasibility study. BMC Health Serv Res. 2008 Apr 1;8:70. doi: 10.1186/1472-6963-8-70.

Attachment(s): None
Related Forms: None
Date First Effective & (Revision/Review dates): 1/16
Distribution: MHCS Intranet

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.