Pharmacy & Therapeutics Committee Meeting
Private Dining Room
August 13, 2015 7:00 a.m.

Agenda Items — Individual Responsible

1. Call to Order — Richard Pesce, MD

2. Approval of April, 2015 Minutes — Richard Pesce, MD

3. Therapeutic Interchanges and Formulary Decisions — Page
   A. Ketamine – IV infusion for pain .....Nathan Schatzman, MD…….5-7
   B. Afrezza® (inhaled insulin).... .....…..Karen Babb, PharmD…….....8-9
   C. Extended Release Morphine Formulary Interchange.....Patrick Ellis, PharmD…..…...10
   D. Entresto® (sacubitril/valsartan) ..... …….11-12
   E. Kengreal® (cangrelor)…..... ….....13-14
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   G. Panhematin® (hemin). .....….…...17
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   I. "GI Cocktail" – Formulary Substitution ….....…….…...19
   J. PCSK9 Inhibitors – *information only*….....…….…...20
   K. Combigan® Formulary Interchange….....…….…...21

4. MUE
   A. Pharmacy Discharge Service ..... Patrick Ellis, PharmD.....22-23

5. Medication Safety/Quality
   A. Estimated GFR Equations (MDRD, CKD-EPI, etc.)..... ..Patrick Ellis, PharmD.....24-26
   B. Prescription Ear Products – FDA decision.....27

6. Policy, Procedure & Protocols
   A. IV Levothyroxine – appropriate use…. ..... Patrick Ellis, PharmD…...28-29
   B. Electrolyte Protocol – phosphate administration…. .....…...

7. Nutrition Support Team
   A. ENFit Connector ..... ....Brian Jones, RD……..…....30
   B. Ensure High Protein .....…...31

8. Adjournment

Next Meeting will be October 8, 2015 at 7:00 AM in the Private Dining Room

**PHARMACY AND THERAPEUTICS COMMITTEE**

DATE: June 25, 2015 CALLED TO ORDER: 7:00 A.M.
LOCATION: Private Dining Room ADJOURNED: 8:00 A.M.

| **Members Present**: | | | **Members Absent**: | | **Guests**: |
|---|---|---|---|---|---|
| Richard Pesce, M.D..<br>David Dodson, M.D.<br>Samuel Currin, M.D.<br>Mark Anderson, MD<br>Allen Atchley, M.D<br>Michael Harper, M.D | Karen Babb, PharmD<br>Patrick Ellis, PharmD<br>Lila Heet, PharmD<br>Rhonda Poulson, RN<br>Vickie Burger, Lab | Sandy Vredeveld, DPh<br>Hannah Walker, RN<br>Brian Jones, RD | Diona Brown, RN<br>William Oellerich, M.D.<br>Shannon Harris, RN<br>Michael Stipanov, M.D.<br>Scott Harbaugh, Finance<br>Michelle Denham, RN<br>Karen Regal, Supply Chain | Rodney Elliott, PhT<br>Nan Payne, RN<br>Kevin Lewis, M.D<br>Melissa Roden, RN | Matthew Russell, PharmD<br>Megan Whittier, PharmD<br>Tatum Daniel, 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 9, 2015 minutes were approved as submitted. | | Complete |
| **Therapeutic Interchanges and Formulary Decisions** | The following medications were reviewed:<br>1. **Custodial HTK (cardioplegia)** – An update was provided regarding the use of Custodial HTK as a cardioplegia solution (approved for trial use in minimally invasive cases October 2014). Per David Middleton use beyond the trial population will not occur and single dose blood cardioplegia will be trialed for all patients. Recommended to continue to allow restricted use per the October 2014 decision.<br>2. **Class Review – Antitussives**: The CHI antitussive class review was reviewed. To comply with CHI's suggested formulary the following modifications to formulary were recommended: removal of Tussionex, triple combination products, Delsym, Hycodan. The updated formulary interchange table was reviewed.<br>3. **Vitamins – class review:** The CHI vitamins class review was reviewed. The CHI class review is largely consistent with our existing formulary. Due to low use the following drugs were recommended for removal from formulary: Vitamin A injection, Vitamin C injection, ergocalciferol drops, calcium carbonate liquid formulation. In addition, Patrick explained that due to a recent price increase of phytonadione tablets he recommended that the hospital stop using the tablet formulation and instead use a liquid formulation compounded by the inpatient pharmacy (1 mg/ml liquid).<br>4. **Respiratory Formulary Interchange –** Patrick reviewed an updated therapeutic interchange list to incorporate newer products that have been released to the market. The formulary drugs of choice remain unchanged and the newer agents will be substituted to a therapeutically equivalent dose of a comparable formulary agent.<br>5. **Corlanor® (ivabradine) –** New heart rate lowering agent indicated for a specific subset of HF patients. Studies have demonstrated a reduction in HF readmissions but no mortality benefit has been shown in clinical trials. Dr. Atchley recommended that based on current data that patients on stable therapy should not have their therapy interrupted but at this point it has no obvious role for new starts in the hospital setting. | 1. Information - current use reserved for trial use as previously approved.<br>2. Formulary interchange approved<br>3. Formulary interchange approved<br>4. Formulary interchange approved<br>5. Not approved for formulary addition | Complete<br>Complete<br>Complete<br>Complete<br>Complete |

| AGENDA ITEM | FINDINGS OR CONCLUSION | ACTION, RESPONSIBILITY | STATUS |
|---|---|---|---|
| | 6. **Opdivo® (nivolumab) – I**mmune modulating monoclonal antibody indicated for the treatment of advanced melanoma and squamous NSCLC. Dr. Stipanov recommended that this be added to formulary for outpatient use due to its unique mechanism of action and the promising data that has demonstrated superior survival rates as compared to standard regimens for numerous oncology diagnoses. | 6. Approved formulary addition | Complete |
| | 7. **Dyloject® (diclofenac injectable) –** Injectable formulation of diclofenac (NSAID). Data was reviewed which has failed to demonstrate any statistically significant difference in regard to pain control or safety as compared to ketorolac. It was recommended to not add this agent to formulary and to interchange a therapeutically equivalent dose of ketorolac when/if ordered. | 7. Not approved for formulary addition | Complete |
| | 8. **Soliris® (eculizumab) –** The draft Soliris inpatient protocol was reviewed. Patrick also reviewed with Drs. Chamberlain and Stipanov and both approved of the content and formatting. The protocol would allow for a single dose to be administered if the appropriate clinical criteria (as outlined in the protocol) are met. Dr. Pesce recommended that the protocol be approved for use. | 8. Protocol approved | Complete |
| | 9. **Berinert® (C1 esterase inhibitor) –** C1 esterase inhibitor indicated for treatment of acute attacks of hereditary angioedema and off label use for severe ACE inhibitor associated angioedema. It was requested by Dr. Schatzman to add this to formulary for patients presenting with severe ACE induced angioedema or hereditary angiodema since no other reliable therapies exist for patients with airway compromise. Patrick recommended that if approved to formulary to only carry 3 vials (1500 units) since this would approximate a 20 unit/kg dose for a non-obese patient. Dr. Pesce also recommended that this be added to formulary and to limit formulary as recommended by Patrick. | 9. Approved for formulary addition | Complete |
| | 10. **Vitamin D analogues – formulary interchange –** Due to low use Patrick recommended that only one of the vitamin D analogues remain on formulary (doxercalciferol, paracalcitol). Due to cost it was recommended to only utilize paracalcitol and therapeutically interchange all orders for doxercalciferol to a therapeutically equivalent dose of the formulary agent. It was also recommended to remove both of the injectable formulations of the vitamin D analogues from formulary due to very low use. Dr. Chamberlain support this approach to these medications. | 10. Formulary interchange approved | Complete |
| | **11. Symbyax – formulary interchange –** Combination olanzapine + fluoxetine product. Due to low use it was recommended to allow a formulary interchange utilizing the individual drug components per the manufacturer recommendations for converting from individual components to the combination product. | 11. Formulary interchange approved | Complete |
| | 12. **Ketamine infusion for pain control –** Patrick explained a request from Dr. Bartlett (anesthesia) to evaluate the possibility of utilizing sub-anesthetic doses of ketamine for a small subset of post-operative patients (opioid tolerant spine patients, etc.). The committee felt that this was a reasonable request and further discussion will occur with a potential protocol to be discussed at the August meeting with input from anesthesia. | 12. Information – added to August agenda for further discussion | Pending |
| **Medication Use Evaluation** | **Narcan®** (naloxone) – An evaluation of all inpatient use of naloxone was reviewed to assess usage trends and opioid safety opportunities. The evaluation examined the precipitating causes necessitating the need for opioid reversal to assess for potential trends and opportunities related to opioid prescribing practices. Patrick explained that the two most common specialties associated with highest naloxone usage were the hospitalists and orthopedic surgery – as expected to the high volume of patients seen by these specialties. Among the hospitalist managed patients IV hydromorphone use was the most commonly implicated medication requiring eventual reversal with naloxone. Despite doses of 0.5-1 mg in | Information – Hospitalist order set to be edited to include hydromorphone | Complete |

| AGENDA ITEM | FINDINGS OR CONCLUSION | ACTION, RESPONSIBILITY | STATUS |
|---|---|---|---|
| | all cases there were still 9 patients receiving hydromorphone who required naloxone for opioid reversal. Patrick suggested adding hydromorphone to the hospitalist admission orders with an option for opioid naïve (0.2-0.4 mg) and non-opioid naïve (0.5-1 mg) dosing. Dr. Dodson agreed that this seemed like a reasonable approach to help improve safety of hydromorphone dosing. Among the orthopedic surgery patients no clear trends were observed with the exception of polypharmacy being the leading cause of over sedation among this population of patients. It was noted that after widespread adoption of intra-operative use of local anesthetic tissue infiltration, the use of naloxone among total joint replacement patients has dropped considerably. Patrick also updated the committee on multi-disciplinary work that is ongoing to add standardized sedation assessments to the existing pain management policies for all patients receiving opioids. | | |
| **Medication Safety/Quality** | • **ADR Review (Jan-April 2015):** Karen reviewed ADR data for this time period. One category 2 ADR was discussed but the committee felt that this patient did not meet criteria for MedWatch reporting. No other trends were observed other than narcotics being a major contributor to inpatient ADRs which was part of the previous naloxone MUE discussion.<br>• **Buprenex®** (buprenorphine): Patrick raised for discussion some safety concerns related to an increased trend in observed ADRs related to buprenorphine. Six ADRs have been reported over the past 6 months in patients receiving buprenorphine. All of these ADRs were in post-operative spine patients and equated to a 20% ADR rate among these patients (reactions included hallucinations, over-sedation, psychosis). Dr. Pesce and the other members of the committee felt that there was not an obvious therapeutic need for buprenorphine and due to the potency of this medication (buprenorphine 0.3 mg = morphine 10 mg) and longer duration of effect as compared to other injectable opioids that this should be removed from formulary due to safety concerns. | Information<br><br>Approved for formulary removal | Complete<br><br>Complete |
| **Policy, Procedure & Protocols** | **Inpatient IV Iron Dosing Protocol:** A new IV iron dosing protocol was presented that offers a new dosing strategy for ferric gluconate complex that would allow this to be used as an alternative to iron dextran for total body iron replenishment. The publication that evaluated this dosing approach was reviewed and the committee recommended the approval of this new protocol and dosing approach. | Protocol approved | Complete |
| **Nutrition Support Team** | • **Food and Drug Policy –** Brian explained that this policy was up for periodic review and no significant changes were made to the content of this policy. Recommended for approval.<br>• **Chyle Diet –** An updated standard chyle diet was presented for use in patients with chyle leaks. Brian explained that physicians can request modifications to this standard diet if they feel changes are clinically appropriate otherwise this diet would serve as the new standard.<br>• **Oral Nutrition Supplements Med Pass Program –** Brian updated the committee on work that is ongoing to improve wound healing and overall nutritional status in patients by incorporating the use of formulary nutritional supplements to be used by all patients when oral medications are administered to patients instead of juice or other products. | | |

There being no further business, the meeting was adjourned at 8:00 A.M. The next P&T meeting is **August 13, 2015 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

DukeMedicine

**Policy Name:** Ketamine Adminstration for Pain (Continuous Intravenous Infusions) -Adults

**Effective Date:** 12/05/14

**Policy Primary:**

**Status**: Published

**Final Approval:**
**Approved by:** **Date**:
**Approved by:** DUH Clinical Practice Council **Date**:

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

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

Indications include: postoperative pain, neuropathic pain and acute or chronic pain

**Level**: Interdependent - asterisked [*] items require an order from a health care practitioner licensed to prescribe medical therapy.

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

**Competencies/Skills**:

**Required Resources**:

**Policy Statement**:
**Purpose:** To provide guidance in the care of patients receiving Ketamine as an infusion for treatment of pain.

## Initial Patient Assessment

1. Assess patient according to the Duke University Process Standard for Pain Management.
2. Assess patient for risk of adverse event. Caution is strongly advised in the administration of Ketamine in patients with any of the following:
    a. Cardiovascular or respiratory compromise
    b. Psychosis, post-traumatic stress disorder (PTSD) or schizophrenia
    c. For any concerns, contact the Acute Pain Service (APS) physician (970-8507).

## Initiating Therapy

1. Review MD Order and prepare for administration.(Ordering Ketamine is restricted to the Anesthesia Acute Pain Service physicians).
    a. Obtain Ketamine infusion from Pharmacy. The standard drip concentration 10 mg per ml (10mg/ml) (2500mg/250ml). Pharmacy will send portless infusion tubing (SAP # 349461) with each bag of ketamine to reduce the risk of diversion.
    b. Ketamione infusion bags will be contained in a plastic lock box for security. ONLY portless infusion tubing will be used for ketamine infusions. If the infusion does not have a plastic lock box, the box may be obtained from Equipment Distribution.
    c. The infusion pumps may be "locked" by activating the "Lock switch" in the back, to prevent accidental change in dose delivery.
    d. Losing the key to the plastic lock box is considered the same as losing a narcotic or PCA key. If a key is lost, the OA must be notified for consideration of a replacement key.
    e. Therapy initiation per acute pain service only. Dosage adjustment per Anesthesia Acute Pain Service physicians only.
    f. *Dosing recommendations may include a one time infusion (over 30 minutes) of 0.25-0.5 mg/kg every 6 hours as needed for pain control. The lower dose is typically selected and increased based upon response.
    g. *For a continuous infusion, a rate of 0.1 – 0.35 mg/kg/hour with 0.25 mg/kg/hour being the typical starting dose. The infusion rate may be titrated up and down based upon clinical response and criteria established by the physician.
    Increases in the infusion rate can be initiated every 8 - 12 hours if clinically indicated and with physician order.
    h. *A benzodiazepine is commonly prescribed with the ketamine to reduce the incidence of hallucinations.

C. **Patient Monitoring during Initial Administration and With Dose Change**

1. Monitor respiratory rate, oxygenation saturation, heart rate, level of pain and sedation (using RASS) by the frequency below for route of therapy.
    a. IV ketamine: Monitor within 60 minutes of initiation of IV therapy and within 60 minutes of any increase in dose.

D. **Routine Patient Monitoring**

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

**Documentation**

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

**Reportable Conditions:**

Notify Medical team and ordering MD if any of the following occur:

1. RASS ≤-2 or ≥ 2.
2. Psychological side effects i.e. hallucinations, vivid dreams, aggressive behavior.
3. Sustained hypertension (>20% increase in blood pressure).
4. Increased pain level or unrelieved pain

**FORMULARY REVIEW**

**GENERIC NAME:** Human Insulin (rDNA origin)

**BRAND NAME:** AFREZZA

**THERAPEUTICS CLASS:** INHALED INSULIN

**SOUND-/LOOK-ALIKE NAMES**: Abraxane, Abreva, Afaxin, Afluia, Afrin, Alexa, Atralin, Afresa

**INDICATIONS:** Glycemic control in patients with Type 1 and Type 2 diabetes mellitus

**CLINICAL PHARMACOLOGY**: Afrezza is a dry powder formulation of recombinant human regular insulin administered via oral inhalation. The metabolism and elimination are comparable to regular human insulin. Afrezza works as an ultrarapid-acting insulin and is given at the beginning of a meal in conjunction with a traditional long-acting basal insulin therapy.

**PHARMACOKINETICS**: Administered as a fine, dry-powdered formulation by oral inhalation. It works about as quickly as injected rapid-acting insulin, but has a shorter duration of less than 3 hours.

| | **Novolog (insulin aspart)** | **Afrezza (inhaled insulin)** |
|---|---|---|
| Onset | 10-20 minutes | 15-30 minutes |
| Peak | 40-50 minutes | 53 minutes (median; standard deviation 74 minutes) |
| Duration | 3-5 hours | 160 minutes (2.6hrs) |

**COMPARATIVE EFFICACY:**

Type 1 DM: Two Phase III clinical trials comparing efficacy and safety of Afrezza (24 and 52 week trials).
In the 24 week, non-inferiority trial, Afrezza was compared to SC rapid-acting analog insulin (aspart) with both groups receiving basal insulin of isophane insulin human, insulin glargine, or insulin determir. The primary efficacy endpoint was the mean change from baseline HbA1c concentration. The secondary efficacy endpoint was the mean change in FPG concentration from baseline to the endpoint. The HbA1c reductions from baseline were 7.9% with a mean change of -0.21% in the Afrezza group (95% CI, -0.33% to -0.09%) vs -0.40% in the aspart insulin group (95% CI, -0.52% to -0.28%). The FPG (Fasting Plasma Glucose) levels were -25.27 mg/dL in the Afrezza group and -10.15 mg/mL in the aspart insulin group.
In the 52-week trial, patients were assigned to Afrezza or insulin (aspart) with both groups receiving insulin glargine. The primary efficacy endpoint was the mean change from baseline HbA1c concentration. The secondary efficacy endpoint was the mean change in FPG concentration from baseline to the endpoint. The HbA1c reductions from mean baseline were comparable in both groups with 8.4%, and a mean change of -0.13% (95% CI, -0.24% to -0.01%) in the Afrezza group vs -0.37% (95% CI, -0.49% to -0.25%) in the aspart insulin group. The FPG levels were -35.5 mg/mL in the Afrezza group and -20.6 mg/mL in the aspart insulin group.

Type 2 DM: Two Phase III clinical trials comparing efficacy and safety of Afrezza (24 and 52 week trials).
In the 24 week, superiority trial, patients were assigned to either 10 units of inhaled insulin or non-insulin containing Technosphere powder (as placebo). The primary efficacy endpoint was a change in HbA1c from baseline to study end, and the secondary endpoints were achieving an HbA1c goal and changes from baseline in FPG and weight. The primary efficacy endpoint showed that Afrezza was superior to placebo with a lower HbA1c and a between-group difference of -0.40% (95% CI, -0.57% to -0.23%). The secondary endpoint the FPG reduction and HbA1c goals greater in the Afrezza group than the placebo group, but there was more weight gain in the Afrezza group than the placebo[3].
In the 52 week, comparative trial, patients were assigned to either Afrezza plus SC basal insulin or premixed biphasic rapid-acting insulin analog with 70% insulin aspart protamine suspension and 30% insulin aspart (BPR 70/30) given twice daily. The primary efficacy endpoint was the change in HbA1c from baseline to study end, and the secondary endpoints were HbA1c goal achievement, FPG change, and weight change. The primary endpoint showed that Afrezza was non-inferior to BPR 70/30 with a mean change from baseline in the Afrezza group of -0.59% and -0.79% in the BPR 70/30 group, resulting in a between-group difference of 0.12% (95% CI, -0.05% to 0.29%). For the secondary endpoints, the 22.1% in the Afrezza group compared to 26.8% in the BPR 70/30 group reached the HbA1c goals. The FPG change was greater in the Afrezza group than the BPR 70/30 group, with -26.7 mg/dL to -12.9 mg/dL, respectively. There was also more weight gain in the BPR 70/30 group than the Afrezza group with 2.5 kg in the BPR 70/30 group (95% CI, 1.9-3.0) and 0.9 kg in the Afrezza group (95% CI, 0.3-1.5).

**CONTRAINDICATIONS, WARNINGS, AND PRECAUTIONS**: ***Black Box Warning***: ASTHMA, COPD, PULMONARY DISEASE (risk of ***acute broncospasm***); Precautions: breast-feeding, children, diabetic ketoacidosis, hypokalemia, infection, lung cancer, pregnancy, renal failure, surgery, thyroid disease, vomiting.

**REMS:** The purpose of the AFREZZA REMS is to inform healthcare providers about the following risks:

- Risk of acute bronchospasm in patients with chronic lung disease
- Contraindicated in patients with chronic lung disease such as asthma or COPD
- Need to evaluate all patients for lung disease before starting AFREZZA

Before initiating AFREZZA, perform

- a detailed medical history
- physical examination, and
- spirometry ($FEV_1$)

**ADVERSE REACTIONS:** Hypoglycemia, cough, sore throat, diabetic ketoacidosis, decreased pulmonary function test, headache, nausea, diarrhea, fatigue

**DRUG INTERACTIONS**: Gatifloxacin (severe), Thiazolidinediones (major), Androgens, ACEIs, ARBs, Beta-Blockers, Corticosteroids, Lithium, Salicylates, Tacrolimus, Thiazide Diuretics

**DOSING**: Type 1 DM: 0.5-0.6 units/kg/day (average dose); Type 2 DM: 0.2-0.6 units/kg/day (average dose)[1]

| SC Prandial (mealtime) Insulin dose | Afrezza dose |
|---|---|
| • < or = 4 units | • 4 units (one 4-unit cartridge) |
| • 5-8 units | • 8 units (one 8-unit cartridge) |
| • 9-12 units | • 12 units (one 12-unit cartridge) |
| • 13-16 units | • 16 units (one 4-unit cartridge and one 12-unit cartridge) |
| • 17-20 units | • 20 units (one 8-unit cartridge and one 12-unit cartridge) |
| • 21-24 units | • 24 units (two 12-unit cartridges) |

Dose Conversion to SC mealtime insulin (Novolog): Convert unit-per-unit to Novolog dose. Ex. 4 units Afrezza mealtime insulin dose = 4 units Novolog mealtime dose

**PRODUCT AVAILABILITY**: 4-unit, 8-unit, and 12-unit Human Recombinant Inhalation Powder[1]
**COST**: $2.91 per 4 unit cartridge

**DRUG SAFTERY/REMS**: Risk of ***acute broncospasm*** in patients with chronic lung disease; Contraindicated in patients with chronic lung disease such as asthma or COPD; ALL patients are required to perform a detailed medical history, physical exam, and spirometry (FEV1) before initiating Afrezza.

**PLACE IN THERAPY:** According to the American Diabetes Association (ADA), most patients with T1DM should be treated with a multiple-dose insulin regimen or continuous subcutaneous insulin therapy. For patients with T2DM, insulin is recommended as add-on to an oral antidiabetic agent when an oral agent alone does not provide adequate glycemic control. Insulin inhalation powder was not specifically discussed in this guidance.

**CONCLUSION:** Afrezza is a safe and effective alternative with a less invasive administration for patients with type 1 and type 2 diabetes that can be used as prandial insulin coverage in conjunction with basal insulin therapy. It is recommended to NOT add this drug to formulary and automatically substitute all orders for inhaled insulin on a unit-per-unit basis to Novolog.

**FORMULARY SUBSTITUTION**

**Extended Release Morphine Equivalents**

Background:
Currently there are 4 timed-release morphine products on the market as noted in the following table. They can be given on an every 8-12 hour basis, with two products having an indication for 24 hour dosing due to release characteristics. The every 24 hour dosed agents can also be given at lesser time intervals.

Pharmcokinetics & how supplied:

| **Product** | Oramorph® (Q8-12 hr dosing) | MS Contin® (Q8-12 hr dosing) | Kadian® (Q12-24 hr dosing) | Avinza® (Q24 hr dosing) |
|---|---|---|---|---|
| **Time to peak (hrs)** | 3.75 | 3.48 | 8 | 30 mins* |
| **How supplied** | 15, 30, 60, 100 | 15, 30, 60, 100, 200 | 10, 20, 30, 40, 50, 60, 70, 80, 100, 130, 150, 200 | 30, 45, 60, 75, 90, 120 |

* capsules consist of an immediate release component that rapidly achieves a morphine concentration and an extended release component that maintains the morphine plasma concentrations throughout the 24 hour dosing interval.

| **Kadian®** | **MS Contin®** | **Kadian®** | **MS Contin®** | **Avinza®** | **MS Contin®** |
|---|---|---|---|---|---|
| Q 24 hr | Q 8-12 hr | Q 12 hr | Q 8-12 hr | Q 24 hr | Q 12 hr |
| 10 mg Q 24 | * | 10 mg Q 12 | 15 mg Q 12 | 30 Q 24 | 15 mg Q12 |
| 20 mg Q 24 | 15 mg Q12 | 20 mg Q 12 | 15 mg Q 12 | 45 Q 24 | 15 mg Q8 |
| 30 mg Q 24 | 15 mg Q12 | 30 mg Q 12 | 30 mg Q 12 | 60 Q 24 | 30 mg Q12 |
| 40 mg Q 24 | 15 mg Q12 | 40 mg Q 12 | 30 mg Q 8 | 75 Q 24 | * |
| 50 mg Q 24 | 15 mg Q8 | 50 mg Q 12 | 30 mg Q 8 | 90 Q 24 | 30 mg Q8 |
| 60 mg Q 24 | 30 mg Q12 | 60 mg Q 12 | 60 mg Q 12 | 120 Q 24 | 60 mg Q12 |
| 70 mg Q 24 | 30 mg Q12 | 70 mg Q 12 | 45 mg Q 8 | | |
| 80 mg Q 24 | 30 mg Q8 | 80 mg Q 12 | 75 mg Q 12 | | |
| 100 mg Q 24 | 30 mg Q8 | 100 mg Q 12 | 100 mg Q 12 | | |
| 130 mg Q 24 | 45 mg Q8 | 130 mg Q 12 | * | | |
| 150 mg Q 24 | * | 150 mg Q 12 | * | | |
| 200 mg Q 24 | 100 mg Q12 | 200 mg Q 12 | * | | |

* A comparable MS Contin® dose (within 10 mg of total 24 hour morphine dose) is not possible. prescriber to be contacted for alternative orders or patient to utilize home supply dispensed by pharmacy.
Oramorph will be substituted on a 1:1 basis and administered at the same dosing interval.

Annual usage – all extended release morphine products:

- Ms Contin® - 4960 doses per year (all strengths)
- Kadian® - 230 doses per year (all strengths)
- Avinza® - 31 doses per year (all strengths)

Recommendation:
MS Contin® is by far the highest utilized timed-release morphine product based on annual usage. Despite low usage of the other available products supplies for each product must currently be maintained in order to supply these medications when ordered despite their low usage. It is proposed to formulary interchange orders for Kadian®, Avinza®, and Oramorph® as outlined in the above table. The above table converts all other products to a comparable dose of MS Contin (dosed every 8 or 12 hours) when possible. In no situation will a substitution result in more than a 10 mg difference in total morphine dose per 24 hours and when this is not possible by utilizing available strengths of MS Contin® (example: Avinza® 75 mg, etc.) the prescriber will be contacted for alternative orders or utilization of the patient's home supply will be arranged. In situations in which the total dose of morphine exceeds 200 mg per 24 hours then no substitution will be performed and the prescriber will be contacted for alternative orders or utilization of the patient's home supply.

**FORMULARY REVIEW**

**GENERIC NAME:** SACUBITRIL/VALSARTAN (LCZ696)

**PROPRIETARY NAME:** ENTRESTO (Novartis)

**INDICATIONS:** Sacubitril/Valsartan is indicated for patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization.

**CLINICAL PHARMACOLOGY:** Management of heart failure with reduced ejection fraction is multimodal with medications from various classes including angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers (ARBs), beta-blockers, mineralocorticosteroid antagonists, and diuretics. Activation of the angiotensin II type 1 receptor contributes to elevated blood pressure through vasoconstriction and aldosterone secretion, which leads to sodium and water retention.

Neprilysin is an enzyme expressed in the kidney that is responsible for the degradation of several endogenous substances, including C-type natriuretic peptide, atrial natriuretic peptide, B-type natriuretic peptide (BNP), endothelin-1, kinin peptides, opioid peptides, substance P, amyloid beta protein, gastrin, and angiotensin I. Natriuretic peptides (type A and B) promote vasodilation and natriuresis, inhibit abnormal growth of the ventricles, suppress the renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system, inhibit the release and action of vasopressin, and augment the parasympathetic nervous system. Accumulation of some of these substances reduces blood pressure and theoretically improves cardiovascular outcomes. Sacubitril is a prodrug that is rapidly metabolized to the active biologically active inhibitor of neprilysin.

The rationale for combination angiotensin receptor and neprilysin blockade is to achieve the dual neurohormonal modulation of RAAS and neprilysin without the increased risk of angioedema. The use of valsartan, an ARB, avoids concomitant inhibition of bradykinin degradation when added to neprilysin inhibitors.

**PHARMACOKINETICS:** Following oral administration, the peak plasma concentrations of sacubitril, its metabolite, and valsartan are reached in 0.5, 2, and 1.5 hours. Oral absolute bioavailability of sacubitril is estimated to be $\geq$ 60%. Valsartan when combined with sacubitril is more bioavailable than valsartan in other marketed tablet formulations (26 mg, 51 mg, and 103 mg when combined with sacubitril = 40 mg, 80 mg, and 160 mg of valsartan in other marketed formulations). Steady state concentrations are reached in 3 days. Food has no clinically significant effect on the exposure of sacubitri/valsartan.

**COMPARATIVE EFFICACY:**
**Drug:** Sacubitril/valsartan vs Enalapril
**Reference:** McMurray JJ, et al, 2014(PARADIGM-HF)
**Study Design:** Randomized, double-blind, active-controlled, multicenter study
**Study Funding:** Novartis
**Patients:** 8,442 patients 18 years and older with heart failure NYHA functional class II to IV; left ventricular ejection fraction (LVEF) 35% or lower; plasma BNP 150 pg/mL or higher or NT-proBNP 600 pg/mL or higher at screening or BNP 100 pg/mL or higher (NT-proBNP 400 pg/mL or higher) and a hospitalization within the previous 12 months for heart failure; previous treatment for at least 4 weeks with stable dose of an ACE inhibitor or ARB equivalent to enalapril 10 mg/day; and treatment with a stable dose of a beta-blocker for at least 4 weeks (unless contraindicated or not tolerated).

**Results:**

- Proportion of patients with the primary composite outcome of death from cardiovascular causes or hospitalization for heart failure at 27 months was 21.8% in the sacubitril/valsartan group and 26.5% in the enalapril group group (hazard ratio [HR], 0.9; 95% confidence interval [CI], 0.73 to 0.87; $P < 0.001$); NNT was 21.3.
- Proportion of patients dying from cardiovascular causes at 27 months was 13.3% in the study group and 16.5% in the enalapril group (HR, 0.8; 95% CI, 0.71 to 0.89; $P < 0.001$); NNT was 31.25.
- Proportion of patients hospitalized for heart failure at 27 months was 12.8% in the study group and 15.6% in the enalapril group (HR, 0.79; 95% CI, 0.71 to 0.89; $P < 0.001$); NNT was 35.7.
- Proportion of patients dying from any cause at 27 months was 17% in the study group and 19.8% in the enalapril group (HR 0.84; 95% CI, 0.76 to 0.93; $P < 0.001$); NNT was 35.7.

**ADVERSE REACTIONS:** The study drug was discontinued in 17.8% of patients receiving sacubitril/valsartan compared with 19.8% of those receiving enalapril. Summary of adverse reactions are detailed below.

| | *Sacubitril/valsartan* | *Enalapril* | *P value* |
|---|---|---|---|
| Hypotension (symptomatic) | 14% | 9.2% | < 0.001 |
| Elevated Scr (≥ 2.5) | 3.3% | 4.5% | < 0.007 |
| Elevated potassium (> 6) | 4.3% | 5.6% | 0.15 |
| Cough | 11.3% | 14.3% | <0.001 |
| Angioedema* | 19 patients | 10 patients | |

**no statistically significant difference and no patient in either group experienced airway compromise*

**DRUG INTERACTIONS:** Sacubitril/valsartan is a weak inhibitor of cytochrome P450 (CYP-450) 2C9. Warfarin, a drug commonly used in patients with heart failure, is a substrate of CYP2C9. A drug-drug interaction study showed no significant increase in the exposure of warfarin or significant increases in partial thromboplastin time and international normalized ratio.

**BLACK BOX WARNING:** Fetal toxicity. When pregnancy is detected, discontinue as soon as possible. Drugs that act directly on the renin angiotensin system can cause injury and death to the developing fetus.

**CONTRAINDICATIONS / PRECAUTIONS:**

- ACE inhibitors: Contraindicated with the concomitant use of ACE inhibitors due to the increased risk of angioedema. Do not administer sacubitril/valsartan within 36 hours of switching to or from an ACE inhibitor. Sacubitril/valsartan is also contraindicated in patients with a history of ACE inhibitor induced angioedema and in those with ARB induced angioedema.
- Aliskerin: contraindicated with the concomitant use of aliskerin in patients with diabetes. Avoid concomitant use of aliskerin in patients with renal impairment (CrCl < 60 ml/min).
- Avoid concomitant use of sacubitril/valsartan and other ARBs as this would result in duplicate ARB therapy.
- Hyperkalemia can occur during treatment and caution should be advised when used concomitantly with other potassium sparing medications.

**DOSING:**
Starting dose: 49/51 mg BID; dose should be doubled after 2-4 weeks to the target maintenance dose of 97/103 mg BID
Patients not currently taking ACE or ARB or taking a low dose of these agents: 24/26 mg BID and the dose should be doubled every 2-4 weeks until the target dose of 97/103 mg BID is achieved.

**COST:**
$5.88 per tablet; $11.76 per day of therapy

**CONCLUSION:** Sacubitril/valsartan is a new drug combination for the treatment of chronic heart failure. It was shown to reduce the rate of hospitalization in patients with heart failure (number needed to treat [NNT] 35.7), reduce mortality from cardiovascular causes (NNT 31.3), and the combination of the two (NNT 21.3). Rates of adverse events are similar to patients treated with enalapril, with potentially increased rates of hypotension; but patients were pretreated with both sacubitril/valsartan and enalapril to eliminate any patient who could not tolerate either drug. The adverse effects of valsartan are well known, but the long-term safety of sacubitril is unknown. Common criticisms of the pivotal PARADIGM-HF trial include the chosen dose of enalapril 10 mg twice daily, although guidelines delineate the dose of enalapril used across trials averaged 16.6 mg/day, and it is similar to the dose used in the SOLVD-Treatment trial. Head-to-head trials show synergistic reduction in blood pressure with sacubitril/valsartan compared with valsartan alone.

The natriuretic peptide augmentation resulting from neprilysin inhibition has demonstrated significant improvements in both morbidity and mortality over enalapril as evidenced by the results of the PARADIGM HF trial. It is recommended to add sacubitril/valsartan to hospital formulary.

**FORMULARY REVIEW**

**GENERIC NAME:** CANGRELOR

**PROPRIETARY NAME:** KENGREAL (The Medicines Company)

**INDICATIONS:** Cangrelor, a $P2Y_{12}$ platelet inhibitor, is indicated as an adjunct to percutaneous coronary intervention (PCI) for reducing the risk of periprocedural myocardial infarction (MI), repeat coronary revascularization, and stent thrombosis (ST) in patients who have not been treated with a $P2Y_{12}$ platelet inhibitor and are not being given a glycoprotein IIb/IIIa inhibitor.

**CLINICAL PHARMACOLOGY:**
Cangrelor is an intravenous, direct $P2Y_{12}$ platelet receptor inhibitor that blocks adenosine diphosphate (ADP) -induced platelet activation and aggregation, reducing the incidence of ischemic events in patients with acute coronary syndrome and patients undergoing PCI.

**PHARMACOKINETICS:** Cangrelor's plasma half-life is approximately 3 to 6 minutes, and has a clinical half-life of less than 5 minutes. Its volume of distribution is 3.68 to 3.9 L. It reaches $C_{max}$ within 2 minutes after administration of an intravenous bolus followed by an infusion. It is metabolized by dephosphorylation to its active metabolite in the circulation, which has negligible anti-platelet activity. Its metabolism is independent of hepatic function, and does not interfere with other drugs that require hepatic enzymes. Cangrelor binds selectively and reversibly to the $P2Y_{12}$ receptor to prevent further signaling and platelet activation. After discontinuation, the anti-platelet effect decreases rapidly and platelet function returns to normal within 1 hour.

**ADVERSE REACTIONS:** The most common adverse reaction in PCI-treated patients was bleeding, and was more frequent than clopidogrel in all categories within both Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Arteries (GUSTO) bleeding and Thrombolysis in Myocardial Infarction (TIMI) bleeding although none of these differences reached statistical significance. Transient dyspnea occurred significantly more frequently with cangrelor than with clopidogrel (1.2% vs. 0.3%).

**COMPARATIVE SAFETY & EFFICACY:** The CHAMPION PHOENIX trial was a randomized, double-blind, active-controlled, double-dummy, multicenter, superiority study of antiplatelet therapy for patients with coronary atherosclerosis who required PCI for stable angina, non-ST-segment elevation acute coronary syndrome (ACS) or ST-segment elevation myocardial infarction (STEMI). In the cangrelor treatment arm (n = 5472), patients were randomized to receive a cangrelor 30 mcg/kg bolus followed by a cangrelor 4 mcg/kg/min infusion for at least 2 hours or for the duration of the procedure with a placebo 300 mg or 600 mg (74.3%). Following infusion, patients received clopidogrel 600 mg. In the clopidogrel treatment arm (n = 5470), patients received placebo bolus and infusion, and clopidogrel 300 mg or 600 mg (74.4%). Following infusion, patients received placebo tablets. All patients received aspirin 75 mg to 325 mg and clopidogrel 75 mg for 48 hours post-procedure, after which an alternative P2Y12 inhibitor could be used at investigator's discretion. Periprocedural anticoagulants, unfractionated heparin, low molecular weight heparin or fondaparinux could be used at the discretion of the investigator, but glycoprotein IIb/IIIa inhibitors were only allowed as rescue therapy during PCI. The primary endpoint was the collective of death from any cause, MI, ischemia-driven revascularization or stent thrombosis within 48 hours of randomization. This occurred in 4.7% of the cangrelor group and 5.9% in the clopidogrel group (CI: 0.66 to 0.93; $p = 0.005$). Secondary endpoint was incidence of stent thrombosis at 48 hours. Results of the secondary endpoint were 0.8% in the cangrelor arm, and 1.4% in the clopidogrel arm (CI 0.43 to 0.9; $p = 0.01$).

The BRIDGE trial was a two-phase trial, the first of which was to find the optimal dose of cangrelor to achieve antiplatelet effect after the cessation of oral P2Y12 antiplatelet therapy. Phase two of the BRIDGE trial was a prospective, randomized, double-blind trial comparing cangrelor IV infusion to placebo to assess the ability of cangrelor to maintain platelet reactivity in patients with an acute coronary syndrome or treated with a coronary stent and receiving a thienopyridine awaiting a planned, non-emergent CABG. The primary efficacy end point was platelet reactivity, assessed daily. Secondary safety endpoints included other bleeding outcomes at time of drug discontinuation and at CABG 30-day postop. A dose of 0.75 μg/kg/min was found to meet the endpoint of 60% platelet inhibition. Median infusion time of cangrelor was 2.8 days vs 3.4 days for placebo. The primary efficacy endpoint of the proportion of patients showing platelet reactivity <240 PRU throughout the infusion was higher in the cangrelor group (98.8 vs 19.0%; $p < 0.001$). Adjustment for expected days to surgery and duration of infusion did not change the effect of cangrelor. After discontinuation of infusion, PRU levels and percentage of patients with continued platelet inhibition were similar (279.7 vs 297.8; p = NS and 26.9 vs 20.0%; p = NS, respectively), yielding the desired result of expected platelet function return at cangrelor discontinuation. Major hemorrhage as defined above was not significantly different between cangrelor and placebo (11.8 vs 10.4%; p = NS).

**CONTRAINDICATIONS:** Cangrelor is contraindicated in those with significant active bleeding or hypersensitivity to cangrelor.

**WARNINGS AND PRECAUTIONS:** As a class effect of $P2Y_{12}$ platelet inhibitors, cangrelor can increase the risk of bleeding.

**DRUG INTERACTIONS:** Cangrelor is not a prodrug and does not require hepatic activation, unlike other oral ADP receptor antagonists; therefore, interactions with drugs that utilize cytochrome P450 metabolism are not expected to inhibit efficacy. There is an increased risk of bleeding with concomitant use of other medications that inhibit platelet adhesion (eg, salicylates, clopidogrel, prasugrel, ticagrelor, ticlopidine, unfractionated and low molecular weight heparins, direct thrombin inhibitors, factor $X_a$ inhibitors, warfarin). Clopidogrel and prasugrel, irreversible platelet inhibitors, should be given after cangrelor discontinuation. The antiplatelet effects of these drugs are blunted when given during cangrelor infusion. Sustained platelet inhibition from clopidogrel did not occur when given with cangrelor, and prasugrel demonstrated limited platelet reactivity when given with cangrelor. These effects were not seen with the reversible platelet inhibitor, ticagrelor (Brilinta).

**DOSING:**

PCI: Bolus dose of 30 mcg/kg over <1 minute; infusion rate 4 mcg/kg/min once bolus is complete for length of PCI or 2 hours, whichever is longer. The bolus should be administered prior to PCI and the maintenance infusion. At the end of cangrelor infusion, an oral P2Y12 platelet inhibitor should be initiated to maintain platelet inhibition. Prasugrel 60 mg or clopidogrel 600 mg may be administered after discontinuation of the cangrelor infusion but should not be administered prior to cangrelor discontinuation. Ticagrelor 180 mg may be administered at any time during or immediately after discontinuation of cangrelor infusion. A maximum weight-based dose has not been established.

Bridge: infusion rate of 0.75 mcg/kg/min * (unlabeled indication)

**CONCLUSION:** Cangrelor is an option for those patients who are unable to take oral P2Y12 inhibitors either due to intubation, nausea/vomiting, or poor absorption due to other causes.

**FORMULARY REVIEW**

**GENERIC NAME:** RAMUCIRUMAB

**PROPRIETARY NAME:** *Cyramza* (Eli Lilly)

**INDICATIONS:**

- For the treatment of gastric or gastro-esophageal junction adenocarcinoma
    - Monotherapy for the treatment of advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after fluoropyrimidine or platinum containing chemotherapy – OR – as combination therapy with paclitaxel.
- For the treatment of patients with metastatic NSCLC in combination with docetaxel, with disease progression on or after platinum based chemotherapy
- For the treatment of metastatic colorectal cancer with disease progression on or after prior therapy with bevacizumab, oxaliplatin, and a fluoropyrimidine, in combination with ironotecan, folinic acid, and 5-FU.

**CLINICAL PHARMACOLOGY:** Ramucirumab is a fully human monoclonal antibody in the immunoglobulin G1 class that is active against vascular endothelial growth factor receptor-2 (VEGFR-2). Ramucirumab blocks binding of all ligands (VEGF-A, VEGF-C, and VEGF-D) to the VEGFR-2; the action of special interest is the blockade of VEGF-A to VEGFR-2, which leads to interruption of activation of endothelial cells that are crucial for tumor growth and survival.

**PHARMACOKINETICS:** Steady state is reached after the fourth infusion when ramucirumab is dosed on a weekly basis, with an accumulation ratio of approximately 1.5 and negligible accumulation beyond that point. The terminal half-life of ramucirumab at steady state ranges from 200 to 300 hours for doses of 8 to 16 mg/kg. There is a large degree of inter-patient variability with regard to pharmacokinetic parameters.

**BLACK BOX WARNINGS:**

- Hemorrhage: Increased risk of hemorrhage and GI hemorrhage, including severe and sometimes fatal hemorrhagic events. Permanently discontinue in patients who experience severe bleeding.
- Gastrointestinal perforation: Increased risk of gastrointestinal perforation. Permanently discontinue in patients who experience a gastrointestinal perforation.
- Impaired wound healing: Impaired wound healing can occur with antibodies inhibiting the VEGF pathway. Discontinue therapy in patients with impaired wound healing and withhold therapy prior to surgery. Discontinue if a patient develops wound healing complications.

**WARNINGS / PRECAUTIONS (in addition to Black Box Warnings):**

- Arterial thromboembolic events including MI, cardiac arrest, CVA, and cerebral ischemia occurred in clinical trials (1.7% in gastric cancer study).
- Hypertension: Increased incidence of severe hypertension as compared to placebo. Blood pressure should be monitored every 2 weeks or more as indicated during treatment.
- Infusion related reactions: rigors/tremors, back pain/spasms, chest pain, chills, flushing, dyspnea, wheezing, hypoxia, and paresthesias. In severe cases, symptoms included bronchospasm, supraventricular tachycardia, and hypotension.
- Reversible posterior Leukoencephalopathy Syndrome - < 0.1%
- Proteinuria including nephrotic syndrome (greater even
- Thyroid dysfunction
- Embyrofetal toxicity

**ADVERSE REACTIONS:** Adverse reactions that occurred at a rate of at least 5% and at least 2% greater than placebo include hypertension (16%), diarrhea (14%), headache (9%), and hyponatremia (6%). Grade 3 or 4 adverse reactions include hypertension (8%), hyponatremia (3%), and diarrhea (1%). The most common severe reactions reported include anemia (3.8%) and intestinal obstruction (2.1%).(1)

**DRUG INTERACTIONS:** Specific drug-drug interaction studies have not been performed.

**DOSING:**

- Gastric cancer: 8 mg/kg every 2 weeks

- NSCLC: 10 mg/kg on day 1 of a 21 day cycle prior to docetaxel infusion.
- Colorectal cancer: 8 mg/kg every 2 weeks, prior to FOLFIRI administration

Infusion related reactions – dose should be reduced by 50% for grade 1 or 2 IRRs and permanently discontinued for grade 3 or 4 IRRs.

Pre-medications: Before each infusion, all patients should be pre-medicated with diphenhydramine and acetaminophen and dexamethasone should be added for patients who have experienced a grade 1 or 2 infusion reaction to ramucirumab.

**COST (based on 75 kg patient):** $1,020 per 100 mg vial
8 mg/kg = 600 mg per dose → $6,120 per dose ($12,240 per month)
10 mg/kg = 750 mg per dose → $8,160 per dose (per cycle)

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

**CONCLUSION:** Ramucirumab is a first in the VEGFR-2 class that is indicated for the treatment of advanced gastric and gastroesophageal cancers; it has also been shown to be effective for the treatment of non–small cell lung cancers. It has a long half-life that allows for biweekly dosing and is efficacious well below the maximum tolerated dose. It has been recommended by Dr. Stipanov to add to formulary for outpatient use when clinically appropriate.

**FORMULARY REVIEW**

**GENERIC NAME:** HEMIN

**PROPRIETARY NAME:** PANHEMATIN (Recordati Rare Diseases)

**INDICATIONS:** For the treatment of recurrent attacks of acute intermittent porphyria related to the menstrual cycle or other patients with acute intermittent porphyria, porphyria variegate, or hereditary coproporphyria.

**CLINICAL PHARMACOLOGY:** Hemin inhibits the enzyme (delta)-aminolevulinic acid synthetase. Heme acts to limit the hepatic and/or marrow synthesis of porphyrin. In normal patients, heme inhibits this enzyme and limits the rate of the porphyrin/heme biosynthetic pathway. Administration of hemin results in effects similar to heme and limits the hepatic and/or marrow synthesis of porphyrin. The exact mechanism by which hemin improves symptoms in patients with acute episodes of the hepatic porphyrias has not been determined. Hemin therapy is intended to prevent an attack from reaching the critical stage of neuronal degeneration; it is not effective in repairing neuronal damage nor is hemin therapy curative. After stopping therapy, symptoms generally return although in some cases remission is prolonged. Some neurological symptoms have improved weeks to months after therapy although little or no response was noted at the time of treatment.

**PHARMACOKINETICS:** Hemin is administered by intravenous infusion. Data on the pharmacokinetics of hemin in humans are limited. After intravenous infusion of hemin in non-jaundiced patients, an increase in fecal urobilinogen can be observed which is roughly proportional to the amount of hemin administered. Therefore, an enterohepatic pathway is considered to be a route of elimination. Bilirubin metabolites are also excreted in the urine. Other aspects of human pharmacokinetics have not been defined.

**ADVERSE REACTIONS:** Iron overload and increased serum ferritin have been observed with post-marketing use of hemin. Monitor iron and serum ferritin in patients receiving multiple injections of hemin. Phlebitis with or without leukocytosis and with or without mild fever has occurred after administration of hemin through small arm veins. Cases of thrombocytopenia and coagulopathy (including prolonged prothrombin time and prolonged partial thromboplastin time) in patients receiving hemin have been included in post-marketing and literature reports

**BLACK BOX WARNINGS:**

- Appropriate use: Should only be used after an appropriate period of alternate therapy (carbohydrate loading) has been tried. Intended to prevent porphyria attacks from becoming critical.
- Experienced physician: Should be administered under the supervision of a physician experienced in the management of porphyrias.

**WARNINGS/PRECAUTIONS:** A large arm vein or a central venous catheter should be utilized for the administration to avoid the possibility of phlebitis. Panhematin is a product of human plasma and may potentially contatin infectious agents which could transmit disease.

**DRUG INTERACTIONS:** There are no known significant interactions.

**DOSING:** Before administering an appropriate period of alternate therapy (i.e., 400 g glucose/day for 1 to 2 days) must be considered. If improvement is unsatisfactory for the treatment of acute attacks of porphyria, an intravenous infusion of Panhematin containing a dose of 1-4 mg/kg/day of hematin should be given over a period of 10-15 minutes for 3-4 days based on the clinical signs. In more severe cases this dose may be repeated no earlier than every 12 hours. No more than 6mg/kg should be given in any 24 hour period.

**COST:** $6,559 per each 313 mg vial; Typical dose (4 mg/kg x 4 days; 75 kg patient) = $26,236 per course of treatment

**CONCLUSION:** Panhematin is overall an infrequently used medication for the treatment of recurrent attacks of acute intermittent porphyria. Acute attacks of porphyria should be treated urgently with Hemin or glucose to avoid prolonged illness and fatal complications. CHI Memorial recently began treating a patient with diagnosed porphyria which has necessitated the need to utilize Panhematin for treatment of this patient's acute porphyria attacks. Therefore, it is recommended to add this drug to formulary and restricted to the Hematology service. Panhematin will not be stocked but will be ordered on an as needed basis when necessary.

**FORMULARY REVIEW**

**GENERIC NAME:** DALBAVANCIN

**PROPRIETARY NAME:** *Dalvance* (Durata Therapeutics)

**INDICATIONS:** Dalbavancin is indicated for the treatment of adult patients with acute bacterial skin and skin structure infections (ABSSSI) caused by susceptible isolates of the following gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, *Streptococcus agalactiae*, and *Streptococcus anginosus* (including *Streptococcus intermedius* and *Streptococcus constellatus*).

**CLINICAL PHARMACOLOGY:** Dalbavancin is an antibacterial drug and works by binding to the D-alanyl-D-alanine terminus of the stem pentapeptide in the bacterial cell wall peptidoglycan, which prevents crosslinking. This interferes with bacterial cell wall synthesis.

**PHARMACOKINETICS:** The pharmacokinetics of dalbavancin can be best described using a 3-compartment model. After a single intravenous (IV) infusion of dalbavancin 1,000 mg, mean plasma concentrations were greater than 35 mg/L for 7 days. Plasma protein binding is approximately 93% and is not affected by drug concentration, renal impairment, or hepatic impairment. The metabolism of dalbavancin is largely unknown. Dalbavancin is not a substrate, inhibitor, or inducer of cytochrome P450 isoenzymes based on in vitro studies using human microsomal enzymes and hepatocytes. In the urine of healthy subjects, the hydroxy-dalbavancin metabolite of dalbavancin has been observed; however, quantifiable concentrations of the hydroxy-dalbavancin metabolite have not been detected in human plasma. Following a single dose of dalbavancin 500 or 1,000 mg, the mean plasma clearance was reduced 47% in patients with severe (less than 30 mL/min) renal impairment compared with healthy patients. Patients with severe renal impairment required a reduced dalbavancin dose.

**ADVERSE REACTIONS:** Common adverse reactions in patients treated with dalbavancin were nausea (5.5%), headache (4.7%), and diarrhea (4.4%). Adverse reactions lasted for a median of 4 days. Proportion of patients in clinical trials that discontinued treatment due to adverse events was 3% for dalbavancin and 2.8% for the comparator treatment.

**DRUG INTERACTIONS:** No clinical drug-drug interaction studies have been conducted with dalbavancin. Coadministration of vancomycin and anesthetic agents has been associated with erythema and histamine-like flushing and anaphylactoid reactions. Concurrent and/or sequential systemic or topical use of other potentially neurotoxic and/or nephrotoxic drugs (eg, amphotericin B, aminoglycosides, bacitracin, polymyxin B, colistin, viomycin, cisplatin), when indicated, requires careful monitoring for toxic effects.

**DOSING:** For treatment of adults with ABSSSI from susceptible gram-positive microorganisms, the recommended 2-dose regimen is dalbavancin 1,000 mg followed 1 week later by dalbavancin 500 mg. After reconstitution and dilution, dalbavancin is to be administered via IV infusion over 30 minutes.

**PRODUCT AVAILABILITY & COST:** Dalbavancin was approved for marketing in the United States on May 23, 2014. Un-reconstituted dalbavancin is supplied in single-use, clear glass vial, as a sterile, lyophilized, preservative-free, white to off-white to pale yellow powder equivalent to anhydrous dalbavancin 500 mg. Vials are supplied as a single unit. Un-reconstituted dalbavancin vials are stored at controlled room temperature at 25°C (77°F); excursions are permitted to 15°C to 30°C (59°F to 86°F).

Cost: $1,418 per 500 mg vial

**WARNINGS & PRECAUTIONS:** Dalbavancin should be administered over 30 minutes to minimize the risk of infusion-related reactions. Rapid IV infusinos can cause reactions that resemble red man syndrome, including flushing of the upper body, urticarial, pruritis, and/or rash.

**CONCLUSION:** Dalbavancin is a semisynthetic lipoglycopeptide antibacterial indicated for ABSSSI caused by certain susceptible bacterial strains. Dalbavancin has a pharmacokinetic profile that allows for once-weekly dosing; therefore, only 2 dalbavancin IV infusions, separated by 1 week, are required for the treatment of cellulitis bacterial infection. Due to the cost and data only available for treatment of cellulitis it is recommended to designate this drug NON-FORMULARY pending new data and/or indications. However, non-formulary use may be considered on a case by case basis for special circumstances for the treatment of off-labeled indications per ID and pharmacy approval.

**FORMULARY REVIEW**

**GI COCKTAIL**

**Background:**
The "GI cocktail" is a generic term for a combination of an antacid (Mylanta), an anticholinergic (Donnatal), and in some recipes a local anesthetic may also be included (viscous lidocaine) which is frequently used in emergency departments for treatment of dyspepsia. Currently at Memorial the GI cocktail consists of 2 Donnatal tablets (atropine, hyoscyamine, phenobarbital) in addition to 30 ml of Mylanta.

Recently the price of Donnatal tablets increased to $8.23 per tablet. Based on historical Donnatal usage this increase in price will represent an annual expense of ~ $17,000 per year. This represents an $11,000 increase in annual Donnatal expense. All Donnatal use is currently for GI cocktail orders.

Donnatal – atropine sulfate 0.0194 mg, hyoscyamine sulfate 0.1037 mg, phenobarbital 16.2 mg, scopolamine 0.0065 mg

**Clinical Efficacy of "GI Cocktail**
The efficacy of "GI Cocktail" was evaluated in a prospective, randomized, double-blind study. The efficacy of an antacid alone, an antacid plus an anticholinergic, and a combination of an antacid, an antispasmodic, and a local anesthetic were assessed in adult patients whose treating physician ordered a GI cocktail. Participants received 30 cc of Mylanta alone, Mylanta with 10 cc of Donnatal, or Mylanta with Donnatal plus 10 cc of 2% viscous lidocaine. Pain was assessed with a 100-mm visual analog scale. Of 120 patients, 113 completed the protocol (38, 37, 38 in the 3 groups, respectively). The groups were similar in age, gender, previous antacid use, and initial pain severity. Thirty minutes after administration of the study medications, pain decreased significantly in each group. However, pain relief did not differ significantly among the groups. The authors note that there are additional costs to purchase and mix a cocktail and that side effects, such as exacerbation of glaucoma or urinary retention, can occur with anticholinergics.

**Recommendation:**
The recent increase in price associated with Donnatal and the lack of superior efficacy as compared to antacid monotherapy brings into question the cost effectiveness of continuing to include this product as part of the hospital's "GI cocktail". This information was also shared with Drs. Champion and Visser and they agreed that the need for Donnatal appears to be unnecessary and they were agreeable to removing Donnatal from the GI cocktail and hospital formulary. All orders for GI cocktail will be substituted to antacid monotherapy. Hyoscamine or viscous lidocaine may be given in addition to an antacid at the physician's discretion for treatment of dyspepsia by separate physician order.

# Proprotein Convertase Subtilisin Kexin Type 9 (PCSK9) Inhibitors

Background:
Genetic studies surrounding mutations with proprotein convertase subilisin/kexin type 9 (PCSK9) revealed relationships between PCSK9, LDL levels, and CVD risk. Patients with gain-of-function PCSK9 mutations are more likely to have hypercholesterolemia, and patients with loss-of-function PCSK9 mutations have a lower CVD risk and low LDL levels. Manufacturers have developed 3 monoclonal antibodies to block the action of PCSK9. These agents have shown them to be effective in reducing LDL cholesterol 40% - 80%.

Mechanism of Action:
Low density lipoprotein (LDL) receptors on the liver remove LDL from the circulating blood. PCSK9 is a regulatory serine protease that binds to LDL receptors to mark them for degradation. PCSK9 inhibitors bind to PCSK9 to prevent degradation of the LDL receptors thereby increasing the amount of LDL removed from the blood.

Indications:
-adults with heterozygous familial hypercholesterolemia
-patients with clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL-C

Concerns:
PCSK9 is expressed in the liver, small intestine, kidney, and the central nervous system. Some research has suggested the possibility of a higher risk of hemorrhagic stroke, cancer, viral infection, and new- onset T2DM due to low LDL levels and interactions with the LDL receptor. The clinical outcome data regarding mortality and the endpoints listed above will be available in 2017/18.

Alirocumab (Praluent) will initially ONLY be available through specialty pharmacy.

| **Agent** | alirocumab (Praluent) | evolocumab (Repatha) | bococizumab |
|---|---|---|---|
| **Manufacturer** | Sanofi and Regeneron | Amgen | Pfizer |
| **Approval Status** | FDA approved (7/24/15) | Under FDA Review | Clinical Trials |
| **Dosage Strength** | 75 -150 mg SC once every 2 weeks | 140 mg SC once every 2 weeks - or- 240 mg SC monthly | 150 mg twice monthly -or- 300 mg once monthly |
| **Adverse Reactions** | itching, pain, swelling, bruising at the injection site, nasopharyngitis, flu, hypersensitivity vasculitis | | |
| **Drug Interactions** | Statin therapy causes a significant increase in plasma PCSK9 concentrations. May or may not be clinically significant. | | |
| **Pricing** | WAC: $1,120 for a 28-day supply | | |
| **Clinical Outcomes** | ODYSSEY- OUTCOMES → January 2018 | SPIRE 1 & 2 → August 2017 | FOURIER → Feb 2018 |

References:

Praluent [package insert]. Bridgewater, NJ: Sanofi Company; 2015. http://products.sanofi.us/praluent/ praluent.pdf.
Werner C, Hoffmann M, Winkler K, Bohm M, Laufs U. Risk prediction with proprotein convertase subtilisin/kexin type 9 (PCSK9) in patients with stable coronary disease on statin treatment. Vascul Pharmacol. 2014 Aug;62(2):94-102.
Norata G, Tibolla G, Catapano A. PCSK9 inhibition for the treatment of hypercholesterolemia: promises and emerging challenges. Vascul Pharmacol. 2014; 62: 103-111.
Marais A, Kim J, Wasserman S, Lambert G. PCSK9 inhibition in LDL cholesterol reduction: genetics and therapeutic implications of very low plasma lipoprotein levels. Pharmacol Ther. 2015 Jan;145:58-66.
Sahebkar A, Simental-Mendía, Guerrero-Romero, Golledge J, Watts G. Effect of statin therapy on plasma PCSK9 concentrations: a systematic review and meta-analysis of clinical trials. *Diabetes Obes Metab*. 2015 Jul 17. doi: 10.1111/dom.12536.

## FORMULARY INTERCHANGE

### COMBIGAN® opthalmic (brimonidine/timolol)

**Background:** Combigan® is a combination eye drop containing brominidine 0.2% and timolol 0.5% used for the reduction of intraocular pressure in patients with open-angle glaucoma or ocular hypertension who require adjunctive or replacement therapy due to inadequate control of intraocular pressure. Recent price increases of Combigan® have resulted in the cost for each patient specific bottle at $116.30. The separate ingredients of each product are commercially available at the same concentration in separate single patient specific bottles at a cost of $4.71 per patient.

**Recommendation:** Designate Combigan® as non-formulary and utilize the separate products (brimonidine 0.2% and timolol 0.5%) as an automatic formulary interchange. Estimated annual savings: $11,577

**Interchange:**
Combigan® 2 drops per day to affected eye(s) → brimonidine 0.2% + timolol 0.5% 2 drops of each to affected eye(s)

**Pharmacist Discharge Medication Reconciliation Review and Discharge Counseling**

*Project Summary and Results*

Background:

In January 2014, a pilot project was conducted to assess the value of utilizing pharmacists to assist with discharge transition of care including discharge medication review and patient education/counseling. Following the three month proof of concept pilot on one medical-surgical floor, a process was developed in which the LACE index scoring tool was used to screen patients for appropriateness to receive pharmacist medication counseling at discharge. The LACE tool was chosen to target high risk patients who were most likely to benefit from pharmacy involvement at the point of hospital discharge. The elements of the LACE tool are length of stay (L), admission status (A), comorbidities (C), and Emergency Department visits in the six months preceding the hospitalization (E) (Table 1) (Van Walraven C, 2010). Scores range from 0 to a maximum of 19, with each score representing a risk of readmission or death in the 30 days following discharge. Data from the proof of concept pilot demonstrated that patients with an average LACE score of at least 13 were more likely to require pharmacist intervention at discharge. A LACE score of 13 corresponds to a 20% risk of death or 30 day hospital readmission.

The service was expanded to include all three medical-surgical floors which represented around one third of the inpatient beds. Pharmacists were available Monday through Friday from 8:00 a.m. until 5:30 p.m. Patients were screened for eligibility to receive medication review and education from a pharmacist at the time of discharge. Eligibility criteria included age greater than 18, discharged to home, mentally and physically capable of receiving counseling, and a LACE score of at least 13. Patients were excluded if they were discharged anywhere other than home, less than 18 years of age, were unable or unwilling to receive counseling, or had a LACE score of less than 13.

Pharmacist responsibilities & process:

The service was expanded to include all three medical-surgical floors which represented around one third of the inpatient beds. Pharmacists were available Monday through Friday from 8:00 a.m. until 5:30 p.m. Patients were screened for eligibility to receive medication review and education from a pharmacist at the time of discharge. Eligibility criteria included age greater than 18, discharged to home, mentally and physically capable of receiving counseling, and a LACE score of at least 13. Patients were excluded if they were discharged anywhere other than home, less than 18 years of age, were unable or unwilling to receive counseling, or had a LACE score of less than 13.

Results:

The average LACE of 14 represents approximately a 25% readmit rate according to the LACE index scoring tool. Our control population had a LACE score average of 14.5 and a readmission rate of approximately 24.5%. This helps validate the use of the LACE score as an applicable screening tool at our institution. As far as the authors are aware, our study is the first to offer pharmacist counseling to patients with any diagnosis and not focused specifically on a targeted population.

During the study period time frame of April 2014 through March 2015, 2,538 patients were discharged from the participating medical-surgical floors who had a LACE score of at least 13. Of these 2,538 patients, 803 patients were excluded and 1,735 patients were included. The patients who were included in the study results were divided into a control group or intervention group with the control group defined as patients who met eligibility criteria but did not receive counseling by a pharmacist at discharge (control n=922 intervention n=813). When the data on readmission or death within 30 days was reviewed, the control group had 224 patients (24.3%) readmitted and 22 patients (2.4%) died while the intervention group had 137 patients (16.8%) readmitted and nine patients (1.2%) died (Figure 1). Of the 813 patients in the intervention group, 229 patients (28.2%) received a pharmacist intervention in addition to medication education and counseling, and approximately 292 potential adverse drug events were documented and avoided.

**Figure 1. Demographic Data with 30-day Readmission and Death Rates**

| Factor | Total | Control | Intervention | p-value |
|---|---|---|---|---|
| Patients (n=) | 1735 | 922 | 813 | |
| Age (years, average) | | 69.4 | 70 | NS |
| Sex (% Male) | | 53 | 50 | NS |
| Race (% White) | | 84.6 | 83.7 | NS |
| LACE Score (average) | | 14.54 | 14.53 | NS |
| Readmission Rate (%) | | 24.3 | 16.8 | 0.0002 |
| Death Rate (%) | | 2.39 | 1.23 | 0.13 |

**Figure 2. Description of pharmacist intervention types**

| Intervention Type | Percentage of total interventions (%) |
|---|---|
| Drug-Drug Interaction | 3.4 |
| Drug Optimization | 18.2 |
| Medication omission | 9.93 |
| Medication reconciliation error | 46.9 |
| Prescription Access | 9.24 |

Discussion:

The results of this evaluation of a new pharmacy service indicates that utilizing pharmacists as part of a multi-disciplinary discharge process has the potential to positively impact patient care. Approximately 30% of patients that received discharge medication review and counseling required pharmacist intervention with the types of interventions described in Figure 2. The targeted patient population (LACE $\geq$ 13) frequently had multiple comorbidities and medications to treat these various conditions which can complicate the accurate reconciliation of discharge medication plans. The review of these medication plans by a pharmacist prior to discharge provided the opportunity to refine and correct any medication discrepancies and communicate these medications plans to the patient or patient's care giver prior to discharge from the facility. Despite the documented benefits of this multidisciplinary approach to patient discharge many opportunities for improvement are needed to better bridge the patient's care from the hospital to their ultimate transition to outpatient care. Improving communication of discharge medication plans and ensuring outpatient follow up to primacy care providers would likely further reduce the readmission risk in this high risk patient population.

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July 16, 2015

Patrick Ellis, Pharm D.
2525 DeSales Avenue
Chattanooga, TN 37404

Dear Patrick,

Enclosed with this letter please find articles which describe the superiority of the Chronic Kidney Disease Epidemiology Collaborative (CKD-EC) equation in comparison to the Cockcroft-Gault and Modified Diet in Renal Disease (MDRD) equations.

Importantly for Memorial Hospital, the article by Parsh, et.al. found that the choice of the equation used to calculate the GFR predicted adverse outcomes after PCI. The CKD-EC equation best discriminated the risk of acute kidney injury, new requirement for dialysis, transfusion and mortality.

The casual relationship of post-PCI bleeding and overall mortality has been well documented. The calculation of the GFR by the other equations resulted in large discrepancies in drug dosing recommendations for antiplatelet and antithrombotic medications used during PCI.

Currently the Kidney Disease: Improving Global Outcomes Guidelines recommend the use of the CKD-CE equation because of its superior accuracy, precision and less bias than the Cockcroft-Gault or MDRD equations.

Considering the incidence of bleeding, incidence of contrast induced nephropathy and cardiovascular mortality at Memorial Hospital, it appears that a change from the Cockcroft-Gault equation (currently used by pathology and pharmacy) could result in a significant reduction in bleeding and cardiovascular mortality.

I have discussed the equations with Drs. Nilesh Patel and Mandeep Grewal. Both nephrologists expressed support for the CKD-EC equation.

Sincerely,

Leonard J. Hays, MD, FACC, FSCAI

## Comparison of Risk Prediction Using the CKD-EPI Equation and the MDRD Study Equation for Estimated Glomerular Filtration Rate

*JAMA.* 2012;307(18):1941-1951.

**Context** The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation more accurately estimates glomerular filtration rate (GFR) than the Modification of Diet in Renal Disease (MDRD) Study equation using the same variables, especially at higher GFR, but definitive evidence of its risk implications in diverse settings is lacking.

**Objective** To evaluate risk implications of estimated GFR using the CKD-EPI equation compared with the MDRD Study equation in populations with a broad range of demographic and clinical characteristics.

**Design, Setting, and Participants** A meta-analysis of data from 1.1 million adults (aged ≥ 18 years) from 25 general population cohorts, 7 high-risk cohorts (of vascular disease), and 13 CKD cohorts. Data transfer and analyses were conducted between March 2011 and March 2012.

**Main Outcome Measures** All-cause mortality (84 482 deaths from 40 cohorts), cardiovascular mortality (22 176 events from 28 cohorts), and end-stage renal disease (ESRD) (7644 events from 21 cohorts) during 9.4 million person-years of follow-up; the median of mean follow-up time across cohorts was 7.4 years (interquartile range, 4.2-10.5 years).

**Results** Estimated GFR was classified into 6 categories (≥90, 60-89, 45-59, 30-44, 15-29, and <15 mL/min/1.73 $m^2$) by both equations. Compared with the MDRD Study equation, 24.4% and 0.6% of participants from general population cohorts were reclassified to a higher and lower estimated GFR category, respectively, by the CKD-EPI equation, and the prevalence of CKD stages 3 to 5 (estimated GFR <60 mL/min/1.73 $m^2$) was reduced from 8.7% to 6.3%. In estimated GFR of 45 to 59 mL/min/1.73 $m^2$ by the MDRD Study equation, 34.7% of participants were reclassified to estimated GFR of 60 to 89 mL/min/1.73 $m^2$ by the CKD-EPI equation and had lower incidence rates (per 1000 person-years) for the outcomes of interest (9.9 vs 34.5 for all-cause mortality, 2.7 vs 13.0 for cardiovascular mortality, and 0.5 vs 0.8 for ESRD) compared with those not reclassified. The corresponding adjusted hazard ratios were 0.80 (95% CI, 0.74-0.86) for all-cause mortality, 0.73 (95% CI, 0.65-0.82) for cardiovascular mortality, and 0.49 (95% CI, 0.27-0.88) for ESRD. Similar findings were observed in other estimated GFR categories by the MDRD Study equation. Net reclassification improvement based on estimated GFR categories was significantly positive for all outcomes (range, 0.06-0.13; all $P <$ .001). Net reclassification improvement was similarly positive in most subgroups defined by age (<65 years and ≥65 years), sex, race/ethnicity (white, Asian, and black), and presence or absence of diabetes and hypertension. The results in the high-risk and CKD cohorts were largely consistent with the general population cohorts.

**Conclusion** The CKD-EPI equation classified fewer individuals as having CKD and more accurately categorized the risk for mortality and ESRD than did the MDRD Study equation across a broad range of populations.

**Choice of Estimated Glomerular Filtration Rate Equation Impacts Drug-Dosing Recommendations and Risk Stratification in Patients with Chronic Kidney Disease Undergoing Percutaneous Coronary Interventions**
*JACC. 2015; 65(25): 2714-2723.*

**Background** Multiple equations exist to estimate glomerular filtration rate (GFR); however, there is no consensus on which is superior for risk classification in patients with chronic kidney disease (CKD) undergoing percutaneous coronary intervention (PCI).
**Objectives** The goals of this study were to identify which equation to estimate GFR is superior for predicting adverse outcomes after PCI and to examine how equation selection would impact drug-dosing recommendations.
**Methods** Estimated GFR (eGFR) was calculated with the Cockcroft-Gault, Modification of Diet in Renal Disease Study (MDRD), and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations for 128,805 patients undergoing PCI in the state of Michigan. Agreement between patient pre-PCI eGFR estimates and resultant CKD stage classifications, their ability to discriminate post-procedural in-hospital clinical outcomes, and the impact of equation choice on dosing recommendations for commonly used antiplatelet and antithrombotic medications were investigated.
**Results** CKD-EPI best discriminated post-PCI mortality by receiver operator characteristic analysis. There was wide variability in eGFR, which persisted after grouping by CKD stages. Reclassification by CKD-EPI resulted in net reclassification index improvement for acute kidney injury and new requirement for dialysis. Equation choice affected drug-dosing recommendations, with the formulas agreeing for only 50.3%, 40.0%, and 34.3% of potentially impacted patients for eGFR cutoffs of <60, <50, and <30 ml/min/1.73 m2, respectively.
**Conclusions** Different eGFR equations result in CKD stage reclassification that has major clinical implications for predicting adverse outcomes after PCI and drug-dosing recommendations. Our results support the use of CKD-EPI for risk stratification among patients undergoing PCI.

**TABLE 1 Equations for Estimating GFR and CrCl**

| Name | Equation | Author, Year (Ref. #) | Developmental Cohort Summary |
|---|---|---|---|
| Cockcroft-Gault | $CrCl = [(140 - age) \times weight^{*}] / 72 \times SCr$ ($\times$ 0.85 if female) | Cockcroft and Gault, 1976 (4) | n = 249, mean age not provided, % male = 100, % black = 0, % diabetic not provided, average weight = 72 kg, mean CrCl not provided |
| MDRD | $eGFR = 175 \times SCr^{-1.154} \times age^{-0.203} \times 0.742$ (if female) $\times$ 1.21 (if black) | Levey et al., 1999 (5) | n = 1,628, mean age = 50.6 ± 12.7 yrs, % male = 60, % black = 12, % diabetic = 6, mean weight = 79.6 ± 16.8 kg, mean GFR = 39.8 |
| CKD-EPI | $eGFR = 141 \times \min(SCr/\kappa,1)^{\alpha} \times \max(SCr/\kappa,1)^{-1.209} \times 0.993^{Age} \times 1.018$ (if female) $\times$ 1.159 (if black)† | Levey et al., 2009 (6) | n = 5,504, mean age = 47 ± 15 yrs, % male = 57, % black = 32, % diabetic = 29, average weight = 82 ± 0 kg, mean GFR = 68 ± 40 |
| BIS1 | $eGFR = 3736 \times SCr^{-0.87} \times age^{-0.95} \times 0.82$ (if female) | Schaeffner et al., 2012 (7) | n = 570, mean age = 78.5 yrs, % male 57.2, % black = 0, mean weight = 77.3 kg, mean GFR = 60.3 |

*CrCl by Cockcroft-Gault was calculated twice, with weight defined as actual body weight and as ideal body weight (based on Devine formula [15]). †$\kappa$ = 0.7 for females and 0.9 for males; $\alpha$ = -0.329 for females and -0.411 for males.
BIS1 = Berlin Initiative Study 1; CKD-EPI = Chronic Kidney Disease Epidemiology Collaboration; CrCl = creatinine clearance (ml/min); eGFR = estimated glomerular filtration rate (in ml/min/1.73 m$^2$); GFR = glomerular filtration rate; max = maximum of SCr/$\kappa$ or 1; min = minimum of Scr/$\kappa$ or 1; MDRD = Modification of Diet in Renal Disease; SCr = serum creatinine (in mg/dl).

FDA News Release

# FDA takes action against unapproved prescription ear drop products

Products lack safety, effectiveness and quality

## For Immediate Release

July 1, 2015

## Release

The U.S. Food and Drug Administration today announced its intention to take enforcement action against companies that manufacture and/or distribute certain unapproved prescription ear drop products (known as otic products) labeled to relieve ear pain, infection, and inflammation.

The unapproved prescription ear drops contain active ingredients such as benzocaine and hydrocortisone, and have not been evaluated by the FDA for safety, effectiveness and quality. The labels on these products do not disclose that they lack FDA approval, and health care professionals may not be aware of their unapproved status.

In a federal register notice published today, the agency informed the companies that they must stop manufacturing these unapproved prescription otic products or be subject to enforcement actions, including seizure, injunction and/or criminal proceedings. Today's action does not affect FDA-approved prescription otic products, or legally marketed otic products sold over-the-counter.

Unapproved prescription otic drug products containing the following ingredients are covered by this action:

- benzocaine;
- benzocaine and antipyrine;
- benzocaine, antipyrine, and zinc acetate;
- benzocaine, chloroxylenol, and hydrocortisone;
- chloroxylenol and pramoxine; and
- chloroxylenol, pramoxine, and hydrocortisone.

"Taking enforcement actions against these unapproved products will protect patients from unnecessary risks," said Cynthia Schnedar, director of the Office of Compliance in the FDA's Center for Drug Evaluation and Research. "There are many FDA-approved prescription products to treat ear infections, so we expect little or no impact on patients from the removal of these unapproved and potentially unsafe products."

Unapproved prescription otic drug products are frequently given to young children suffering from ear infections and other conditions that cause ear pain and swelling. Patients taking unapproved drugs may be at greater risk because there is no proven safety or effectiveness information. These products may be contaminated or manufactured incorrectly, which could result in patients receiving the wrong dose, even when administered according to the labeled directions for use.

Companies making and selling unapproved otic drug products covered by this action that are not currently listed with the FDA must stop manufacturing and shipping the products immediately. Companies that wish to market the drug products covered by this action can submit a new drug application (NDA) or an abbreviated new drug application (ANDA) for the FDA to consider approval of these products.

**IV LEVOTHYROXINE**
**Review of Appropriate Use**

Background:
The use of IV levothyroxine is often utilized for patients admitted to the ICU and/or strict NPO status and unable to tolerate oral administration of levothyroxine maintenance therapy. IV levothyroxine is now only available from a single manufacturer and the price has now increased to $83.73 per vial. Due to the increased cost other strategies may need to be considered such as expansion of current IV to ORAL criteria or limiting use to only patients who are strict NPO and/or unable to tolerate any medications via oral or enteral administration.

Pharmacokinetics:
Oral absorption variable (40-80% as compared to IV formulation)
Half life: 6-7 days (euthyroid patients), 9-10 days (hypothyroid patients), 3-4 days (hyperthyroid patients)

Historical purchases, usage, cost:
Total spend (previous 12 months): $106,861
Total doses: 1542
Patient location: ICU patients – 47%

Enteral administration of levothyroxine:
When combined with continuous enteral nutrition, levothyroxine sodium may bind to enteral feeding tubes, resulting in decreased drug efficacy. Manessis et al. found that the use of percutaneous endoscopic gastrostomy tubes may result in significant levothyroxine adsorption. However, the extent of the adsorption is likely clinically insignificant and may be attributed to drug lost during crushing and transfer. Co-administration with food may decrease absorption and increase fecal elimination. *For use for less than seven days*, no medication administration changes are needed. *For use for seven days or longer*, tube feedings should be held one hour before and after administration of a dose. Thyroid function should be monitored weekly (grade 2B).

Wohlt PD, et al. Recommendations for the use of medications with continuous enteral nutrition. *Am J Health-Syst Pharm. 2009;16:1458-67*

Current IV to ORAL policy: (see next page)

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

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**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

# ENFit Connectors

**Pharmacy and Therapeutics Presentation – 8/15**

**The Problem**

**Healthcare tubing was created to have universal connections. A patient can have as many as 40 connectors leaving room for error.**

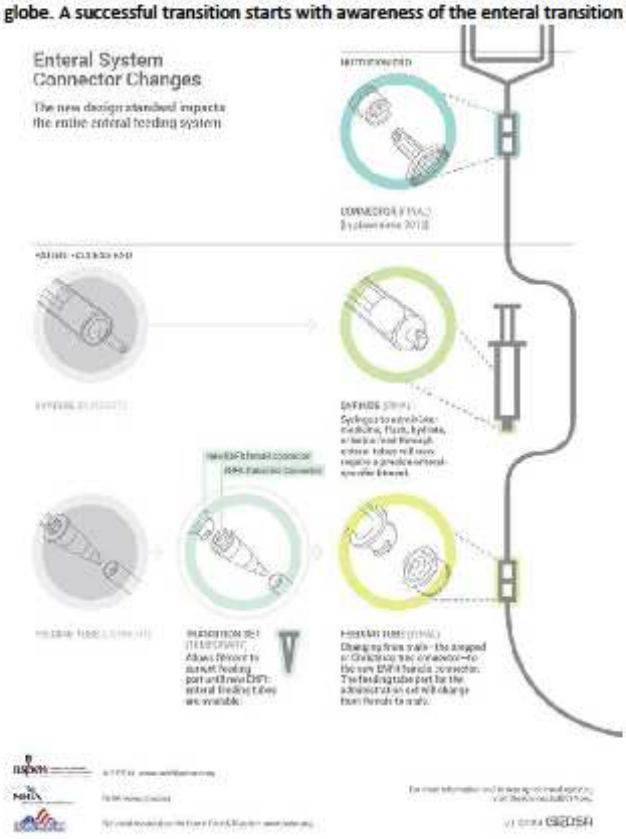
**<u>Causes of Connection-related Injuries:</u>**

- **The luer (universal) connector**
- **Workarounds (rigging)**
- **Providers in "automatic" mode due to stress, fatigue or distractions.**
- **Poor lighting and other environmental factors.**
- **"Spaghetti syndrome" and not tracing tubing connections**
- **Less-than-optimal reporting – fear of repercussions and legal action**

**ISO (international standardization organization) along with the WHO, FDA, ISMP, JC, etc have developed standards for medical device companies to design safe connectors. Enteral Tubing are the first of several upcoming international standards in medical device tubing connection standards.**

**The Solution**

**Reducing the risk of misconnection requires a complete design change with correlating standards established and adopted across the industry and around the globe. A successful transition starts with awareness of the enteral transition plan and devices affected.**




**The final 2 phases include the adaptation to an ENFit syringe and utilization of ENFit feeding tubes (G tubes, DHT etc). We will form an interdisciplinary team including representation from nutrition, nursing, education, pharmacy and supply chain to ensure education is completed and timelines/altered workflows are communicated.**

# Summary Review of Ensure High Protein

*High protein and low fat nutrition supplement*

**Proprietary Name:** Ensure High Protein for Muscle Health
Abbott Laboratories Nutrition
Product of USA

**Indications/Use:**

- Halal
- Kosher
- Gluten free
- Suitable for lactose intolerance
- Low Residue
- Suitable for those patients on controlled carbohydrate diets
- Provides optimal kcal/protein ratio for obese patients
- Will be optimal for use with our upcoming "Med Pass" program
- Low sugar/high protein can be optimal for bariatric surgery patients

**Nutrition Information:**

**ENSURE HIGH PROTEIN FOR MUSCLE HEALTH**

| Technical Data (Vanilla) | |
|---|---|
| Nutrient Density (Cal/mL) | 0.67 |
| Protein (% Cal) | 41 |
| Carbohydrate (% Cal) | 48 |
| Fat (% Cal) | 11 |
| Kosher, Halal | Yes |
| Gluten-free | Yes |
| Suitable for Lactose Intolerance* | Yes |
| Low-Residue | Yes |

| Nutrition Information (Vanilla) | 8 fl oz (237 mL) | % DV |
|---|---|---|
| Calories | 160 | |
| Protein, g | 16 | 32 |
| Total Carbohydrate, g | 19 | 6 |
| Dietary Fiber, g | <1 | <4 |
| Sugars, g | 4 | |
| Total Fat, g | 2 | 3 |
| Saturated Fat, g | 0.5 | 3 |
| *Trans* Fat, g | 0 | |
| Cholesterol, mg | 20 | 7 |
| Vitamin A, IU | 1500 | 30 |
| Vitamin D, IU | 120 | 30 |
| Vitamin E, IU | 27 | 90 |
| Vitamin K, mcg | 24 | 30 |
| Vitamin C, mg | 60 | 100 |
| Folic acid, mcg | 240 | 60 |
| Thiamin, mg | 0.45 | 30 |
| Riboflavin, mg | 0.51 | 30 |
| Vitamin $B_6$, mg | 0.6 | 30 |
| Vitamin $B_{12}$, mcg | 1.8 | 30 |
| Niacin, mg | 6 | 30 |
| Choline, mg | 0 | 0 |
| Biotin, mcg | 90 | 30 |
| Pantothenic Acid, mg | 3 | 30 |
| Sodium, mg | 130 | 5 |
| Potassium, mg | 160 | 5 |

| | 8 fl oz (237 mL) | % DV |
|---|---|---|
| Calcium, mg | 300 | 30 |
| Phosphorus, mg | 250 | 25 |
| Magnesium, mg | 60 | 15 |
| Iodine, mg | 37.5 | 25 |
| Manganese, mg | 0.4 | 20 |
| Copper, mg | 0 | 0 |
| Zinc, mg | 5.3 | 35 |
| Iron, mg | 7.2 | 40 |
| Selenium, mcg | 21 | 30 |
| Chromium, mcg | 48 | 40 |
| Molybdenum, mcg | 38 | 40 |