Pharmacy & Therapeutics Committee Meeting
Private Dining Room
October 13, 2016 7:00 a.m.

Agenda Items — Individual Responsible

1. Call to Order — Richard Pesce, MD

2. Approval of August, 2016 Minutes — Richard Pesce, MD

Next Meeting will be December 8, 2016 at 7:00 AM in the Private Dining Room

PHARMACY AND THERAPEUTICS COMMITTEE

DATE: August 11, 2016 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. David Dodson, M.D. Samuel Currin, M.D. Mark Anderson, MD Allen Atchley, M.D. Richard Yap, M.D. Avni Kapadia, M.D. Jeffrey Mullins, M.D.	Sandy Vredeveld, DPh Patrick Ellis, PharmD Lila Heet, PharmD Rhonda Poulson, RN Melissa Roden, RN Patty Hicks, RN Susan Fuchs, RD Linda Johnson PharmD Jamie Barrie, PharmD Rodney Elliott, CPhT	Nan Payne, RN Shannon Harris, RN Michael Stipanov, M.D. Nathan Chamberlain, M.D. Nathan Schatzman, M.D. Karen Babb, PharmD Scott Harbaugh, Finance	Meredith Tate, PharmD Justin Reinert, PharmD Jenny Gibson, PharmD Nasar Ansari, student

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 April 14, 2016 minutes were approved as submitted.		Complete
Therapeutic Interchanges and Formulary Decisions	The following medications were reviewed: 1. **CHI MUE Committee Decision Brief**: The medications that were reviewed at the April, May, and June national MUE committee meetings were reviewed with the committee. No updates will be required for any of the medications currently on Memorial's formulary based on the MUE committee's formulary decisions. 2. **Respiratory Formulary Interchange** – A few changes were recommended to the existing inhaled respiratory formulary interchange due to the removal of Foradil (formoterol) from the market. Brovana (aformoterol) will be utilized as the sole long acting beta agonist on formulary and all other agents within this class would be automatically substituted to a therapeutically equivalent dose of Brovana. Additionally, it was suggested to remove Atrovent MDI (substitute to ipratropium neb) due to low utilization of this product. 3. **Anti-muscarinic medications (overactive bladder)** – A review of the available medications within this class were reviewed. Due to similar efficacy of the various agents within this class it was recommended by Patrick to modify the formulary for this class (remove oxybutynin, tolterodine) and to utilize Sanctura (trospium) now that it is the most cost-effective agent within this class – auto-sub all other drugs to a therapeutically equivalent dose of trospium. Dr. Jeff Mullins (urology) supported this recommendation. 4. **PPI for Tube Administration** – Due to contracting changes (only Protonix granules now on contract) it has been recommended by CHI for all sites to re-evaluate their formularies for alternatives to Nexium suspension (current formulary medication). Due to previous issues with clogged feeding tubes it was recommended to not add Protonix	Information only Therapeutic Interchange approved Therapeutic Interchange approved Approved – Nexium suspension removed from formulary	Complete Complete Complete Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	granules back to the formulary. Patrick suggested that as an alternative patients may be maintained on IV therapy when IV access is available or utilize a compounded formulation of omeprazole solution for patients requiring PPI therapy with no IV access.		
	5. **Nucynta ER Formulary Interchange** – Patrick presented a proposed interchange that would allow auto-substitution of immediate release Nucynta (tapentadol) for all home medication orders for Nucynta ER to provide continuity of care for patients admitted on the ER formulation.	Therapeutic Interchange approved	Complete
	6. **Tresiba® (insulin degludec)** – Ultra-long acting insulin formulation. Patrick reviewed the PK/PD differences as compared to other long acting insulins (Levemir, Lantus). Due to the longer duration of effect a recent CHI MUE committee review suggested a conversion of half of the total daily units of Tresiba converted to a twice daily dose of Levemir (example: Tresiba 40 units DAILY → Levemir 20 units BID). This was supported by the Hospitalist members of the committee and it was recommended to auto-substitute all orders for Tresiba to Levemir as indicated above and Patrick will provide education to the Hospitalists at their monthly education meetings.	Therapeutic Interchange approved	Complete
	7. **Briviact® (brivaracetam)** – Recommended by Dr. Kadrie for addition to formulary. Levetiracetam analog indicated for treatment of partial onset seizures. Although similar to Keppra (levetiracetam) no head to head studies exist to accurately compare the efficacy of these two similar agents. However, clinical trials have demonstrated Briviact to be effective as an add-on therapy for seizure control for patients intolerant of Keppra secondary to behavioral side effects. Patrick recommended this agent be added to formulary and new inpatient starts restricted to neurology.	Approved with restrictions (neurology)	Complete
	8. **Darzalex (daratumumab)** – Anti-CD38 monoclonal antibody indicated for treatment of multiple myeloma. This medication was recently requested by TN Oncology for outpatient formulary addition for its labeled indication. Data indicates that this medication is effective for patients with refractory myeloma and it is currently the only monoclonal antibody available for treatment of this oncology diagnosis. Dr. Stipanov recommended that this be added to the outpatient formulary.	Approved – outpatient infusion only	Complete
Medication Safety	**ADR Review**: Patrick reviewed the summary of reported ADR's from February – April 2016. No significant trends have been observed although the incidence of opioid ADR's related to over-sedation appear to be on the decline since the therapeutic duplication policy and order set changes were implemented in April. Patrick did report a significant ADR related to canagliflozin (DKA requiring hospitalization and ICU management). The FDA has encouraged the reporting of these DKA events with the SGLT2 inhibitors and this ADR will be reported to the FDA's medwatch program. Although the SGLT2 inhibitors are not on formulary the hospital does allow the continuation of these medications using patients' own supply. Dr. Pesce recommended that the hospital no longer allow the continuation of medications within this class due to the risk of DKA, urinary tract infections, and volume depletion.	Approved to no longer permit continuation of SGLT2 inhibitors (dapagliflozin, canagliflozin, etc.)	Complete
	Surgical Management – NOACs: The use of the newer novel oral anticoagulants were discussed and the challenges of managing acute surgical needs. An orthopedic surgeon recently expressed frustration/concern over the use of these medications and the delays that	Information only; Patrick to provide education	Complete

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	can be caused while awaiting return of normal coagulation status. The physician members of the committee discussed the physician's concerns and felt that since every clinical situation is unique (urgency of surgery, renal function, etc.) it would be difficult to expand on the hospital's current "Antithrombotic Reversal & Surgical Management Recommendations" that are distributed to physicians and other relevant clinical staff. Dr. Currin recommended a letter be drafted to the physician to explain that each case would need to be uniquely considered and the existing hospital recommendations should be utilized to guide the decision making process in regard to if reversal should be attempted or an appropriate delay should be observed prior to surgical intervention. Patrick stated that he would work with Sherry Fusco to try to arrange a time for him to educate this group on the available hospital resources.		
Medication Use Evaluation	**Medications and Inpatient falls:** An evaluation was performed to assess medication impact on inpatient falls over a 6 month time period. The evaluation confirmed that only 1.6% of all inpatient falls were related to the use of a sedative/hypnotic medication which affirms the effectiveness of the existing policy regarding the use of these medications. There was a trend toward higher fall rates in patients receiving drugs such as benzodiazepines with many of these being scheduled doses of home med orders. This information will be shared with the falls team for further discussion.	Information only; data to be shared with falls committee	Complete
Antimicrobial Stewardship	**Pneumonia Admission Orders:** Linda shared a draft of proposed changes to the hospital's pneumonia standing orders as recommended by the Antibiotic Stewardship Committee. All respiratory isolates for calendar year 2015 were analyzed to determine the optimal agents or combination of agents to be utilized as empiric choices on the pneumonia orders. This data has demonstrated that non-ICU patients can achieve desirable susceptibility (>90%) with only one gram negative drug (cefepime or pip/tazo) with the addition of vancomycin due to high rates of MRSA among respiratory isolates. ICU patients who are more critically ill are proposed to use the same strategy with the addition of tobramycin in order to achieve susceptibilities closer to 100%. Fluoroquinolones no longer appear to be useful as an add-on therapy to cefepime or pip/tazo. Patrick explained that this would result in more ICU patients receiving tobramycin and he would discuss this with Dr. Chamberlain to get nephrology input on this proposed change. **Antibiotic Dose Adjustments** – Linda reviewed some proposed additions (ampicillin, amp/sulb, ceftaroline, ceftazidime/avibactam, ceftolozane/tazobactam) and modifications (cefepime, aztreonam) to the drugs eligible for automatic renal adjustments by pharmacy.	Approved pending ASP committee final review; Patrick to discuss with nephrology Approved	Pending Complete
Nutrition Support Team	**Malnutrition Platform** – Susan presented a brief overview of the planned implementation of the comprehensive malnutrition platform developed by Sodexo. This new program will help to coordinate the identification, documentation, and intervention of patients that are malnourished to aid with earlier intervention, improved collaboration, decreased LOS, decreased readmissions, and improved financial outcomes. Susan asked the committee for input on a physician champion for this work and Dr. Currin recommended Dr. Bill Fritsch for this role. Susan also recommended that the interpretive information that is reported along with prealbumin results be removed due to data demonstrating that prealbmuin is not a good	Information only	Pending

AGENDA ITEM	FINDINGS OR CONCLUSION	ACTION, RESPONSIBILITY	STATUS
	indicator of a patient's nutritional status. The physicians supported this request and Susan will follow up with the appropriate parties in lab to suggest this change.		

There being no further business, the meeting was adjourned at 8:00 A.M. The next P&T meeting is **October 13, 2016 at 7:00 a.m.**

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

Approved by,
Richard Pesce, M.D. Chairman

MEDICATION USE AND EVALUATION COMMITTEE DECISION SUMMARY: September 2016

Executive Summary

Medication Name	Discussion Purpose	Decision(s)	Implementation Timeline
sacubitril/valsartan (Entresto®) *reduces the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure and reduced ejection infraction*	To provide clarification requested by markets	Cardiovascular surgeons were added to the restriction criteria. **Restrictions** • Restricted to cardiologists "***or cardiovascular surgeons***" for initiation of therapy (new inpatient starts) • Restricted to patients with NYHA class II to IV HF with reduced EF	The clarification language is effective immediately; the original decision implementation timeline remains (60 days from original MUE approval date of Aug. 16, 2016)
Bupivacaine liposome injection suspension (Exparel®) *an intra-operative depot pain medication*	To respond to market exception and extension requests	6-month extension to implement non-formulary status approved for: • CHI Health (6 months beginning 10/1/2016 was requested) 12-month extension to implement non-formulary status approved for: • KentuckyOne Health-St. Joseph Lexington Hospitals (2 total) • CHI St Luke's Baylor St Luke's Medical Center • CHI St. Luke's Health Sugar Land Hospital Sites are required to share a six-month progress report (by procedure). Decreasing utilization is expected with progression to non-formulary status.	Timeline begins Oct. 1 for CHI Health Timeline begins Sept. 12 for other markets
Brexpiprazole (Rexulti®) *an antipsychotic drug used as an adjunctive treatment for adults with major depressive disorder*	To implement therapeutic interchange	**Non-Formulary:** Brexpiprazole (Rexulti®) **Formulary, Unrestricted:** aripiprazole (Abilify®)	60 days from 9/12/2016
Inhaled corticosteroids *inhaled medicines for chronic treatment of asthma*	To implement therapeutic interchange	**Formulary, Unrestricted:** Mometasone/formoterol (Dulera®) Mometasone furoate (Asmanex®) **Non-Formulary:** Beclometasone dipropionate HFA (QVAR)	60 days from 9/12 2016

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 four ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

		Budesonide Flexhaler (Pulmicort Flexhaler®) Ciclesonide (Alvesco®) Flunisolide (AeroSpan®) Fluticasone (Flovent®) Fluticasone Furoate (Arnuity Ellipta®) Budesonide/formoterol fumarate dehydrate (Symbicort®) Fluticasone/Salmeterol (Advair HFA® and Adavir Diskus®) Fluticasone/vilanterol (Breo Ellipta®)	
Clevidipine (Cleviprex®), nicardipine (Cardene®) and nitroprusside (Nitropress®) *anti-hypertension drugs, used to treat high blood pressure and chest pain*	To determine formulary status and implement therapeutic interchange	**Formulary, Unrestricted:** Nicardipine **Non-Formulary:** Clevidipine Sodium Nitroprusside	90 days from 9/12/2016
Antimuscarinic *urinary agents to treat overactive bladder*	To implement therapeutic interchange	**Formulary, Unrestricted:** Oxybutynin IR (Immediate-Release Ditropan®) Oxybutynin ER (Extended-Release) Ditropan XL®) Trospium IR (Sanctura®) Mirabegron (Myrbetriq®) **Non-Formulary:** Oxybutynin topical gel (Gelnique®) Oxybutynin transdermal patch (Oxytrol®) Fesoterodine (Toviaz®) Tolterodine (Detrol®) Tolterodine ER (Extended-Release Detrol LA®) Darifenacin ER (Enablex®) Trospium ER (Sanctura XR®) Solifenacin (VESIcare®)	60 days from 9/12/2016
Ciprofloxacin otic suspension (Ciprodex®) *used to treat bacterial ear infections*	To implement therapeutic interchange	**Formulary, Unrestricted:** Ciprofloxacin (Ciloxan®) 0.3% ophthalmic solution Dexamethasone 0.1% ophthalmic solution (to be used in combination **Non-Formulary:** Ciprofloxacin 0.3% and dexamethasone 0.1% OTIC Suspension (Ciprodex®)	60 days from 9/12/2016
Phenazopyridine *relieves symptoms caused by urinary tract infections and other urinary problems*	To implement therapeutic interchange	**Formulary, Unrestricted:** Phenazopyridine 95 mg tablets **Non-Formulary:** Phenazopyridine 100 mg tablets	60 days from 9/12/2016

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 four ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

		Phenazopyridine 200 mg tablets	

Acetaminophen (OFIRMEV®)
an injectable analgesic when oral route is not available
	To determine Formulary Status	**Formulary, Restricted:**
		Restrictions
		• 24 hours automatic stop (Max)
		• Automatic conversion from IV to PO by pharmacy (if patient meets criteria)
		• Perioperative use only
		
		Service Line Support
		• Cardiovascular and Orthopedic Service Lines will:
		  • Develop and mandate national multi-modal therapy protocols; Cardiovascular Surgery and Orthopedic Service Lines will have access to product based on multi-modal pain protocols
		  • SLs will report data with outcomes at 6 months and 12 months to MUE with MUE review at 18 months
		  • SL results will guide help guide multi-modal pain protocol development for all of CHI (SLs, patients/indications, physician specialties)
		Note: Per normal process, markets may implement or retain more restrictive formulary status.
			60 days from 9/13/2016

Infliximab-dyyb (Inflectra®) *a biosimilar for (infliximab) REMICADE®; immunosuppressant to treat patients with moderately to severely active Crohn's disease who have not responded to conventional therapy*	To determine Formulary Status	Decision/Discussion tabled until next MUE meeting to allow for additional information to become available(product availability and pricing	N/A
Cabazitaxel (Jevtana®) *an anti-cancer medication to treat advanced prostate cancer with progression after treatment with conventional therapy*	To determine Formulary Status	**Formulary, Restricted:** **Restrictions** • Outpatient use • In combination with prednisone • For the treatment of hormone-refractory metastatic prostate cancer (mHRPC)	60 days from 9/13/2016

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 four ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

		• In patients who have been previously treated with a docetaxel-containing regimen (as indicated by FDA) • Ordered by oncologist	
Vedolizumab (Entyvio®) *used to treat chronic, inflammatory bowel disease (ulcerative colitis) and Crohn's disease*	To determine Formulary Status	**Non-Formulary:** for Inpatients **Formulary, Restricted:** **Restrictions** • Outpatient setting • Restricted to GI services or other specialty if GI services are not available in a market • Adults >18 years of age • Moderate to severe UC or UD who have previously failed or were intolerant to at least one conventional treatment	60 days from 9/13/2016
Regadenoson (Lexiscan®) *used for cardiac stress tests*	To determine Formulary Status	**CV service line will work with all markets to reduce use of pharmacologic stress tests in favor of exercise stress test** **Formulary, Unrestricted:** adenosine (Adenoscan®) regadenoson (Lexiscan®) dipyridamole (Persantine®) Dobutamine (Dobutrex®)	60 days from 9/13/2016
Ophthalmic antihistamines *eye medications used to treat hay fever symptoms such as runny eyes and redness*	To implement a therapeutic interchange	**Formulary, Unrestricted:** Ketotifen (Zaditor®) **Non-Formulary:** azelastine (Optivar®) epinastine (Elestat®) olopatadine (Patanol®, Pataday®) emedastine (Emadine®)	60 days from 9/13/2016
Ophthalmic prostaglandins *eye medications used to reduce intraocular pressure in people who have glaucoma or ocular hypertension*	To implement a therapeutic interchange	**Formulary, Unrestricted:** Latanoprost (Xalatan®) **Non-Formulary:** Travopost (Izba®, Travatan Z®) Zioptan (Tafluprost®) Bimatoprost (Lumigan®, Latisse®)	60 days from 9/13/2016

Members Present: see attached Attendance Roster
See Committee Meeting Packet with references: CHI MUE Committee Compiled Packet 09 12 2016 final

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 four ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

Medication Use and Evaluation Committee Decision Summary

1. **Follow up from August Decision: Clarification of Restrictions for sacubitril/valsartan (ENTRESTO™)**

Drug Summary

Sacubitril/valsartan (ENTRESTO™) is a combination of sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin receptor blocker (ARB). It is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction. In one study sacubitril/valsartan was superior to enalapril in reducing the risk of the combined endpoint of cardiovascular death or hospitalization for heart failure.

CLARIFICATION TO MUE COMMITTEE DECISION/NEW DECISION

The decision in August was to classify sacubitril/valsartan as Formulary, Restricted

Restrictions

- Restricted to cardiologists for initiation of therapy (new inpatient starts)
- Restricted to patients with NYHA class II to IV HF with reduced EF

The clarification in September is to modify the language of the Restrictions to include cardiovascular surgeons as follows:

Restrictions

- Restricted to cardiologists "***or cardiovascular surgeons***" for initiation of therapy (new inpatient starts)
- Restricted to patients with NYHA class II to IV HF with reduced EF

There were no changes in the Guidelines or Implementation timeline.

Guidelines:

- Required washout period of 36 hours for patients switched to ENTRESTO™ from an ACE inhibitor
- Cardiology consult to be placed prior to initiation for new start patients
- Any practitioner may continue the medication in a patient previously on a stable dose prior to admission.
- If a patient is to be discharged with this medication, prior authorization should be obtained prior to discharge due to its high drug cost to ensure that therapy will not be interrupted.

Implementation: 60 days from approval if not already in place

ACTION: A motion was made and seconded to clarify the Restriction to include cardiovascular surgeons (above).

Voting: FOR: 23
AGAINST: 0
ABSENT: 1

2. **Extension and Exception Requests related to liposomal bupivacaine liposomal injectable suspension (Exparel®)**

Drug Summary

Liposomal bupivacaine liposomal injectable suspension (Exparel®) is an amide-type local anesthetic in an encapsulated liposomal formulation developed with the goal of providing a longer duration of anesthesia compared with its nonliposomal counterpart, bupivacaine hydrochloride or other local anesthetics. The product utilizes the DepoFoam® drug delivery system consisting of an aqueous suspension of multivesicular liposomes containing bupivacaine in a honeycomb-like structure that allows for a more gradual release. The FDA approved bupivacaine liposomal in October 2011 for single-dose infiltration into the surgical site for postoperative analgesia.

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 four ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

ORIGINAL MUE COMMITTEE DECISION FROM MARCH 2016

The MUE Committee rejected the addition of liposomal bupivacaine to the CHI formulary with the decision to make liposomal bupivacaine a non-formulary product.
March 2016 ACTION: A motion was made and seconded to not add liposomal bupivacaine to the formulary.
Voting: FOR: 16; AGAINST: 6; ABSENT: 2
In addition, the MUE Committee recommended that the MUE co-chairs will work to create a reference document for physicians and other stakeholders that includes data and alternatives to the indicated uses of liposomal bupivacaine.
Clinical Alternatives to liposomal bupivacaine.
Accessed at Folder: 2016 03 (March) Alternatives to liposomal bupivacaine
Document: CHI Division Alternatives to Exparel May 10 2016 ver 2

September MUE Actions were necessary to address one extension request and three exception requests

a. **Extension Request from CHI Health**
CHI Health Representatives presented a request from the CHI Health Pharmacy and Therapeutics Committee to modify a previously submitted exception request to an extension request, requesting that a six month extension start October 1, 2016. CHI Health P&T will move liposomal bupivacaine (Exparel®) to non-formulary status at the conclusion of the extension period (April 1, 2017).

ACTION: **A motion was made and seconded to grant the extension request (6 months) as requested**

Voting: FOR: 23
AGAINST: 0
ABSENT: 1

b. **Exception Requests (three total) from CHI KentuckyOne Health, St Joseph and St Joseph East Hospitals (Lexington); CHI St Luke's Health Baylor St Luke's Medical Center; CHI St Luke's Health Sugar Land Hospital.**
Representatives from each market presented an exception request.

ACTION 1: **A motion was made and seconded to reject the three exception requests.**

Voting: FOR: 23
AGAINST: 0
ABSENT: 1

ACTION 2: **A motion was made and seconded to convert the three exception requests to three extension requests with an extension period of 12 months (1 year). Further, each market is provide a status update (utilization) in 6 months (April MUE).**

Voting: FOR: 23
AGAINST: 0
ABSENT: 1

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 four ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

3. Brexpiprazole (Rexulti®)

Product Review and Therapeutic Interchange

Brexpiprazole is an atypical antipsychotic drug in the class dopamine system stabilizers. It is a partial dopamine agonist, comparable to aripiprazole, but with a unique receptor binding profile and low adverse effects. Both brexpiprazole and aripiprazole have indications for schizophrenia and adjunctive treatment of depression. A head to head trial with bexpiprazole 3mg and aripiprazole 15mg showed that both agents have rapid onset of effect, improvements in PANSS (positive and negative syndrome scale), and other efficacy measure improvements in patients with acute schizophrenia.

MUE COMMITTEE DECISION

The Decision is to therapeutically interchange brexpiprazole to aripiprazole.

Non-Formulary:

Brexpiprazole (Rexulti®)

Formulary, Unrestricted:

aripiprazole (Abilify®)

THERAPEUTIC INTERCHANGE OR GUIDELINES

Ordered	Provided
Brexpiprazole 1mg	Aripiprazole 5mg
Brexpiprazole 2mg	Aripiprazole 10mg
Brexpiprazole 3mg	Aripiprazole 15mg
Brexpiprazole 4mg	Aripiprazole 30mg

Implementation: 60 days from approval if not already in place.

ACTION: **A motion was made and seconded to accept the above recommendations.**
Voting: FOR: 22
AGAINST: 0
ABSENT: 2

4. Therapeutic Interchange for inhaled corticosteroids

Product Review and Therapeutic Interchange

Numerous placebo controlled trials have demonstrated the efficacy of inhaled corticosteroid agents in the treatment of asthma, and these agents are considered the most effective agents in the long-term management of the disease. The results of head-to-head trials directly comparing the inhaled corticosteroids products have not demonstrated one agent to be significantly more effective than another, regardless of the potency or dosage form of the inhaled corticosteroid agent used.

While Dulera® (mometasone/formoterol) is not indicated for the treatment of COPD, there are two identical phase 3, randomized, placebo-controlled, multi-center, multinational, double-blind studies that have evaluated the efficacy and safety of this agent in in patients with moderate to very severe COPD. The trial found Dulera® to be well tolerated during the one year of treatment and there were no notable differences in the incidence or types of adverse events (AEs) between the Dulera® and mometasone or formoterol groups. Additionally, the National Institute for Heath and Clinical Excellence (NICE) in their review of ICS concludes "if a combination device is chosen then the least costly device that is suitable for the individual is recommended".

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 four ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

MUE COMMITTEE DECISION

Implement a therapeutic interchange to recommended substitution for adult patients.

Formulary, Unrestricted:

Mometasone/formoterol (Dulera®)
Mometasone furoate (Asmanex®) are Formulary Status

Non-Formulary:

Beclomethasone HFA (QVAR®)
Budesonide Flexhaler (Pulmicort Flexhaler®)
Ciclesonide (Alvesco®)
Flunisolide (AeroSpan®) Inhaler
FLUTICASONE (Flovent®)
Fluticasone furoate (Arnuity Ellipta®)
Budesonide/formoterol (Symbicort®)
Fluticasone/salmeterol (Advair HFA® and Advair Diskus®)
Fluticasone/vilanterol (Breo Ellipta®)

THERAPEUTIC INTERCHANGE CONVERSIONS

Asmanex® Conversion

Prescribed Therapy	Asmanex® Twisthaler	Asmanex® HFA
Inhaled low-dose corticosteroids	220mcg /inhalation – 1 inhalation once daily	100 mcg /inhalation- 1 inhalation BID
Inhaled medium-dose corticosteroids	220mcg /inhalation – 2 inhalations once daily	100mcg /inhalation- 2 inhalations BID
Inhaled high-dose corticosteroids	220mcg /inhalation – >2 inhalations once daily	200mcg /inhalations- 2 inhalations BID

Inhaled Corticosteroid (HFA) Daily Dose Comparison:

LOW DOSE (HFA)	
Beclomethasone HFA (QVAR®)[4] 40mcg/inhalation – 2-5 inhalations/day	Mometasone HFA (Asmanex®)[5] 100 mcg /inhalation- 1 inhalation BID
Beclomethasone HFA (QVAR®) 80mcg/inhalation – 1-2 inhalations/day	
Fluticasone HFA (Flovent®)[6] 44mcg/inhalation- 1-5 inhalations/day	
Fluticasone HFA (Flovent®) 110 mcg/inhalation- 1-2 inhalations/day	
Fluticasone HFA (Flovent®) 220 mcg/inhalation- 1 inhalations/day	
Ciclesonide MDI (Alvesco®)[7] 80mcg/inhalation- 2-3 inhalations/day	
Ciclesonide MDI (Alvesco®) 160mcg/inhalation- 1 inhalations/day	
MEDIUM DOSE (HFA)	
Beclomethasone HFA (QVAR®) 40mcg/inhalation – 6-12 inhalations/day	Mometasone HFA (Asmanex®) 200mcg /inhalation- 1 inhalations BID
Beclomethasone HFA (QVAR®) 80mcg/inhalation – 3-6 inhalations/day	
Fluticasone HFA (Flovent®) 44mcg/inhalation- 6-10 inhalations/day	

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 four ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

Fluticasone HFA (Flovent®) 110 mcg/inhalation- 3-4 inhalations/day	
Fluticasone HFA (Flovent®) 220 mcg/inhalation- 2 inhalations/day	
Ciclesonide MDI (Alvesco®) 80mcg/inhalation- 4-8 inhalations/day	
Ciclesonide MDI (Alvesco®) 160mcg/inhalation- 2-4 inhalations/day	
HIGH DOSE (HFA)	
Beclomethasone HFA (QVAR®) 40mcg/inhalation – >12 inhalations/day	Mometasone HFA (Asmanex®) 200mcg /inhalations- 2 inhalations BID
Beclomethasone HFA (QVAR®) 80mcg/inhalation – >6 inhalations/day	
Fluticasone HFA (Flovent®) 44mcg/inhalation- 11-15 inhalations/day	
Fluticasone HFA (Flovent®) 110 mcg/inhalation- 5-6 inhalations/day	
Fluticasone HFA (Flovent®) 220 mcg/inhalation- 3 or more inhalations/day	
Ciclesonide MDI (Alvesco®) 80mcg/inhalation- > 8 inhalations/day	
Ciclesonide MDI (Alvesco®) 160mcg/inhalation- > 4 inhalations/day	

INHALED CORTICOSTEROID (DRY POWDER) DOSE COMPARISON:

Ordered Product and Dose	Substitution Product and Dose
LOW DOSE (Dry Powder Inhaler)[8]	
Budesonide DPI (Pulmicort®)[9] 90mcg/inhalation -1-3 inhalations BID	Mometasone DPI (Asmanex®)[10] 220mcg /inhalation -1 inhalation once daily
Fluticasone DPI (Flovent® Diskus)[11] 50mcg/inhalation -1-2 inhalations BID	
Fluticasone DPI (Arnuity Ellipta®)[12] 100mcg/inhalation once daily	
MEDIUM DOSE (Dry Powder Inhaler)[8]	
Budesonide DPI (Pulmicort®) 180mcg/inhalation - 2 inhalations BID	Mometasone DPI (Asmanex®) 220mcg /inhalation -2 inhalations once daily
Fluticasone DPI (Flovent® Diskus) 50mcg/inhalation -3-5 inhalations BID	
Fluticasone DPI (Arnuity Ellipta®) 200mcg/inhalation once daily	
HIGH DOSE (Dry Powder Inhaler)[8]	
Budesonide DPI (Pulmicort®) 180mcg/inhalation – >2 inhalations BID	Mometasone DPI (Asmanex®) 220mcg /inhalation - >2 inhalations once daily
Fluticasone DPI (Flovent® Diskus) 50mcg/inhalation >5 inhalations BID	

COMBINATION PRODUCT DOSE COMPARISONS

Ordered Product and Dose	Substitution Product and Dose
Advair® Diskus[13]	**Dulera®[14]**
Fluticasone 100 mcg/Salmeterol 50 mcg 1 inhalation BID	Mometasone 100 mcg/Formoterol 5 mcg 2 inhalations BID
Fluticasone 250 mcg /Salmeterol 50 mcg 1 inhalation BID	Mometasone 200 mcg/Formoterol 5 mcg 2 inhalations BID
Fluticasone 500 mcg/Salmeterol 50 mcg	Mometasone 200 mcg/Formoterol 5 mcg

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 four ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

1 inhalation BID	2 inhalations BID (+/- Asmanex® 220 - 1 inhalation BID)
Ordered Product and Dose	**Substitution Product and Dose**
Advair® HFA[16]	**Dulera®**
Fluticasone 45 mcg/Salmeterol 21 mcg 2 inhalation BID	Mometasone 100 mcg/Formoterol 5 mcg 2 inhalations BID
Fluticasone 115 mcg /Salmeterol 21 mcg 2 inhalation BID	Mometasone 200 mcg/Formoterol 5 mcg 2 inhalations BID
Fluticasone 230 mcg /Salmeterol 21 mcg 2 inhalation BID	
Symbicort®[17]	**Dulera®**
Budesonide 80 mcg/Formoterol 4.5 mcg 2 Inhalations BID	Mometasone 100 mcg/Formoterol 5 mcg 2 inhalations BID
Budesonide 160 mcg/Formoterol 4.5 mcg 2 Inhalations BID	Mometasone 200 mcg/Formoterol 5 mcg 2 inhalations BID
Breo Ellipta®[18]	**Dulera®**
Fluticasone 100 mcg/Vilanterol 25 mcg 1 inhalation daily	Mometasone 100 mcg/Formoterol 5 mcg 2 inhalations BID

*Facilities may consider using spacers for the administration of Dulera® due to the increased corticosteroid doses and for patient administration ease.

Implementation: 60 days from approval if not already in place.

ACTION: A motion was made and seconded to accept the recommendations.

Voting: FOR: 22
AGAINST: 0
ABSENT: 2

5. **Product Monograph/Therapeutic Interchange for clevidine (Cleviprex®), nicardipine (Cardene®), and nitroprusside (Nitropress®)**

Product Review and Therapeutic Interchange

When compared to current accepted therapies, the ECLIPSE trial demonstrated that clevidipine is as efficacious as nicardipine and not superior, and more efficacious than nitroglycerin and sodium nitroprusside in treating perioperative hypertension, while 30-day rates of major clinical events were comparable when compared all three of these agents. Based on this review, the addition of clevidipine to formulary is not warranted and nicardipine should be the primary medication used.

MUE COMMITTEE DECISION

Implement a therapeutic interchange utilizing nicardipine rather than clevidipine or sodium nitroprusside.

Formulary, Unrestricted:
Nicardipine

Non-Formulary:
Clevidipine
Sodium Nitroprusside

Note: facilities may opt to keep limited stock of Sodium Nitroprusside for specific clinical indications.

Implementation: 90 days from approval if not already in place.

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 four ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

ACTION: A motion was made and seconded to accept the above recommendations.
Voting: FOR: 22
AGAINST: 0
ABSENT: 2

6. **Therapeutic Interchange for antimuscarinic (urinary)**

Product Review and Therapeutic Interchange

There are currently six antimuscarinic agents and one β3 selective adrenergic receptor agonist available to treat overactive bladder. There are limited head-to head trials comparing these agents in treating OAB. Most of the trials have compared oxybutynin with tolterodine and in a few cases some of the newer agents. Differences in efficacy and tolerability profiles provide various treatment options. When considering pharmacologic therapy, consideration should be given to the use of agents with low potential to cause cognitive adverse events, low potential for interaction with concomitant medication, and cost.[2, 8] Oxybutynin is a gold-standard first line agent for OAB. It is available in immediate release forms that can be cut and crushed as well as an oral liquid formulary. The extended release product is also low cost and has similar efficacy to other agents in the class. Trospium is the only quaternary amine in the class. This gives advantages of a lower side effect profile (due to reduced CNS penetration) and fewer drug-drug interactions because of little to no metabolism. The long acting agents are preferred to short acting due to fewer adverse reactions. The β3 adrenergic receptor agonist mirabegron, is a new agent in this class. It has no listed contraindications, and is an alternative for patients who experience intolerable side effects to antimuscarinics.[24, 26]

MUE COMMITTEE DECISION

Implement a therapeutic interchange program for antimuscarinic (urinary) agents.

Formulary, Unrestricted:

Oxybutynin IR (Immediate-Release) (Ditropan)
Oxybutynin ER (Extended-Release) (Ditropan XL)
Trospium IR (Sanctura)
Mirabegron (Myrbetriq)

Non-Formulary:

Oxybutynin topical gel (Gelnique)
Oxybutynin transdermal patch (Oxytrol)
Fesoterodine (Toviaz)
Tolterodine (Detrol)
Tolterodine ER (Detrol LA)
Darifenacin ER (Enablex)
Trospium ER (Sanctura XR)
Solifenacin (VESIcare)

THERAPEUTIC INTERCHANGE OR GUIDELINES	
Ordered	**Provided**
Any of the below for feeding tube administration	Oxybutynin (Ditropan) 5 mg per feeding tube TID
Oxybutynin IR 5 mg TID	** FORMULARY **
Oxybutynin ER (Ditropan XL) 5-15mg q day	** FORMULARY **
Oxybutynin topical gel (Gelnique)	Oxybutynin ER (Ditropan XL) 15mg q day
Oxybutynin transdermal patch (Oxytrol)	Oxybutynin ER (Ditropan XL) 15mg q day
Fesoterodine (Toviaz) 4-8 mg q day	Trospium (Sanctura) 20 mg BID or if CrCl <30 20mg daily
Tolterodine (Detrol) 1-2 mg BID	Trospium (Sanctura) 20 mg BID or if CrCl <30 20mg daily
Tolterodine ER (Detrol LA) 2-4 mg q day	Trospium (Sanctura) 20 mg BID or if CrCl <30 20mg daily
Darifenacin ER (Enablex) 7.5-15 mg	Trospium (Sanctura) 20 mg BID or if CrCl <30 20mg daily
Trospium IR (Sanctura) 20 mg BID	** FORMULARY **
Trospium ER (Sanctura XR) 60 mg q day	Trospium (Sanctura) 20 mg BID or if CrCl <30 20mg daily
Solifenacin (VESIcare) 5-10mg q day	Trospium (Sanctura) 20 mg BID or if CrCl <30 20mg daily
Mirabegron (Myrbetriq) 25mg-50mg q day	** FORMULARY **

Implementation: 60 days from approval if not already in place.

ACTION: A motion was made and seconded to accept the above recommendations.
Voting: FOR: 22
AGAINST: 0
ABSENT: 2

7. **Therapeutic Interchange for ciprofloxacin otic suspension (Ciprodex®)**
Product Review and Therapeutic Interchange
Ciprodex is an expensive agent that would appear to be at least as effective if not more effective than current treatment of AOMT with ofloxacin, in terms of fewer treatment failures, earlier resolution of AOMT, better overall therapeutic response, and reduction of granulation tissue. Support for the addition of the corticosteroid also comes from the fact that Ciprodex has resulted in a faster clinical response when compared with ciprofloxacin alone. Comparison of dexamethasone to hydrocortisone in a murine model suggests that dexamethasone may be more effective than hydrocortisone for the treatment of granulation tissue resulting from external and middle ear inflammatory conditions. The use of an economic model demonstrating the cost-effectiveness of Ciprodex versus ofloxacin has several major limitations.
The PCC would recommend that Ciprodex NOT be added to the CHI formulary. The information available demonstrates that Ciprodex is an effective and safe agent when used for treatment of acute otitis media with otorrhea in children with tympanostomy tubes and suggests that it has particular advantages over other agents currently approved for this indication. However, due to the availability of limited comparative evidence supporting the use of Ciprodex and its high cost relative to other agents, it is recommended that the much less costly generically available products ciprofloxacin 0.3% ophthalmic solution and dexamethasone 0.1% ophthalmic solution be used instead for this indication. Intraoperative use of this particular preparation has not been studied; intraoperative use of ciprofloxacin and other antibiotic and/or corticosteroid preparations have demonstrated that they are effective at significantly lowering the incidence of early post-tympanostomy tube otorrhea.

MUE COMMITTEE DECISION
Implement a therapeutic interchange from ciprofloxacin 0.3% and dexamethasone 0.1% OTIC Suspension (CiproDex®) to ciprofloxacin 0.3% ophthalmic solution and dexamethasone 0.1% ophthalmic solution

Formulary, Unrestricted:
Ciprofloxacin (Ciloxan®) 0.3% ophthalmic solution and Dexamethasone 0.1% ophthalmic solution
Non-Formulary:
Ciprofloxacin 0.3% and dexamethasone 0.1% OTIC Suspension (CiproDex®)

THERAPEUTIC INTERCHANGE	
Ordered	**Provided**
Ciprofloxacin 0.3% and dexamethasone 0.1% OTIC Suspension (CiproDex®) 4 drops intra aurally twice daily	Ciprofloxacin (Ciloxan®) 0.3% ophthalmic solution (2 drops) plus dexamethasone 0.1% ophthalmic solution (2 drops) given intra aurally twice daily

Implementation: 60 days from approval if not already in place.

ACTION: A motion was made and seconded to accept the above recommendations.
Voting: FOR: 15
AGAINST: 7
ABSENT: 2

8. **Therapeutic Interchange for phenazopyridine**
Phenazopyridine is a urinary analgesic that has been used for over 40 years. It is indicated to relieve symptoms such as pain, burning, urgency and/or frequency, and other discomforts due to irritation of the lower urinary tract. Phenazopyridine 95 mg is available over-the-counter whereas the 100 mg and 200 mg tablets are available by prescription only.

MUE COMMITTEE DECISION
Formulary, Unrestricted:
Phenazopyridine 95 mg tablets

Non-formulary:
Phenazopyridine 100 mg and 200 mg tablets

THERAPEUTIC INTERCHANGE	
Ordered	**Provided**
Phenazopyridine 100 mg TID	1 tablet of 95 mg TID (Dose=95 mg)
Phenazopyridine 200 mg TID	2 tablets of 95 mg TID (Dose=190 mg)

Implementation: 60 days from approval if not already in place.

ACTION: A motion was made and seconded to accept the above recommendations.
Voting: FOR: 23
AGAINST: 0
ABSENT: 1

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 four ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

9. acetaminophen (OFIRMEV®)

Product Review

There is extensive data and many years of non-U.S. clinical experience that support the safety and efficacy of IV acetaminophen in the treatment of pain and fever, but only a small number of studies were head-to-head or active-controlled trials. In the acute pain conditions studied, IV acetaminophen is comparable to oral acetaminophen, IV morphine and oral NSAID in terms of magnitude of pain reduction. The advantages of IV acetaminophen when used for short periods include a slightly faster onset of action and a more effective initial 2-hour antipyretic effect than oral acetaminophen; potential decreased risk of adverse events relative to injectable morphine (although this finding requires better designed trials for confirmation); and lower risk of gastrointestinal adverse events relative to oral NSAIDs. Compared with PCA morphine alone, the combination of IV acetaminophen plus morphine postoperatively may lower opioid requirements to a relatively small degree, but seems to have to no effect on the incidence of opioid-related gastrointestinal effects.

IV acetaminophen use in the postoperative setting has a quicker onset of analgesia than oral acetaminophen and can be used when oral or rectal administration of medication is not possible or is impractical. IV acetaminophen lacks certain contraindications and boxed warnings listed for opioid analgesics and NSAIDs, and is an alternative analgesic when opioids and NSAIDs are inappropriate.

MUE COMMITTEE DECISION

Formulary, Restricted:

acetaminophen (OFIRMEV®)

Restrictions

- 24 hours automatic stop (Max)
- Conversion from IV to PO by pharmacy (if patient meets criteria)
- Perioperative use only

Service Line Support

- Cardiovascular and Orthopedic Service Lines will:
  - Develop and mandate national multi-modal therapy protocols; Cardiovascular Surgery and Orthopedic Service Lines will have access to product based on multi-modal pain protocols
  - SLs will report data with outcomes at 6 months and 12 months to MUE with MUE review at 18 months
  - SL results will guide the decision for all of CHI (SLs, patients/indications, physician specialties)

Implementation: 60 days from approval if not already in place.

ACTION: A motion was made and seconded to accept the above recommendations.

Voting: FOR: 16
AGAINST: 7
ABSENT: 1

10. cabazitaxel (JEVTANA®)

Product Review

Cabazitaxel is a semisynthetic compound that exhibits antitumor activity by binding tubulin and stabilizing microtubules, which interferes with mitosis. In vitro, cabazitaxel has also produced antiproliferative activity in docetaxel-resistant and other resistant cell lines expressing the multidrug-resistance (mdr-1) gene. The TROPIC study

is a phase 3, randomized controlled trial that compared cabazitaxel with mitoxantrone, each in combination with prednisone, in patients with castration-resistant metastatic prostate cancer after progression on docetaxel therapy. Results showed that cabazitaxel increased overall survival (OS) by 3 months (15.1 vs. 12.7 months, P < 0.001) and progression free survival by 1.4 months (2.1 vs. 1.4 months, P < 0.001). Due to the high risk of adverse effects proper monitoring is required throughout therapy. In addition, cabazitaxel contains a black box warning for neutropenia and infusion reactions. Infusion reactions are mediated by the diluent polysorbate 80. Therefore, patients with a history of reactions to medications formulated in polysorbate 80 (ex. docetaxel) should not receive cabazitaxel.

MUE COMMITTEE DECISION
Formulary, Restricted:
cabazitaxel (JEVTANA®)
Restrictions

- Outpatient use
- In combination with prednisone
- For the treatment of hormone-refractory metastatic prostate cancer (mHRPC)
- In patients who have been previously treated with a docetaxel-containing regimen (as indicated by FDA)
- Ordered by oncologist

Additional recommendation: Include OP Reimbursement information with monograph

Implementation: 60 days from approval if not already in place.

ACTION: A motion was made and seconded to accept the above recommendations.
Voting: FOR: 22
AGAINST: 0
ABSENT: 2

11. vedolizumab (Entyvio®)
Product Review
Vedolizumab is an anti-α4β7 integrin monoclonal antibody (mAb), for the treatment of Crohn's disease (CD) and ulcerative colitis (UC) in adults with moderately to severely active disease who have had an inadequate response with, or were intolerant to anti-tumor necrosis factor (TNF) agents, or had an inadequate response with, or demonstrated dependence on corticosteroids[1,2] . Vedolizumab is the second integrin-receptor antagonist to be approved in the United States. Natalizumab (Tysabri®) was the first integrin receptor antagonist approved for the treatment of CD but was withdrawn from the market after several reports of Progressive Multifocal Leukoencephalopathy (PML).

Considering relatively limited efficacy data, lack of long-term safety data, time-consuming administration requiring dose monitoring, inconvenience to patients, nursing costs, and substantial cost of the medication itself, vedolizumab should not be recommended as an addition to the formulary. This medication would be better suited for outpatient prescribing by gastroenterologists during clinic visits for administration at an outpatient infusion center. Eligible patients would be adult patients > 18 years of age with moderate-to-severe UC or CD who have previously failed or were intolerant to at least one conventional treatment (i.e. glucocorticoid, immunomodulator, or TNF-α antagonist), or demonstrated dependence on corticosteroids.

MUE COMMITTEE DECISION
Non-Formulary for Inpatients
vedolizumab (Entyvio®)

Formulary, Restricted
vedolizumab (Entyvio®)

Restrictions
- GI Service OR other specialty if no GI Service
- Outpatient setting
- Adult patients > 18 years of age
- Moderate-to-severe UC or CD who have previously failed or were intolerant to at least one conventional treatment

Implementation: 60 days from approval if not already in place.

ACTION: A motion was made and seconded to accept the above recommendations.
Voting: FOR: 22
AGAINST: 0
ABSENT: 2

12. regadenoson (Lexiscan®)
Product Review
Radionuclide myocardial perfusion imaging (MPI) is used in the detection and risk stratification of coronary artery disease (CAD). MPI evaluates coronary blood flow at rest and during stress with the use of radionuclide agents that show areas of reduced perfusion and restrictions in coronary blood flow. Exercise is the preferred method of cardiac stress testing; however, when a patient is not able to exercise, pharmacologic agents (adenosine, regadenoson, dipyridamole or dobutamine) are used to increase coronary blood flow. The vasodilators adenosine and regadenoson have traditionally been considered the agents of choice for pharmacologic stress testing. Other agents that have been used include dobutamine and dipyridamole.

MUE COMMITTEE DECISION
Approve option endorsed by the CV Service Line:
Use exercise testing first unless contraindicated.
If contraindicated, acceptable indications for pharmacologic stress testing are:
1. Left bundle branch block
2. Ventricular paced rhythm
3. Inability to exercise due to severe claudication, severe arthritis, gait disturbances (walker, cane)
4. Mental or physical impairment leading to inability to exercise adequately

Note: Any pharmacologic stress testing agent may be used (adenosine, regadenoson, dipyridamole or dobutamine).

Formulary, Unrestricted:
- adenosine
- regadenoson
- dipyridamole

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 four ways: 1) approve with no changes 2) approve with more restrictions 3) request an extension, exception or appeal per the MUE process.

- Dobutamine

Implementation: 60 days from approval if not already in place.

ACTION: A motion was made and seconded to accept the above recommendations.
Voting: FOR: 22
AGAINST: 0
ABSENT: 2

13. Therapeutic Interchange for ophthalmic antihistamines

Ophthalmic antihistamine that is used for allergic conjunctivitis, allergic rhinitis, and itching prophylaxis. Ketotifen demonstrates similar efficacy and safety as the other ophthalmic antihistamines. The adverse effect and drug interaction profile is limited and similar across all similar agents to ketotifen.

MUE COMMITTEE DECISION
Formulary, Unrestricted:
Ketotifen (Zaditor®)

Non-Formulary:
Azelastine (Optivar®)
Epinastine (Elestat®)
Olopatadine (Patanol®, Pataday®)
Emedastine (Emadine®)

THERAPEUTIC INTERCHANGE	
Ordered	**Provided**
Azelastine 1 drop in each eye twice daily	Ketotifen 1 drop in each eye twice daily
Epinastine 1 drop in each eye twice daily	Ketotifen 1 drop in each eye twice daily
Olopatadine 0.1% 1 drop in each eye twice daily	Ketotifen 1 drop in each eye twice daily
Olopatadine 0.2% 1 drop in each eye once daily	Ketotifen 1 drop in each eye twice daily
Emedastine 1 drop in each eye four times daily	Ketotifen 1 drop in each eye twice daily

Implementation: 60 days from approval if not already in place.

ACTION: A motion was made and seconded to accept the above recommendations.
Voting: FOR: 22
AGAINST: 0
ABSENT: 2

14. Therapeutic Interchange for ophthalmic prostaglandins

Ophthalmic prostaglandin agonists are used for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma and ocular hypertension. In addition, prostaglandin agonist agents have been used concomitantly with another ophthalmic products to achieve greater IOP-lowering effect.

MUE COMMITTEE DECISION
Formulary, Unrestricted:

Latanoprost (Xalatan®)

Non-Formulary:
Travoprost (Izba®, Travatan Z®)
Zioptan (Tafluprost®)
Bimatoprost (Lumigan®, Latisse®)

THERAPEUTIC INTERCHANGE	
Ordered	**Provided**
Travoprost (Izba®, Travatan Z®) 1 drop daily to affected eye	Latanoprost (Xalatan®) 1 drop daily to affected eye
Zioptan (Tafluprost®) 1 drop daily to affected eye	Latanoprost (Xalatan®) 1 drop daily to affected eye
Bimatoprost (Lumigan®, Latisse®) 1 drop daily to affected eye	Latanoprost (Xalatan®) 1 drop daily to affected eye

ACTION: A motion was made and seconded to accept the above recommendations.
Voting: FOR: 22
AGAINST: 0
ABSENT: 2

Implementation: 60 days from approval if not already in place.

FORMULARY REVIEW

GENERIC NAME: BREXPIPRAZOLE

PROPRIETARY NAME: *Rexulti* (Otsuka)

THERAPEUTIC CLASS: Atypical antipsychotic

SIMILAR DRUGS: Abilify (aripiprazole)

INDICATIONS

FDA Approved
Treatment of schizophrenia (monotherapy)
Treatment of major depression (adjunctive therapy)
Non-FDA Approved
N/A

MECHANISM OF ACTION: Brexpiprazole may exert its therapeutic effects through a combination of partial agonist activity at dopaminergic D-2 receptors and serotonergic 5-HT1A receptors, and antagonist activity at serotonergisc5-HT2A receptors. It is also a partial agonist at D-3 receptors and an antagonist at a1A, a1B, a1D, and a2C alpha receptors, as well as 5-HT2B, 5-HT7, histamine H-1, and muscarinic M-1 receptors. Actions at muscarinic, alpha-1, and histamine receptors likely explain some of the adverse effects for antipsychotics such as orthostatic hypotension and somnolence.

PHARMACOKINETICS:

Absorption	Oral bioavailability 95%. Absorption is not affected by food
Distribution	Large volume of distribution. >99% protein bound
Metabolism	Mainly metabolized by CYP3A4 and CYP2D6. Major metabolite: DM-3411. DM-3411 does not contribute to the therapeutic effects. T1/2=91hrs.
Elimination	25% urine & 46% feces. <1% is excreted unchanged in the urine and ~14% is excreted unchanged in the feces.

SPECIAL POPULATIONS:

Pregnancy	May cause extrapyramidal and/or withdrawal symptoms in neonates with third trimester exposure. Only recommended when benefits outweigh risks.
Lactation	Brexpiprazole is excreted in the milk of lactating rats, but not studied in humans. Due to lack of evidence, consider other alternatives such as olanzapine or quetiapine.
Pediatrics	Safety and efficacy have not been established.
Geriatrics	Same as adult dosing. Advised to initiate treatment at lower end of dosing range.
Hepatic Impairment	**Mild:** No dose adjustments needed. **Moderate/Severe:** Maximum recommended dose for schizophrenia is 3mg PO once daily and for major depression is 2mg PO once daily.
Renal Impairment	**CrCL ≥ 60:** No adjustments needed. **CrCl < 60:** Maximum recommended dose for schizophrenia is 3mg PO once daily and for major depression is 2mg PO once daily.

CLINICAL STUDIES:

STUDY ONE: The ABC's of dopamine receptor partial agonists-aripiprazole, brexpiprazole and cariprazine: the 15- min challenge to sort these agents out	
METHODS	
Study Design	Review of placebo-controlled trials with three dopamine receptor partial agonists.
Study Funding	Leslie Citrome
Patient Enrollment Inclusion	Patients taking brexpiprazole, aripiprazole, or cariprazine.
Treatment Plan	To determine the similarities and differences of three dopamine receptor partial agonists that have been approved for the treatment of schizophrenia as well as other disorders.
RESULTS	
Outcomes Summary	Based on NNT derived from placebo-controlled trials, brexpiprazole has better efficacy compared to aripiprazole when treating schizophrenia, but worse when treating major depressive disorder.

Primary Endpoint (Schizophrenia)	NNT for response (derived from placebo-controlled trials and based of a 30% or greater decrease in PANSS): Aripiprazole: 8 Brexpiprazole: 7 Cariprazine: 10
Adverse Events	Akathisia, weight gain, somnolence, and extrapyramidal symptoms.
Author's Conclusion	Schizophrenia, bipolar disorder, and major depressive disorder are heterogeneous disorders and patient tolerability and response to these medications can vary, therefore treatment should be individualized to each specific patient.

STUDY TWO: The effect of brexpiprazole (OPC-34712) and aripiprazole in adult patients with acute schizophrenia: results from a randomized, exploratory study	
METHODS	
Study Design	Six-week, phase IIIb, exploratory, open-label, multicenter, flexible-dose study in adult patients carried out between 2/27/14 and 7/25/14 at 19 sites across the United States.
Study Funding	Otsuka Pharmaceutical Commercialization and Development Inc. and H. Lundbeck A/S.
Patient Enrollment Inclusion	Adult patients (18-65yrs) with a DSM-IV-TR diagnosis of schizophrenia confirmed by the Mini International Neurophsychiatric Interview for Schizophrenia and Psychotic Disorders were recruited. In the investigator's opinion, patients might potentially benefit from hospitalization or continued hospitalization with brexpiprazole or aripiprazole monothereapy for the treatment of a current acute relapse of schizophrenia. Experiencing an acute exacerbation of psychotic symptoms and marked deterioration of usual function: PANSS total score of 80 or more, score of 4 or more at screening on two or more PANSS items of hallucinatory behavior, unusual thought content, conceptual disorganization, or suspiciousness; and Clinical Global Impression-Severity of Illness Scale (CGI-S) score 4 or more.
Treatment Plan	Patients who would benefit from hospitalization/continued hospitalization for acute relapse of schizophrenia were enrolled and randomized to target doses of open- label brexpiprazole 3 mg/day or aripiprazole 15 mg/day for 6 weeks.
RESULTS	
Outcomes Summary	Improvements in the PANSS total score, supported by the CGI-S and CGI-I results, were observed as early as week 1 in both treatment groups. The early improvements observed for a number of the efficacy measures suggest that both brexpiprazole and aripiprazole may have a rapid onset of action even when patients are being titrated to their target dose. In this study, the mean changes from baseline in impulsivity scores were small. However, reductions in impulsivity scores as measured by BIS-11 were observed with brexpiprazole, with no change being observed for aripiprazole, suggesting improvements in impulsive personality traits in the brexpiprazole group, but not in the aripiprazole group. No meaningful worsening in cognitive function was observed in either treatment group.
Primary Endpoint	Patients treated with brexpiprazole (n = 64) or aripiprazole (n = 33) showed reductions in symptoms of schizophrenia as assessed by Positive and Negative Syndrome Scale total score (− 22.9 and − 19.4, respectively, both demonstrating statistical significance). A modest reduction in impulsivity was observed with brexpiprazole, but not aripiprazole (mean change in the Barratt Impulsiveness Scale 11-item total score: − 2.7 (P=0.0392 for brexpiprazole) and 0.1(P=0.9716 for aripiprazole)).
Adverse Events	A similar percentage of patients in both groups reported at least one treatment-emergent adverse event. The most frequent being akathisia, weight increase, headache, dyspepsia, dry mouth, nausea, pain in extremity, constipation, diarrhea, back pain, sedation, muscle spasms, and toothache.
Author's Conclusion	Within-group improvements in PANSS total score from baseline to week 6 were observed for both brexpiprazole and aripiprazole (Least squares mean change at week 6 was -22.9 (from 94.1) for brexpiprazole and -19.4 (from 93.3) for aripiprazole). Clinically relevant improvements in psychopathology were observed in patients with acute schizophrenia treated with brexpiprazole or aripiprazole. Brexpiprazole was well tolerated, with a lower incidence of akathisia than aripiprazole.

STUDY THREE: Adjunctive Brexpiprazole in Patients With Major Depressive Disorder and Irritability: An Exploratory Study	
METHODS	
Study Design	Interventional, exploratory study, open-label, flexible-dose
Study Funding	Supported by H. Lundbeck A/S, and Otsuka Pharmaceutical Development & Commercialization, Inc.
Patient Enrollment Inclusion	Men and women between 18-65 yrs, been diagnosed with MDD according to DSM-IV-TR criteria, current major depressive episode (MDE) had to be confirmed using the Mini International Neuropsychiatric Interview, have displayed an inadequate response to at least 1 antidepressant treatment, presented a MADRS total score of greater than 18, CGI-S score of greater than or equal to 3, and a 30-item inventory of depressive symptomatology,clinical version (IDS-C_{30}), item 6 (irritable mood) score of greater than or equal to 2. Current MDE treatment should have been more than 10 weeks.
Treatment Plan	6 weeks of treatment with current therapy in addition to brexpiprazole (target 3mg/day).
RESULTS	
Outcomes Summary	54 patients were treated with adjunctive brexpiprazole. From baseline to week 6: clinically relevant improvements were observed in Sheehan Irritability Score total (P<0.0001) and irritable mood scores (P<0.0001), Kellner symptom questionnaire total and anger-hostility subscale scores (P<0.0001)), and IDS-C30, item 6 score (P<0.0001). Irritability symptoms worsened after brexpiprazole discontinuation, assessed at week 10. All scores improved and less patients developed anger attacks during treatment.

Primary Endpoint	Irritability, hostility, and anger all indicated an improvement of distress, irritability, and anger-hostility symptoms during treatment with adjunctive brexpiprazole. 15 out of 17 pts having anger attacks prior to treatment stopped having anger attacks after 6 weeks of brexpiprazole treatment. Depressive symptoms indicated an improvement of irritability, anger-hostility, and other residual depressive symptoms during treatment with adjunctive brexpiprazole.
Adverse Events	43 pts (79.6%) had a treatment-emergent adverse event (TEAE), with 2 leading to withdrawal. Most common TEAE was akathisia (20.45), followed by headache, dry mouth, fatigue, increased appetite, insomnia, diarrhea, dizziness, fall, somnolence, and weight increase (all greater than 5%).
Author's Conclusion	Adjunctive treatment with brexpiprazole may represent a strategy for patients with MDD and inadequate response to antidepressant treatment who have symptoms of irritability.

GUIDELINE:

Indication	Recommendation	Alternative agents
Schizophrenia	Atypical Antipsychotics (Aripiprazole, ziprasidone, olanzapine, clozapine,risperidone, quetiapine, paliperdone, asenapine, iloperidone, lurasidone).	Typical antipsychotics (chlorpromazine, thioridazine, mesoridazine, loxapine, molindone, perphenazine, trifluoperazine, fluphenazine, haloperidol), then brexpiprazole.
Major Depressive Disorder (adjunct)	SSRIs, SNRIs, bupropion, trazodone, mirtazapine.	TCAs, MAOIs, nefazodone, antiphsychotics (aripiprazole, olanzapine/fluoxetine, brexpiprazole).

COMPARATIVE EFFICACY FOR ADULTS:

	Aripiprazole	Brexpiprazole	Cariprazine
Schizophrenia	Starting dose: 10-15mg/day Recommended dose: 10-15mg/day Maximum dose: 30mg/day	Starting dose: 1mg/day Recommended dose: 2-4mg/day Maximum dose: 4mg/day	Starting dose: 1.5 mg/day Recommended dose: 1.5-6mg/day
Major Depressive Disorder	Starting dose: 2-5mg/day Recommended dose: 5-10mg/day Maximum dose: 15mg/day	Starting dose: 0.5-1mg/day Recommended dose: 2mg/day Maximum dose: 3mg/day	Not Applicable
Bipolar Mania	Starting dose: 15 mg/day Recommended dose: 15mg/day Maximum dose: 30mg/day	Not Applicable	Starting dose: 1.5 mg/day Recommended dose: 3-6mg/day

CONTRAINDICATIONS: Known hypersensitivity to brexpiprazole or any of its components.

WARNING AND PRECAUTIONS:

- Cerebrovascular adverse reactions in elderly patients with dementia related psychosis: Increased incidence of cerebrovascular adverse reactions (TIA, stroke).
- Leukopenia, neutropenia, and agranulocytosis: Perform CBC in patients with pre-existing low WBC or history of leukopenia or neutropenia. Consider D/C'ing Rexulti if a clinically significant decrease in WBC occurs in absence of other factors.
- Metabolic changes: Monitor for hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain.
- Neuroleptic malignant syndrome: Manage with immediate D/C'ing and close monitoring.
- Orthostatic hypotension and syncope: Monitor HR and BP and warn patients with known cardiovascular or cerebrovascular disease, and risk of dehydration or syncope.
- Seizures: Use cautiously in patients with a history of seizures or with conditions that lower the seizure threshold.
- Tardive dyskinesia: D/C is clinically appropriate.
- Black box warning for:
  - -Increased mortality in elderly patients with dementia related psychosis
  - -Suicidal thoughts and behaviors.

ADVERSE REACTIONS: The most common adverse reactions reported by patients with major depressive disorder treated with brexpiprazole included constipation, fatigue, nasopharyngitis, increased appetite, weight gain, decreased blood cortisol, akathisia, headache, somnolence, tremor, dizziness, anxiety, and restlessness. The most common adverse reactions reported by patients with psychosis treated with brexpiprazole included dyspepsia, diarrhea, increased weight, increased blood creatinine phosphokinase, akathisia, tremor, and sedation.

DRUG INTERACTIONS: Brexpiprazole is metabolized by the CYP2D6 and CYP3A4 isozymes. Individuals who are poor CYP2D6 metabolizers and patients receiving drugs that inhibit CYP2D6 or CYP3A4 may have higher serum levels of brexpiprazole, whereas patients receiving drugs that are inducers of CYP3A4 may have decreased serum levels of brexpiprazole.

DOSING AND ADMINISTRATION:

Adult Dosing/ Indication	Aripiprazole	Brexpiprazole	Cariprazine
Schizophrenia	10-15mg/day	2-4mg/day	1.5-6mg/day
Major Depressive Disorder	5-10mg/day	2mg/day	N/A
Bipolar Mania	15mg/day	N/A	3-6mg/day
Pediatric Dosing/ Indication	**Aripiprazole**	**Brexpiprazole**	**Cariprazine**
Schizophrenia	N/A	N/A	N/A
Major Depressive Disorder	10yrs and older: 2mg daily, titrate by 5mg daily. Max dose is 30 mg.	N/A	N/A
Bipolar Mania	10yrs and older: 2mg daily, titrate by 5mg daily. Max dose is 30 mg.	N/A	N/A
Administration	**Aripiprazole**	**Brexpiprazole**	**Cariprazine**
	Tablets **Oral disintegrating tablets** **Oral solution** **Short-acting IM injection** **Long-acting IM injection (schizophrenia only)**	**Tablets**	**Capsules**
Dose Adjustments	**Aripiprazole**	**Brexpiprazole**	**Cariprazine**
Hepatic Impairment	N/A	**Moderate/Severe:** Maximum recommended dose for schizophrenia is 3mg PO once daily and for major depression is 2mg PO once daily.	**Mild/Moderate:** No adjustments necessary. Severe: Cariprazine is NOT recommended.
Renal Impairment	N/A	**CrCL ≥ 60:** No adjustments needed. **CrCl < 60:** Maximum recommended dose for schizophrenia is 3mg PO once daily and for major depression is 2mg PO once daily.	**CrCL ≥ 30:** No adjustments needed. **CrCl < 30:** Cariprazine is NOT recommended.
Geriatrics	Same as adult dose.	Same as adult dose.	Same as adult dose.
Pregnancy and Lactation	N/A	N/A	N/A
Pediatrics and neonatal	10yrs and older: 2mg daily, titrate by 5mg daily. Max dose is 30 mg.	N/A	N/A

PRODUCT AVAILABILITY:

Availability/How Supplied	**Packages of 30 oral tablets in strengths of 0.25mg, 0.5mg, 1mg, 2mg, 3mg and 4mg.**

PHARMACOECONOMICS/COST:
Rexulti cost per dose: $29.64
Aripiprazole cost per dose: $5.67

CONCLUSION:
Brexpiprazole has shown clinically relevant improvements in patients with acute schizophrenia, similar to aripiprazole, and was well tolerated with a lower incidence of akathisia. In addition, adjunctive treatment with brexpiprazole has been proven to reduce depressive symptoms and irritability for patients with MDD. However, due to the cost and only slight advantage of this medication over current therapies, it may not be a feasible option for first line treatment for schizophrenia or assisting in the treatment of major depressive disorder.

RECOMMENDATION:

☒Non-Formulary

Use preferred recommended agents prior to attempting brexpiprazole

THERAPEUTIC INTERCHANGE OR GUIDELINES - Both brexpiprazole and aripiprazole have indications for schizophrenia and adjunctive treatment of depression. In a head to head trial, bexpiprazole 3mg vs aripiprazole 15mg showed rapid onset of effect, improvements in PANSS (positive and negative syndrome scale), and other efficacy measure improvements for both agents in patients with acute schizophrenia.

Ordered	**Provided**
Brexpiprazole 1mg	Aripiprazole 5mg
Brexpiprazole 2mg	Aripiprazole 10mg
Brexpiprazole 3mg	Aripiprazole 15mg
Brexpiprazole 4mg	Aripiprazole 30mg

DRUG CLASS REVIEW

Phenazopyridine products

GENERIC NAME: Phenazopyridine

PROPRIETARY NAMES: Azo-Gesic®, Azo-Septic®, Azo-Standard®, Uristat®, Pyridium®, Baridium®, Phenazo 95®

THERAPEUTIC CLASS: Urinary analgesics

SIMILAR DRUGS: None

SOUND-/LOOK-ALIKE NAMES: None

INDICATION: Phenazopyridine is indicated to relieve symptoms such as pain, burning, urgency and/or frequency, and other discomforts due to irritation of the urinary tract mucosa caused by infection, trauma, surgery, endoscopic procedures, or the passage of sounds or catheters.

CLINICAL PHARMACOLOGY: Phenazopyridine is excreted in the urine where it exerts a topical analgesic effect on the mucosa of the urinary tract. This action helps to relieve pain, burning, urgency, and frequency. The precise mechanism of action is not known.

PHARMACOKINETICS: The pharmacokinetic properties of phenazopyridine have not been determined.

Absorption: not determined
Distribution: not determined
Elimination: following oral administration, the kidneys rapidly excrete phenazopyridine with as much as 65% of an oral dose being excreted unchanged in the urine.
Specific Populations: not determined

CLINICAL STUDIES: Phenazopyridine is a pre- 1938 drug with no existing FDA approval based upon a new drug application (NDA). It has been used as a urinary tract analgesic for over 40 years and no recent adequate and well-controlled clinical trials exist that support its safety and efficacy.

CONTRAINDICATIONS:
- Hypersensitivity to any component of phenazopyridine or its ingredients.
- Renal insufficiency or any liver disease.

WARNING AND PRECAUTIONS:
- May stain fabric, clothing, and contact lenses
- May interfere with urinalysis based on spectrometry or color reactions
- Patients with glucose-6-phosphate dehydrogenase deficiency

DOSING AND ADMINISTRATION:
The recommended dose is 200 mg three times daily after meals as needed. Over-the-counter dose administration should not exceed 2 days when used concomitantly with an antibacterial agent for the treatment of urinary tract infection.

DOSING ADJUSTMENTS:

GERIATRICS:
Safety and efficacy in patients greater than 65 years of age have not been established

RENAL IMPAIRMENT:
Mild renal failure (GFR greater than 50 mL/min): It has been recommended that the dosage interval be increased to every 8 to 16 hours.
Moderate to severe renal failure (GFR less than 50 mL/min): phenazopyridine should not be used.

HEPATIC IMPAIRMENT:
There are no dosage adjustments or precautions provided in the manufacturer's labeling.

PREGNANCY AND LACTATION:
Pregnancy Category B – Reproduction studies have been performed in rats at doses up to 50 mg/kg/day and have revealed no evidence of impaired fertility or harm to the fetus due to phenazopyridine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. No information is available on the appearance of phenazopyridine or its metabolites in human milk.

RECOMMENDED MONITORING:
- Pain, burring, urgency, or frequency
- Yellowing of the skin or sclera

PRODUCT AVAILABILITY:
- 95 mg tablet
- 100 mg tablet
- 200 mg tablet

PHARMACOECONOMICS/COST

	Dosing Unit	Cost		
		Cost/tablet	Cost/course (200 mg TID x 2 days)	Cost/year
Phenazopyridine	**95 mg**	**$0.19**	**$2.28**	**$1,121**
Phenazopyridine	**100 mg**	**$1.67**	**$20.04**	**$3,507**
Phenazopyridine	**200 mg**	**$2.47**	**$14.82**	**$4,693**

Potential cost savings if 95 mg tablets were utilized as a formulary substitution: $3,500 annual savings

In order to mitigate the high cost of this medication it is recommended that the inpatient pharmacy will stock phenazopyridine 95 mg. The table below will address the therapeutic interchange and utilization of the 95 mg strength.

Dose prescribed	Dosing unit used	Dose provided
100 mg TID	**1 tablet of 95 mg TID**	**95 mg TID**
200 mg TID	**2 tablets of 95 mg TID**	**190 mg TID**

CONCLUSION:
Phenazopyridine is available in 95mg, 100mg, and 200mg dosage tablets. The 95mg strength tablet is available over-the-counter whereas the 100mg and 200mg strength tablets are available by prescription only. However, all three strength tablets are used for symptomatic relief of dysuria. Currently, CHI Franciscan Health has the 100mg and 200mg on formulary. As can be seen by the breakdown cost of phenazopyridine, roughly $7,000 can be saved annually by interchanging 95mg tablets for 100mg and 200mg tablets. Utilizing 95mg tablets will yield 190mg vs 200mg, but this is not a clinically significant difference.

RECOMMENDATION:
Recommend interchanging phenazopyridine 100mg and 200mg tablets with 95mg tablets using the therapeutic interchange above.

Formulary: 95 mg tablets

DRUG CLASS REVIEW

DPP-4 Inhibitors for Type 2 Diabetes Mellitus

GENERIC AND PROPRIETARY NAMES

- Alogliptin (Nesina)
- Linagliptin (Tradjenta)
- Saxagliptin (Onglyza)
- Sitagliptin (Januvia)

THERAPEUTIC CLASS

There are four dipeptidyl-peptidase 4 (DPP-4) inhibitors currently available in the United States: alogliptin, linagliptin, saxagliptin, and sitagliptin. Of the four, alogliptin is the only agent generically available.

INDICATIONS

- All DPP-4 inhibitors are indicated as monotherapy and combination therapy as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
- DPP-4 inhibitors should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis

CLINICAL PHARMACOLOGY

DPP-4 inhibitors exert their action through inhibiting the metabolism of endogenous hormones such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) which are released from the GI tract in response to the ingestion of food. Prolonging the activity of these hormones leads to an increase in insulin release, an inhibition of glucagon release, a reduction in gastric emptying leading to satiety, and a reduction in weight.

PHARMACOKINETICS

	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin
Bioavailability	≈100%	30%	Not reported	87%
Time to maximum conc.	1-2 hrs	1.5 hrs	2 hours; 4 hrs (active metabolite)	1-4 hrs
t ½	21 hrs	12 hrs	2.4 hrs; 3.1 hrs (active metabolite)	12.4 hrs
Protein binding	20%	70-80% (concentration dependent)	Negligible	38%
Volume of distribution	417 L	1110 L (extensively distributes into tissues)	Not reported	198 L
Metabolism	Minimally metabolized to inactivate metabolites	Undergoes minimal metabolism; 90% drug recovered as unchanged parent compound. The remainder undergoes hydroxylation or oxidation as inactive metabolite	Primarily via CYP3A4/5. Major metabolite is half as potent as parent	Undergoes limited metabolism via CYP3A4 and CYP2C8
Elimination	Renal 76% and feces 13%	Enterohepatic system; urine 5% and feces 80%	Renal and hepatic	Urine 87% and feces 13%
Fraction excreted unchanged in urine	60-70%	See metabolism above	Not reported	79%

SPECIAL POPULATIONS

Special Populations	DPP-4 Inhibitors
Pregnancy	Pregnancy category B
Lactation	Unknown if excreted in human milk
Pediatrics	Safety and effectiveness in patients < 18 have not been established
Geriatrics	No difference in safety or effectiveness observed between subjects ≥ 65 years old and younger
Hepatic Impairment	No dosage adjustment
Renal Impairment	See dosage adjustment below for sitagliptin, saxagliptin, and alogliptin. No dosage adjustment for linagliptin.

CLINICAL STUDIES

According to the most current guidelines available for the management of diabetes published by the American Diabetes Association (ADA), DPP-4 inhibitors, along with 5 other classes, should be considered as an adjunct to metformin in patients who do not achieve their HbA_{1c} target after 3 months. Patient specific parameters, such as desired reduction in hemoglobin A_{1c} (HbA_{1c}), cost, comorbidities, and drug characteristics, should guide the selection of adjunctive agents. The ADA cannot recommend one DPP-4 inhibitor over another due to the lack of direct comparative studies among agents within the DPP-4 inhibitor class. Because of this, clinicians may rely on data from available meta-analyses that pool results from large number of placebo-controlled and act comparator studies published for each agent.

In 2012, a meta-analysis and systemic review summarized the findings from studies of glucagon-like peptide 1 receptor agonists and DPP-4 inhibitors. Studies were selected for inclusion if they were randomized controlled trials of 12-52 weeks' duration with a change from baseline in HbA_{1c} as the primary endpoint. The random effects meta-analysis examined HbA_{1c}, fasting blood glucose (FBG), and body weight for individual therapies, but did not compare effects between therapies. The results from the analysis are listed in the table 1.

Table 1

Agent	Total No. Studies	Total ITT Population	Active-Txt ITT Population	Mean Change in HbA_{1C} from Baseline (%)	Mean Change in FBG from Baseline (mmol/L)	Mean Change in Weight from Baseline (kg)
Alogliptin	5	2503	1976	–0.69 [–0.85 to –0.54]	–0.97 [–1.27 to –0.67]	–0.30 [–0.90 to +0.30]
Linagliptin	9	5177	3221	–0.60 [–0.75 to –0.46]	–1.04 [–1.59 to –0.49]	Not reported
Saxagliptin	7	3187	1566	–0.68 [–0.78 to –0.57]	–0.72 [–0.95 to –0.50]	–0.64 [–1.11 to –0.16]
Sitagliptin	23	> 10,893	> 5274	–0.67 [–0.75 to –0.60]	–0.87 [–0.98 to –0.76]	–0.29 [–0.61 to +0.03]

In 2015, a meta-analysis evaluated the HbA_{1C} response to each DPP-4 inhibitor within 1 year of therapy. The analysis included 98 RCTs of DPP-4 inhibitors (alogliptin, linagliptin, saxagliptin, sitagliptin, and vidagliptin). Reductions in HbA_{1C} from baseline based on individual agents were quantified using a random effects model. Results from the analysis are shown in table 2.

Table 2*

Agent	Total No. Study Arms	Mean Change in HbA_{1C} from Baseline (%)	P value	I^2 (%)
Alogliptin	11	−0.76 (95% CI, −0.86 to −0.66)	p<0.0001	90
Linagliptin	13	−0.55 (95% CI, −0.65 to −0.45)	p<0.0001	90
Saxagliptin	13	−0.70 (95% CI, −0.79 to −0.62)	p<0.0001	86
Sitagliptin	37	−0.79 (95% CI, −0.87 to −0.71)	p<0.0001	94

*Results of vidagliptin were not included

COMPARATIVE EFFICACY

The efficacy and safety of saxagliptin and sitagliptin as an adjunct to metformin was investigated in a randomized, double-blind, parallel group study that lasted 18 weeks. The study demonstrated that saxagliptin plus metformin was not inferior to sitagliptin plus metformin in reducing primary endpoints. Both agents were well tolerated and were associated with low and comparable rates of hypoglycemia. [8]

Agent	Saxagliptin 5 mg QD (n=403)	Sitagliptin 100 mg QD (n=398)	Mean Difference Between-Groups
Mean change in HBA_{1c} (%)	–0.52	–0.62	0.09 (95% CI, –0.1 to 0.2)
Mean change in FPG (mmol/L)	–0.60	–0.90	0.30 (95% CI, 0.08 to 0.53)
Mean change in weight (kg)	–0.4	–0.4	No difference

CONTRAINDICATIONS

- Alogliptin : History of a serious hypersensitivity reaction to alogliptin-containing products, such as anaphylaxis, angioedema or severe cutaneous adverse reactions
- Linagliptin : History of hypersensitivity reaction to linagliptin, such as anaphylaxis, angioedema, exfoliative skin conditions, urticaria, or bronchial hyperreactivity

- Saxagliptin : History of a serious hypersensitivity reaction (e.g., anaphylaxis, angioedema, exfoliative skin conditions) to saxagliptin
- Sitagliptin : History of a serious hypersensitivity reaction to sitagliptin, such as anaphylaxis or angioedema

WARNING AND PRECAUTIONS

	Alogliptin	Linagliptin	Saxagliptin	Sitagliptin
Acute pancreatitis	X	X	X	X
Heart failure	X		X	
Hypersensitivity	X	X	X	X
Hepatic effects	X			
Hypoglycemia	X	X	X	X
Arthralgia	X	X	X	X
Macrovascular outcomes	X	X	X	X
Acute renal failure				X

ADVERSE REACTIONS

- Alogliptin:
  - Most common adverse reactions (≥ 4%) are nasopharyngitis, headache and upper respiratory tract infection
- Linagliptin:
  - Adverse reactions reported ≥5% of patients treated with linagliptin and more commonly than in patients treated with placebo included nasopharyngitis
  - Hypoglycemia more commonly reported in patients treated with combination of linagliptin and sulfonylurea compared with those treated with combination of placebo and sulfonylurea
- Saxagliptin:
  - Adverse reactions reported ≥5% of patients treated with saxagliptin and more commonly than in patients treated with placebo are upper respiratory tract infection, and headaches
  - Peripheral edema was reported more commonly in patients treated with the combination of saxagliptin and a TZD than in patients treated with combination of placebo and TZD
- Sitagliptin:
  - Adverse reactions reported in ≥ 5% of patients treated with sitagliptin and more commonly than in patients treated with placebo are: upper respiratory tract infection, nasopharyngitis and headache
  - In the add-on to sulfonylurea and add-on to insulin studies, hypoglycemia was also more commonly reported in patients treated with sitagliptin compared to placebo

DOSING AND ADMINISTRATION

Agent	Usual Dose	Dosage Adjustment in Renal Insufficiency		
		CrCl ≥ 50 mL/min	CrCl ≥ 30 to < 50 mL/min	CrCl < 30 mL/min or ESRD requiring dialysis
Alogliptin	25 mg once daily	No dosage adjustment	12.5 mg once daily	6.25 mg once daily without regard to time of dialysis
Linagliptin	5 mg once daily	No dosage adjustment	No dosage adjustment	No dosage adjustment
Saxagliptin	2.5 mg or 5 mg once daily	No dosage adjustment	2.5 mg once daily	2.5 mg once daily
Sitagliptin	100 mg once daily	No dosage adjustment	50 mg once daily	25 mg once daily without regard to time of dialysis

Administration:

- All 4 agents may be taken with or without food
- Swallow saxagliptin tablets whole – do not split or cut tabs

Drug Interactions:

- There are no drug interactions requiring dosage adjustment of sitagliptin or alogliptin with co-administered drugs
- Reduce the dose of saxagliptin to 2.5 mg if taken concurrently with a strong CYP3A4/5 inhibitor (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin)
- Co-administration of linagliptin and CYP3A4 or P-gp inducers is not recommended

PHARMACOECONOMICS/COST

Product (Drug)	Strength and form (30 tabs)	Contract/GPO Price
Alogliptin	6.25 mg tab	$159.36 ($5.31 per tab)
	12.5 mg tab	
	25 mg tab	
Linagliptin	5 mg tab	$305.73 ($10.19 per tab)
Saxagliptin	2.5 mg tab	$311.06 ($10.37 per tab)
	5 mg tab	
Sitagliptin*	25 mg tab	$293.82 ($9.79 per tab)
	50 mg tab	
	100 mg tab	

*On formulary

Potential Cost Savings if alogliptin utilized as formulary agent: $5,300 annual savings

CONCLUSION

Results of meta-analyses demonstrate similar reductions in glycemic parameters between agents in the DPP-4 inhibitor class. Only one head-to-head trial comparing agents within this class is available. This trial showed comparable efficacy and safety between sitagliptin and saxagliptin as adjunct to metformin.

The DPP-4 inhibitors discussed differ in regards to pharmacokinetic properties, dosage adjustment in renal impairment, and drug interactions. Linagliptin is the only agent that does not require dosage adjustment for renal impairment. Sitagliptin and alogliptin do not require dosage adjustment for drug interactions. Reduce the dose of saxagliptin to 2.5 mg if taken with a strong CYP3A4/5 inhibitor. Co-administration of linagliptin and CYP3A4/P-gp inducers is not recommended. Additionally, alogliptin and saxagliptin should be used with caution in patient with heart failure.

RECOMMENDATION

There is a lack of compelling evidence to support the use of one DPP-4 inhibitor over another since these agents have similar side effects and efficacy. These agents have similar warnings and precautions with a few notable exceptions. These agents also have different pharmacokinetic properties and dosage adjustment requirements. Alogliptin is the only agent that is available in a generic formulation. The cost per single alogliptin tablet is $5.31 compared to $9.79 per tablet of sitagliptin. Considering these factors, replacing sitagliptin with alogliptin seems reasonable.

☒Formulary (Alogliptin)

☒Non-Formulary (Linagliptin, saxagliptin, sitagliptin) with substitution to a therapeutically equivalent dose of alogliptin as indicated below

THERAPEUTIC INTERCHANGE OR GUIDELINES

If you order	*Pharmacy will interchange to*
Linagliptin 5 mg once daily	Alogliptin 25 mg once daily or adjusted for renal function
Saxagliptin 2.5 mg once daily	Alogliptin 25 mg once daily or adjusted for renal function
Saxagliptin 5 mg once daily	Alogliptin 25 mg once daily or adjusted for renal function
Sitagliptin 100 mg once daily	Alogliptin 25 mg once daily or adjusted for renal function
Sitagliptin 50 mg once daily	Alogliptin 12.5 mg once daily or adjusted for renal function
Sitagliptin 25 mg once daily	Alogliptin 6.25 mg once daily or adjusted for renal

Agent	**Usual Dose**	**Dosage Adjustment in Renal Insufficiency**		
		CrCl ≥ 50 mL/min	**CrCl ≥ 30 to < 50 mL/min**	**CrCl < 30 mL/min or ESRD requiring dialysis**
Alogliptin [1]	25 mg once daily	No dosage adjustment	12.5 mg once daily	6.25 mg once daily without regard to time of dialysis

FORMULARY REVIEW

GENERIC NAME: VEDOLIZUMAB

PROPRIETARY NAME: *Entyvio* (Takeda Pharmaceuticals)

INDICATIONS: Vedolizumab is an anti-α4β7 integrin monoclonal antibody (mAb), for the treatment of Crohn's disease (CD) and ulcerative colitis (UC) in adults with moderately to severely active disease who have had an inadequate response with, or were intolerant to anti-tumor necrosis factor (TNF) agents, or had an inadequate response with, or demonstrated dependence on corticosteroids.

FDA Approved
Ulcerative Colitis (Adults ≥ 18 years) Entyvio® (Vedolizumab) is indicated for: ▪ inducing and maintaining clinical response, ▪ inducing and maintaining clinical remission, ▪ improving the endoscopic appearance of the mucosa, and ▪ achieving corticosteroid-free remission in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids. **Crohn's Disease (Adults ≥ 18 years)** Entyvio® (Vedolizumab) is indicated for: ▪ achieving clinical response, ▪ achieving clinical remission, and ▪ achieving corticosteroid-free remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to a tumor necrosis factor (TNF) blocker or immunomodulator; or had an inadequate response with, were intolerant to, or demonstrated dependence on corticosteroids.
Non-FDA Approved
There were no studies supporting off-label uses for Vedolizumab.

CLINICAL PHARMACOLOGY: Vedolizumab is a humanized immunoglobulin monoclonal antibody against α4β7 integrin that selectively inhibits adhesion of α4β7 integrin expressing cells to Mucosal Vascular Addressing Cell Adhesion Molecule 1 (MAdCAM-1). By blocking the interaction between α4β7 and MAdCAM-1, leukocyte binding to the endothelial surface is inhibited, consequently inhibiting migration of memory T-lymphocytes across the endothelium into inflamed gastrointestinal parenchymal tissue. The binding is selective for α4β7, resulting in inhibition of the α4β7–MAdCAM-1 interaction in the gastrointestinal tract without affecting systemic immunosuppression. The humanized IgG1 monoclonal antibody, vedolizumab, is produced in Chinese hamster ovary cells which are engineered using recombinant DNA technologies. The interaction of the α4β7 integrin with MAdCAM-1 has been implicated as an important contributor to the chronic inflammation that is a hallmark of ulcerative colitis and Crohn's disease.

Vedolizumab is the second integrin-receptor antagonist to be approved in the United States. Natalizumab (Tysabri®) was the first integrin receptor antagonist approved for the treatment of CD but was withdrawn from the market after several reports of Progressive Multifocal Leukoencephalopathy (PML). It has since been reintroduced to the market with a surveillance program. To date, vedolizumab has not been associated with PML. However, post marketing studies monitoring for this adverse effect are ongoing and the expected completion date for the study is 2021.

PHARMACOKINETICS: Similar pharmacokinetic parameters have been reported in patients with UC and CD. In a dose-ranging study, 36 patients with UC were administered vedolizumab as a 30–60 min intravenous infusion at doses of 2, 6, or 10 mg/kg at weeks 0, 2, and 4 (induction phase) and week 12 (maintenance phase).[12] With each of these doses, maximum serum concentration and area under the curve were considered dose dependent. Serum concentrations declined in a linear manner when concentrations ranged from 1 to 10 μg/mL, with a nonlinear decline thereafter. Across all doses, the mean half-life ranged from 15–22 days.

These pharmacokinetic parameters were confirmed in phase III trials, when 300 mg of vedolizumab was administered as a 30 min intravenous infusion at weeks 0, 2, 6, and then every 4 or 8 weeks thereafter to patients with UC and CD. Trough serum concentrations

declined in a linear fashion from week 6 to week 46 from 26.3 to 11.2 μg/mL (UC) and from 27.4 to 13 μg/mL (CD), and the serum half-life was determined to be nearly 25 days.

CLINICAL TRIALS: The FDA approval of vedolizumab for UC and CD was based on results from three prospective, randomized, multi-center, phase III trials (GEMINI 1, GEMINI 2, and GEMINI 3). GEMINI 1 and 2 were integrated trials with similar study design and methodology and consisted of both induction and maintenance phase studies in UC and CD, respectively, while GEMINI 3 was an induction phase study in CD. In each of these trials, patients had moderate to severe disease with treatment failure to glucocorticoids and immunomodulators (GEMINI 1, 2) or TNF-α inhibitors (GEMINI 1, 2, 3). Moderate-quality evidence suggests that vedolizumab is efficacious in the induction and maintenance of remission of UC (NNT=9 for clinical remission at week 6; NNT=7 for maintaining durable clinical remission). In Crohn's disease, vedolizumab showed inconsistent efficacy in inducing remission at week 6 (NNT=13 in one trial; no benefit in another trial). It also achieved clinical remission temporarily but did not show durable benefit (or gain FDA approval) for maintenance of remission. It lacked benefit in inducing clinical response or remission in TNF antagonist failures by week 6.

ADVERSE REACTIONS: The most serious adverse reactions reported in clinical studies of vedolizumab have included serious infections, malignancies, and anaphylaxis. The most common adverse reactions (incidence ≥3% and ≥1% higher than placebo) have been nasopharyngitis, headache, arthralgia, nausea, pyrexia, upper respiratory tract infection, fatigue, cough, bronchitis, influenza, back pain, rash, pruritus, sinusitis, oropharyngeal pain, and pain in extremities.

DRUG INTERACTIONS:

Interacting Drug	Effect
Natalizumab	Because of the potential for increased risk of PML and other infections, avoid the concomitant use of ENTYVIO® with Natalizumab.
TNF Blockers	Because of the potential for increased risk of infections, avoid the concomitant use of ENTYVIO® with TNF blockers
Live Vaccines	Vedolizumab may enhance the adverse/toxic effect of Live Vaccines. Vedolizumab may diminish the therapeutic effect of Live Vaccines. Management: Prior to initiating treatment with Entyvio®, all patients should be brought up to date with all immunizations according to current immunization guidelines. Avoid concurrent use of live organism vaccines with Vedolizumab; live-attenuated vaccines should not be given for at least 3 months after therapy.

CONTRAINDICATIONS: Vedolizumab is contraindicated in patients who have had a known serious or severe hypersensitivity reaction to Vedolizumab (Entyvio®) or any of its excipients (such as dyspnea, bronchospasm, urticaria, flushing, rash and increased heart rate).

DOSING & ADMINISTRATION:

Adult Dosing/Indication	The recommended dosage of Vedolizumab in adults with ulcerative colitis or Crohn's disease is 300 mg administered by intravenous infusion at zero, two and six weeks and then every eight weeks thereafter. Discontinue therapy in patients who show no evidence of therapeutic benefit by Week 14.
Pediatric Dosing/Indication	The safety and efficacy of Vedolizumab in pediatric patients below the age of 18 have not been established
Administration	For intravenous use only. Reconstitute prior to use. Administer as intravenous infusion over 30 minutes. Do *not* administer by rapid IV injection (IV push or bolus). After the infusion is complete, flush with 30 mL of sterile 0.9% Sodium Chloride injection. Should be administered by a healthcare professional prepared to manage hypersensitivity reactions including anaphylaxis, if they occur.

RECOMMENDED MONITORING

▪ Observe patients during infusion (until complete) and monitor for hypersensitivity reactions; LFTs; tuberculosis screening according to local practice; signs/symptoms of infection; any new onset or worsening of neurological signs and symptoms.
▪ Assess therapeutic benefit; if none noted after treatment course reconsider use. ▪ Monitor for signs and symptoms of infusion-related reactions or hypersensitivity, infections especially respiratory and nasal, neurologic changes, and elevated LFTs. ▪ All immunizations should be up to date prior to initiation of treatment.

PHARMACOECONOMICS/COST: The cost of a 300 mg vial of vedolizumab in the US is $5011.76.

Based on the recommended dosing of 300 mg on weeks 0, 2, 6, and then every 8 weeks thereafter, the cost of vedolizumab for the **initial year of treatment is approximately $43,334** and for **subsequent years approximately $28,917**.

To account for individual drug reimbursement, vedolizumab should only be administered in an outpatient infusion clinic setting. The manufacturer of vedolizumab does provide support for copayment assistance for those with private insurance, identification of independent patient support foundations for possible financial assistance for those with Medicare/Medicaid, and determination of patient assistance qualification for those without insurance.

DRUG SAFETY/RISK EVALUATION AND MITIGATION STRATEGY (REMS): No REMS is anticipated to be required for vedolizumab.

CONCLUSION: Considering relatively limited efficacy data, lack of long-term safety data, time-consuming administration requiring dose monitoring, inconvenience to patients, nursing costs, and substantial cost of the medication itself (price for 300-mg reconstitutable vedolizumab is $5011.76), vedolizumab should not be recommended as an addition to the inpatient formulary. This medication would be better suited for outpatient prescribing by gastroenterologists during clinic visits for administration at an outpatient infusion center. Eligible patients would be adult patients > 18 years of age with moderate-to-severe UC or CD who have previously failed or were intolerant to at least one conventional treatment (i.e. glucocorticoid, immunomodulator, or TNF-α antagonist), or demonstrated dependence on corticosteroids.

RECOMMENDATION:

Formulary, restricted: outpatient infusion use ONLY for below indications

- Diagnosis of moderately to severely active Ulcerative colitis (UC) or Crohn's Disease (CD)
  AND *One* of the following:

    1. History of failure, inadequate response, or intolerance to at least **one** of the following therapies:
        a) Tumor necrosis factor (TNF) blocker - failure of preferred agent(s) as designated by patient specific insurance medical necessity requirements.
        b) Immunomodulator (azathioprine, mercaptopurin, etc.)

    2. Corticosteroids
        a) History of failure, inadequate response, or intolerance, to corticosteroids,
        b) Corticosteroid dependent (unable to successfully taper corticosteroids without a return of the symptoms of CD or UC).

BIOSIMILAR MEDICATIONS – INTRODUCTION & REVIEW

What are biosimilar products?
Biosimilars are a type of biological product that is licensed (approved) by the FDA because they are highly similar to an already FDA-approved biological product, known as the biological reference product (RP) and have been shown to have no clinically meaningful differences from the RP. Minor differences in clinically inactive components are allowed, but there must be no clinically meaningful differences between the biosimilar and the RP it was compared to in terms of the safety, purity, and potency of the product. Biological products are made from a variety of natural sources and, like drugs, biological products are used to either treat or cure diseases and medical conditions, prevent diseases, or diagnose diseases. Biological products can be made of sugars, proteins, nucleic acids, complex combinations of these substances, or may be living entities such as cells and tissues. Due to the complexity of biologics and the lack of access to proprietary manufacturing data, developers reverse engineer the RP to create a biological product that is highly similar to the RP. Therefore, the structural and manufacturing complexity of biologic therapies and the requirement for proprietary knowledge preclude duplication, whereas the simpler structures of small molecule products and the ability to replicate the patented production process have facilitated development of generic versions which are identical copies of the originator or RP.

The FDA will only approve a biosimilar product if it has the same mechanism of action, route of administration, dosage form, and strength as the RP. Additionally, a biosimilar can only be approved for the indication(s) and conditions of use that have been previously approved for the RP.

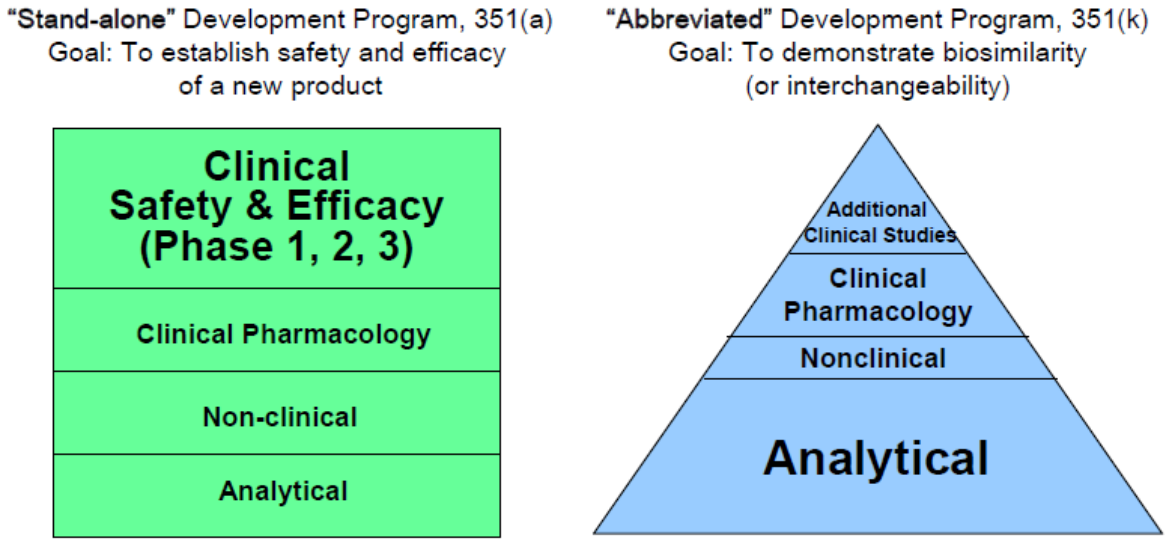
How are biosimilars and interchangeable biosimilars approved?
The Patient Protection and Affordable Care Act (Affordable Care Act), signed into law by President Obama on March 23, 2010, amended the Public Health Service Act (PHS Act) to create an abbreviated licensure pathway for biological products that are demonstrated to be "biosimilar" to or "interchangeable" with an FDA-licensed (approved) biological product. This pathway is provided in the part of the Affordable Care Act known as the *Biologics Price Competition and Innovation Act of 2009 (BPCI Act)*. Applications for biosimilar approvals are submitted under section 351(k) of the PHS Act in order to demonstrate that the proposed product is biosimilar to the RP. For licensure, a proposed biosimilar relies on comparative data with the RP, as well as publicly available information regarding the FDA's previous determination that the RP is safe, pure, and potent. In comparison, the RP is a licensed biologic approved under section 351(a) of the PHS Act as a "stand-alone" application that contains all information and data necessary to demonstrate that the proposed product is safe, pure, and potent.

What data does the FDA review to determine biosimilarity and interchangeability?
The manufacturer's application for a biosimilar or interchangeable biological product must include, among other things, information demonstrating biosimilarity based upon data from:

- Analytical studies demonstrating that the biological product is "highly similar" to the RP notwithstanding minor differences in clinically inactive components. If a molecule is known to have multiple biological activities, each should be demonstrated to be highly similar between the proposed biosimilar product and the RP.
- Animal studies (including the assessment of toxicity)
- A clinical study or studies (including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate safety, purity, and potency in 1 or more appropriate conditions of use for which the RP is licensed and for which licensure is sought for the biosimilar product.

How do the goals of drug development differ between biosimilar and "stand-alone" products?
The goal of "stand-alone" development is to demonstrate that the proposed product is safe and efficacious. Drug development starts with preclinical research, moves to phase 1, 2 and culminates in phase 3 "pivotal" trials to show safety and efficacy. The biosimilar pathway does differ in that the goal is to demonstrate biosimilarity between the proposed product and a RP with analytical similarity data serving as the foundation of biosimilar development. The goal is not to independently establish safety and effectiveness of the product (this is the responsibility of the RP approved via 351(a) pathway) but instead the FDA has outlined a stepwise approach to generate data in support of a demonstration of biosimilarity using a "totality of the evidence" approach meaning that there is no one pivotal study that demonstrates biosimilarity. However, approval of a proposed biosimilar product is based on the integration of various information and the totality of the evidence submitted by the biosimilar sponsor to provide an overall assessment that the proposed product is biosimilar to the RP.

Despite the differing pathways of drug development, the FDA requires licensed biosimilar and interchangeable biological products to meet the agency's rigorous standards of safety and efficacy. Per the FDA, this means patients and health care professionals will be able to rely upon the safety and effectiveness of the biosimilar or interchangeable product, just as they would the RP.



What are interchangeable products and what additional data is required for this designation? Interchangeable products are both biosimilar to an FDA-approved RP, and can be expected to produce the same clinical result as the RP in any given patient. For interchangeable products, the application must include information that demonstrates that the risk in terms of safety or diminished effectiveness of alternating between use of the proposed interchangeable product and the RP is not greater than the risk of using the RP without alternating or switching. Because of these additional standards, an interchangeable biological product may be substituted for the RP (subject to state pharmacy laws) by a pharmacist without the intervention of the health care provider who prescribed the RP.

Extrapolation of data

Biosimilars and interchangeable biological products can only be approved for indications of use that have been previously approved for the RP. However, under the abbreviated 351(k) pathway, the potential exists for a biosimilar or interchangeable biological product to be approved for one or more of the conditions of use for which the RP is labeled based upon extrapolation of data intended to demonstrate biosimilarity in one condition of use. Once these requirements are fulfilled, extrapolation of biosimilar approval to other indications for which the RP are approved is permitted without the need for further clinical trials, as long as this is scientifically justifiable. Such justification requires that the mechanism(s) of action of the RP in question should be similar across indications, and also comparable between the RP and the biosimilar. Likewise, the pharmacokinetics, immunogenecity and safety of the RP should be similar across indications and comparable between the RP in the clinically tested population(s). For example, infliximab-dyyb (infliximab biosimilar) was only evaluated clinically for the treatment of rheumatoid arthritis and ankylosing spondylitis but was approved for the same FDA approved indications as the RP, infliximab (crohn's, ulcerative colitis, psoriatic arthritis, and plaque psoriasis). These additional indication approvals were based on extrapolation of all necessary data including PK, mechanism of action(s) for each indication, immunogenecity, and toxicity data.

Prescribing biosimilars and interchangeables

Health care professionals can prescribe biosimilar and interchangeable products just as they would prescribe other medications by writing the proprietary name or nonproprietary name on the prescription. A biosimilar can be approved only for those indications and condition(s) of use previously approved for the RP, but a biosimilar can be approved for fewer than all the indications and condition(s) of use approved for the RP. Therefore, it is important for health care professionals to review the product labeling (prescribing information) to determine which conditions of use and routes of administration the biosimilar was approved for. Because interchangeable products have met additional criteria for approval, they may be substituted at the pharmacy without the intervention of a healthcare provider (subject to state pharmacy laws). Currently, there is only one biosimilar approved and available for use in the U.S. - Zarxio (filgrastim-sndz), which is biosimilar to Neupogen (filgrastim). A biosimilar product for infliximab has been FDA approved (infliximab-dyyb), however it is not currently available for purchase in the U.S.

Reimbursement

Medicare Part B payment for newly approved drugs and biologicals will be available once the product is approved by the FDA. CMS will incorporate biosimilars that are approved under the abbreviated biological approval pathway in the Average Sales Price (ASP) payment methodology. Initially, once the manufacturer's wholesale acquisition cost (WAC) is available, Medicare will pay 106% of the WAC for the product until ASP information is available. Once ASP information is available for the biosimilar product, Medicare payment will equal the ASP for the biosimilar product plus 6% of the ASP for the RP.

CMS will also create a separate reimbursement code to distinguish the biosimilar from the RP. Additionally, all biosimilars for a specific product will be reimbursed with the same J-code under Medicare Part B regardless of manufacturer.

FORMULARY REVIEW

GENERIC NAME: INFLIXIMAB-dyyb

PROPRIETARY NAME: *Inflectra* (Celltrion/Pfizer)

INDICATIONS: Infliximab-dyyb (CT-P13) is a biosimilar version of Remicade® that is a monoclonal antibody targeted against tumor necrosis factor alpha (TNF_{alpha}). CT-P13 is only the second biosimilar and the first monoclonal antibody to be approved by the FDA under the new abbreviated pathway for biologic products that are demonstrated to be "biosimilar" to an FDA licensed biological reference product (RP).

FDA Approved
• **Crohn's Disease***
• **Pediatric Crohn's Disease***
• **Ulcerative Colitis***
• **Rheumatoid Arthritis**
• **Ankylosing Spondylitis**
• **Psoriatic Arthritis***
• **Plaque Psoriasis***

***** Approval based on extrapolation of data on safety and efficacy across indications

CLINICAL PHARMACOLOGY: Infliximab is a chimeric IgG1k monoclonal antibody that binds to and inhibits the binding of TNFα, thus interfering with its endogenous activity. TNFα is responsible for many biological activities that play a role in inflammatory autoimmune disorders. These activities include induction of inflammatory cytokines IL-1 and IL-6, enhanced leukocyte migration, activation of neutrophils and eosinophils, fibroblast proliferation, induction of acute phase reactants, and increased synthesis of prostaglandins.Vedolizumab is the second integrin-receptor antagonist to be approved in the United States. Natalizumab (Tysabri®) was the first integrin receptor antagonist approved for the treatment of CD but was withdrawn from the market after several reports of Progressive Multifocal Leukoencephalopathy (PML). It has since been reintroduced to the market with a surveillance program. To date, vedolizumab has not been associated with PML. However, post marketing studies monitoring for this adverse effect are ongoing and the expected completion date for the study is 2021.

PHARMACOKINETICS: Infliximab is primarily distributed within the vascular department with a V_d: 3 to 6 L. The volume of distribution is increased when co-administered with corticosteroids. There is no evidence of accumulation but elevated serum concentrations have been seen following multiple doses of infliximab in patients also receiving concurrent methotrexate. There is a linear relationship between dose and C_{max} and AUC following IV infusions of 1-20 mg/kg. The onset ranges from 3 days to 2 weeks with a quicker onset generally seen with Crohn's disease. A long elimination half-life (8-12 days) produces an extended duration of action varying from 6-12 weeks for RA and 8-48 weeks in Crohn's disease.These pharmacokinetic parameters were confirmed in phase III trials, when 300 mg of vedolizumab was administered as a 30 min intravenous infusion at weeks 0, 2, 6, and then every 4 or 8 weeks thereafter to patients with UC and CD. Trough serum concentrations declined in a linear fashion from week 6 to week 46 from 26.3 to 11.2 µg/mL (UC) and from 27.4 to 13 µg/mL (CD), and the serum half-life was determined to be nearly 25 days.

CLINICAL STUDIES (evaluating safety, efficacy, immunogenicity of CT-P13): Biosimilarity between CT-P13 and its reference product (Remicade®) was demonstrated by comprehensive physiochemical, non-clinical and clinical studies including two randomized, double-blind, parallel group studies as outlined below (PLANETAS, PLANETRA). In addition, extension studies of both trials were conducted to investigate longer term safety and efficacy of extended CT-P13 treatment over 2 years and the efficacy and safety of switching from the reference product (RP) Remicade® to CT-P13 for 1 year.

RHEUMATOID ARTHRTITIS & ANKYLOSING SPONDYLITIS: CT-P13 was evaluated clinically in two similarly designed phase III randomized, double-blind, multicenter, parallel group studies for the treatment indications of ankylosing spondylitis (PLANETAS) and rheumatoid arthritis (PLANETRA). Both studies demonstrated that CT-P13 and the RP have highly comparable efficacy, pharmacokinetics, safety, and immunogenicity for the specified study timeframes. Additionally, two extension studies of PLANETRA and PLANETAS studies were conducted to determine longer term efficacy (additional year) of CT-P13 and the efficacy and safety of switching from the RP to CT-P13 for patients previously on stable regimens with the RP. These extension studies both confirmed continued efficacy and safety of therapy with CT-P13 as well as no notable differences in response rates, adverse events, or immunogenicity for the patients switched to the biosimilar product.

INFLAMMATORY BOWEL DISEASE: No manufacturer sponsored studies were conducted to independently evaluate clinical efficacy for inflammatory bowel indications. These additional diagnoses were approved using extrapolation of the data available for treatment of AS and RA. Extrapolation of biosimilar approval to other indications for which the RP are approved is permitted without the need for further clinical trials as long as this is scientifically justifiable. This justification requires that that mechanism(s) of action of the RP in question should be similar across indications, and also comparable between the RP and the biosimilar. Additionally, the pharmacokinetics, immunogenicity and safety of the RP should be similar across indications and comparable between the RP in the clinically tested population(s). Despite the lack of data for these GI indications, numerous observational studies have evaluated the safety, efficacy, and immunogenicity of CT-P13 for the treatment of inflammatory bowel disorders.

The summary of evidence tends to support the clinical efficacy and safety of the use of infliximab-dyyb in both infliximab naïve patients and those being switched from infliximab reference product to the biosimilar for the treatment of inflammatory bowel disorders (further discussion regarding switching below). All studies show similar rates of clinical response and remission along with comparable rates of adverse events. No unexpected adverse events or issues related to immunogenicity were observed. However, many of these studies are observational and have small patient populations and short follow-up times. Currently, CT-P13 is the only anti-TNF biosimilar for infusion use approved for treatment of IBD and the current real-world efficacy and safety data as outlined above appears to support extrapolation to CD and UC indications. However, additional data should be forthcoming as other more robust randomized clinical trials are completed which should further independently demonstrate efficacy for these IBD indications.

PSORIATIC INDICATIONS (Psoriatic Arthritis, Plaque Psoriasis): No observational or manufacturer sponsored studies were conducted to independently evaluate clinical efficacy for inflammatory bowel indications.

INTERCHANGEABILITY/SWITCHING BETWEEN REFERENCE PRODUCT & BIOSIMILAR: CT-P13 was approved via the FDA's abbreviated pathway for biosimilar drug development, however it was not approved as an interchangeable biosimilar. The abbreviated approval pathway for biosimilars has established a pathway for biological products to demonstrate similar efficacy and safety with the RP. The federal law has differentiated the approval of products into two stages: (1) the "biosimilar" has to provide evidence of basic similarity to the reference product, and (2) an additional approval status called "interchangeable biosimilar" which is required to allow for unlimited transition/substitution from the RP without the authorization of the provider who prescribed the RP (subject to state laws). The FDA requires that interchangeable biosimilars demonstrate that there is no increased risk associated (safety or diminished efficacy) with alternating or switching between the interchangeable product and the reference product compared with using only the RP without such alternation or switch. It is important to note that at this time the FDA has yet to clarify the requirements of the interchangeable biosimilar approval pathway and they recommend that drug sponsors utilize a two-step process for first obtaining biosimilar approval and then later submitting a supplement with new data to support interchangeability.

Despite the lack of an interchangeable biosimilar designation, several studies (observational cohort studies, extension studies of randomized controlled trials, etc.) have evaluated single-way transition studies from the RP (Remicade®) to CT-P13 to examine safety, effectiveness, and immunogenicity of switching between products. These studies are outlined below.

Switchability of CT-P13: summary of current literature				
Country (Study)	**Patient Information**	**Indication**	**Efficacy Summary**	**Summary/Author Conclusion**
16 countries (PLANETRA)[7]	302 158 = maintenance group 144 = switch group	RA	Based on ACR 25/50/70, DAS28s-ESR, DAS28-CRP, EUALAR-ESR, and EULA-CRP, a highly similar efficacy between the switch and maintenance group was demonstrated.	In the switch group, there were no notable differences in response rates, adverse events, or immunogenicity between the end of the PLANETRA study and week 102 of the extension study, suggesting that switching from INX to CT-P13 in patients with RA will not have any detrimental effects on efficacy or safety.
8 countries (PLANETAS)[4,5]	174 88 = maintenance group 86 = switch group	AS	Based on ASAS 20/40, ASAS partial remission rate, BASDAI, BASFI, BASMI, and chest expansion, a highly similar efficacy between the switch and maintenance group was demonstrated	In the switch group, there were no notable differences in response rates, adverse events, or immunogenicity between the end of the PLANETAS study and the completion of the extension study. Immunogenicity profiles were comparable and safety profiles were generally comparable following transition from RP to CT-P13
South Korea[10]	CD (59: 32 infliximab-naïve, 27 switch) UC (51: 42 infliximab-naïve, 9 switch)	IBD	Naïve: • Response: 95.5% in CD and 91.3% in UC patients at week 30 • Remission: 77.3% in CD and 47.8% in UC patients at week 30	CT-P13 appears to have comparable efficacy, safety, and interchangeability with its originator in the treatment of IBD. Further prospective studies with long-term follow up periods will be needed to confirm the biosimilarity of CT-P13.

			Switch: • Efficacy was maintained for 92.6% of CD and 66.7% of UC patients	
South Korea[11]	CD (83: 43 infliximab-naïve, 40 switch) FCD (12: 8 infliximab-naïve, 4 switch) UC (78: 62 infliximab-naïve, 16 switch)	IBD	Naïve: • Response: 79.5% in CD and 66.7% in FCD, and in 72.2% UC patients at week 30 • Remission: 59.0% in CD and 50% in FCD, and in 37% UC patients at week 30 Switch: • Efficacy was maintained for 80.6% of CD, 50% of FCD, and 45.5% of UC patients	There were no meaningful differences observed for the proportions of IBD patients experiencing TEAEs in the infliximab-naïve group compared with the switch group. Overall, 32/46 patients (69.5%) who switched from infliximab to CT-P13 achieved or maintained remission through visits two to six with a majority of these patients having the diagnosis of CD. Comparisons with historical data published for infliximab suggest that clinical outcomes such as safety and efficacy are comparable for both CT-P13 and the reference product.
South Korea[12]	CD (11: 8 infliximab-naïve, 5 switch) UC (9: 5 infliximab-naïve, 4 switch)	IBD	Naïve: • Response and Remission: 87.5% in IBD patients at week 8 Switch: • Efficacy was maintained for 88.9% of patients as compared to the RP	One UC patient experienced arthralgia and CT-P13 was discontinued for this reason. Only one patient with UC experienced loss of response during the study. CT-P13 may have biosimilarity and interchangeability with its originator in IBD although a large, randomized, double-blind, prospective study is needed.
Poland[18]	32 switch (CD) 7 switch (UC)	Pediatric CD, UC	Switch: Median Pediatric Chrohn's Disease Activity Index Calculator • At the initiation of infiliximab RP= 48 (Severe) • Immediately before switching to CT-P13 = 8.5 (Remission) • Before the second CT-P13 infusion = 7.5 (Remission) The median population maintained remission after their initial change from RP to the biosimilar product.	Evaluation efficacy of last biosimilar doses of all patients revealed rates of clinical remission of 88 and 57% for CD and UC patients, respectively. Last follow-up assessment of patients who continued with biosimilar therapy showed that 16/20 (80%) CD patients and all 4 UC individuals were in remission. One infusion reaction to infliximab biosimilar was observed in a CD patient, which led to treatment discontinuation. The incidence of sporadic mild adverse events prior to and after switching did not differ significantly and was consistent with the safety profile of the infliximab molecule.
Finland[19]	39 switch	RA	Switch: No statistical differences were reported with regard to AUC for pain (VAS), fatigue, PtGlob, PtAct, HAQ DrGlob, ESR, CRPafter CT-P13 administration for 11 months	Generally well tolerated. Adverse events were similar in all groups with no statistical differences or immediately observable safety signals. The clinical effectiveness of CT-P13 in both patient reported outcomes and disease activity measures was comparable to infliximab during the first year of switching, with no immediate safety signals observed. It was noted by the authors that subjective reasons (negative expectations) may play a role among discontinuations of biosimilars and larger patient numbers and longer follow up are necessary for confirming this clinical experience.

Interchangeability/Switching Summary**:** Currently the data available in regard to switching between products is limited to mostly observational cohort studies from other countries and the two above mentioned extension studies of the PLANETAS and PLANETRA clinical trials. However, the above studies do provide some insight on the safety, effectiveness, and immunogenicity experience with switching from the infliximab RP to CT-P13. As demonstrated in the summary table above, there currently appear to be no immediate concerns for those patients who experience a switch in therapy. However it is important to note that all of the reported studies, with the exception of the PLANET extension studies, are observational studies that lacked proper power and strong study designs and the need for stronger head-to-head clinical trials is apparent. The European experience with CT-P13 will continue to provide additional insight on the feasibility of switching patients to the more economical biosimilar version of infliximab. One such study is the Norwegian NOR-SWITCH study which is a randomized, double-blind trial to compare the safety and efficacy of continued reference product infliximab

compared to switching therapy to CT-P13. This study is designed to evaluate the safety and efficacy of switching from RP to CT-P13 in 500 patients with RA, AS, UC, CD, Ps, and AS. In addition to the NOR-SWITCH trial, two other randomized clinical trials are underway. One study will focus on CD patients in 19 countries, while the other will focus on RA patients in Japan. Despite the results of these more robust clinical evaluations not being available at this time the data from Asia and Europe do suggest similar efficacy and safety when patients are transitioned from the reference product infliximab to the biosimilar version of infliximab.

CONTRAINDICATIONS: Infliximab-dyyb at doses greater than 5 mg/kg is contraindicated in patients to moderate to severe heart failure. Infliximab has been associated with increased risk of death and hospitalization due to worsening heart failure at doses of 10 mg/kg. Infliximab is also contraindicated in patients with known hypersensitivity reactions to infliximab products or murine proteins.

ADVERSE REACTIONS: **Adverse reactions included in the package insert for infliximab-dyyb are those reported in the package insert of infliximab RP (Remicade)

DRUG INTERACTIONS:

Interacting Drug	Effect
Anakinra	**Increased risk of serious infection and neutropenia.**
Abatacept	**Increased risk of serious infection.**
CYP450 Substrates	**Infliximab products may affect the formation of CYP450 enzymes. Closely monitor patients being treated with drug products that are substrates of CYP450 enzymes during the initiation and discontinuation of infliximab-dyyb.**
Live Vaccines	**Do not give live vaccines during treatment with infliximab-dyyb or to infants exposed to infliximab-dyyb in utero for at least 6 months after birth.**
Tocilizumab	**Avoid due to increased risk of immunosuppression and infection.**

DOSING AND ADMINISTRATION

Adult Dosing/Indication	Crohn's Disease, Ulcerative Colitis, Psoriatic Arthritis, Plaque Psoriasis • Induction: 5 mg/kg IV at 0,2,and 6 weeks • Maintenance: 5 mg/kg IV every 8 weeks, can consider 10 mg/kg for those with inadequate response • Patients who do not response by week 14 are unlikely to respond and discontinuation should be considered Rheumatoid Arthritis • Induction: 3 mg/kg IV at weeks 0, 2, and 6 • Maintenance: 3 mg/kg IV every 8 weeks • Should be given in combination with MTX • 10 mg/kg can be considered for patients with inadequate response at intervals of up to every 4 weeks Ankylosing Spondylitis • 5 mg/kg IV at weeks 0, 2, and 6 followed by 5 mg/kg every 6 weeks
Pediatric Dosing/Indication	For pediatric patients aged 6 years and older, the recommended dose is 5 mg/kg IV at weeks 0, 2, and 6 for induction followed by a maintenance regimen of 5 mg/kg every 8 weeks.
Administration	Pre-medication with antihistamines, acetaminophen, and/or corticosteroids should be considered prior to administration of infliximab-dyyb to reduce the incidence of infusion related reactions. In the event of an infusion related reaction, slowing or suspending the infusion and reinitiating at a lower rate my help to improve symptoms. Infliximab-dyyb is reconstituted using 10 mL Sterile Water for Injection. The resulting solution is the diluted in 250 mL 0.9% Sodium Chloride. No other diluents should be used. The final concentration should range between 0.4 mg/mL to 4 mg/mL. The dose should be administered within 3 hours of reconstitution and over a period of at least 2 hours. An infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (≤ 1.2 μm pore size) should be used.

RECOMMENDED MONITORING

All patients should be evaluated for active tuberculosis and tested for latent infection prior to initiation of therapy and periodically during treatment with infliximab-dyyb.
Patients taking infliximab-dyyb should be monitored for signs/symptoms of infection with prompt workups and antimicrobial therapy when necessary.
LFTs should be monitored and therapy discontinued if > 5 times ULN.
Monitor for signs/symptoms of lulus-like syndrome, malignancy, and hypersensitivity.

PRODUCT AVAILABILITY: Infliximab-dyyb is only available as 100 mg infliximab-dyyb in a 20 mL vial for injection for intravenous use.

PHARMACOECONOMICS/COST: Cost data for infliximab-dyyb is currently unavailable although early indications suggest this should be available at approximately a 20-30% cheaper acquisition cost as compared to the Remicade® acquisition cost.

Total Remicade® expenditures for FY16: $2,796,254

Comparative Cost (Remicade®)

Remicade® (cost per vial)	Cost per vial
Remicade (infliximab) 100 mg vial	$1019.22

CONCLUSION

Infliximab-dyyb (CT-P13) is a biosimilar version of Remicade® that is a monoclonal antibody targeted against tumor necrosis factor alpha (TNF_{alpha}). CT-P13 is only the second biosimilar and the first monoclonal antibody to be approved by the FDA under the new abbreviated pathway for biologic products that are demonstrated to be "biosimilar" to an FDA licensed biological reference product (RP). CT-P13 demonstrated biosimilarity through analytical, non-clinical and clinical research to have no clinically meaningful differences in terms of safety and effectiveness from the reference product, Remicade®. Although this product is not designated as an interchangeable biosimilar (conversion from RP to biosimilar without the authorization of the provider) several smaller studies evaluating switching between products do suggest similar efficacy and safety when patients are transitioned from the RP to CT-P13.

CT-P13 was evaluated clinically in two similarly designed phase III randomized, double-blind, multicenter, parallel group studies for the treatment indications of ankylosing spondylitis (PLANETAS) and rheumatoid arthritis (PLANETRA). Both studies demonstrated that CT-P13 and the RP have highly comparable efficacy, pharmacokinetics, safety, and immunogenicity for the specified study timeframes. Additionally, extension studies of both trials also confirmed continued efficacy and safety of therapy with CT-P13 as well as no notable differences in response rates, adverse events, or immunogenicity for the patients switched to the biosimilar product.

No manufacturer sponsored studies were conducted to independently evaluate clinical efficacy for inflammatory bowel disorder (IBD) indications or the other approved indications. These additional diagnoses were approved using extrapolation of the data available for treatment of AS and RA. Despite the lack of data, numerous observational studies have evaluated the safety, efficacy, and immunogenicity of CT-P13 for the treatment of IBD which affirms the clinical efficacy and safety in both infliximab naïve patients and those being switched from the RP to the biosimilar.

Overall, the available data does demonstrate that CT-P13 is an effective therapy and the biosimilar approval of this product does support that it is highly similar from a safety and efficacy standpoint to Remicade® and could reasonably be utilized for any of its labeled indications. The issue of interchangeability and switching between products is somewhat less clear although the limited evidence available at this time does suggest that patients can be safely switched between products.

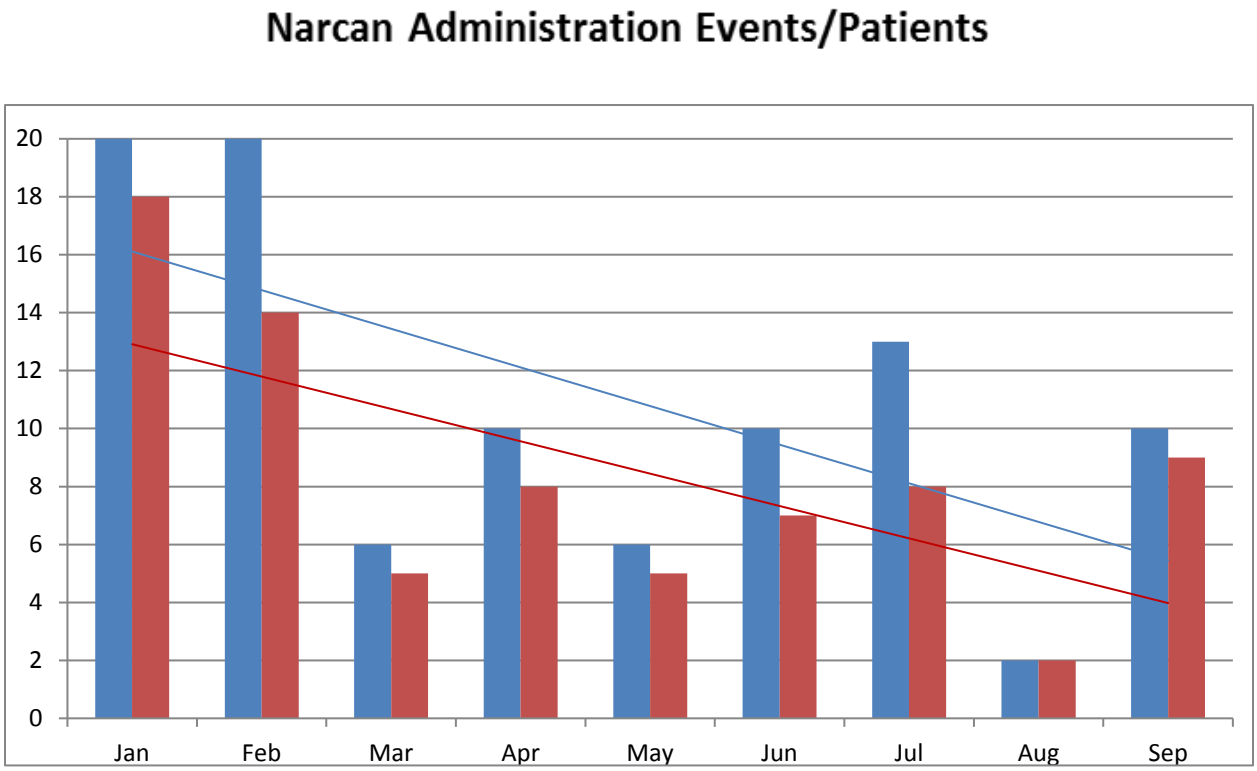
RECOMMENDATION

Formulary, restricted to outpatient use only. The most cost-effective agent will be used for new starts (Remicade naïve patients) once the pricing of the biosimilar has been determined.

For existing patients, local markets are encouraged to discuss this product with their providers and encourage the transition of existing Remicade® patients to Inflectra® when possible.

OPIOID SAFETY – NALOXONE ADMINISTRATION

January – September 2016



Pyxis Report Date	Narcan Admin events	# patients
Jan	20	18
Feb	20	14
Mar	6	5
Apr	10	8
May	6	5
Jun	10	7
Jul	13	8
Aug	2	2
Sep	10	9
Oct		
Nov		
Dec		

CATHOLIC HEALTH INITIATIVES
Memorial Health Care System
2525 deSales Avenue Chattanooga, TN 37404
2051 Hamill Road Hixson, TN 37343

(Order Set: 1829) Revised: (1/20/2016)

WEIGHT:
HEIGHT:

DATE/TIME ORDERED

DILTIAZEM PROTOCOL (CARDIZEM)
For Use with MD order only to Standardize Administration

Indications:
Atrial Fibrillation with sustained (> 30 minutes) HR >120.

Contraindications:
(Clarify with MD prior to starting medication if any of the following are present)

- *EF < 30% and uncompensated heart failure requiring therapy such as inotropes or IV diuretics*
- *History of symptomatic bradycardia*
- *History of 2nd or 3rd degree AV block*
- *Systolic BP < 100 mm Hg*
- *Prior Diltiazem allergy*

1. Continuous EKG monitoring.
2. Vital signs including blood pressure prior to administration, 15 minutes after each bolus and Q 1 hour X 2, then Q 4 hours during the infusion.
3. **Initial dose 0.25 mg/kg (maximum 25 mg) IV bolus over 2 minutes.** Heart rate should slow in 2-7 minutes. If patient is on beta-blocker or amiodarone, reduce dose by 50%.
4. **Immediately follow bolus with Diltiazem drip (concentration = 1mg/ml). Obtain pre-mixed drip from Pyxis. Start at 10 mg/hr (10 ml/hr).**
5. If HR > 120 after 30 minutes of 10 mg/hr drip, **rebolus with 10 mg Diltiazem IV over 2 minutes and increase drip by 5 mg/hr to 15 mg/hr (maximum dose).**
6. If HR remains uncontrolled (> 120) after 1 hour with drip at 15 mg/hr, notify MD for further treatment.
7. **If systolic BP drops below 100 mmHg, stop drug until systolic BP > 100. When systolic BP > 100, restart drip at 1/2 the previous rate unless the patient was symptomatic with the drop in BP. Hypotension has been shown to resolve in 1-3 hours.**
8. **If patient develops symptomatic hypotension (diaphoresis, dizziness, light-headedness, shortness of breath or chest pain) stop the drip. Call the MD and give Calcium Gluconate 1 gm IV piggyback over 30 minutes.**

Note: Because the average effective half-life of IV Diltiazem is 3 1/2 hours, dose reductions (weaning) should not be done more often than every 4 hours and dose increases require repeat bolus.

Physician Signature:_____ Date:_____ Time:_____

Diltiazem protocol - proposed edits

3. Initial dose 0.25 mg/kg (maximum 20 mg) IV bolus over 2 minutes. Heart rate should slow in 2-7 minutes. If patient is on a beta-blocker or amiodarone, reduce dose by 50%.

4. Immediately follow bolus with Diltiazem drip (concentration = 1 mg/1 ml) at 10 mg/hr (10 ml/hr).

5. If HR > 120 after 30 minutes (following initial bolus and drip at 10 mg/hr) give additional loading dose of 0.35 mg/kg (maximum 25 mg) IV bolus over 2 minutes. Following bolus, increase drip by 5 mg/hr to 15 mg/hr (maximum dose).

6. If HR remains uncontrolled (> 120) after 1 hour with drip at 15 mg/hr, notify MD for further treatment.

7. If systolic BP drops below 90 mmHg, stop drug until systolic BP > 90. When systolic BP > 90, restart drip at ½ the previous rate unless the patient was symptomatic with the drop in BP. Hypotension has been shown to resolve in 1-3 hours.

8. If HR < 90 decrease infusion by 5 mg/hr and if HR < 80 decrease infusion rate by an additional 50%.

9. If HR < 60 at any point during infusion stop the infusion and resume at ½ the previous rate when HR > 90. If at any point HR < 50 stop the infusion and notify MD for further instructions.

10. If patient converts to normal sinus rhythm (NSR) stop the infusion. If the patient's rhythm converts out of NSR and HR > 90 resume at previous rate. If the infusion has been stopped for > 2 hours a repeat bolus dose may be necessary – contact physician for orders if HR does not respond to the restarted infusion.

Renal Adjustment/Dose Optimization

Protocol Addition

Clindamycin (IV)		
Standard Dose	600mg IV q8h	No adjustment for renal dysfunction
Necrotizing fasciitis	900mg IV q8h	

CATHOLIC HEALTH INITIATIVES

Memorial Health Care System

POLICY

Title: **INTRAVENOUS TO ORAL THERAPY - PHARMACY**		
	Page 1 of 1	
Policy Number: PHRM-0535	Date Last Reviewed/ Revised: 3/14	Valid Until: 3/17
Department(s) Affected: Pharmacy	Review Period: every 3 years	

OUTCOME:

Transition patients who meet clinical criteria from IV to Oral Therapy.

POLICY:

A pharmacist may use established criteria to evaluate targeted IV antibiotic and antifungal therapies, proton pump inhibitors (PPIs), histamine 2 receptor antagonists (H2 blockers) and other Pharmacy and Therapeutics committee approved medications for potential conversion to oral (PO) therapy.

CRITERIA FOR INCLUSIOIN:

- Taking other oral medications by mouth
- Afebrile for at least 24 hours (T<100.4)
- WBC that is normalizing (<15K), or a known, non-infectious reason can be identified for WBC count (i.e., steroids) – *applies to antibiotics & antifungals only*
- Functioning GI tract (eating full liquids or better)
- Non ICU setting

CRITERIA FOR EXCLUSION:

- Patient has not yet received at least 24 hour duration of IV therapy
- ICU
- NPO
- Active GI bleed – *applies to PPI's and H2 blockers only*
- Febrile neutropenia – *applies to antibiotics & antifungals only*
- Patient with recent nausea or vomiting (antiemetic use within the last 24 hours)
- GI obstruction or non-functioning GI tract
- Inability to swallow

MEDICATIONS PERTAINING TO THIS POLICY:

Antibiotics: azithromycin, ciprofloxacin, clindamycin, doxycycline, fluconazole, levofloxacin, linezolid, metronidazole
Gastrointestinal agents: famotidine, pantoprazole
Miscellaneous agents: levetiracetam, folic acid, multivitamin, thiamine, levothyroxine

---

Key Contact: Patrick Ellis, Pharmacy Review Team
Approved/Reviewed by: Sandy Vredeveld, Director Pharmacy; Lila Heet, Manager Pharmacy
Date First Effective/Revisions: 12/20/88, 5/07, 12/07 **Revised:** 1/10 (1/13) (3/14)
Distribution: MHCS Intranet

CHI Memorial
Imagine better health.℠

POLICY

Title: **ANTICOAGULATION MANAGEMENT**			
Page 1 of 3			
Policy Number: MM-05401		Date Last reviewed/Revised: 12/14	Valid Until: 12/17
Department(s) Affected: All Clinical Areas		Review Period: every 3 years	

OUTCOME: To reduce the likelihood of patient harm associated with the use of anticoagulation therapy.

PURPOSE:
To implement a defined anticoagulant management program to individualize the care provided to each patient receiving anticoagulant therapy.

Proposed edit: automatic adjustment of *ANY* prophylactic dose of LMWH – including 30 mg BID dosing

d. Low Molecular Weight Heparins (enoxaparin): Lovenox (enoxaparin) dosing protocol available for physician use. The hospital approved dosing for renal failure (CrCl < 30 ml/min), dosing in the elderly (age ≥ 70 yrs), and dosing in obese patients (BMI > 50 kg/m2) is as follows:
   i. Renal failure (prophylaxis): Doses of 40 mg daily are automatically reduced by pharmacy to 30 mg daily.
   ii. Renal failure (treatment dose): Pharmacy may automatically adjust patients with CrCL < 30 ml/min to 1 mg/kg once daily. If CrCl < 20 ml/min, pharmacy will order an anti-Xa level to determine if once daily dosing with enoxaparin is appropriate. Abnormal lab results will be communicated directly to physician.
   iii. Obesity (prophylaxis): Recommended dose of 40 mg BID.
   iv. Obesity (treatment): Actual body weight to be used for dosing in patients >150 kg. Anti-Xa levels will be monitored following 3rd dose to ensure adequate dosing for patients > 190 kg.

POLICY

Title: FORMULARY			
		Page 1 of 2	
Policy Number: MM-05428		Date Last reviewed/Revised: 7/14	Valid Until: 7/17
Department(s) Affected: Pharmacy, Clinical Staff		Review Period: every 3 years	

OUTCOME:

The formulary system is operated under the Pharmacy and Therapeutics Committee to promote rational, safe, and cost-effective use of medications at Memorial Health Care System.

DEFINITIONS:

The Formulary system is an ongoing process whereby an organization's pharmacy and medical staff, working through the Pharmacy and Therapeutics Committee, evaluate and select medications that are routinely available for use within the organization. The list of formulary medications is maintained in Meditech and reviewed at least annually, or when new information becomes available. Medications which are acquired from sources other than the hospital, e.g., from patients or from specialty pharmacies will not be allowed to be administered during hospitalization. *Exceptions:* If Pharmacy is unable to supply an ordered drug and the patient/practitioner has a supply of the drug*, or if the medication is received or coordinated thru Memorial's Patient Assistance Program it can be used if Memorial's Pharmacy identifies, labels, and dispenses the drug.

*Medications previously designated as non-formulary by the Pharmacy and Therapeutics Committee will not be allowed to be used during hospitalization unless no other alternatives exist due to allergies or other patient specific scenarios as deemed appropriate by Director of Pharmacy, Pharmacy Clinical Coordinator, or designee.

POLICY:

Adding or Deleting Drugs to/from the Formulary

A medical staff member or pharmacist may request drugs to be added to or deleted from the formulary by completing a "Formulary Addition Request". These forms can be obtained from the Pharmacy. "Formulary Addition Requests" must be received in the department at least three weeks prior to the next Pharmacy and Therapeutics meeting. The committee meets bi-monthly. An expedited approval process may be implemented if necessary.

Non-formulary drug requests are reviewed bi-monthly at P&T. Routine drug class reviews may also occur at the Pharmacy and Therapeutics meeting leading to formulary additions or deletions.

The Pharmacy and Therapeutics Committee will utilize the following criteria in making decisions on formulary issues:

- Need in relation to the diseases and conditions treated at Memorial Health Care System
- Effectiveness
- Drug Interactions
- Toxicity
- Pharmacokinetic properties
- Bioequivalence
- Pharmaceutical equivalence
- Risks

CATHOLIC HEALTH INITIATIVES

Memorial Health Care System

Chattanooga, Tennessee

POLICY

Title: **RENAL DOSING ADJUSTMENTS**		
		Page 1 of 1
Policy Number: PHRM – POL- 0579	Date Last Revised: 9/13	Valid Until: 9/16
Department(s) Affected: Pharmacy	Review Period: every 3 years	

OUTCOME:

To ensure appropriate medication dosing based on patient's renal function and optimize pharmacodynamics and pharmacokinetic properties of renally eliminated medications while decreasing toxicities associated with inappropriate dosing.

POLICY:

Pharmacists may automatically adjust the dose of renally eliminated antimicrobials, anticoagulants, and other medications as approved per the Pharmacy and Therapeutics committee after evaluation of a patient's renal function. In instances where a renal dosage change is warranted, but the medication is not included for automatic dosage adjustment, the pharmacist may contact the prescriber with the recommended dosage change.

PROCEDURE:

1. A pharmacist may evaluate a patient's medication profile for renally eliminated medications. If relevant renal labs have not been ordered within 24 hours of the medication order, the pharmacist may order a basic metabolic profile (BMP) in order to complete this evaluation.

2. During the evaluation, the pharmacist may assess the doses of renally eliminated medications. Based on the patient's calculated creatinine clearance and clinical status, the pharmacist may make necessary adjustments. In instances where a renal dosage adjustment is warranted, but the medication is not approved for automatic adjustment, the pharmacist may contact the prescriber recommending a dosage change.

3. When an automatic dosage adjustment is made, the pharmacist will write the new order as "Per Therapeutics Committee." The pharmacist will also write a brief progress note communicating the patient's relevant clinical history and the therapeutic rationale of the dosage change.

4. The pharmacist will follow up on dosage adjustments as appropriate, evaluating subsequent changes in patient's renal function and clinical status. If relevant renal labs have not been ordered within 48 hours after a dosage adjustment, the pharmacist may order a basic metabolic profile (BMP).

5. If any dosage adjustment made by a pharmacist is subsequently changed by a prescriber, the pharmacist will make not further automatic adjustments on that medication during the current admission, unless otherwise directed.

Workgroup/Committee Chair/Key Contact: Patrick Ellis, Pharm D., Clinical Coordinator
Approved/Reviewed by: Sandy Vredeveld, Director Pharmacy
Reference(s): ASHP Guidelines
Date First Effective/Revisions: 9/13
Distribution: MHCS Intranet

CHI Memorial
Imagine better health.℠

POLICY

Title: **24 HOUR STOP ON ROUTINE PERI-OPERATIVE ANTIBIOTIC PROPHYLAXIS**		
	Page 1 of 1	
Policy Number: MM-05433	Date Last Reviewed/Revised: 9/13	Valid Until: 9/16
Department(s) Affected: All Clinical Areas	Review Period: every 3 years	

OUTCOME:

Ensure adherence to evidence-based practice regarding management of routine, peri-operative antibiotic prophylaxis in patients with uneventful clinical course.

POLICY:

Routine, peri-operative prophylactic antibiotics will be automatically stopped after 24 hours for patients whose clinical course does not suggest infection. *The 24 hour time frame will include the first documented peri-operative dose given by Surgery.*

For exceptions to this policy,

A. The physician must write an order to continue antibiotic therapy.

B. Medical record documentation by the physician must state indication for continuation of antibiotics beyond the automatic 24 hour stop time. Indications might include but are not limited to: abscess, sepsis, surgical site or wound infection, or osteomyelitis.

If it is unclear whether antibiotics are for routine prophylaxis or for treatment of infection, the pharmacist will contact the surgeon for clarification before any changes are made.

Key Contact: Patrick Ellis, Pharmacy Review Team
Approved/Reviewed by: **Sandy Vredeveld, Director of Pharmacy; Diona Brown, Chief Nurse Executive**
Approved by Pharmacy & Therapeutics Committee: 10-11-08, 12-9-10
Approved by Medical Executive Committee: 10-28-08
Approved by Nursing Professional Practice Council: 01/04/2011
Reference(s): SCIP Guidelines
Date First Effective/Revisions: 10/08, (12/10) (9/13)
Distribution: MHCS Intranet