Pharmacy & Therapeutics Committee Meeting
Private Dining Room
August 10, 2017 7:00 a.m.

Next Meeting will be October 12, 2017 at 7:00 AM in the Private Dining Room

PHARMACY AND THERAPEUTICS COMMITTEE

DATE: April 13, 2017 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. (Phone)	Sandy Vredeveld, DPh	Nan Payne, RN	Shane Church, PharmD
David Dodson, M.D.	Patrick Ellis, PharmD	Nathan Schatzman, M.D	Justin Reinert, PharmD
Mark Anderson, MD	Lila Heet, PharmD	Shannon Harris, RN	Jenny Gibson, PharmD
Allen Atchley, M.D.	Susan Fuchs, RD	Michael Stipanov, M.D.	Brianna Qualls, Student
Richard Yap, M.D.	Karen Babb, PharmD	Scott Harbaugh, Finance	
Helen Kuroki, MD	Melissa Roden, RN	Jeffrey Mullins, M.D	
F. Hamilton, M.D.	Rodney Elliott	Jamie Barrie, PharmD	
Avni Kapadia, M.D.	Petra Green, RN	Patty Hicks, RN	
Nathan Chamberlain, M.D	Elvira Smith, RN		

This meeting will be convened under the protection of the Tennessee Statute 63-6-219 and the Health Care Quality Improvement Act of 1986, Public Law 99-660. All information, case reviews, meeting minutes, statistics and correspondence are confidential and protected. Included in that protection are those that are involved in the review of the information. Any discussion of this information outside the realm of Peer Review constitutes a breach and violates the protection of the persons involved in the breach.

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
Minutes	The February 9, 2017 minutes were approved as submitted.	Approved	Complete
CHI MUE Committee	The following medications were reviewed: **CHI MUE Committee Decision Brief**: The medications that were reviewed at the March national MUE committee meeting were reviewed with the committee. The only two items that required local P&T review are the following: **A.** **Sotalol:** Sotalol IV injection was designated non-formulary by the national committee. Dr. Dodson pointed out that this is part of the ACLS pathway for treatment of tachycardia with wide QRS. Dr. Pesce and the committee didn't feel this was necessary as other formulary options such as amiodarone and procainaimide are also options for this same indications. **B.** **Dantrolene:** Larger vial size formulation (Ryanodex) designated non-formulary by the national committee. This product is currently non-formulary at Memorial facilities and the committee was in support of the national non-formulary designation. **C.** **Inpatient iron formulary:** No changes to local formulary necessary; current formulary consistent with national decision (ferric gluconate complex OR iron dextran single dose replacement). **D.** **SGLT2 inhibitors:** No changes to local formulary necessary; current formulary consistent with national decision (non-formulary, these meds are held during hospitalization). **E.** **Long acting bronchodilators:** Formulary preferred products and corresponding therapeutic interchanges for LABA (Brovana), LAMA (Spiriva), and LAMA/LABA (Anoro Ellipta) were designated by the national committee. No changes to local formulary necessary; current formulary consistent with national decision.	Non formulary status approved Non formulary status approved No changes necessary No changes necessary No changes necessary	Complete Complete Complete Complete Complete
Therapeutic Interchanges and Formulary Decisions	**1.** **Latuda® (lurasidone) –** New atypical antipsychotic indicated for treatment of bipolar depression and schizophrenia. Recently designated as formulary-restricted by national MUE committee to facilities with inpatient psychiatric care facilities. The committee agreed with this recommendation and supported non-formulary designation for all Memorial facilities. **2.** **Invega® (paliperidone) –** New atypical antipsychotic indicated for treatment of schizoaffective and schizophrenia (major metabolite of risperidone). Recently designated as formulary-restricted by national MUE	Non-formulary status Non-formulary status	Complete Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	committee to facilities with inpatient psychiatric care facilities. The committee agreed with this recommendation and supported non-formulary designation for all Memorial facilities. An optional therapeutic substitution was offered by CHI although Patrick suggested that due to PK/PD differences between the formulations to designate this as non-formulary and work through non-formulary processes when patients are unable to supply their own home medication for dispensing during hospitalization.		
	3. **Relistor® (methylnaltrexone) Therapeutic Interchange –** A potential therapeutic interchange (Relistor → Movantik) was proposed for patients with Relistor orders that are able to tolerate oral medications. This interchange was previously supported and approved by CHI national MUE committee in 2016. Justin reviewed a recent evaluation of Relistor utilization and discovered that 38% of patients that were prescribed Relistor were taking other oral medications at the time of the Relistor order and could have potentially received Movantik as an alternative therapy (significant cost savings opportunity). The majority of all use (70%) was from hospitalist and ED providers. The committee was supportive of this automatic therapeutic interchange and recommended this be approved and implemented at Memorial facilities. Patrick explained that he was still awaiting feedback from GI providers on this interchange and until this feedback is received he suggested that this interchange not involve GI providers and this decision would be modified to include these providers or not based on this specialty's feedback.	Therapeutic interchange approved	Complete
	4. **Reopro® (abciximab) –** Due to minimal use and routine wasting of expired product, Patrick has previously discussed the formulary status of Reopro with the interventional cardiologists. The invasive cardiology committee agreed with the recommendation for formulary removal. Further changes to this class of medications are currently being considered by the national MUE committee and national CV service line with further discussion planned for the May MUE committee meeting.	Removal from formulary approved	Complete
Medication Safety & Policy	1. **Hypertonic saline (3% NS) –** Follow up discussion from previous meeting. Patrick reviewed a proposed policy for use of hypertonic saline. The policy detailed ordering requirements, lab monitoring requirements, criteria for stopping infusion (Na+ increase limits), as well as nursing documentation and monitoring requirements. Additionally, a draft order set was presented that incorporates the various policy requirements that would be required for non-nephrology or critical care physicians to order hypertonic saline for treatment of hyponatremia. Dr. Chamberlain expressed support for both proposed documents (policy and order set) and also suggested that appropriate use criteria also be included on the order set to highlight when this therapy should be utilized (hyponatremia with symptoms). He agreed to help Patrick develop this verbiage. Additional discussion revolved around restricting to critical care areas only, however the committee supported the documents as written without including any additional restrictions to particular patient care units. Patrick agreed to provide education to the hospitalists via their routine monthly staff meetings.	Policy & order set approved, additional education to be provided to hospitalists	Complete
	2. **Perioperative medication management –** The updated pre-operative anesthesia orders were reviewed by the committee. Dr. Schatzman, although not in attendance, expressed continued concerns regarding the holding of ACE/ARBs without further communication with MEC and expanded education to surgery providers. The committee still strongly supported this initiative from a patient safety standpoint and Patrick agreed to assist with any additional education needs for eventual inclusion regarding perioperative holding of ACE/ARBs. Dr. Schatzman plans to present this to MEC on April 25th for further discussion. Temporarily the holding of ACE/ARBs statement will be removed from this order set until education plan in place.	Changes pending Dr. Schatzman's MEC discussion	Pending
	3. **PCA smart pump "guardrail" settings** – A recent patient safety event due to a PCA pump programming error (incorrect hydromorphone continuous rate) prompted a review of the existing soft and hard limits for morphine and hydromorphone PCAs. Patrick explained that this review revealed that 45% of all attempted pump	Approved	Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	programs triggered either a soft or hard limit alert. Additionally, the current soft and hard limits were set at levels that did not mirror typical PCA dosing from routinely used order sets. Patrick reviewed potential changes that should lower the number of unnecessary soft limit alerts and readjust these to levels that will render these alerts more useful and prevent more potential programming errors. These changes will further be reviewed with nursing and implemented with the next scheduled pump update.		
	4. Nicardipine IV infusions – Per Dr. Yap's request, the current hospital policy (*Cardiac IV & Continuous Medication Infusion – Patient Placement & Monitoring Policy*) was reviewed for potential inclusion of nicardipine infusion for traditional telemetry units. After discussion, the physician committee members felt uncomfortable from a patient safety standpoint in modifying the existing policy which limits nicardipine to ICU or SSU units only. The committee felt that IV nicardipine infusions should only be utilized for patients with hypertensive urgency and these situations should be confined to ICU areas. Dr. Atchley suggested IV hydralazine be utilized as an IV agent when patients are experiencing intermittent hypertension uncontrolled by traditional oral medications.	Modifications to existing policy not supported	Complete
Medication Use Evaluation	**1. PPI Stress Ulcer Prophylaxis –** A repeat MUE was conducted to reassess the appropriateness of hospital initiated PPI SUP. This re-evaluation showed improved use among ICU patients although non-ICU utilization was not improved with 80% of all newly initiated use inappropriate (mostly hospitalist providers). Dr. Hamilton suggested re-education for hospitalists with focus on increased risk of Clostridium difficile infection (CDI) in patients on acid suppression therapies. Jenny also explained that ~50% of all inappropriate use originated from 5 hospitalist providers. Melissa suggested letters be sent to these 5 physicians alerting them of their outlier status in regard to PPI prescribing and this was supported by Dr. Hamilton. Patrick has already begun re-education for providers and this will continue until all hospitalist providers have received this education on PPI use and increased CDI risk.	Education plan in place	Complete
	2. Glycemic Control – Shane briefly reviewed data from his residency project evaluating glycemic control for hospitalized patients with ICD-10 diagnosis of diabetes. The data has shown a high incidence of hyperglycemia (> 180 mg/dl & > 250 mg/dl) particularly among patients admitted on home insulin regimens. A pilot is currently underway in which pharmacy is working closely with hospitalist providers when hyperglycemia has been identified using the pharmacy's clinical surveillance system.	Information only	Complete
Nutrition Support	**Diet Manual –** Annual review per policy. There has been no changes of the current Nutrition Care Manual by the Academy of Nutrition and Dietetics since March 2016. Location of the NCM is on MNet, manual discs available per policy in case of emergency. Current attachment to our Diet Manual Policy includes diets that are exceptions to the Nutrition Care Manual. The very restrictive GI Soft Diet that was requested by a physician that no longer practices at Memorial was removed from the exception list.	Approved	Complete
Protocols	**IV Iron Replacement (max dose consideration) –** Patrick reviewed a proposed revision to add a 1.5 gram max dose to the IV Iron Replacement Protocol. A few recent large doses per the standard dose calculation prompted a review of the literature in regard to maximum total iron replacement doses. Although a clear literature recommendation doesn't exist the majority of evidence seems to suggest a 1.5 gram per total dose maximum. This was reviewed with Dr. Stipanov and he agreed with this suggested modification.	Approved	Complete
	Nicotine Replacement Protocol – Justin reviewed the current NRT protocol and explained that some modifications appear to be needed. The committee agreed with the option to add PRN lozenges as a standard in addition to patch therapies which is consistent with consensus recommendations from USPHS. Additionally, the committee supported Patrick's suggestion to investigate the possibility of automatically initiating the NRT protocol for any patients that are agreeable to cessation therapy while hospitalized without the need for specific physician order (similar to flu vaccination process). Patrick will discuss with Nan Payne to see if a previous MEC approval will allow this or if this	Approved	Pending

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	will require additional MEC approval. If approved, Patrick will work with clinical informatics to assess feasibility of incorporating this into our current EMR.		

There being no further business, the meeting was adjourned at 8:00 A.M. The next P&T meeting is **June 8, 2017 at 7:00 a.m.**

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

Approved by,
Richard Pesce, M.D. Chairman

MEDICATION USE AND EVALUATION COMMITTEE DECISION BRIEF: May 2017

Executive Summary

May MUE Decision(s)

NOTE: Per MUE normal process, markets may implement or retain more restrictive formulary status.

Medication Name	*Medication Used for*	Formulary Status Decision				Comments/Restrictions/Therapeutic Interchange	Timeline to Implement
		Formulary, Unrestricted	Formulary, Restricted	Non-Formulary	Do Not Stock		
Glycoprotein IIb/IIIa Inhibitor Class Review	*platelet aggregation inhibition*	**tirofiban** (Aggrastat®)	**abciximab** (ReoPro®)	**eptifibatide** (Integrilin®)		abciximab (ReoPro®) is restricted to patients with severe renal impairment (CrCl < 30mL/min) or receiving dialysis when tirofiban is not appropriate or those undergoing neurovascular procedures	90 days from 5/16/2017
Chemotherapy-Induced Nausea and Vomiting (CINV) Treatment Review	*chemotherapy-induced nausea/vomiting (CINV)*	ondansetron (Zofran®) olanzapine (Zyprexa®)	palonosetron (Aloxi®) fosaprepitant (EMEND® for Injection)	granisetron (KYTRIL®) aprepitant (EMEND®) rolapitant (VARUBI™) netupitant/ palonosetron (Akynzeo •)		Palonosetron is restricted to outpatient use unless use meets listed criteria due to reimbursement Fosaprepitant is restricted based on CINV risk Note: Outpatient use may be determined by the entity based on reimbursement considerations	60 days from 5/16/2017
ocrelizumab (Ocrevus®)	*Multiple sclerosis (MS)*		ocrelizumab (Ocrevus®)			Restrict to administration in outpatient infusion centers only with product ordered by/referred by neurologist (Information regarding availability of MS-trained neurologist may be needed)	30 days from 5/16/2017

Attendance Roster: 2017 MUE Attendance Roster Cumulative 05 16 2017 updated
Voting Roster: Voting Record May 2017 updated
Items above are listed in same order as they appear in the Committee Meeting Packet: CHI MUE Committee Compiled Packet 05 16 2017 Final

MEDICATION USE AND EVALUATION COMMITTEE DECISION BRIEF: July 2017

Executive Summary

July MUE Decision(s)

NOTE: Per MUE normal process, markets may implement or retain more restrictive formulary status.

Medication Name	*Medication Used for*	Formulary Status Decision				Comments/Restrictions/Therapeutic Interchange	Timeline to Implement
		Formulary, Unrestricted	Formulary, Restricted	Non-Formulary	Do Not Stock		
Gram Positive Organism Treatment Review		**clindamycin** **doxycycline** **minocycline** **rifampin** **TMP/SMX** **vancomycin**	**ceftaroline (Teflaro®)** **daptomycin (Cubicin®)** **linezolid (Zyvox®)** **oritavancin (ORBACTIV®)** **tigecycline (Tygacil®)**	**dalbavancin (DALVANCE®)** **quinupristin/ dalfopristin (Synercid®)** **tedizolid (SIVEXTRO®)** **telavancin (VIBATIV®)**		**Restrictions** **See SELECTION CRITERIA FOR RESTRICTED GRAM POSITIVE ANTIBIOTICS (IN May 2017 MUE Packet)** Selection criteria identified for specific situations such as resistance, treatment failure, hypersensitivity/allergy, and salvage.	60 days from 7/18/2017
Long-acting Somatostatin Analogs	*symptoms due to tumors*		**Lanreotide LAR (SOMATULINE® DEPOT)** **octreotide LAR (Sandostatin® LAR Depot)** **pasireotide LAR (Signifor® LAR)**			**Restrictions** Restrict to outpatient infusion use only for patients with FDA approved indications or payer approved off-label indications subsequent to insurance approval/pre-authorization.	60 days from 7/18/2017

Note: The Decision Brief summarizes the decisions of the national CHI Medication Use and Evaluation (MUE) Committee. Local P&Ts may act on MUE Decisions in one of three ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

Medication Name	*Medication Used for*	Formulary Status Decision				Comments/Restrictions/Therapeutic Interchange	Timeline to Implement
		Formulary, Unrestricted	Formulary, Restricted	Non-Formulary	Do Not Stock		
abatacept (Orencia®)	*Rheumatoid arthritis (RA)*		**abatacept (Orencia®) Intravenous Formulation**	**abatacept (Orencia®) Subcutaneous Formulation**		**Restrictions (IV Formulation)** Restrict to outpatient infusion for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or pre-authorization.	60 days from 7/18/2017
Therapeutic Interchange for brexpiprazole to aripiprazole (Update from 9/2016)	*Schizophrenia and major depressive disorders*	**aripiprazole** (9/2016 decision)		**brexpiprazole** (9/2016 decision)		Update Therapeutic Interchange for brexpiprazole 4mg to aripiprazole 20mg (from 30mg previously). Therapeutically interchange brexpiprazole to aripiprazole **THERAPEUTIC INTERCHANGE** **Ordered** → **Provide** brexpiprazole 1mg → aripiprazole 5mg brexpiprazole 2mg → aripiprazole 10mg brexpiprazole 3mg → aripiprazole 15mg brexpiprazole 4mg → aripiprazole 20mg	Immediately
belimumab (Benlysta®)	*Systemic lupus erythematous (SLE)*		**belimumab (Benlysta®)**			**Restrictions** Restricted to outpatient infusion for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or pre-authorization	60 days from 7/18/2017
mivacurium (Mivacron®)	*Adjunct to general anesthesia to relax skeletal muscles*			**mivacuronium (Mivacron®)**			Immediately
bezlotoxumab (ZINPLAVA®)	*Reducing the recurrence of Clostridium difficile infection*			**bezlotoxumab (Zinplava®)**			90 days from 7/18/2017

Medication Name	*Medication Used for*	Formulary Status Decision				Comments/Restrictions/Therapeutic Interchange	Timeline to Implement
		Formulary, Unrestricted	Formulary, Restricted	Non-Formulary	Do Not Stock		
Therapeutic Interchange for ophthalmic proparacaine to tetracaine	*topical anesthetic for eye for various eye procedures*	**tetracaine** 0.5% ophthalmic solution **proparacaine** 0.5% ophthalmic solution				A therapeutic interchange from proparacaine to tetracaine was proposed. The proposal was not approved due to concern with transient stinging/burning associated with tetracaine. As a result, both products remain as Formulary, Unrestricted per MUE decision. A local facility may consider the proposed therapeutic interchange since it is a more restrictive option; the information in the July MUE packet may be used as a reference.	Therapeutic Interchange Not Approved
obinutuzumab (GAZYVA®)	*Chronic lymphocytic leukemia and follicular lymphoma*		**obinutuzumab** (GAZYVA®)			**Restrictions** Outpatient infusion for FDA-approved indications or payer-approved off-label subsequent to insurance approval or pre-authorization.	60 days from 7/18/2017
Medication Dose Rounding Guideline	*Guideline for appropriate dose adjustments and reducing waste*					Dose Rounding Guidelines for Adult Patients: Clinical effect (response or toxicity/side effects) unlikely with minimal dose rounding (5-10%) but may significantly reduce medication waste	90 days from 7/18/2017
Phosphodiesterase Type 5 (PDE5) Inhibitors	*Pulmonary Arterial Hypertension (PAH)*		**sildenafil** (Revatio®)	**tadalafil** (Adcirca®) **tadalafil** (Cialis®) 5mg for benign prostatic hypertrophy (BPH)	**sildenafil** (Viagra®) **tadalafil** (Cialis®) 20mg **vardenafil** (Levitra®, Staxyn®)	**Restrictions** Sildenafil (Revatio®) is restricted to treatment of pulmonary arterial hypertension (PAH) only	60 days from 7/18/2017

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Medication Name	*Medication Used for*	Formulary Status Decision				Comments/Restrictions/Therapeutic Interchange	Timeline to Implement
		Formulary, Unrestricted	Formulary, Restricted	Non-Formulary	Do Not Stock		
Anesthesia Gases	*general anesthesia*	**sevoflurane (Ultane®, Sojourn®)** **isoflurane (Forane®, Terrell®)**	**desflurane (Suprane®)**			**Restrictions provided by anesthesia** **Case selection factors:** – Neurological surgery that is high risk for acute post op complications and early post op mental acuity is required for a timely diagnosis (e.g. carotid endarterectomy, cerebral aneurysm clipping, intracranial bleeding) – Surgical cases that require muscle paralysis/weakness with a patient that cannot tolerate neuromuscular blocking agents. (e.g. myasthenia gravis) **Patient selection factors:** – Any case that involves a super obese patient (BMI over 50) – Morbid or severe morbid obesity (BMI over 40) undergoing a case longer than 3 hours – Patient with a clear history of significant difficulty/complications related to emergence from anesthesia	120 days from 7/18/2017

Medication Name	*Medication Used for*	Formulary Status Decision				Comments/Restrictions/Therapeutic Interchange	Timeline to Implement
		Formulary, Unrestricted	Formulary, Restricted	Non-Formulary	Do Not Stock		
Glycoprotein IIb/IIIa Inhibitor Class Review	*platelet aggregation inhibition* *Modification to May 2017 Decision: add restrictions for abciximab (ReoPro®) only*		**abciximab** (ReoPro®)			**No change in formulary status of tirofiban (Aggrastat®), abciximab (ReoPro®), or eptifibatide (Integrilin®); modification to restrictions for abciximab (ReoPro®) only. (See May 2017 decision summary below.)** **Restrictions** **Update to abciximab (ReoPro®) Restrictions per request from CVSL:** **abciximab (ReoPro®) is restricted to patients with at least one of the following conditions or situations** **1) severe renal impairment (CrCl < 30mL/min) or extremely poor renal function (GFR < 30)** **2) receiving dialysis when tirofiban is not appropriate** **3) undergoing neurovascular procedures** **4) STEMI patients with visible thrombus** **5) insulin-dependent diabetes** **In addition, requirements to monitor utilization of abciximab (ReoPro®) were established. Monitor utilization for 6 months; if increase, local leadership will initiate chart review or audit of cases to evaluate compliance with restrictions**	**Immediately**
	Original MUE Decision (May 2017)						
	Medication Used for	**Formulary Status Decision**				**Comments/Restrictions/Therapeutic Interchange**	**Timeline to Implement**
		Formulary, Unrestricted	**Formulary, Restricted**	**Non-Formulary**	**Do Not Stock**		
	platelet aggregation inhibition	**tirofiban** (Aggrastat®)	**abciximab** (ReoPro®)	**eptifibatide** (Integrilin®)		**Restrictions (Original)** abciximab (ReoPro®) is restricted to patients: 1) with severe renal impairment (CrCl < 30mL/min) 2) receiving dialysis when tirofiban is not appropriate 3) undergoing neurovascular procedures	**90 days from 5/16/2017**

Note: The Decision Brief summarizes the decisions of the national CHI Medication Use and Evaluation (MUE) Committee. Local P&Ts may act on MUE Decisions in one of three ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

FORMULARY REVIEW

GENERIC NAME: OCRELIZUMAB (Genentech)

PROPRIETARY NAME: *Ocrevus*

INDICATIONS:

FDA Approved:
Treatment of adult patients with relapsing or primary progressive forms of multiple sclerosis.

THERAPEUTIC CATEGORY:
Monoclonal Antibody

PHARMACOKINETICS:

	Ocrelizumab
Absorption	Administered intravenously
Distribution	Central Volume of Distribution = 2.78 L; Peripheral volume and intercompartment clearance were estimated at 2.68 L and 0.29 L/day, respectively.
Metabolism	The metabolism of OCREVUS has not been directly studied because antibodies are cleared principally by catabolism.
Excretion	Constant clearance was estimated at 0.17 L/day, and initial time-dependent clearance at 0.05 L/day, which declined with a half-life of 33 weeks. The terminal elimination half-life was 26 days.
Cmax (mg/L)	212 mcg/mL in patients with RMS (600 mg infusion) and 141 mcg/mL in patients with PPMS (two 300 mg infusions administered within two weeks)
Bioavailability (%)	100%
t ½ (hr)	The terminal elimination half-life was 26 days.
Vd (L/kg)	Central Volume of Distribution = 2.78 L; Peripheral volume and intercompartment clearance were estimated at 2.68 L and 0.29 L/day, respectively.
AUC (mg*h/L)	3,510 mcg/mL per day
Protein binding (%)	N/A
Dose adjustment in renal insufficiency	None
Dose adjustment in geriatric patients	None
Dose adjustment in hepatic insufficiency	None

CLINICAL STUDIES:

Ocrelizumab versus Interferon Beta-1a in Relapsing Multiple Sclerosis – Two Identical Studies Performed				
Trial design	Randomized, double-blind, double-dummy, active comparator-controlled clinical trial			
Intervention	Ocrelizumab 600 mg IV every 24 weeks x 96 weeks vs. Interferon beta-1a (Rebif) 44 mcg three times weekly for 96 weeks			
Inclusion	MS patients who had experienced at least one relapse within the prior year, or two relapses within the prior two years, and had an Expanded Disability Status Scale (EDSS) score from 0 to 5.5. Patients with primary progressive forms of multiple sclerosis (MS) were excluded.			
Demographics	Demographics were balanced among each treatment group in both studies with regard to mean age; male vs. female; mean time from diagnosis to randomization; mean number of relapses in previous years; mean EDSS score; proportion of patients not treated with non-steroid therapy for MS in 2 years prior to study; baseline proportion of patients that had one or more T1 Gd-enhancing lesions.			
Endpoints	**Study 1**		**Study 2**	
	OCREVUS 600 mg every 24 weeks N=410	REBIF 44 mcg three times a week N=411	OCREVUS 600 mg every 24 weeks N=417	REBIF 44 mcg three times a week N=418
Clinical Endpoints				
Annualized Relapse Rate (Primary Endpoint) Relative Reduction	0.156	0.292	0.155	0.290
	46% (p<0.0001)		47% (p<0.0001)	
Proportion Relapse-free	83%	71%	82%	72%
Proportion of Patients with 12-week Confirmed Disability Progression1 Risk Reduction (Pooled Analysis2)	9.8% OCREVUS vs 15.2% REBIF			
	40%; p=0.0006			
MRI Endpoints				

Mean number of T1 Gd-enhancing lesions per MRI Relative Reduction	0.016	0.286	0.021	0.416
	94% (p<0.0001)		95% (p<0.0001)	
Mean number of new and/or enlarging T2 hyperintense lesions per MRI Relative Reduction	0.323	1.413	0.325	1.904
	77% (p<0.0001)		83% (p<0.0001)	

1 Defined as an increase of 1.0 point or more from the baseline Expanded Disability Status Scale (EDSS) score for patients with baseline score of 5.5 or less, or 0.5 or more when the baseline score is greater than 5.5, Kaplan-Meier estimates at Week 96.

Ocrelizumab versus Placebo in Primary Progressive Multiple Sclerosis	
Trial design	Randomized, double-blind, placebo-controlled clinical trial
Intervention	Patients were randomized 2:1 to receive either OCREVUS 600 mg or placebo as two 300 mg intravenous infusions 2 weeks apart every 24 weeks for at least 120 weeks.
Inclusion	Selection criteria required a baseline EDSS of 3 to 6.5 and a score of 2 or greater for the EDSS pyramidal functional system due to lower extremity findings.
Demographics	The baseline demographic and disease characteristics were balanced between the two treatment groups. At baseline, the mean age of patients was 45; 49% were female. The mean time since symptom onset was 6.7 years, the mean EDSS score was 4.7, and 26% had one or more T1 Gd-enhancing lesions at baseline; 88% of patients had not been treated previously with a non-steroid treatment for MS. The time to onset of disability progression confirmed at 12 weeks after onset was significantly longer for OCREVUS-treated patients than for placebo-treated patients.

Endpoints	**Study 3**	
	OCREVUS 600 mg (two 300 mg infusions two weeks apart every 24 weeks) N=488	Placebo N=244
Clinical Outcomes		
Proportion of patients with 12-week Confirmed Disability Progression1	32.9%	39.3%
Risk reduction	24%; p=0.0321	
MRI Endpoints		
Mean change in volume of T2 lesions, from baseline to Week 120 (cm3)	-0.39	0.79
	p<0.0001	

COMPARATIVE EFFICACY:

Ocrelizumab represents a new approach to management of Multiple Sclerosis as it is thought to act on the immune system's B-cells rather than the T-cells which have been the target of traditional immunomodulatory therapy such as Interferon Beta-1a, its head-to-head comparator in the pivotal clinical trials that supported FDA approval of Ocrelizumab and other therapies such as Tysabri (. In these trials, Ocrelizumab demonstrated statistically significant superiority to Interferon Beta-1a in prevention of disease relapse and progression endpoints.

CONTRAINDICATIONS:

• Active Hepatitis B Virus infection
• A history of life-threatening infusion reaction to Ocrelizumab

DRUG INTERACTIONS:

Interacting Drug	**Effect**
Immunosuppressive or Immune-Modulating Therapies	The concomitant use of OCREVUS and other immune-modulating or immunosuppressive therapies, including immunosuppressant doses of corticosteroids, is expected to increase the risk of immunosuppression. Consider the risk of additive immune system effects when coadministering immunosuppressive therapies with OCREVUS. When switching from drugs with prolonged immune effects, such as daclizumab, fingolimod, natalizumab, teriflunomide, or mitoxantrone, consider the duration and mode of action of these drugs because of additive immunosuppressive effects when initiating OCREVUS.

DOSING AND ADMINISTRATION:

Required pre-meds and assessment prior to ALL infusions:

- Infection Assessment:

- Prior to every infusion of OCREVUS, determine whether there is an active infection. In case of active infection, delay infusion of OCREVUS until the infection resolves.

- Recommended Premedication:
  - Pre-medicate with 100 mg of methylprednisolone (or an equivalent corticosteroid) administered intravenously approximately 30 minutes prior to each OCREVUS infusion to reduce the frequency and severity of infusion reactions. Pre-medicate with an antihistamine (e.g., diphenhydramine) approximately 30-60 minutes prior to each OCREVUS infusion to further reduce the frequency and severity of infusion reactions.
  - The addition of an antipyretic (e.g., acetaminophen) may also be considered.

Administration:

- Administer under the close supervision of an experienced healthcare professional with access to appropriate medical support to manage severe reactions such as serious infusion reactions.
- Initial dose: 300 mg intravenous infusion, followed two weeks later by a second 300 mg intravenous infusion.
- Subsequent doses: single 600 mg intravenous infusion every 6 months.
- Observe the patient for at least one hour after the completion of the infusion.

		Amount and Volume	**Infusion Rate and Duration**
Initial Dose (two infusions)	Infusion 1	300 mg in 250 mL	• Start at 30 mL per hour • Increase by 30 mL per hour every 30 minutes • Maximum: 180 mL per hour • Duration: 2.5 hours or longer
	Infusion 2 (2 weeks later)	300 mg in 250 mL	
Subsequent Doses (one infusion)	One infusion every 6 months[2]	600 mg in 500 mL	• Start at 40 mL per hour • Increase by 40 mL per hour every 30 minutes • Maximum: 200 mL per hour • Duration: 3.5 hours or longer

DOSING ADJUSTMENTS:
No dose adjustments required for renal or hepatic impairment

WARNING AND PRECAUTIONS

Warning and Precautions	
Infusion Reactions	Can cause infusion reactions, which can include pruritus, rash, urticaria, erythema, bronchospasm, throat irritation, oropharyngeal pain, dyspnea, pharyngeal or laryngeal edema, flushing, hypotension, pyrexia, fatigue, headache, dizziness, nausea, and tachycardia. In multiple sclerosis (MS) clinical trials, the incidence of infusion reactions in OCREVUS-treated patients [who received methylprednisolone (or an equivalent steroid) and possibly other pre-medication to reduce the risk of infusion reactions prior to each infusion] was 34 to 40%, with the highest incidence with the first infusion. There were no fatal infusion reactions, but 0.3% of OCREVUS-treated MS patients experienced infusion reactions that were serious, some requiring hospitalization. Observe patients treated with OCREVUS for infusion reactions during the infusion and for at least one hour after completion of the infusion. Inform patients that infusion reactions can occur up to 24 hours after the infusion. Reducing the Risk of Infusion Reactions and Managing Infusion Reactions: Administer pre-medication (e.g., methylprednisolone or an equivalent corticosteroid, and an antihistamine) to reduce the frequency and severity of infusion reactions. The addition of an antipyretic (e.g., acetaminophen) may also be considered. Management recommendations for infusion reactions depend on the type and severity of the reaction. For life-threatening infusion reactions, immediately and permanently stop OCREVUS and administer appropriate supportive treatment. For less severe infusion reactions, management may involve temporarily stopping the infusion, reducing the infusion rate, and/or administering symptomatic treatment.
Infections	A higher proportion of OCREVUS-treated patients experienced infections compared to patients taking REBIF or placebo. In RMS trials, 58% of OCREVUS-treated patients experienced one or more infections compared to 52% of REBIF-treated patients. In the PPMS trial, 70% of OCREVUS-treated patients experienced one or more infections compared to 68% of patients on placebo. OCREVUS increased the risk for upper respiratory tract infections, lower respiratory tract infections, skin infections, and herpes-related infections. OCREVUS was not associated with an increased risk of serious infections in MS patients. Delay OCREVUS administration in patients with an active infection until the infection is resolved. Respiratory Tract Infections: A higher proportion of OCREVUS-treated patients experienced respiratory tract infections compared to patients taking REBIF or placebo. In RMS trials, 40% of OCREVUS-treated patients experienced upper respiratory tract infections

	compared to 33% of REBIF-treated patients, and 8% of OCREVUS-treated patients experienced lower respiratory tract infections compared to 5% of REBIF-treated patients. In the PPMS trial, 49% of OCREVUS-treated patients experienced upper respiratory tract infections compared to 43% of patients on placebo and 10% of OCREVUS-treated patients experienced lower respiratory tract infections compared to 9% of patients on placebo. The infections were predominantly mild to moderate and consisted mostly of upper respiratory tract infections and bronchitis. Herpes: In active-controlled (RMS) clinical trials, herpes infections were reported more frequently in OCREVUS treated patients than in REBIF-treated patients, including herpes zoster (2.1% vs. 1.0%), herpes simplex (0.7% vs. 0.1%), oral herpes (3.0% vs. 2.2%), genital herpes (0.1% vs. 0%), and herpes virus infection (0.1% vs. 0%). Infections were predominantly mild to moderate in severity. There were no reports of disseminated herpes. In the placebo-controlled (PPMS) clinical trial, oral herpes was reported more frequently in the OCREVUS treated patients than in the patients on placebo (2.7% vs 0.8%). Progressive Multifocal Leukoencephalopathy (PML): PML is an opportunistic viral infection of the brain caused by the John Cunningham (JC) virus that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. Although no cases of PML were identified in OCREVUS clinical trials, JC virus infection resulting in PML has been observed in patients treated with other anti-CD20 antibodies and other MS therapies and has been associated with some risk factors (e.g., immunocompromised patients, polytherapy with immunosuppressants). At the first sign or symptom suggestive of PML, withhold OCREVUS and perform an appropriate diagnostic evaluation. MRI findings may be apparent before clinical signs or symptoms. Typical symptoms associated with PML are diverse, progress over days to weeks, and include progressive weakness on one side of the body or clumsiness of limbs, disturbance of vision, and changes in thinking, memory, and orientation leading to confusion and personality changes. Hepatitis B Virus (HBV) Reactivation: There were no reports of hepatitis B reactivation in MS patients treated with OCREVUS. Fulminant hepatitis, hepatic failure, and death caused by HBV reactivation have occurred in patients treated with other anti-CD20 antibodies. Perform HBV screening in all patients before initiation of treatment with OCREVUS. Do not administer OCREVUS to patients with active HBV confirmed by positive results for HBsAg and anti-HB tests. For patients who are negative for surface antigen [HBsAg] and positive for HB core antibody [HBcAb+] or are carriers of HBV [HBsAg+], consult liver disease experts before starting and during treatment. Possible Increased Risk of Immunosuppressant Effects with Other Immunosuppressants: When initiating OCREVUS after an immunosuppressive therapy or initiating an immunosuppressive therapy after OCREVUS, consider the potential for increased immunosuppressive effects. OCREVUS has not been studied in combination with other MS therapies. Vaccinations: Administer all immunizations according to immunization guidelines at least 6 weeks prior to initiation of OCREVUS. The safety of immunization with live or live-attenuated vaccines following OCREVUS therapy has not been studied, and vaccination with live-attenuated or live vaccines is not recommended during treatment and until Bcell repletion. No data are available on the effects of live or non-live vaccination in patients receiving OCREVUS.
Malignancies	An increased risk of malignancy with OCREVUS may exist. In controlled trials, malignancies, including breast cancer, occurred more frequently in OCREVUS-treated patients. Breast cancer occurred in 6 of 781 females treated with OCREVUS and none of 668 females treated with REBIF or placebo. Patients should follow standard breast cancer screening guidelines.

ADVERSE REACTIONS

Adverse Reactions	**OCREVUS 600 mg IV Every 24 Weeks[1] (n=486) %**	**Placebo (n=239) %**
Upper respiratory tract infections	49	43
Infusion reactions	40	26
Skin infections	14	11
Lower respiratory tract infections	10	9
Cough	7	3
Diarrhea	6	5
Edema peripheral	6	5
Herpes virus associated infections	5	4

PHARMACOECONOMICS/COST:
Cost per vial (300 mg vial): $16,250
Annual cost (1200 mg per year; 600 mg every 6 months): $65,000

CONCLUSION & RECOMMENDATION:
Ocrelizumab (Ocrevus) represents a new approach to management of MS as it is thought to act on the immune system's B-cells rather than the T-cells which have been the target of traditional immunomodulatory therapies such as Interferon Beta-1a, its head-to-head comparator in the pivotal clinical trials that supported FDA approval of Ocrelizumab. In these trials, Ocrelizumab demonstrated statistically significant superiority to Interferon Beta-1a in prevention of disease relapse and progression endpoints. Ocrelizumab is the first drug ever approved by the FDA for treatment of Primary-Progressive MS, the more aggressive form of the disease.

The CHI MUE committee recommendation is to classify this agent as "formulary, restricted" for outpatient infusion utilization only for patients subsequent to insurance approval/prior authorization.

FORMULARY REVIEW

GENERIC NAME: BEZLOTOXUMAB

PROPRIETARY NAME: *Zinplava* (Merck)

INDICATIONS:
Bezlotoxumab is approved by the Food and Drug Administration (FDA) to reduce the recurrence of *Clostridium difficile* infection in patients 18 years or older receiving antibacterial drug treatment for *C. difficile* infection and at high risk for *C. difficile* infection recurrence.

CLINICAL PHARMACOLOGY:
Zinplava (bezlotoxumab) is a human monoclonal antibody that binds to *C. difficile* toxin B and neutralizes its effects. Bezlotoxumab does not impact *C. difficile* toxin A. Although both toxins, A and B, produced by *Clostridium difficile* are known to act synergistically, toxin B is essential for virulence of *Clostridium difficile.*

PHARMACOKINETICS:
The pharmacokinetics of bezlotoxumab were studied in 1515 CDI patients in two Phase 3 trials. Based on a population PK analysis, the geometric mean (%CV) clearance of bezlotoxumab was 0.317 L/day (41%), with a mean volume of distribution of 7.33 L (16%), and elimination half-life (t½) of approximately 19 days (28%). These findings are consistent with PK characteristics of typical human monoclonal antibodies, which have low clearance, small volume of distribution, and long half-life. The clearance of bezlotoxumab increased with increasing body weight; the resulting exposure differences are adequately addressed by the administration of a weight-based dose (10mg/kg).

As a monoclonal antibody, bezlotoxumab is degraded into small peptides and individual amino acids through protein catabolism. Thus, bezlotoxumab is not expected to be metabolized by the liver or excreted by the kidney. Bezlotoxumab is not a substrate of hepatic metabolic enzymes or transporters. The target of bezlotoxumab is an exogenous toxin but not a cytokine modulator. Therefore, bezlotoxumab is not expected to inhibit or induce metabolic enzymes or transporters.

ADVERSE REACTIONS:
Serious Adverse Events (SAE) from MODIFY 1 & MODIFY 2 Trials (All results are bezlotoxumab vs. placebo)

Study	Total Patients	Patients with >1 event	Cardiac failure*	Diarrhea	Abdominal Pain	Respiratory Failure
Combined Trial Results (MODIFY 1 &2)	786 vs. 781	231 (29.4%) vs. 255 (32.7%)	17 (2.2%) vs. 7 (1%)	16 (2%) vs. 12 (1.5%)	7 (0.9%) vs. 4 (0.5%)	5 (0.6%) vs. 6 (0.8%)

Common Adverse Events (CAE) from MODIFY 1 & MODIFY 2 Trials (All results are bezlotoxumab vs. placebo)

Study	Total Patients	Patients with >1 event	Nausea / Vomiting	Pyrexia	Headache	Cough / Dyspnea
Combined Trial Results (MODIFY 1 &2)	786 vs. 781	485 (61.7%) vs. 478 (61.2%)	83 (11%) vs. 60 (7.5%)	36 (4.7%) vs. 27 (3.5%)	35 (4.4%) vs. 24 (3.1%)	34 (0.6%) vs. 21 (0.8%)

The most common adverse reactions following treatment with Zinplava (reported in ≥4% of patients within the first 4 weeks of infusion and with a frequency greater than placebo) were nausea/vomitting (11% vs7.5%), pyrexia (5% vs 3%), and headache (4% vs 3%). All other common adverse events were not significantly different between bezlotoxumab and placebo.

DRUG INTERACTIONS:
No metabolic drug-drug interactions with bezlotoxumab are expected because bezlotoxumab is eliminated by catabolism. Coadministration of other drugs simultaneously through the same infusion line is not recommended.

CLINICAL STUDIES & COMPARATIVE EFFICACY:

All results are bezlotoxumab vs. placebo

	Study	N=	Patient Population	Primary Endpoints	Clinical Cure	Global Cure (clinical cure with no recurrence)	CDI recurrence
Placebo-controlled Trials (MODIFY 1)	MODIFY 1 (REF) Double-blind Randomized (2015) 12wk duration	386 vs. 395	Adult patients presenting with primary or secondary *C. difficile* infection currently receiving standard of care antibiotic therapy* for 10-14 days. Patients with chronic diarrhea disease or planned surgery were excluded.	Recurrent CDI during 12 weeks of follow up.	299 (77.5%) vs. 327 (82.8%) p = 0.0622	232 (60.1%) vs. 218 (55.2%) p = 0.1647	67 (17.4%) vs. 109 (27.6%) p = 0.0006
Placebo-controlled Trials (MODIFY 2)	MODIFY 2 (REF) Double-blind Randomized (2016) 12wk duration	395 vs. 378	Adult patients presenting with primary or secondary *C. difficile* infection currently receiving standard of care antibiotic therapy* for 10-14 days. Patients with chronic diarrhea disease or planned surgery were excluded.	Recurrent CDI during 12 weeks of follow up.	326 (82.5%) vs. 294 (77.8%) p = 0.0973	264 (66.8%) vs. 197 (52.1%) p <0.0001	62 (15.7%) vs. 97 (25.7%) p = 0.0006

**Antibiotic therapy with metronidazole, vancomycin or fidaxomicin.*

DOSING AND ADMINISTRATION:

The recommended dose of Zinplava is a single dose of 10 mg/kg administered as an intravenous infusion over 60 minutes. The safety and efficacy of repeat administration of Zinplava in patients with CDI have not been studied.

Administer the diluted solution as an intravenous infusion over 60 minutes using a sterile, non-pyrogenic, low-protein binding 0.2 micron to 5 micron in-line or add-on filter. The diluted solution can be infused via a central line or peripheral catheter. Do not administer Zinplava as an intravenous push or bolus. Do not co-administer other drugs simultaneously through the same infusion line.

RECOMMENDED MONITORING:

Appropriate observation and medical treatment should always be readily available in case of an anaphylactic event following the administration of the antibody.

PHARMACOECONOMICS/COST:

Drug	Cost
Zinplava (bezlotoxumab)	$3,800.00 / vial

CONCLUSION & RECOMMENDATION:

Zinplava (bezlotoxumab) is the first human monoclonal antibody indicated to reduce the recurrence of CDI in adult patients. The product does not treat CDI as it is not an antibacterial agent but rather a toxin-binding antibody that reduces recurrence of CDI. The overall safety profile of this agent is similar to placebo with the exception of CHF. There are no dosing adjustments necessary.

The cost of this branded antibody is $3,800 per 1000mg vial. Given the 10% reduction in recurrence, using this product on every CDI admission would cost $38,000 to prevent 1 recurrence of CDI. More importantly, the follow-up period for recurrence in both studies was too short to assess recurrence rate after the patient has cleared the antibody (4 half-lives = 80 days, study period was 85 days). With no information or recommendation on repeat dosing of this product, it is likely recurrence will occur in

patients that receive future antibiotics after antibody clearance. Therefore, the utility of this agent to prevent recurrence in the inpatient setting is not justified. Clinical practice for treatment of inpatient CDI at our institutions will continue to follow guidance from the IDSA and SHEA; first line agents; metronidazole, vancomycin, or fidaxomicin for the first and second episodes, followed by consideration for fecal transplant thereafter. The role of this medication after fecal transplant has yet to be established.

It is the recommendation of the Memorial Antibiotic Stewardship Committee and that of the national MUE committee to designate this medication non-formulary at all Memorial facilities.

FORMULARY REVIEW

GENERIC NAME: MIVACURIUM

PROPRIETARY NAME: Mivacron (Abbvie)

THERAPEUTIC CLASS:
Neuromuscular blocking agent, nondepolarizing

INDICATIONS:
Adjunct to general anesthesia to facilitate tracheal intubation and to provide skeletal muscle relaxation during surgery or mechanical ventilation

CLINICAL PHARMACOLOGY:
Neuromuscular blocking agents are classified as either depolarizing or nondepolarizing. Depolarizing agents act as acetylcholine agonists, binding to acetylcholine receptors and causing prolonged depolarization of the muscle end-plate. Nondepolarizing agents, like mivacurium, bind competitively to cholinergic receptors on the motor end-plate to antagonize the action of acetylcholine, resulting in a block of neuromuscular transmission and muscle relaxation.

PHARMACOKINETICS:

	Ultra Short-acting	**Short-acting**	**Intermediate-acting**			
	Succinylcholine	**Mivacurium**	**Rocuronium**	**Vecuronium**	**Cisatracurium**	**Atracurium**
Onset of action*	IM: 2 to 3 min IV: <60 seconds	1.5 to 3 min	1 to 4 min	2.5 to 5 min	2 to 5 min	2 to 5 min
Duration of action*	IM: 10 to 30 min IV ~4 to 6 min	15 to 20 min	~30 min	25 to 40 min	35 to 45 min	20 to 35 min
t ½	< 1 min	~2 min	1.4 to 2.4 hr	80 to 90 min	22 to 29 min	20 min
Vd	--	0.067 to 0.772 L/kg	0.22 to 0.26 L/kg	0.3 to 0.4 L/kg	0.145 L/kg	0.1 L/kg
Protein binding (%)	--	--	~30%	60 to 80%	--	--
Metabolism	Rapid hydrolysis via plasma cholinesterase; inactive metabolites	Rapid hydrolysis via plasma cholinesterase; inactive metabolites	Minimal	Active metabolite with half activity of parent drug	Rapid nonenzymatic degradation (Hofmann elimination)	Ester hydrolysis and Hofmann elimination
Elimination	Urine	Urine; bile	Feces 31%; urine 26%	Feces 40 to 75%; urine 30%	Urine 95%; feces 4%	Urine <5%
Fraction excreted unchanged in urine	~10%	~7%	--	30%	<10%	--

SPECIAL POPULATIONS:

	Succinylcholine	**Mivacurium**	**Rocuronium**	**Vecuronium**	**Cisatracurium**	**Atracurium**
Renal Impairment	No dosage adjustment provided	Risk of prolonged effect; dosing based on clinical response	No dosage adjustment necessary	No dosage adjustment necessary	Slower onset to effect; may need to extend interval between dose and intubation attempt	No dosage adjustment necessary
Hepatic Impairment	No dosage adjustment provided	Risk of prolonged effect; dosing based on clinical response	No dosage adjustment provided; lower doses may be necessary with liver disease	No dosage adjustment provided; lower doses may be necessary with liver disease	No dosage adjustment necessary	No dosage adjustment necessary
Obesity	Dose based on TBW	Dose based on IBW	Dose based on IBW – indication specific	Dose based on IBW – indication specific	No dosage adjustment provided	Dose based on IBW or AdjBW
Geriatrics	No dosage adjustment necessary	May require decreased infusion rates	No dosage adjustment necessary	No dosage adjustment provided; should	No dosage adjustment necessary	No dosage adjustment necessary

				use lower end of dosing range		
Pediatrics	Dosing available for neonates, infants, and children	Dosing available for children ≥2 years old	Dosing available for neonates, infants, and children	Dosing available for infants and children	Dosing available for infants and children	Dosing available for infants and children
Pregnancy	Category C	Category C	Category C	Category C	Category B	Category C
Lactation	Unknown if excreted in breast milk	Unknown if excreted in breast milk	Unknown if excreted in breast milk	Unknown if excreted in breast milk	Unknown if excreted in breast milk	Unknown if excreted in breast milk

CLINICAL STUDIES:

Efficacy and safety of divided dose administration of mivacurium for 90-second tracheal intubation				
METHODS				
Study Design	Randomized, double-blind, multicenter			
Study Funding	Supported by Glaxo-Wellcome Co.			
Patient Enrollment Inclusion	ASA physical status I and II, 18-65 years old, scheduled for low to moderate risk surgical procedures requiring tracheal intubation, within 30% of IBW			
Patient Enrollment Exclusion	History of any of the following: malignant hyperthermia; major thermal injury; chronic alcoholism or drug abuse; psychiatric, neurologic, neuromuscular, or cardiovascular diseases; significant hepatic or renal impairment; anatomical characteristics recognized for difficult intubation; exposure to drugs known to affect neuromuscular function; narrow angle glaucoma, disorders of plasma cholinesterase			
Baseline Characteristics	Demographics (age, sex, weight, ASA class) were comparable between the 2 groups			
Outcome Measures	Efficacy: tracheal intubation conditions graded by blinded observer; train-of-four response Safety: mean arterial pressure, heart rate			
Statistical Analyses	Chi-square or Fisher's Exact tests to compare intubation grades on the first attempt Summary statistics for all vital signs data Paired and upaired t-tests to compare mean arterial pressure and heart rate up to 5 min after intubation; alpha = 0.05			
Treatment Plan	200 patients premedicated with 1 to 2 mg midazolam and 2 mcg/kg fentanyl; anesthesia induced with 2 mg/kg propofol; randomized into 2 groups Group A: received 0.15 mg/kg followed in 30 seconds by 0.1 mg/kg mivacurium Group B: received 1.5 mg/kg succinylcholine preceded 2 min earlier by 50 mcg/kg d-rubocurarine			
RESULTS				
Outcomes Summary	Successful intubation achieved in 90/91 in Group A and 96/97 in Group B			
	Intubation grade at 90 seconds	**Group A (n = 91)**	**Group B (n = 97)**	**p-value**
	Excellent	51 (56%)	81(84%)	p <0.0001
	Good	38 (42%)	10 (10%)	NS
	Poor	1 (1%)	1 (1%)	NS
	No possible	1 (1%)	1 (1%)	NS
	Excellent and good combined	89 (98%)	91 (94%)	NS
	Train-of-Four Response	**Group A**	**Group B**	**p-value**
	Max suppression of TOF (mean ± SD, min)	4.6 ± 2.1	1.8 ± 0.6	NS
	Beginning recovery (mean ± SD, min)	13.0 ± 4.1	5.3 ± 1.7	NS
	Safety - Changes in mean arterial pressure and heart rate were similar between the 2 groups - In general, the average mean arterial pressure decreased after induction of anesthesia and administration of either mivacurium or succinylcholine but increased after intubation - In general, heart rates remained stable during induction and administration of mivacurium or succinylcholine - Cutaneous flushing observed in 6% in mivacurium group and none in the succinylcholine group			
Author's Conclusion	When succinylcholine is not desirable, mivacurium provides good to excellent intubation conditions 90 seconds after initial dose without significant changes in mean arterial pressure or heart rate. It can be an appropriate alternative for short surgical procedures. This conclusion does not apply to rapid sequence intubation.			

COMPARATIVE EFFICACY:

There are no known meta-analyses and systematic reviews published that compare mivacurium to other neuromuscular blocking agents. In order to assess the efficacy and safety of mivacurium, conclusions must be drawn from smaller trials. A 1995 randomized trial compared the intubation conditions of mivacurium with vecuronium and rocuronium in anesthetized patients. This study found that intubating conditions were better for rocuronium compared to mivacurium or vecuronium. This was due to a significantly shorter average onset of action of rocuronium (172 s) compared to vecuronium (192 s) and mivacurium (229 s). However, recovery time for mivacurium was significantly shorter (6 min) compared to rocuronium (11 min) and vecuronium (14 min), suggesting mivacurium may be most beneficial if rapid recovery is required.

A randomized trial published in 2001 compared equi-lasting doses of rocuronium and mivacurium in 60 patients undergoing gynecological laparoscopy. The mean onset time was longer for mivacurium (1.9 ± 0.4 min) than for rocuronium (1.3 ± 0.3

min). However, there was no statistical difference in intubation conditions between the 2 drugs. More patients required maintenance doses with mivacurium (22/30) compared to rocuronium (14/30). Rocuronium was associated with a more favorable adverse event profile. Mivacurium had more hemodynamic instability, and 14/30 patients experienced erythema vs. 0/30 in the rocuronium group.

Another study from 2007 compared rocuronium and mivacurium in 50 patients undergoing day case anesthesia. This study resulted in good or excellent intubation conditions for both mivacurium (8% good, 92% excellent) and rocuronium (100% excellent). Unlike previous trials, there was no significant difference between mivacurium and rocuronium regarding time to onset and recovery of muscle relaxation. Therefore, the authors concluded that rocuronium would be an appropriate alternative to mivacurium for short procedures.

The Clinical Practice Guidelines for Sustained Neuromuscular Blockade in the Adult Critically Ill Patient by the Society for Critical Care Medicine do not recommend which neuromuscular blocking agents should be used in intensive care units. The preferred agent depends on the indication, patient-specific factors, and drug-specific factors. For example, cisatracurium is the only neuromuscular blocking agent studied in patients with ARDS. These guidelines do not list mivacurium as a preferred agent for any indication.

WARNING AND PRECAUTIONS:
Mivacurium should be administered in carefully adjusted dosage by or under the supervision of experienced clinicians. It should not be administered unless personnel and facilities for resuscitation and life support and an antagonist of mivacurium are immediately available. Use of a peripheral nerve stimulator to monitor drug effects is recommended. It is important to note that mivacurium has no effect on consciousness, pain threshold, or cerebration. Therefore, neuromuscular block should not be induced before unconsciousness.

Warning and Precautions	
Anaphylaxis	Precautions should be taken in those who have had previous reactions to other neuromuscular blocking agents; cross-reactivity has been reported in this drug class
Bradycardia	Mivacurium has no clinically significant effects on heart rate; will not counteract bradycardia produced by many anesthetic agents or by vagal stimulation
Burn injury	Resistance may occur, which would require increased doses; patients may also have reduced plasma cholinesterase activity that requires dose reduction
Cardiovascular disease and increased sensitivity to histamine (ex. asthma)	Use with caution in these patients; reduce initial dosage and inject slowly (over 60 seconds). Carefully monitor hemodynamic status and maintain adequate hydration.
Antagonism of neuromuscular blockade	Increased doses may be required with the following conditions: acid-base and/or electrolyte abnormalities, demyelinating lesions, peripheral neuropathies, denervation, and muscle trauma
Diminished plasma cholinesterase activity	Prolonged neuromuscular blockade may occur with the following conditions: plasma cholinesterase genetic abnormalities, malignant tumors, infections, anemia, decompensated heart disease, peptic ulcer, and myxedema
Potentiation of neuromuscular blockade	Decreased doses may be required with the following conditions: Acid-base and/or electrolyte abnormalities, cachexia, carcinomatosis, debilitation, neuromuscular diseases, Eaton-Lambert syndrome, myasthenia gravis, and myasthenic syndrome
Renal or hepatic impairment	Use with caution; prolonged neuromuscular blockade may occur
Obesity	More likely to experience clinically significant transient decreases in mean arterial pressure when dose based on actual body weight; initial dose should be determined using IBW
Malignant hyperthermia	Mivacurium did not trigger malignant hyperthermia in animal studies but has not been studied in susceptible human patients; clinicians should be prepared to recognize and treat malignant hyperthermia in any patient undergoing general anesthesia

ADVERSE REACTIONS:

Adverse Reactions	
Cardiovascular	
Flushing	16%
Other: hypotension, tachycardia, bradycardia, cardiac arrhythmia, phlebitis	<1%
Respiratory: bronchospasm, wheezing, hypoxemia	<1%
Dermatological: rash, urticarial, erythema, injection site reaction	<1%
General: prolonged drug effect	<1%
Neurologic: dizziness	<1%
Musculoskeletal: muscle spasms	<1%

DRUG INTERACTIONS:

As with other agents in this class, the neuromuscular blocking action of mivacurium may be potentiated by concomitant administration of certain medications. Dose reductions of mivacurium may be required in combination with these medications. In particular, it is recommended to reduce the mivacurium continuous infusion rate by ≤35% to 40% or reduce the bolus dose by ≤25% with the administration of isoflurane or enflurane. Conversely, chronic administration of phenytoin or carbamazepine may antagonize the effect of neuromuscular blocking agents, resulting in slightly shorter durations of action and higher infusion rate requirements.

In addition to enhancing neuromuscular blocking effects, the addition of systemic corticosteroids also increases muscle weakness and the risk of myopathies. Neuromuscular blocking agents may increase the risk for arrhythmias for patients on digoxin.

DOSING AND ADMINISTRATION:

Adult Dosing/Indication**	**Intermittent bolus** -Initial: 0.15 mg/kg over 5 to 15 seconds **or** 0.2 mg/kg over 30 **or** 0.15 mg/kg followed in 30 seconds by 0.1 mg/kg -Maintenance: 0.1 mg/kg at ~15 min intervals **Continuous infusion** -Initial: 9 to 10 mcg/kg/min upon evidence of spontaneous recovery from initial bolus dose -Usual infusion rate: 5 to 7 mcg/kg/min under balanced anesthesia -Lower initial infusion rate should be used if continuous infusion is initiated simultaneously with initial dose
Pediatric Dosing/Indication (2 to 12 years)**	**Intermittent bolus:** 0.2 mg/kg over 5 to 15 seconds **Continuous infusion:** 14 mcg/kg/min
Administration	IV administration only as bolus and/or continuous infusion

**Dose to effect; doses must be individualized due to interpatient variability

DOSING ADJUSTMENTS:

Concomitant inhalational anesthetics	Consider reduction of mivacurium continuous infusion rate by ≤35% to 40% or reduction of bolus dose by ≤25% with concomitant isoflurane or enflurane at steady state
Burn patients	Administer test dose of 0.015 to 0.02 mg/kg, then follow with appropriate dosing and monitoring
Cachectic or immobile patients	Administer test dose of 0.015 to 0.02 mg/kg, then follow with appropriate dosing and monitoring
Cardiovascular disease	Initial bolus dose: ≤0.15 mg/kg over 60 seconds
Increased sensitivity to histamine (ex. asthma)	Initial bolus dose: ≤0.15 mg/kg over 60 seconds
Reduced plasma cholinesterase activity	Initial doses >0.03 mg/kg not recommended in patients homozygous for atypical plasma cholinesterase gene; neuromuscular blockade may be prolonged and intensified.
Hepatic Impairment	Mild to severe impairment: initial bolus dose 0.15 mg/kg; clinically effective duration of block may be about 3 times longer in patients with ESLD; subsequent dosing based on clinical response. Decrease infusion rates by as much as 50% depending on degree of impairment.
Renal Impairment	Mild to severe impairment: initial bolus dose 0.15 mg/kg; clinically effective duration of block may be about 1.5 times longer in patients with ESRD; subsequent dosing based on clinical response.
Geriatrics	Adult dosing; may require decreased infusion rates or smaller/less frequent maintenance bolus dose.
Obesity	Dose obese patients (weight ≥30% more than IBW) based on IBW.
Pregnancy	Pregnancy category C; no adverse events observed in animal reproduction studies. Use if potential benefit justifies potential risk to fetus. Neuromuscular blockade may be prolonged and intensified due to lower plasma cholinesterase concentrations in pregnancy so adjustment of dose may be necessary.
Lactation	Unknown if excreted in breast milk; manufacturer recommends exercising caution when administering to breast-feeding women.
Pediatrics (2 to 12 years)	Intermittent bolus: 0.2 mg/kg over 5 to 15 seconds Continuous infusion: 14 mcg/kg/min
Toxicity	No maximum dose identified.

PHARMACOECONOMICS/COST:

Product (Name, Size, ABC Item #)	HPB Contract	Cost Per Vial
MIVACRON 10MG/5ML SDV 10X5ML, 10174386	☐	$ 211.60
MIVACRON 20 MG SDV 10X10 ML, 10172967	☐	$ 27.63
ATRACURIUM 100 MG-10 ML MDV 10X10 ML	☒	$ 8.79
ATRACURIUM BESY INJ 50MG-5ML SDV 10X5ML	☒	$ 3.89
CISATRACURIUM BESYL INJ 10MG 10X5ML	☒	$ 6.98
CISATRACURIUM BESYL INJ 200MG 10X20ML	☒	$ 134.18
CISATRACURIUM BESYL INJ 20MG 10X10ML	☒	$ 12.47
PANCURONIUM 1 MG/ML VL 25X10 ML	☒	$ 4.16
ROCURONIUM 10 MG-ML VL 10X10 ML	☒	$ 4.25
ROCURONIUM 10 MG-ML VL 10X5ML	☒	$ 2.17
VECURONIUM 10 MG VL 10	☒	$ 4.58
VECURONIUM 20 MG VL 10	☒	$ 8.77

CONCLUSION:

Mivacurium is a short-acting, nondepolarizing neuromuscular blocking agent originally approved by the FDA in 1992. It has the shortest duration of action of the nondepolarizing agents, which might be preferred for neuromuscular blockade during short procedures. However, it has a longer onset of action compared to succinylcholine and high-dose rocuronium, making it less ideal for rapid sequence intubation. Mivacurium has not been widely studied for prolonged use in the intensive care setting. As this drug was off the US market for about 10 years, there are few studies available to compare the efficacy and safety of mivacurium to other neuromuscular blocking agents. Therefore, there is a lack of compelling evidence to support the use of mivacurium over other neuromuscular blocking agents that are already available.

The national MUE committee recommended that this agent be non-formulary at the July 2017 meeting.

FORMULARY REVIEW

GENERIC NAME: OBINUTUZUMAB

PROPRIETARY NAME: Gazyva (Genentech)

THERAPEUTIC CLASS:
Monoclonal antibody

INDICATIONS:

FDA Approved
Chronic lymphocytic leukemia (CLL) in treatment-naïve adults in combination with chlorambucil.
Combination therapy with obinutuzumab and bendamustine for the treatment of patients with follicular lymphoma (FL) who relapsed after, or are refractory to, a rituximab-containing regimen.
Non-FDA Approved
First-line therapy for FL in combination with CHOP or CVP

CLINICAL PHARMACOLOGY: The cell surface antigen CD20 is commonly expressed on B-cell precursors and mature B cells, making them an ideal target for malignancies in this hematopoietic cell lineage. However, in the course of treatment of indolent B-cell malignancies, patients typically fail to achieve complete response or relapse and become refractory to current therapy, including specific type I anti-CD20 monoclonal antibodies. Obinutuzumab is a novel glycoengineered type II anti-CD20 monoclonal antibody intended to have improved efficacy over previous type I monoclonal antibodies. In general, anti-CD20 antibodies induce apoptosis through varying degrees of activation of the complement-dependent cytotoxicity (CDC), antibody-dependent cellular cytotoxicity (ADCC), and direct cell death.

PHARMACOKINETICS:

Absorption	Administered intravenously
Distribution	Geometric mean (CV%) volume of distribution = 4.1-4.3 L
Metabolism	Not reported
Excretion	Clearance after target-mediate drug disposition (TMDD) = 0.08 – 0.11 L/day; terminal half-life elimination was approximately 26.4-36.8 days.
Cmax (mg/L)	Not reported
Bioavailability (%)	100%
t ½ (hr)	In patients with CLL and NHL, the terminal half-life elimination was approximately 26.4 and 36.8 days, respectively.
Vd (L/kg)	In patients with CLL and NHL, the volume of distribution was approximately 0.11 L/day and 0.08 L/day, respectively.
Dose adjustment in renal insufficiency	None; obinutuzumab has not been studied in patients with baseline CrCl < 30 mL/min.
Dose adjustment in geriatric patients	None
Dose adjustment in hepatic insufficiency	Obinutuzumab has not been studied in patients with hepatic impairment.

CLINICAL STUDIES:

Obinutuzumab plus Chlorambucil in Patients with CLL and Coexisting Conditions	
Trial design	Prospective, multicenter, open label, 3-arm, randomized phase III trial
Intervention	Chlorambucil monotherapy (0.5 mg/kg PO on days 1 and 15 of each cycle) vs. obinutuzumab (1000 mg IV on days 1, 8, and 15 of cycle 1 and on day 1 of cycles 2 through 6) with chlorambucil vs. rituximab 375 mg/m^2 IV on day 1 of cycle 1 and 500 mg/m^2 on day 1 of cycles 2 through 6) with chlorambucil. All arms received these respective regimens in six 28-day cycles. Response was assessed three months following the end of treatment.
Inclusion	Patients with CD20-positive and previously untreated CLL (Binet Stage C or symptomatic disease), and a Cumulative Illness Rating Scale (CIRS) > 6 (range, 0-56) or CrCl 30-69 mL/min.
Demographics	Multinational study conducted in 26 countries; 189 centers enrolled patients. Median age of patients was 73 years, CrCl of 62 mL/min, and CIRS score of 8 at baseline.

Endpoints	**Chlorambucil monotherapy**	**Obinutuzumab + Chlorambuc**	**Rituximab + Chlorambucil**	**HR, 95% CI; p-value**
Median Progression-Free Survival	11.1 months 11.1 months	26.7 months 26.7 months	16.3 months 15.2 months	HR 0.18; CI 0.13-0.24; p<0.001 HR 0.44; CI 0.34-0.57; p<0.001 HR 0.39; CI 0.31-0.49; p<0.001
Overall Response Rate	33.1%	78.2%	66.3%	p<0.001
Complete Response	0%	28.2%	8.8%	
Partial Response	31.4%	55%	58.4%	
Median Duration of Response	4.7 months	22.4 months	9.7 months	

Median Overall Survival (Not Reached)	NR	NR	NR	
Rate of Death at Cutoff	20% 20%	9% 8%	 15% 12%	HR 0.41; CI 0.3-0.74; p=0.002 HR 0.66; CI 0.39-1.11; p=0.11 HR 0.66; CI 0.41-1.06; p=0.08

Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN)	
Trial design	Open label, randomized, multicenter, phase 3 study
Intervention	Obinutuzumab 1000 mg IV on days 1, 8 and 15 of cycle 1 and then on day 1 of cycles 2 through 6 with bendamustine 90 mg/m^2/day IV on days 1 and 2 of cycles 1 through 6; after complete (CR), partial response (PR) or stable disease (SD) patients received obinutuzumab maintenance therapy of 1000 mg IV every 2 months for 2 years or until PD versus bendamustine monotherapy 120 mg/m^2 IV on days 1 and 2 for all cycles. Response was monitored post-induction, then every three months for two years, then every 6 months.
Inclusion	Patients with CD20-positive indolent NHL (including follicular lymphoma of grades 1–3a, marginal zone lymphoma, small lymphocytic lymphoma, and Waldenström's macroglobulinaemia) refractory to a rituximab-containing regimen. Rituximab-refractory was defined as a patient that did not response to rituximab as monotherapy or a chemotherapy regimen containing rituximab OR a patient that progressed within six months of completion of last dose of a rituximab-containing regimen. Patients had at least one bi-dimensionally measurable lesion, ECOG performance status of 0 to 2, and an estimated life expectancy of about five years.
Demographics	Multinational study conducted in 83 hospital and community sites in 14 countries. Median age of patients was 63 years with a median of two prior therapies.

Endpoint	**Obinutuzumab + bendamustine (n = 194)**	**Bendamustine (n = 202)**	**HR, 95% CI; p-value**
Median Progression-Free Survival by IRC (95% CI)	29.2 months (20.2-NR)	14 months (11.7-16)	0.52, (0.39-0.70); p<0.0001
Median Progression-Free Survival (95% CI)	Not reached (22.5-NR)	14.9 months (12.8-16.6)	0.55, (0.40-0.74); p=0.0001
Median Duration of Response	Not reached	13.2 months	0·42, (0·29–0·61)
Median Overall Survival	Not reached	Not reached	0.82, (0.52-1.30); p=0.4017

COMPARATIVE EFFICACY:
Obinutuzumab represents an alternative approach to the treatment of chronic lymphocytic leukemia. The combination of obinutuzumab and chlorambucil provided a statistically and clinically significant benefit in progression-free survival when compared to chlorambucil alone or in combination of rituximab and chlorambucil.

ADVERSE REACTIONS:

Adverse Reactions	
Gastrointestinal	Nausea, vomiting, diarrhea, constipation, decreased appetite
Hematologic and Oncologic	Neutropenia, thrombocytopenia, anemia
Infection	Upper respiratory tract infection, sinusitis, urinary tract infection
Neuromuscular & skeletal	Arthralgia
Respiratory	Cough
Skin	Infusion related reaction
Systemic	Fatigue, pyrexia, asthenia

The most common adverse reactions reported with obinutuzumab therapy include infusion reactions, neutropenia, thrombocytopenia, anemia, pyrexia, cough, and musculoskeletal disorder. Of the patients receiving obinutuzumab, 38% experienced infection (similar rate in the chlorambucil arm); 9% were grade 3 to 4 and none were fatal. Patients receiving obinutuzumab reported adverse reactions related to musculoskeletal disorders at a rate of 17% compared with 13% in the chlorambucil arm. Two percent of patients receiving obinutuzumab experienced grade 3 or 4 tumor lysis syndrome.

DRUG INTERACTIONS:
There is no published information regarding drug interactions with obinutuzumab.

DOSING:
Chronic Lymphocytic Leukemia – dose of obinutuzumab to be administered during 6 treatment cycles, each of 28 days duration

Dose of 28-day treatment cycle	**Dose of obinutuzumab**	**Rate of Infusion** (In the absence of infusion reactions/hypersensitivity during previous infusions)

Cycle 1 (loading doses)	Day 1	100 mg	Administer at 25 mg/hr over 4 hours. Do not increase the infusion rate.
	Day 2	900 mg	Administer at 50 mg/hr. The rate of the infusion can be escalated in increments of 50 mg/hr every 30 minutes to a maximum rate of 400 mg/hr.
	Day 8	1000 mg	Infusions can be started at a rate of 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr (if no infusion reaction occurred during previous infusions).
	Day 15	1000 mg	
Cycles 2-6	Day 1	1000 mg	

Follicular Lymphoma – dose of obinutuzumab to be administered during 6 treatment cycles, each of 28 days duration

Dose of 28-day treatment cycle		**Dose of obinutuzumab**	**Rate of Infusion** (In the absence of infusion reactions/hypersensitivity during previous infusions)
Cycle 1 (loading doses)	Day 1	1000 mg	Administer at 50 mg/hr. Infusion rate can be escalated in 50 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.
	Day 8	1000 mg	Infusions can be started at a rate of 100 mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400 mg/hour (if no infusion reaction occurred during previous infusions).
	Day 15	1000 mg	
Cycles 2-6	Day 1	1000 mg	
Monotherapy	Every two months for two years	1000 mg	

DOSING ADJUSTMENTS:

Hepatic Impairment	Obinutuzumab has not been studied in patients with hepatic impairment
Renal Impairment	Obinutuzumab has not been studied in patients with CrCl < 30 mL/min
Geriatrics	None
Pregnancy and Lactation	None
Pediatrics and neonatal	Obinutuzumab has not been studied in the pediatric/neonatal populations
Toxicity	Clinical trials did not assess effects of overdose with obinutuzumab. Doses ranging from 50 mg to 2000 mg per infusion have been administered in clinical trials. For patients who experience overdose, treatment should consist of immediate interruption or reduction of obinutuzumab and supportive therapy

RECOMMENDED MONITORING:

Monitor patients closely during and for at least one hour after infusion.

WARNING AND PRECAUTIONS:

Warning and Precautions	
Hepatitis B Virus (HBV) Reactivation	Patients who are hepatitis B surface antigen (HBsAg) positive and/or are HBsAg negative but are hepatitis B core antibody positive are at risk for HBC reactivation. All patients should be screened for HBV infection (including measuring HBsAg and anti-HBc) prior to starting treatment with Obinutuzumab. If HBV reactivation does occur during treatment with Obinutuzumab, treatment should immediately be stopped and appropriate treatment should be initiated.
Progressive Multifocal Leukoencephalopathy (PML)	PML is an opportunistic viral infection of the brain caused by the John Cunningham (JC) virus that typically only occurs in patients who are immunocompromised, and that usually leads to death or severe disability. PML ha s been observed in patients treated with Obinutuzumab. Therapy should be discontinued and consider discontinuation or reduction of any concomitant chemotherapy or immunosuppressive therapy in patients who develop PML.
Infusion Reactions	Severe and life-threatening infusion reactions can occur with obinutuzumab treatment. 65% of patients with CLL experienced an infusion-related reaction to the first 1000 mg infused of Obinutuzumab. 38% of FL patients experienced a reaction after receiving obinutuzumab on Day 1. Infusion-related reactions can also occur with subsequent infusions. Patients may experience any of the following symptoms during treatment with obinutuzumab: hypotension, tachycardia, dyspnea, bronchospasm, wheezing, nausea, fatigue, flushing, hypertension, headache, pyrexia, and chills. Closely monitor patients during the entire infusion. Reactions can occur within 24 hours of receiving obinutuzumab. **Premedication to administer prior to obinutuzumab infusion to reduce infusion-related reactions:**

Day of treatment cycle	**Patients requiring premedication**	**Premedication**	**Administration**

<table>
<tr><td></td><td>
<table>
<tr><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="3">Cycle 1:

CLL –
Day 1,
Day 2

FL –
Day 1</td><td rowspan="3">All patients</td><td>Intravenous glucocorticoid:
20 mg dexamethasone or
80 mg methylprednisolone</td><td>Completed at least 1 hour prior to obinutuzumab infusion</td></tr>
<tr><td>650-1000 mg acetaminophen</td><td rowspan="2">At least 30 minutes before obinutuzumab infusion</td></tr>
<tr><td>Antihistamine (e.g. 50 mg diphenhydramine)</td></tr>
<tr><td rowspan="5">All subsequent infusions</td><td>All patients</td><td>650-1000 mg acetaminophen</td><td>At least 30 minutes before obinutuzumab infusion</td></tr>
<tr><td>Patients with an IRR (Grade 1 or more) with the previous infusion</td><td>Antihistamine (e.g. 50 mg diphenhydramine)</td><td>At least 30 minutes before obinutuzumab infusion</td></tr>
<tr><td rowspan="3">Patients with a Grade 3 IRR with the previous infusion <u>OR</u> with a lymphocyte count >25 x 10^9/L prior to next treatment</td><td>Intravenous glucocorticoid:
20 mg dexamethasone or
80 mg methylprednisolone</td><td>Completed at least 1 hour prior to obinutuzumab infusion</td></tr>
<tr><td>650-1000 mg acetaminophen</td><td rowspan="2">At least 30 minutes before obinutuzumab infusion</td></tr>
<tr><td>Antihistamine (e.g. 50 mg diphenhydramine)</td></tr>
</table>
Management of infusion-related reactions in CLL and FL patients:
Obinutuzumab infusion should be stopped for any Grade 4 infusion reaction and discontinue should be permanently discontinued. For patient with Grade 3 infusion reactions, obinutuzumab should be paused until symptoms resolve. For Grade 1 or 2 reactions, the infusion can be interrupted or reduced at a slower rate- symptoms should be managed. Patients with preexisting cardiac or pulmonary conditions are at greater risk of experiencing more severe reactions and should be monitored more frequently throughout the infusion. Hypotension can present as part of an infusion reaction, therefore consider withholding antihypertensive treatments for 12 hours prior to, during and for the first hour after administration until blood pressure is stable. The risk versus
benefit of withholding antihypertensive medications should be considered for patients at increased risk of hypertensive crisis,</td></tr>
<tr><td>Tumor Lysis Syndrome (TLS)</td><td>TLS, including fatal cases, has been reported with obinutuzumab. Patients considered high risk for developing TLS (high tumor burden, high circulating lymphocyte count [> 25 x 10^9
/L] or renal impairment) should receive appropriate TLS prophylaxis with antihyperuricemics and hydration prior to treatment with obinutuzumab. When therapy with obinutuzumab has been initiated, appropriate labs associated with TLS should be monitored.</td></tr>
<tr><td>Infections</td><td>During and following obinutuzumab therapy, serious bacterial, fungal, and new or reactivated viral infections can occur. Trials evaluating FL treatment reported that incidence of infection was 66% in the obinutuzumab and bendamustine arm versus 56% in the bendamustine monotherapy arm. Do not administer to patients with an active infection. Those with a history of recurring or chronic infections may be at increased risk of developing an infection. Fatal infections have been reported.</td></tr>
<tr><td>Neutropenia</td><td>Severe and life-threatening and febrile neutropenia have been reported during obinutuzumab therapy. Trials evaluating CLL treatment, the combination of obinutuzumab and chlorambucil resulted in Grade 3 or 3 neutropenia in 33% of the patients. In patients being treated for FL, the incidence of neutropenia was higher in the obinutuzumab plus bendamustine arm at 38% versus bendamustine alone at 32%. For patients that experience severe and long-lasting neutropenia during treatment, antimicrobial prophylaxis should strongly be considered, as well as antiviral and antifungal prophylaxis.</td></tr>
<tr><td>Thrombocytopenia</td><td>During treatment with obinutuzumab and bendamustine, severe and life-threatening thrombocytopenia was reported. Incidence was lower in the obinutuzumab plus bendamustine arm (15%) versus the bendamustine only arm (24%). In patients treated with obinutuzumab and chlorambucil, Grade 3 or 4 thrombocytopenia occurred in 10% of patients. Monitor all patients frequently for thrombocytopenia and hemorrhagic events, especially during the first cycle. Consider subsequent dose delays of obinutuzumab and chemotherapy or dose reductions of chemotherapy. Platelet transfusions may be necessary.</td></tr>
<tr><td>Immunization</td><td>The safety and efficacy of administration of live or attenuated viral vaccines during or following obinutuzumab therapy has not been studied. It is recommended that immunization with live vaccines to be withheld during treatment and until B-cell recovery.</td></tr>
</table>

PRODUCT AVAILABILITY:

Obinutuzumab is supplied as a single-dose vial containing 1000 mg/40 mL (25 mg/mL)

PHARMACOECONOMICS/COST

Product (Drug, Strength, Form)	Contract/GPO Price	NDC
1000 mg/40 mL vial	$5,779.43	50242-070-01

PRODUCT AVAILABILITY AND STORAGE: Obinutuzumab was approved by the Food and Drug Administration on November 1, 2013.(21) Obinutuzumab is available as preservative-free, single-use vials of 1,000 mg per 40 mL (25 mg/mL). Unopened vials should be stored at 2°C to 8°C (36°F to 46°F) in an area protected from light. Although solutions of obinutuzumab should be used immediately after preparation, reconstituted products may be stored for up to 24 hours between 2°C and 8°C (36°F to 46°F).

CONCLUSION & RECOMMENDATION:
Obinutuzumab is a novel monoclonal anti-CD20 antibody. When used in combination with chlorambucil, it improved median progression-free survival in treatment naïve CLL patients with comorbidities (26.7 months), compared to chlorambucil alone (11.1 months) and rituximab with chlorambucil (15.2 months) treatment groups. When used in combination with bendamustine for the treatment of follicular lymphoma in patients who have relapsed after or are no longer response to rituximab-containing regimens, obinutuzumab plus bendamustine had a significantly longer progression-free survival (22.5 months) versus bendamustine alone (14.9 months); however, obinutuzumab combination therapy did not reach median progression-free survival. Infusion reaction is a common adverse event, occurring in greater than half of the patients, especially with the first dose. Pre-medication with a glucocorticoid, antihistamine, and acetaminophen is recommended.

It was recommended at the June 2017 national MUE committee meeting to **approve this for outpatient infusion use only for FDA-approved indications or payer approved off label use subsequent to insurance approval or pre-authorization.**

GP IIb/IIIa Inhibitors

FORMULARY STANDARDIZATION/MODIFICATION

CURRENT FORMULARY AGENT:
Integrilin® (eptifibatide)

BACKGROUND:
The platelet integrin receptor $\alpha_{IIb}\beta_3$ (GPIIb/IIIa) plays a crucial role in thrombosis and hemostasis by mediating interactions between platelets and several ligands, primarily fibrinogen. It is found on platelets and is composed of two separate subunits, α_{IIb} (GPIIb) and β_3 (GPIIIa). When the platelet becomes activated, the receptor undergoes conformational changes and several binding sites for fibrinogen and other ligands are exposed. Fibrinogen binding to the activated GPIIb/IIIa mediates platelet aggregation by crosslinking adjacent platelets. Since fibrinogen binding to the activated receptor GPIIb/IIIa constitutes the final common pathway of platelet aggregation, GPIIb/IIIa antagonists inhibit platelet aggregation independently of the type of platelet agonist. Currently, three GPIIb/IIIa antagonists are available: abciximab (ReoPro®), eptifibatide (Integrilin®) and tirofiban (Aggrastat®).

PRODUCT COMPARISON:
Clinical studies and meta-analyses have demonstrated that all FDA-approved glycoprotein IIb/IIIa inhibitors at current FDA-approved doses have a similar efficacy and safety profile. As such, the current 2014 ACC/AHA guidelines recommend all glycoprotein IIb/IIIa inhibitors equally for the treatment of non-ST elevation-acute coronary syndrome and for PCI in their respective doses.

There are key similarities between tirofiban and eptifibatide, which makes them comparable in this respect (similar onset of action, similar half-life, both bind reversibly to the GPIIb/IIIa receptor, both are adjusted for renal insufficiency). Tirofiban provides the best value on a per-patient treatment cost basis. Other advantages include that it can be stored at room temperature storage, does not require filtration, and the single bolus and infusion can be delivered from the same pre-mixed IV bag. Additionally, according to the National Kidney Foundation's KDOQI guidelines, when a GPIIb/IIIa antagonist is used for ACS in dialysis patients, abciximab and tirofiban should be considered preferred agents, since no dosing changes are required for abciximab, and dialysis-specific dosing recommendations are available for tirofiban. Abciximab is typically used for PCI, as the clearance of the drug is not altered in dialysis patients. There are chronic kidney diseases—but not dialysis—patient studies dealing with this issue. One study reported safety of abciximab for Cr >2.0 mg/dL, while another showed no increase in bleeding for renal failure versus no renal failure for abciximab in PCI. However, increased bleeding with abciximab in renal failure has been reported. Increased bleeding but reduced in-hospital mortality in CKD patients with ACS treated with IIb/IIIa antagonists has also been shown.

RATIONALE FOR FORMULARY MODIFICATION TO AGGRASTAT (tirofiban):
Potential cost savings associated with this class of agents is driven by a market share opportunity through our group purchasing organization, HealthTrust (HPG), for the Market Basket of tirofiban and eptifibatide. Discounts for Aggrastat® will be based on the discount tier associated with the aggregate market share achieved. CHI is attempting to achieve Tier 4 (≥70% Aggregate Market Share) by January 2018 to retain the current 40% off-WAC pricing we have currently. It is estimated that moving from Integrilin® to Aggrastat® the organization stands to save approximately $504,000 (30% savings). Additionally, if facilities work to reduce abciximab (ReoPro®) use where appropriate there is a potential cost savings of approximately $355,000 (60% reduction in use) by moving to Aggrastat®. Note: abciximab was removed from formulary as per the invasive cardiology committees recommendation at the April 2017 P&T meeting.

RECOMMENDATION:
<u>This proposed formulary conversion has been discussed at length with Memorial's Invasive Cardiology Committee and they are agreeable to this formulary interchange. Aggrastat (tirofiban) will be the only GPIIb/IIIa agent on Memorial's formulary.</u>

Aggrastat® (tirofiban)

Review & Clinical Comparison

Dosing:

CrCl > 60 ml/min: **25 mcg/kg** IV bolus within 5 minutes (IVP) and then **0.15 mcg/kg/min** for up to 18 hours
CrCl < 60 ml/min: **25 mcg/kg** IV bolus within 5 minutes and then **0.075 mcg/kg/min** for up to 18 hours

Recommended stock (both stored at room temp):

Bolus vial: 3.75 mg/15 ml vial (250 mcg/ml)
Infusion bag - pre-mix: 5 mg/100 ml NS (50 mcg/ml)
**(1) 100 ml infusion bag can provide a 6 hour infusion in a 90 kg patient*

Aggrastat® (tirofiban HCl) and Integrilin® (eptifibatide) comparison

Brand Name: **Generic Name:** **Manufacturer:**	Aggrastat® Tirofiban hydrochloride Medicure Pharma (Baxter HealthCare Corp.)	Integrilin® Eptifibatide Merck (Patheon Italia S.p.A)
Indications	**Labeled:** Reduce the rate of thrombotic cardiovascular events (combined endpoint of death, myocardial infarction or refractory ischemia/repeat cardiac procedure) in patients with non-ST elevation acute coronary syndrome (NSTE-ACS)	**Labeled:** Treatment of ACS patients managed medically or with percutaneous coronary intervention (PCI) or treatment of patients undergoing PCI (including intracoronary stenting).
	Off Label: primary PCI during STEMI and elective PCI for stable ischemic heart disease	
Mechanism of Action	Antagonist of fibrinogen that binds reversibly to GP IIb/IIIa receptor preventing platelet aggregation	
Pharmacodynamics & Pharmacokinetics	**Molecular class:** Non-peptide **Molecular weight:** Small Molecule (495 Da) **Receptor binding affinity:** High (15 nM) **Receptor binding half-life:** 10-15 sec **Plasma half-life:** 2 hours **Clearance:** Renal	**Molecular class:** Cyclic Heptapeptide **Molecular weight:** Small Molecule (832 Da) **Receptor binding affinity:** Low (120 nM) **Receptor binding half-life:** 10-15 sec **Plasma half-life:** 2.5 hours **Clearance:** Renal
Clinical Efficacy	**See clinical data summaries in Appendix III & IV**	
Dosage Forms	**Premixed Bags/Vials:** • 3.75 mg/15 mL (250 mcg/mL with sodium chloride (concentrated bolus vial) • 5 mg/100 mL (50 mcg/mL) with sodium chloride (bag & vial) • 12.5 mg/250 mL (50 mcg/mL) with sodium chloride (bag)	**Premixed Vials:** • 20mg/10mL (2 mg/mL) vial for single use bolus injection • 75mg/100mL (0.75 mg/mL) vial for single use infusion • 200mg/100mL (2 mg/mL) vial for single use infusion
Storage	Store at 25°C (77°F) with excursions permitted between 15-30°C (59-86°F) Do not freeze & protect from light during storage (comes in light-protective foil pouch).	Refrigerate at 2-8°C (36-46°F) Vials may be transferred to room temperature storage for a period not exceeding 2 months Protect from light until administration

Dosing and Administration	**NSTE-ACS (medically managed or undergoing PCI):** 25 mcg/kg IV bolus within 5 minutes and then 0.15 mcg/kg/min for up to 18 hours No minimum infusion length 1. Bolus delivered via syringe from concentrated bolus vial and infusion comes from infusion bag via infusion pump **OR** 2. Bolus and infusion comes out from the same bag via infusion pump No weight-based dosing cap	**NSTE-ACS:** 180 mcg/kg IV bolus and then 2 mcg/kg/min until discharge or initiation of CABG, up to 72 hrs **PCI:** 180 mcg/kg IV bolus then a second 180 mcg/kg bolus at 10 minutes and 2 mcg/kg/min until discharge or for up to 18-24 hrs. Minimum of 12 hrs recommended Bolus via syringe and infuse via pump Dosing cap at 121kg
Onset	>90% platelet inhibition within 10 minutes of bolus delivery	**Single bolus + infusion:** >80% platelet inhibition 15 min after bolus **Double bolus + infusion:** >90% platelet inhibition 10 min after second bolus
Dosage Adjustments	**Renal:** CrCl ≤60 mL/min, give 25 mcg/kg within 5 minutes and then 0.075 mcg/kg/min **Hemodialysis:** Same as above; Use with Caution	**Renal:** CrCl<50mL/min; reduce the infusion to 1mcg/kg/min **Hemodialysis:** Contraindicated
Adverse Drug Reactions	Bleeding, thrombocytopenia	Bleeding, hypotension, intracranial hemorrhage and stroke, immunogenicity/thrombocytopenia
Contraindications	Known hypersensitivity to any component of Aggrastat History of thrombocytopenia with prior exposure to Aggrastat Active internal bleeding, history of bleeding diathesis, major surgical procedure or severe physical trauma within the previous month	Known hypersensitivity to any component of the product -Bleeding diathesis or bleeding within previous 30 days Severe uncontrolled HTN (BP>200/110mmHg) Major surgery within previous 6 weeks Stroke within 30 days or any history of hemorrhagic stroke Co-administration with other GP IIb/IIIa inhibitor Dependency on renal dialysis

Guideline Excerpts

- **2011 ACCF/AHA PCI Guidelines**

  "Abciximab, double-bolus eptifibatide (180 mcg/kg bolus followed 10 minutes later by a second 180 mcg/kg bolus), and high-bolus dose tirofiban (25 mcg/kg) all result in a high degree of platelet inhibition, have been demonstrated to reduce ischemic complications in patients undergoing PCI, and appear to lead to comparable angiographic and clinical outcomes."

- **2013 ACCF/AHA STEMI Guidelines**

  "It is reasonable to start treatment with an intravenous glycoprotein (GP) IIb/IIIa receptor antagonist such as abciximab, high-bolus-dose tirofiban or double-bolus eptifibatide at the time of primary PCI (with or without stenting or clopidogrel pretreatment) in selected patients with STEMI who are receiving unfractionated heparin (UFH).
  (Level of Evidence: A, B)

- **2014 ACC/AHA NSTE-ACS Guidelines**

  Class I
  In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) and not adequately pre-treated with clopidogrel or ticagrelor, it is useful to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI.
  (Level of Evidence: A)

  Class IIa
  In patients with NSTE-ACS and high-risk features (e.g., elevated troponin) treated with UFH and adequately pretreated with clopidogrel, it is reasonable to administer a GP IIb/IIIa inhibitor (abciximab, double-bolus eptifibatide, or high-dose bolus tirofiban) at the time of PCI.
  (Level of Evidence: B)

  Class IIb
  In patients with NSTE-ACS treated with an early invasive strategy and dual antiplatelet therapy (DAPT) with intermediate/high-risk features (e.g., positive troponin), a GP IIb/IIIa inhibitor may be considered as part of initial antiplatelet therapy. Preferred options are eptifibatide or tirofiban.
  (Level of Evidence: B)

HIV ANTIRETROVIRAL AGENTS
FORMULARY STANDARDIZATION

Background**:**
Due to multiple newer antiretroviral agents now appearing on the market a full review of this class of medications was completed in order to ensure that the most commonly utilized agents were on formulary and to eliminate any agents that are now rarely utilized.

The below has been reviewed by the Antibiotic Stewardship Committee and approved for implementation at all CHI Memorial facilities.

Formulary Medications:

Medications	**Strength**	**Formulation**
Tivicay (dolutegravir)	50mg	Tab
Norvir (ritonavir)	100mg	Tab
Prezista (darunavir)	800mg	Tab
Prezista (darunavir)	600mg	Tab
Ziagen (abacavir)	300mg	Tab
Intelence (etravirine)	100mg	Tab
Epivir (lamivudine) - HBV	100mg	Tab
Epivir (lamivudine)	150mg	Tab
Isentress (raltegravir)	400mg	Tab
Reyataz (atazanavir)	150mg	Cap
Viread (tenofovir)	300mg	Tab
Sustiva (efavirenz)	200mg	Cap
Emtriva (emtricitabine)	200mg	Cap
Genvoya (elvitegravir/cobicistat/ emtricitabine/tenofovir alafenamide)*	150/150/200/10mg	Tab
Kaletra (lopinavir/ritonavir)	200/50mg	Tab
Retrovir (zidovudine)	300mg	Tab

* New addition to formulary

Non-formulary:

Medications	**Strength**	**Formulation**
Truvada (tenofovir/emtricitabine)*	300/200mg	Tab
Atripla (tenofovir/emtricitabine/efavirenz)*	300/200/600mg	Tab
Stribild (cobicistat/elvitegravir/ emtricitabine/tenofovir disoproxil fumarate)*	150/150/200/300mg	Tab
Descovy (emtricitabine/tenofovir alfenamide)*	200/25 mg	Tab
Combivir (lamivudine/zidovudine)*	150/300mg	Tab
Epzicom (abacavir/lamivudine)*	600/300 mg	Tab
Triumeq (abacavir/lamivudine/dolutegravir)*	600/50/300 mg	Tab
Viramune (nevirapine)	200mg	Tab
Reyataz (atazanavir)	200mg	Cap
Epzicom (abacavir/lamivudine)	600/300mg	Tab
Crixivan (indinavir)	200mg	Cap
Lexiva (fosamprenavir)	700mg	Tab
Retrovir (zidovudine)	100mg	Cap
Prezcobix (darunavir/cobicistat)*	800/150 mg	Tab
Videx EC (didanosine)	400mg	Cap
Viracept (nelfinavir)	250mg	Tab
Zerit (stavudine)	20mg	Cap
Zerit (stavudine)	40mg	Cap

* Substitutions as per below

Formulary substitutions:

Atripla: efavirenz 600mg + emtricitabine 200mg + tenofovir 300mg
Truvada: emtricitabine 200mg + tenofovir 300mg
Combivir: lamivudine 150mg + zidovudine 300mg
Epzicom: abacavir 600mg + lamivudine 300mg
Triumeq: abacavir 600mg + lamivudine 300mg + dolutegravir 50mg

Substitutions if patient unable to bring own medication from home:

Stribild → Genvoya 1 tab PO daily
Prezcobix → Darunavir 800mg + ritonavir 100mg PO daily
Descovy → Truvada 1 tab PO daily (normal renal function)

If renal impairment, dose adjust individual components as shown below

Emtricitabine:

CrCl 30-49 mL/min: 200mg q48h
15-29 mL/min: 200mg q72h
<15 mL/min or HD: 200mg q96h

Tenofovir:

CrCl 30-49 mL/min: 300mg q48h
10-29 mL/min: 300mg twice weekly (every 72-96 hours)
HD: 300mg q 7 days

DATE/TIME ORDERED

INSULIN PUMP ORDERS: Subcutaneous

1. Consultations:
   - ☐ Consult Hospitalist Service for insulin pump management
   - ☑ Consult Diabetes Educator

2. Patient to self-administer insulin via subcutaneous insulin pump. If at any time the patient is no longer alert and physically capable, able to work the pump functions, or unwilling to manage the pump during hospitalization the physician should be contacted for further orders for insulin management.

3. Discontinue all other insulin orders

4. Lab orders (if not already ordered):
   - ☑ Hemoglobin A1c (if not already ordered)
   - ☑ Fingerstick blood glucose: AC & HS, 2 AM

5. Hyperglycemia management:
   a. Unexplained hyperglycemia unresponsive to insulin boluses
      Instruct patient to change pump reservoir, infusion set and insertion site. Patient to then bolus for correction. If hyperglycemia is not resolved 2 hours after bolus following cartridge and set change notify MD immediately for alternative insulin orders
   b. Blood glucose > 250 mg/dL x 2
      Contact physician for two consecutive blood glucose values > 250 mg/dL that have not decreased with insulin administration, change in pump settings or insertion of new tubing or site change.

6. Hypoglycemia management:
   a. Mild to Moderate (BG < 70 mg/dL) with no cognitive impairment
      Treat per Hypoglycemia Protocol unless MD has ordered other treatment. DO NOT STOP PUMP.
   b. Severe hypoglycemia - patient unresponsive
      Treat per Hypoglycemia Protocol. CALL MD IMMEDIATELY to determine pump status (may require stopping pump temporarily or changing rates). If nurse determines the insulin infusion should be stopped before physician contacted, remove infusion set from patient.

7. Documentation of patient administered basal, correctional, and nutritional insulin doses
   a. Basal rates: document or verify basal rates in *Assess/Monitor: Blood Glucose* EVERY shift and as needed if there are changes in basal rate.
   b. Bolus doses (correction, nutritional): document time and amount of all boluses in *Assess/Monitor: Blood Glucose*.

8. Pump refills & infusion site management:
   a. Pump refills: Only patients, patient representative or diabetes educator should refill the insulin pump using insulin supplied by the inpatient pharmacy.
   b. Infusion site: Site should be assessed at the beginning of each shift and the patient should change the infusion set at least every 2-3 days.
   c. Pump alarms: Contact diabetes educator immediately for any pump error or alert messages. If diabetes educator not available, the physician should be contacted.

9. Discontinue all other **subcutaneous insulin** orders

DATE/TIME ORDERED

INSULIN PUMP ORDERS: Subcutaneous

10. Continuous subcutaneous insulin administration by pump as follows:
** If diabetes educator not available to complete the below information, continue pump at current settings until pump interrogation can be completed by Diabetes Educator.*

11. **TYPE OF INSULIN:** _____

12. **BASAL RATES:**

TIME	UNITS/ HR	TIME	UNITS/ HR	TIME	UNITS/ HR	TIME	UNITS/ HR
12A-1A		6A-7A		12P-1P		6P-7P	
1A-2A		7A-8A		1P-2P		7P-8P	
2A-3A		8A-9A		2P-3P		8P-9P	
3A-4A		9A-10A		3P-4P		9P-10P	
4A-5A		10A-11A		4P-5P		10P-11P	
5A-6A		11A-12P		5P-6P		11P-12A	

13. **MEAL BOLUSES:**

1 unit per _____ grams CHO from _____ to _____ (times)

1 unit per _____ grams CHO from _____ to _____ (times)

1 unit per _____ grams CHO from _____ to _____ (times)

1 unit per _____ grams CHO from _____ to _____ (times)

14. **CORRECTION BOLUSES:**

1 unit for every ____ mg/dL blood glucose > ____ from ____ to ____ (times)

1 unit for every ____ mg/dL blood glucose > ____ from ____ to ____ (times)

1 unit for every ____ mg/dL blood glucose > ____ from ____ to ____ (times)

1 unit for every ____ mg/dL blood glucose > ____ from ____ to ____ (times)

Correct at: ☐ Meals ☐ HS ☐ Other: _____

15. **ACTIVE INSULIN TIME =** _____ hours

16. **CONSISTENT CARBOHYDRATE DIET:**
☐ 1500 kcal (45 grams CHO/meal) ☐ 2000 kcal (60 grams CHO/meal)
☐ 1800 kcal (60 grams CHO/meal) ☐ Other: _____

Patient Safety Review

SODIUM PHOSPHATE ENEMA (SPE)

ACUTE PHOSPHATE NEPHROPATHY

Background:
A patient safety concern was recently brought to the attention of pharmacy regarding patient safety risks associated with the use of sodium phosphate enemas (SPE). The concern originated from nephrology who indicated they had treated several patients for what they felt was acute nephropathy secondary to sodium phosphate enema administration and particularly in patients with pre-existing renal dysfunction or patients at increased risk of renal complications (elderly, etc.).

Acute Phosphate Nephropathy:
Acute phosphate nephropathy is a form of kidney injury that occurs following the use of bowel purgatives that contain oral sodium phosphate (OSP) or sodium phosphate containing enemas. The mechanism underlying acute phosphate nephropathy most likely relates to a transient but potentially severe increase in serum phosphate and its associated complications (nephrocalcinosis, volume depletion, etc.). In 2006, the FDA issued a warning regarding the potential for AKI in patients who received OSP. However, no specific warnings were issue for the SPE formulation although case reports of AKI associated with this formulation have also been documented in the literature. The bulk of the data documenting acute phosphate nephropathy originates from evaluations of OSP as part of bowel cleansing regimens prior to colonoscopy or other GI surgeries/procedures. However, case reports of AKI related to intermittent use of SPE have typically involved patients receiving multiple doses or patients with pre-existing renal dysfunction (eGFR 25-57 ml/min).

Risk factors for acute phosphate nephropathy:
Risk factors for use of the enema product have not been clearly defined (may also occur in patients with no risk factors) although the FDA black box warning for oral sodium phosphate includes the following: increased age (> 55 years of age), preexisting renal dysfunction, bowel obstruction, active colitis, or dehydration, and the use of medications that affect renal perfusion or function (ACE/ARBs, diuretics, and possibly NSAIDs).

Conclusion & Recommendation:
A brief review of hospital utilization of SPE was performed. There were a few isolated events of transient increased in serum creatinine observed in some patients that received SPE although it is not clear if administration of SPE was the sole precipitating event. Additionally, there were situations observed in which patients with pre-existing renal dysfunction were prescribed single or multiple doses of SPE despite pre-existing renal dysfunction (Scr > 1.5 with some patients with Scr > 2).

Despite a lack of clear recommendations on which patients are at higher risk of acute phosphate nephropathy some consideration should be given to avoidance at least in patients with pre-existing renal dysfunction. However, the limited data that is available at this time doesn't specifically suggest either an eGFR, CrCl, or serum creatinine value that should be utilized to identify this at risk population. A hospital defined parameter should be defined and this information incorporated into physician standing orders that currently utilize SPE as well as prospective screening of SPE use by pharmacy to identify potentially dangerous/inappropriate use of sodium phosphate enemas.

Adverse Drug Reaction (ADR) Summary
September 2016 through February 2017

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.

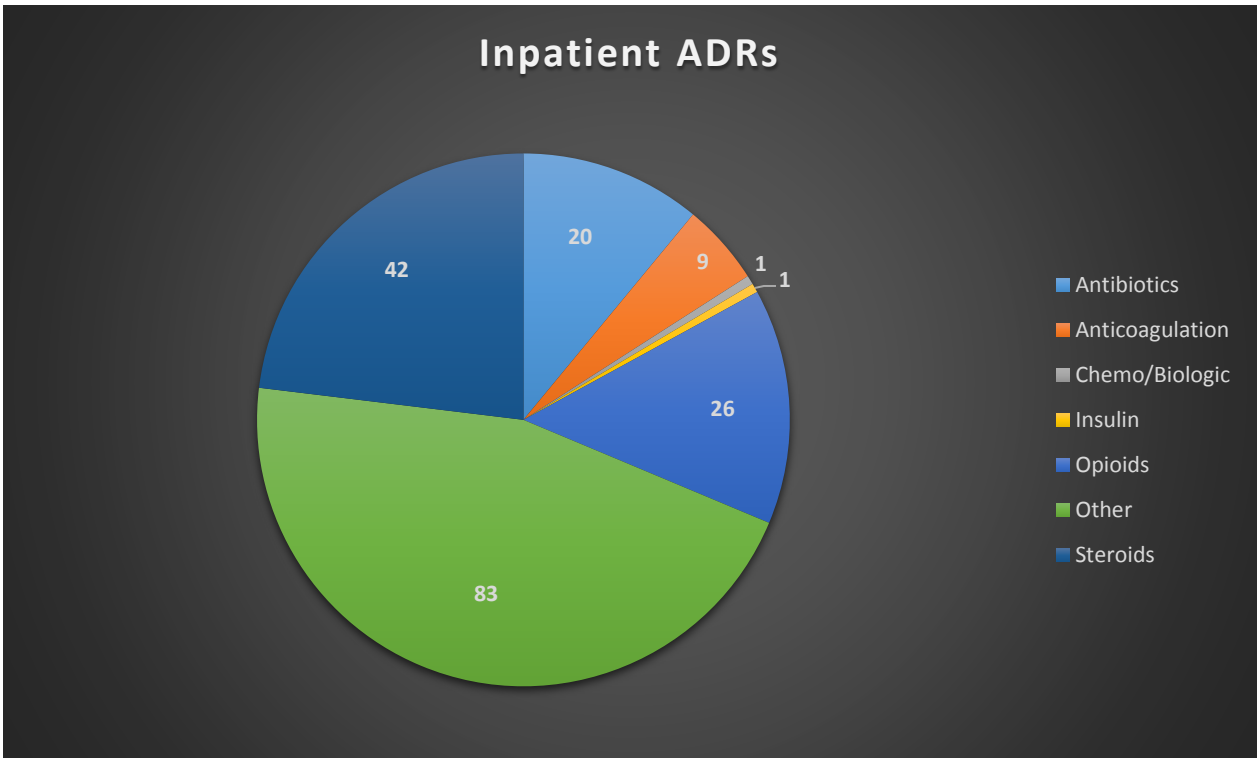
Category 3: A serious or rare ADR which has abnormal characteristics compared with published reports of the reaction (e.g. heparin induced platelet aggregation resulting in limb amputation). ADR's from this category should be reported to the manufacturer and/or the FDA (MedWatch or the Vaccine Adverse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

Inpatient: 182 (25%)
Prior to hospitalization: 551 (75%)
Total: 733

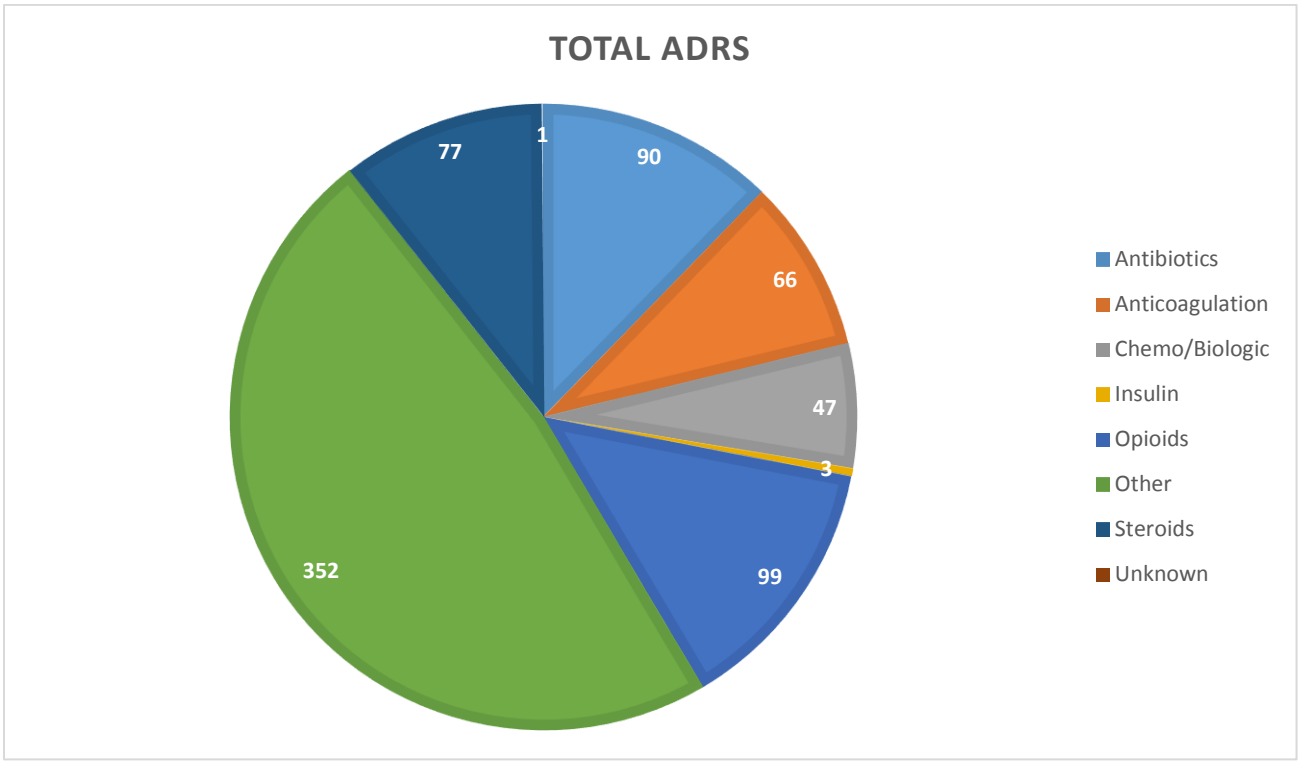
Category 1: 481
Category 2: 249
Category 3: 3

January:
1. Patient received Cubicin (Daptomycin) inpatient and developed Toxic Epidermal Necrolysis.
2. Patient received Plaquenil (Hydroxychloroquine) as outpatient and developed Stevens Johnson Syndrome.

February
1. Patient received Treanda (Bendamustine) and Rituxan (rituximab) as outpatient and developed Stevens Johnson Syndrome.



Antibiotics: Levaquin most common (5) – Rash, Increased INR, Encephalopathy; Rocephin (4) – Rash; Zosyn and Vancomycin (2) – anaphylaxis; Ancef, Azithromycin, Bactrim (1) - Rash
Anticoagulants: Coumadin (Increased INR, Hemoptysis, Hematuria); Eliquis (GI Bleed, Anemia)
Narcotics: Dilaudid (Respiratory distress x 2, Syncope); Oxycodone (withdrawal); Constipation most common
Steroids: Hyperglycemia and leukocytosis most common
Other: Mostly blood pressure medications, diuretics, and benzodiazepines



Antibiotics: Bactrim and Levaquin (AKI and Rash most common); N/V/D reported with several beta-lactams
Anticoagulants: Coumadin, Plavix, Xarelto, Eliquis—various bleeds
Antineoplastics: Pancytopenia, GI Distress, AKI, Neuropathy

** Level 3 Stevens Johnson Syndrome due to Bendeka and Rituxan combination **

Narcotics: AMS, constipation, metabolic encephalopathy, respiratory depression
Steroids: Hyperglycemia and leukocytosis most common

GLYCEMIC MANAGEMENT:

Pharmacists may order or make insulin therapy adjustments for the following conditions when clinically appropriate as indicated below. However, if hospitalist or other provider(s) are currently managing insulin or other therapies for glycemic control any modifications in therapy will be discussed with the provider prior to execution of any of the below therapies.

1.) Sliding scale insulin dose level titration to the next highest level: If blood glucose (BG) > 180 mg/dl two (2) times in 24 hours AND all BG readings > 90 mg/dl

2.) Long-acting insulin

a. ***Patients on home long-acting insulin therapy:*** Pharmacists can resume patient home regimens (or formulary equivalent) upon initiation of TPN therapy if not already continued by other provider. Further dose titrations may be executed daily if patient experiences persistent hyperglycemia (BG > 200 mg/dl x 2 within 24 hour period) in 5-10 unit increments. Total insulin utilization over the previous 24 hours will be reviewed to more accurately determine the needed dose increase. Dose reductions may also be performed in the event of hypoglycemic events or reductions in TPN rate or caloric intake.

b. ***Patients not on home long-acting insulin therapy:*** Pharmacists may begin long-acting insulin therapy for any TPN patient experiencing persistent hyperglycemia (BG > 200 mg/dl x 2 within 24 hour period). The initial dose may be up to 0.1 units/kg and further titrated daily if patient experiences persistent hyperglycemia (BG > 200 mg/dl x 2 within 24 hour period) in 5-10 unit increments up to a total dose of 0.4 units/kg. Titrations beyond this dose will be discussed with the attending physician or other appropriate provider before execution if unable to maintain adequate glycemic control despite the addition of long-acting insulin up to the aforementioned maximum dose. Total insulin utilization over the previous 24 hours will be reviewed to more accurately determine any needed dose increase. Dose reductions may also be performed in the event of hypoglycemic events or reductions in TPN rate or caloric intake.

c. ***Patients on cyclic TPN therapy:*** The substitution of NPH insulin can be considered for patients on cyclic TPN therapy as the duration of effect for this insulin is more appropriate for patients on cyclic TPN.

ORDERS TO PHARMACY:

1. Communicate with Pharmacy regarding discharge or death or changes in orders as soon as these issues are known for the patient receiving TPN so that solutions are not mixed unnecessarily.
2. All TPN orders should be written on a TPN order sheet; orders include labs, referrals and indicators for use. The TPN Initiation order set must be completed on the first day by the physician or pharmacist indicating appropriate indication for TPN.
3. Orders must be received by the Pharmacy by 2 p.m. daily.
   - After order receipt deadline, new TPN orders and changes will be initiated the next day at the hospital standard hang time (8 p.m. – 10 p.m.).
4. When orders are written for changes in therapy that necessitate discontinuing a continuous TPN infusion, $D_{10}W$ will be infused at the same rate until the next hang time, unless the most recent blood glucose is greater than 200.
5. Twenty-four-hour solutions are delivered to the nursing unit at 1800 daily.

POLICY

Title: TITRATING MEDICATIONS		
	Page 1 of 1	
Policy Number: MM-05405	Date Last Reviewed/Revised: 8/16	Valid Until: 8/19
Department(s) Affected: All Clinical Areas	Review Period: every 3 years	

OUTCOME: Patient will receive adequate medication for desired outcome.

POLICY:
Medications will be titrated in a safe and accurate manner as established by Pharmacy recommendations from appropriate drug information sources, physician order and clinical assessment. In the absence of specific MD/Practitioner orders for titrating and tapering certain IV medications, the attached guidelines will be followed and titration instructions will be defined on the eMar. Unless otherwise specified by the physician, all the required titration order elements below will be included within the medical record (eMar) as defined by this policy.

Standard concentrations listed in the attachment will be routinely followed. If standard concentrations are utilized, the nurse can document the rate on the MAR without specifying the concentration. When non-standard concentrations are used, the nurse must have the concentration per ml and rate documented on the MAR.

All titration orders should contain the following:

- Medication name
- Medication route
- Initial infusion rate
- Incremental units the rate can be increased or decreased
- Frequency of incremental dose adjustments
- Maximum infusion rate
- Objective clinical endpoint, to be specified at the time of order*

*Any order without an objective clinical endpoint (BP target, RASS goal, etc.) as defined by the ordering practitioner must be clarified with the prescriber and clarified via written order.

Key Contact: Patrick Ellis, Pharmacy
Approved/Reviewed by: Medication Management Chapter Leader, Nursing Professional Practice Council
Reference(s): Clinical Pharmacology
Joint Commission Standard: MM 04.01.01
Attachment(s): IV Drug Standards Chart
Date First Effective/Revisions: 1/04, 9/08, 11/09, 3/13, 12/14, 1/16, 4/16, 8/16

IV DRUG STANDARDS

Drug Name Brand *(Generic)*	Drug Category	Mixing & Concentration	Pyxis	Dosing *(Titrating & Tapering)*	Precautions or Special Instructions	Dosed as
Angiomax *bivalirudin*	Anticoagulant	250 mg/250 ml NS Concentration = 1 mg/ml Non-procedural use – HIT treatment 250 mg/50 ml NS Concentration = 5 mg/ml Cath lab, procedural use, etc.		Wt Based Protocol: For treatment of HIT or suspected heparin intolerance: See *Angiomax (bivalirudin) Weight Based Dosing Protocol* for starting rates and titration information Dose adjustments depend upon aPTT results (see protocol)	• Initial dose dependent upon patient's renal function • Observe patient for bleeding. • Angiomax weight based protocol in Meditech • d/c all other parenteral anticoagulants • ECMO order set also available for ECMO anticoagulation	mg/kg/hr
Argatroban	Anticoagulant	50 mg/50 ml D_5W Non PVC bag only Concentration = 1 mg/ml		Wt Based Protocol: For treatment of HIT or suspected heparin intolerance: See *Argatroban Orders and Dosing Protocol* for starting rates and titration information Dose adjustments depend upon aPTT results (see protocol)	• Reduce initial dose for hepatic insufficiency • Observe patient for bleeding. • Argatroban usage guidelines in Meditech • d/c all other parenteral anticoagulants	mcg/kg/min
Ativan *lorazepam*	Benzodiazepine Anxiolytic, sedative	50 mg/250 ml D_5W Non PVC bag only Concentration = 0.2 mg/ml		Starting Dose: 0.5 mg/hr Maximum Dose: 10 mg/hr Increase or decrease by 0.5 mg/hr at 30 minute intervals based on parameters as determined by physician	• Patients receiving > 0.1 mg/kg/hr for > 48 hrs should be evaluated for propylene glycol toxicity	mg/hr
Brevibloc *Esmolol*	Beta-blocker Antiarrhythmic	2.5 gm/250 ml NS Premix Concentration = 10 mg/ml	□	Starting Dose: 50 mcg/kg/min Maximum Dose: 300 mcg/kg/min Titrate/taper in 50 mcg/kg/min increments every 5 minutes based on parameters as determined by physician	• Monitor ECG and blood pressure closely during infusion • For SVT load c/ 500 mcg/kg over 1 min up to 3 doses q4min • Contraindicated for bradycardia	mcg/kg/min
Bumex *Bumetanide*	Loop Diuretic	25 mg/100 ml Concentration = 0.25 mg/ml		Starting Dose: 0.25-0.5 mg/hr Maximum Dose: generally 2 mg/hr **continuous infusion – dose titration to be specified by prescriber	• Monitor patient response (edema, SOB, etc.), BUN, Scr, electrolytes	mg/hr
Cardene *Nicardipine*	Calcium Channel Blocker Antihypertensive	25 mg/250 ml NS Concentration = 0.1 mg/ml		Starting Dose: 5 mg/hr Maximum Dose: 15 mg/hr Increase or decrease by 2.5 mg/hr every 5-15 minutes until desired blood pressure (as directed by physician) is reached	• With constant peripheral vein infusion, infusion site should be changed at least every 12 hours • Incompatible c/ HCO_3 and LR	mg/hr
Cardizem *Diltiazem*	Calcium Channel Blocker Antiarrhythmic	100 mg/100 ml NS Concentration = 1mg/ml	□	Starting Dose: 10 mg/hr Maximum Dose: 15 mg/hr See *Diltiazem Protocol* for starting rates, bolus information and titration information or as parameters as determined by physician	May depress cardiac conduction; headache, hypotension, dizziness, flushing or fatigue	mg/hr
Cordarone *Amiodarone*	Antiarrhythmic	Infusion: 500 mg/500 ml D_5W Non PVC bag only Bolus: 150 mg/100 ml D_5W (bolus may be mixed in PVC bag)		Bolus 150mg over 10-30 min, then 1mg/min x 6 hours, then 0.5mg/min x 18 hours or as determined by physician See *Amiodarone IV Protocol*	Should not be given to pts w/bradycardia, AV block, severe hypotension, or severe respiratory failure. Contraindicated in cardiogenic shock Caution in allergies to iodine	mg/min

IV DRUG STANDARDS (continued)

Drug Name Brand *(Generic)*	Drug Category	Mixing & Concentration	Pyxis	Dosing *(Titrating & Tapering)*	Precautions or Special Instructions	Dosed as
Corlopam *Fenoldopam*	Antihypertensive Vasodilator	10 mg/250 ml NS Concentration = 40 mcg/ml		Starting Dose: 0.03-0.1 mcg/kg/min Maximum Dose: 1.6 mcg/kg/min Increase or decrease by 0.05-0.1 mcg/kg/min at 15 minutes intervals until target blood pressure (as determined by physician) is reached	Hypotension, flushing, dizziness, headache, reflex tachycardia, nausea and vomiting Unlabeled use: Renal protection	mcg/kg/min
Diprivan *Propofol*	Sedative-hypnotic	1000 mg/100 ml (lipid emulsion) Concentration = 10mg/ml Change bottle & tubing q 12 hours	□	Starting Dose: 5 mcg/kg/min Max dose: generally 50 mcg/kg/min Increase or decrease by 5 mcg/kg/min at 5-10 minute intervals based on parameters as determined by physician	• Patient MUST be mechanically ventilated while receiving Propofol in the ICU. • Do not bolus • May cause hypotension, profound bradycardia, increase triglycerides, green urine, hiccough • Reduce dose by ½ in elderly	mcg/kg/min
Dobutrex *Dobutamine*	Inotropic agent Cardiac stimulant	500 mg/250 ml D_5W Premix Concentration = 2000 mcg/ml	□	Starting Dose: 2.5 mcg/kg/min Maximum Dose: generally 20 mcg/kg/min Increase or decrease by 2.5 mcg/kg/min every 15 minutes based on parameters determined by physician	HTN, tachycardia, angina, increased ventricular ectopy, hypokalemia, nausea, HA Incompatible with HCO_3	mcg/kg/min
Dopamine	Inotropic agent Cardiac stimulant Vasopressor	400 mg/250 ml D_5W Premix Concentration = 1600 mcg/ml	□	Starting Dose: 2-5 mcg/kg/min Maximum Dose: 20 mcg/kg/min Increase or decrease by 1 mcg/kg/min every 5-15 minutes based on parameters determined by physician	• Tachycardia, palpitations, nausea, vomiting • Caution c/ allergies to sulfites • Inactivated by HCO_3 • Avoid extravasation **	mcg/kg/min
Epinephrine	**Cardiac Stimulant Vasopressor Bronchodilator**	**2 mg/250 ml D_5W Concentration = 8 mcg/ml**		**(Utilize mcg/min dosing unless weight based dosing ordered.)** **MCG/MIN DOSING** Starting Dose: 1-2 mcg/min Maximum Dose: generally 50 mcg/min Increase or decrease by 1 mcg/min at 3-5 minute intervals based on parameters determined by physician **MCG/KG/MIN DOSING** Starting Dose: 0.05-0.1 mcg/kg/min Maximum Dose: 0.5 mcg/kg/min Increase or decrease by 0.05-0.2 mcg/kg/min every 3-5 minutes based on parameters determined by physician	**Vasoconstriction-induced tissue sloughing can occur.**	**mcg/min -OR- mcg/kg/min**
Fentanyl	Narcotic analgesic Anesthesia adjunct	1500 mcg/30 ml* Concentration: 50 mcg/ml *To be infused via PCA pump as continuous infusion	□	Starting Dose: usually 25 mcg/hr Maximum Dose: generally 200 mcg/hr Increase or decrease by 50 mcg/hr at 30 minute intervals until adequate analgesia is maintained	• Observe for respiratory depression, bradycardia, urinary retention • Tolerance can develop with prolonged use • Avoid abrupt cessation	mcg/hr

IV DRUG STANDARDS (continued)

Drug Name Brand *(Generic)*	Drug Category	Mixing & Concentration	Pyxis	Dosing *(Titrating & Tapering)*	Precautions or Special Instructions	Dosed as
Isuprel *isoproterenol*	Inotropic/chronotropic Antiarrhythmic	1 mg/250 ml D5W Concentration = 4 mcg/ml		Starting dose: 2 mcg/min Maximum Dose: generally 10 mcg/min Increase or decrease by 1-2 mcg/min every 15 minutes until desired effect as per physician parameters	• Cadiovascular effects include: sinus tachycardia, atrial and ventricular tachycardia. Fatal ventricular arrhythmias have been seen when heart rates increased above 130 bpm. • May precipitate angina or coronary insufficiency, especially in patients with cardiogenic shock or ischemic heart disease due to increased oxygen demand. • Monitor BP closely. Can initially cause hypertension followed by profound hypotension.	mcg/min
Labetalol *Trandate*	Alpha and Beta-Blocker Antihypertensive	300mg/300 ml D5W Concentration: 1 mg/ml		Starting Dose: 0.5-2 mg/min Maximum Dose: generally 300 mg total dose Increase or decrease by 0.5 mg/min at 10 minute intervals	Monitor B/P closely during direct IV injection and at least every 15 minutes during infusion.	mg/min
Levophed *Norepinephrine*	**Vasopressor**	**4mg/250 ml D_5W Concentration = 16 mcg/ml**		**(Utilize mcg/min dosing unless weight based dosing ordered.)** **MCG/MIN DOSING** Starting Dose: 4 mcg/min Maximum Dose: 80 mcg/min Increase or decrease by 1 mcg/min at 5 minute intervals based on parameters determined by physician **MCG/KG/MIN DOSING** Starting Dose: 0.05 mcg/kg/min Maximum Dose: 1 mcg/kg/min Increase or decrease by 0.02 mcg/kg/min at 5 minute intervals based on parameters determined by physician	• **Avoid extravasation ‡‡** • **Anxiety, N/V, HTN, urinary retention, arrhythmias**	**mcg/min -OR- mcg/kg/min**
Lidocaine	Antiarrhythmic	2 gm/500 ml NS Premix Concentration = 4 mg/ml	□	Starting Dose: 1-2 mg/min Maximum Dose: 4 mg/min Titrate upward per physician order. Tapering: If the drip is infusing faster than 2mg/min OR has been infusing longer than 36 hrs, half the dose for 8 hrs, then discontinue.	• Monitor ECG closely • CNS side effects: dizziness, anxiety, confusion, hallucinations, etc. • Levels may be monitored • Therapeutic levels: 1.5-5 mcg/ml	mg/min
Morphine	Narcotic analgesic	30 mg/30 ml NS (PCA at basal rate) Concentration = 1mg/ml		Starting Dose: 0.5-1 mg/hr Maximum Dose: generally 20 mg/hr Increase or decrease by 0.5-1 mg/hr at 30 minute intervals until adequate analgesia is maintained.	• Observe for respiratory depression, constipation, N/V • Tolerance can develop with prolonged use	mg/hr
Neosynephrine *Phenylephrine*	Vasopressor	10 mg/250 ml D_5W Concentration = 40 mcg/ml Should not be given undiluted all		Starting Dose: (severe hypotension): 40 mcg/min Maximum Dose: generally 360 mcg/min Increase or decrease by 20 mcg/min at	• Avoid extravasation ‡‡ • Use with caution in elderly, bradycardia, partial heart block, hyperthyroid, myocardial disease, severe atherosclerosis • Correct volume deficiency before considering this	mcg/min

IV DRUG STANDARDS (continued)

Drug Name Brand *(Generic)*	Drug Category	Mixing & Concentration	Pyxis	Dosing *(Titrating & Tapering)*	Precautions or Special Instructions	Dosed as
		bolus doses should be mixed in 50 ml NS prior to administration		10 minute intervals based on parameters as determined by physician	drug	
Nimbex *Cisatracurium*	Neuromuscular Blocker (paralytic)	200 mg/100 ml D5W Concentration = 2 mg/ml		Bolus: 150-200 mcg/kg Initial maintenance Dose: 1-3 mcg/kg/min Normal maintenance dose range 0.5-10 mcg/kg/min (max dose generally 10 mcg/kg/min) Monitor depth of blockade every 20 mins initially until stable dose (increase or decrease by 0.5 mcg/kg/min), then every 1 hr according to patient's clinical response with peripheral nerve stimulator or BIS based on parameters as determined by physician.	• Preferred NMBA for patients with multi-system organ failure – organ independent metabolism. • Patients must have sedation and medication for analgesia while on paralytic	mcg/kg/min
Norcuron *Vecuronium*	Neuromuscular Blocker (paralytic)	50 mg/500 ml D5W Concentration = 0.1 mg/ml (100mcg/ml)		Bolus: 80-100 mcg/kg Initial maint. dose: 0.8 – 1.2 mcg/kg/min Normal maintenance dose range: 0.8-1.7 mcg/kg/min (max dose generally 1.7 mcg/kg/min) Monitor depth of blockade every 20 mins initially until stable dose (increase or decrease by 0.3 mcg/kg/min), then every 1 hrs. according to patient's clinical response with peripheral nerve stimulator or BIS based on parameters as determined by physician.	• Dose adjustment not necessary for renal impairment. • Patients must have sedation and medication for analgesia while on paralytic	mcg/kg/min
Precedex *Dexmedetomidine*	Alpha$_2$ agonist Sedative-hypnotic	400 mcg/100 ml NS 400mcg/96cc NS from OR Concentration = 4 mcg/ml	□	Starting Dose: 0.2 mcg/kg/hr Maximum Dose: 2 mcg/kg/hr Increase or decrease by 0.1mcg/kg/hr at 10-15 minute intervals on parameters as determined by physician	• Observe for hypotension and bradycardia with loading dose. Use with caution in patients with advanced heart block. Decreases SNS activity.	mcg/kg/hr
Primacor *Milrinone*	Inotropic agent	20 mg/100 ml D$_5$W Premix Concentration: 200 mcg/ml	□	Starting Dose: 0.375-0.5 mcg/kg/min Maximum Dose: 0.75 mcg/kg/min, not to exceed 1.13 mg/kg/24 hrs Increase or decrease by 0.025 mcg/kg/min every 60 minutes based on parameters determined by phys.	• Has positive inotropic effect with vasodilator activity – may cause hypotension • Forms precipitate with Bumex or Lasix • Should not be used longer than 48 hours	mcg/kg/min
Procainamide	Antiarrhythmic	1 gm/250 ml NS Concentration = 4 mg/ml		Usual Dose: 1-4 mg/min Maximum Dose: 6 mg/min Increase or decrease by 1 mg/min every 15 to 30 minutes until desired effect as per physician parameters	• Decreases HR, monitor ECG, BP • Infusion > 24 hrs: monitor Procainamide and NAPA levels (active metabolite) esp. with renal failure	mg/min
Tridil *Nitroglycerin*	Anti-hypertensive Antianginal Vasodilator	50mg/250 ml D$_5$W Premix Concentration = 200 mcg/ml		Starting Dose: 5 mcg/min Maximum Dose: usually 200 mcg/min Increase by 5 mcg/min every 3-5 minutes	• Headache, hypotension, tachycardia • Do not filter (Gahart, 2004) • Tolerance may develop if administered over 12 hr.	mcg/min

IV DRUG STANDARDS (continued)

Drug Name Brand *(Generic)*	Drug Category	Mixing & Concentration	Pyxis	Dosing *(Titrating & Tapering)*	Precautions or Special Instructions	Dosed as
			□	up to 20 mcg/min based on parameters determined by physician. If no response, increase by 10 mcg/min every 3-5 minutes. Taper per MD order.	• Use extreme caution with inferior MI c/ RV involvement	
Vasopressin *Pitressin*	Vasopressor	20 units/50 ml NS Concentration 0.4 units/ml		Starting Dose: 0.03 units/min Maximum Dose: 0.07 units/min Increase or decrease by 0.005 units/min every 10 – 15 minutes based on parameters as determined by physician	• Minimal information available for dosing in vasodilatory shock. Dosing is research-based. • Must be administered via central line • May also be used for GI hemorrhage (0.2-1 units/min)	units/min
Versed *Midazolam*	Benzodiazepine Sedative-hypnotic Anesthesia adjunct	100 mg/100 ml NS Concentration = 1 mg/ml		Starting Dose: 1-2 mg/hr Maximum Dose: generally 10 mg/hr Increase or decrease by 1 mg/hr at 15 min. intervals based on parameters as determined by physician	• Monitor for respiratory depression and/or hypotension • May be dosed 0.02 – 0.1 mg/kg/hr • Adjust for GFR < 30 ml/min	mg/hr
Zemuron *rocuronium*	Neuromuscular Blocker (paralytic)	250 mg/250 ml NS Concentration = 1 mg/ml		Bolus: 0.6 – 1 mg/kg Initial maint Dose: 8 – 12 mcg/kg/min (max dose generally 16 mcg/kg/min) Monitor depth of blockade every 20 mins initially until stable dose (increase or decrease by 1 mcg/kg/min), then every 1 hrs. according to patient's clinical response with peripheral nerve stimulator or BIS based on parameters as determined by physician.	• Dose adjustment not necessary for renal impairment. • Patients must have sedation and medication for analgesia while on paralytic.	mcg/kg/min

Call IV Team for infiltration of this drug
** May also be dosed in mcg/kg/min