**Pharmacy & Therapeutics Committee Meeting**

SCN Boardroom

February 9, 2023 7:00 a.m.

| Agenda Items | Individual Responsible |
|---|---|
| 1. Call to Order | Nathan Chamberlain, MD |
| 2. Conflict of Interest Disclosure | Rachel Kile, PharmD |
| 3. Approval of December 2022 Minutes | Nathan Chamberlain, MD |



**Next Meeting Date: March 30, 2023 at 7:00 a.m. in SCN Boardroom**

# PHARMACY AND THERAPEUTICS COMMITTEE

DATE: December 15, 2022 CALLED TO ORDER: 7:08 a.m.
LOCATION: Private Dining Room + Zoom ADJOURNED: 7:55 a.m.

| Voting Member Attendance: | | | | Non-Voting Member Attendance: | | Guests: |
|---|---|---|---|---|---|---|
| X | **Nathan Chamberlain, MD- Chairman** | | Matthew Kodsi, MD- Quality | X | **Karen Babb, PharmD- Manager** | **Joseph Oh, Pharmacy Resident** |
| X | **Mark Anderson, MD- Infectious Disease** | | Aditya Mandawat, MD- Cardiology | | Jamie Barrie, PharmD- Manager, HX | **Jordan Tynes, Pharmacy Resident** |
| X | **Justin Blinn, MD- Anesthesiology** | X | **Daniel Marsh, PharmD- Director of Pharmacy** | | Kenneth Dyer, PharmD- Operations Manager | **Hallie Butler, Pharmacy Resident** |
| X | **David Dodson, MD- Hospitalist** | X | **Chad Paxson, MD- Intensivist** | X | **Rodney Elliott- Purchasing** | |
| X | **Karen Frank, RN- Quality** | | James Wahl, MD- Hospitalist, GA | | Lori Hammon, RN- Quality | |
| | Sherry Fusco, RN- CNO | | Richard Yap, MD- Hospitalist | X | **Shannon Harris, RN- Infection Prevention** | |
| | F. Lee Hamilton, MD- Hospitalist | | | X | **Kevin Hopkins, RT- Director of Resp Therapy** | |
| X | **William Haren, MD- Psychiatry** | | | X | **Rachel Kile, PharmD- Clinical Manager** | |
| | | | | | Carey Smith, RPh- Manager, GA | |

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 September minutes were approved as submitted. | Approved | Complete |
| **CommonSpirit Health System P&T Committee** | **November 2022 Decision Brief:** The medication decisions that were approved at the CommonSpirit Health System P&T committee meeting were reviewed. All new system formulary medications or changes were either consistent with existing CHI Memorial formulary decisions or are described in the "Formulary Decisions & Therapeutic Interchanges" section of the minutes below, or will be reviewed at an upcoming P&T committee meeting. | Approved | Complete |
| **Formulary Decisions & Therapeutic Interchanges** | **A. Sublingual Dexmedetomidine (IGALMI)**: Igalmi is a sublingual dexmedetomidine film approved for the treatment of acute agitation due to schizophrenia and bipolar 1 or 2 disorder. In the SERENITY 1 and 2 trials, Igalmi demonstrated significant improvement in agitation after a single dose when compared to placebo. Adverse events included somnolence, hypotension, and dizziness. Due to a lack of comparative data to current therapies for acute agitation in patients with schizophrenia or bipolar 1 and 2 disorder, the place in therapy of Igalmi is unclear. Furthermore, the level of cooperation required to administer a medication sublingually limits administration to patients able or willing to self administer a medication. Finally, the cost of each Igalmi film for administration is $105. It was recommended that Igalmi be a non-formulary product which would align with the system P&T Committee decision. | Approved | Complete |
| | **B. Hydralazine orders**: Following incidences of patients receiving PRN IV hydralazine for appropriate blood pressure parameters resulting in subsequent elevated heart rate issues, it was proposed to add hold instructions in all as needed injectable hydralazine orders for heart rates exceeding 100 beats per minute. P&T committee voting members wished for this to be a selectable, optional parameter within the order panel. Rachel is investigating how to build this into the EHR and will report back to the committee with options. | Approved | Incomplete |
| | **C. IVIG**: Octapharma, the vendor for the current preferred IVIG product Octagam, will terminate its established contract with CommonSpirit Health at the end of this year. It was recommended to approve Privigen to formulary as the preferred IVIG product. Privigen will be acquired at the same cost per gram as Octagam. | Approved | Complete |

| | | | |
|---|---|---|---|
| | Gamunex-C will remain the alternative IVIG product restricted to patients intolerant or unresponsive to Privigen. Additionally, it was recommended to approve Privigen as the preferred outpatient IVIG product, subsequent to insurance approval or prior authorization requirements.<br>**D. Ophthalmic non-anti-infective agents class review:** Fluorometholone(FML) ophthalmic formulations have very low utilization and are dispensed primarily as a patient home supply. Similarly, Lotemax formulations have low utilization. Due to the unlikely impact on patient care, it was recommended to approve both products as non-formulary and to implement an automatic therapeutic interchange of FML and Lotemax (loteprednol) ophthalmic formulations to dexamethasone 0.1% ophthalmic suspension. Dr. Bowers prefers the use of Lotemax for corneal transplants, therefore this may require non-formulary use of Lotemax for this specific indication. Rachel is currently working with Dr. Bowers to evaluate evidence in the use of Lotemax versus dexamethasone in this patient population.<br>**E. Drug shortages:**<br>a. Iron dextran and sodium ferric gluconate are the preferred IV iron products for inpatient use. Both products are currently experiencing a critical shortage. It was recommended to approve the automatic pharmacist therapeutic interchange to substitute iron sucrose (Venofer) 200 mg IV every other day for new orders for IV iron replacement when sodium ferric gluconate and iron dextran are unavailable.<br>b. Injectable lorazepam supply has recovered. The restrictions placed on lorazepam use were implemented to minimize unnecessary usage and ensure appropriate utilization. It was recommended to maintain current injectable lorazepam restrictions in order to maintain supply and continue appropriate use. Additionally, it was proposed to change current benzodiazepine equivalents to the following: Lorazepam 1 mg = Midazolam 2 mg (previously 1 mg) = Diazepam 5 mg. After much discussion, the committee recommended adding additional restriction parameters to IV lorazepam use which include: Agitation in the ICU and unable to take oral medications, and to clarify that use for alcohol withdrawal is for patients unable to take oral medications. Finally, it was recommended to keep lorazepam infusions as non-formulary.<br>c. Injectable diazepam supply has recovered. It was recommended to remove the restrictions for IV diazepam use.<br>**F. Medications for COVID-19:** Bebtelovimab is no longer authorized for emergency use due to lack of efficacy against select Omicron sub-variants. | Approved<br>Approved<br>Approved<br>Approved<br>Approved | Complete<br>Complete<br>Complete<br>Complete |
| **Miscellaneous** | **A. Report: Pharmacist Clinical Interventions, Serious Significance Level:** Rachel reviewed the "serious" significance level interventions made by pharmacist staff. The committee had no recommendations based on this review.<br>**B. Annual Formulary List Review:** The annual formulary list review was completed for the year. | Approved<br>Approved | Complete<br>Complete |

There being no further business, the meeting was adjourned at 7:55 a.m. The next P&T meeting is **February 9, 2023.**

Respectfully submitted,
Daniel Marsh, Director of Pharmacy; Rachel Kile, PharmD, Pharmacy Clinical Manager

Approved by,
Nathan Chamberlain, MD, Chairman

# CSH SYSTEM PHARMACY AND THERAPEUTICS COMMITTEE DECISION BRIEF

**January 2023 Decisions**

NOTE: Local/divisional P&T committees may implement more restrictive statuses

| Medication Name | Medication Used For | Formulary Decision | | | Restrictions and Therapeutic Interchange | Timeline to Implementation |
|---|---|---|---|---|---|---|
| | | Formulary Unrestricted | Formulary Restricted | NonFormulary | | |
| **immune globulin,gamma(IgG)-ifas human/glycine** | Provision of passive immunity and treatment of chronic inflammatory diseases | | | PANZYGA | | Within 60 days of System P&T Committee approval |
| **immune globulin,gamma(IgG)-hipp human/maltose** | Provision of passive immunity and treatment of chronic inflammatory diseases | | | CUTAQUIG | | Within 60 days of System P&T Committee approval |
| **immune globulin,gamma (IgG)/proline/IgA 0 to 50 mcg/mL** | Provision of passive immunity and treatment of chronic inflammatory diseases | | PRIVIGEN | | Restriction Criteria:<br>1. Outpatient Use Only<br>- FDA approved indication<br>- Payer-approved off-label indications subsequent to insurance approval or prior authorization<br>2. Inpatient use only if clinically indicated or unable to wait until after discharge for IVIG administration.<br>3. To utilize IVIG for the second line treatments, the patient has failed alternative therapies (such as oral glucocorticoids) or the patient's comorbidities preclude the use of alternative therapies. The specific reason for use of IVIG should be charted in the patients' medical | Within 90 days of System P&T Committee approval |

| Medication Name | Medication Used For | Formulary Decision | | | Restrictions and Therapeutic Interchange | Timeline to Implementation |
|---|---|---|---|---|---|---|
| | | Formulary Unrestricted | Formulary Restricted | NonFormulary | | |
| | | | | | record with explanation of the medical necessity.<br><br>4. Procurement Guidance:<br>CHI and Centura facilities: CSL Behring is the preferred plasma vendor (Privigen and AlbuRX). Grifols is the secondary plasma product vendor if CSL Behring is unable to supply.<br><br>Dignity Health facilities: Grifols is the preferred plasma products vendor. CSL Behring is the secondary plasma product provider if Grifols is unable to supply. | |
| **immune globulin,gamm(IgG)/maltose/IgA greater than 50 mcg/mL** | Provision of passive immunity and treatment of chronic inflammatory diseases | | | OCTAGAM | | Within 60 days of System P&T Committee approval |
| **risankizumab-rzaa** | The treatment of: (1) moderate-to-severe plaque psoriasis in adults; (2) active psoriatic arthritis in adults; and, (3) moderately to severely active Crohn's disease in adults | | SKYRIZI IV vials | | Restriction Criteria: Outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization. | Within 90 days of System P&T Committee approval |
| | | | | SKYRIZI ON-BODY, 2 syringe kit and pen | | Within 60 days of System P&T Committee approval |
| **canakinumab/PF** | For treating a variety of immune and fever | | ILARIS | | Restriction Criteria: Outpatient setting for FDA-approved indications or | Within 90 days of System P&T |

| Medication Name | Medication Used For | Formulary Decision | | | Restrictions and Therapeutic Interchange | Timeline to Implementation |
|---|---|---|---|---|---|---|
| | | Formulary Unrestricted | Formulary Restricted | NonFormulary | | |
| | related conditions including CAPS, TRAPS, HIDS, MKD, FMF and SJIA | | | | payer-approved off-label indications subsequent to insurance approval or prior authorization. | Committee approval |
| **ranibizumab** | The treatment of age-related neovascular macular degeneration | | LUCENTIS | | Restriction Criteria: Outpatient setting for FDA-approved indications subsequent to insurance approval or prior authorization. If a biosimilar is not available or payor-approved, the reference product may be used. Biosimilars should be used in preference to reference products whenever possible. | Within 90 days of System P&T Committee approval |
| **brolucizumab-dbll** | The treatment of age-related neovascular macular degeneration | | BEOVU | | Restriction Criteria: Outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization<br>- Patients who are refractory to ranibizumab, aflibercept, or bevacizumab; | Within 90 days of System P&T Committee approval |
| **ranibizumab-eqrn** | The treatment of age-related neovascular macular degeneration | | CIMERLI | | Restriction Criteria: Outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization | Within 90 days of System P&T Committee approval |
| **faricimab-svoa** | The treatment of age-related neovascular macular degeneration | | VABYSMO | | Restriction Criteria: Outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization<br>- Patients who are refractory to ranibizumab, aflibercept, or bevacizumab | Within 90 days of System P&T Committee approval |

| Medication Name | Medication Used For | Formulary Decision | | | Restrictions and Therapeutic Interchange | Timeline to Implementation |
|---|---|---|---|---|---|---|
| | | Formulary Unrestricted | Formulary Restricted | NonFormulary | | |
| **aflibercept** | The treatment of age-related neovascular macular degeneration | | EYLEA | | Restriction Criteria: Outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization | Within 90 days of System P&T Committee approval |
| **ranibizumab-nuna** | The treatment of age-related neovascular macular degeneration | | BYOOVIZ | | Restriction Criteria: Outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization. | Within 90 days of System P&T Committee approval |
| **ophthalmic hyaluronate sodium** | Surgical aids used in cataract extraction and intraocular lens implantation during cataract surgery | PROVISC | | | | Within 90 days of System P&T Committee approval |
| | | All HEALON products | | | | Within 90 days of System P&T Committee approval |
| | | | | AMVISC, AMVISC PLUS | | Within 60 days of System P&T Committee approval |
| **ophthalmic chondroitin sulfate A sodium/hyaluronate sodium** | Surgical aids used in cataract extraction and intraocular lens implantation during cataract surgery | DISCOVISC | | | | Within 90 days of System P&T Committee approval |
| | | VISCOAT | | | | Within 90 days of System P&T Committee approval |
| **ophthalmic hypromellose** | Surgical aids used in cataract extraction and intraocular lens | | | OCUCOAT | | Within 60 days of System P&T Committee |

| Medication Name | Medication Used For | Formulary Decision | | | Restrictions and Therapeutic Interchange | Timeline to Implementation |
|---|---|---|---|---|---|---|
| | | Formulary Unrestricted | Formulary Restricted | NonFormulary | | |
| | implantation during cataract surgery | | | | | approval |
| **ofloxacin 0.3% ear drops** | Ear infections | | | OFLOXACIN | Link to therapeutic substitution | Within 90 days of System P&T Committee approval |
| **neomycin sulfate/polymyxin B sulfate/hydrocortisone ear drops** | Ear infections | NEOMYCIN-POLYMYXIN-HYDROCORT | | | | Within 90 days of System P&T Committee approval |
| **ciprofloxacin HCl/fluocinolone acetonide ear drops** | Ear infections | | | OTOVEL | Link to therapeutic substitution | Within 90 days of System P&T Committee approval |
| **hydrocortisone/acetic acid ear drops** | Treatment of superficial infections of the external auditory canal | | | HYDROCORTISONE -ACETIC ACID | Link to therapeutic substitution | Within 90 days of System P&T Committee approval |
| **neomycin sulf/colistin sul/hydrocortisone ac/thonzonium brom ear drops** | Ear infections | | | CORTISPORIN-TC | Link to therapeutic substitution | Within 90 days of System P&T Committee approval |
| **terlipressin** | Hepatorenal syndrome | | | TERLIVAZ | | Within 60 days of System P&T Committee approval |
| **ulipristal acetate** | Emergency contraception | | | ELLA | | Within 60 days of System P&T Committee approval |
| **cysteine HCl** | Parenteral nutrition | | ELCYS | | Restriction Criteria: Neonatal parenteral nutrition | Within 90 days of System P&T Committee |

| Medication Name | Medication Used For | Formulary Decision | | | Restrictions and Therapeutic Interchange | Timeline to Implementation |
|---|---|---|---|---|---|---|
| | | Formulary Unrestricted | Formulary Restricted | NonFormulary | | |
| | | | | | | approval |
| **futibatnib** | To treat intrahepatic cholangiocarcinoma harboring fibroblast growth factor receptor 2 gene fusions or rearrangements | | | LYTGOBI | | Within 60 days of System P&T Committee approval |
| **emapalumab-lzsg** | Primary hemophagocytic lymphohistiocytosis | | GAMIFANT | | Restriction Criteria: Outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization. | Within 90 days of System P&T Committee approval |
| **vutrisiran sodium** | The treatment of patients with polyneuropathy associated with hereditary transthyretin-mediated amyloidosis | | AMVUTTRA | | Restriction Criteria: Outpatient setting for FDA-approved indications or payer-approved off-label indications subsequent to insurance approval or prior authorization. | Within 90 days of System P&T Committee approval |

**THERAPEUTIC INTERCHANGES**

| Otic drops | |
|---|---|
| Ordered | Provided |
| Cortisporin-TC 3.3 mg-3 mg-10 mg-0.5 mg/mL ear drops, suspension | generic neomycin-polymyxin-hydrocort 3.5 mg/mL-10,000 unit/mL-1% ear solutions at the same dose and frequency as ordered |
| ofloxacin 0.3% ear drops | ofloxacin 0.3% eye drops at the same dose and frequency as ordered |
| Otovel 0.3 %-0.025 % (0.25 mL) ear solution (ciprofloxacin and fluocinolone) to | ciprofloxacin 0.3% + dexamethasone 0.1% ophthalmic drops at same number of drops and frequency via otic route |
| hydrocortisone-acetic acid 1 %-2 % ear drops | Substitute with ophthalmic dexamethasone and acetic acid ear solution |
| Ciprodex 0.3 %-0.1 % ear drops, suspension or | ciprofloxacin 0.3% ophthalmic drops + dexamethasone 0.1% drops at same dose and frequency via otic route |

| | |
|---|---|
| ciprofloxacin 0.3 %-dexamethasone 0.1 % ear drops, suspension | |

**FORMULARY REVIEW**

**GENERIC NAME:** IncobotulinumtoxinA

**PROPRIETARY NAME:** *Xeomin®*

**INDICATIONS:**

| **FDA Approved** |
|---|
| ● Chronic sialorrhea in patients 2 years of age and older<br>● Upper limb spasticity in adult patients<br>● Upper limb spasticity in pediatric patients 2 – 17 years old, excluding caused by cerebral palsy<br>● Cervical dystonia<br>● Blepharospasm |

**THERAPEUTIC CATEGORY:**
Botulinum toxin is derived from a neurotoxin produced by the gram-positive bacillus, Clostridium botulinum. It inhibits the release of acetylcholine at presynaptic nerve terminals within the peripheral nervous system. This will induce local paralysis and selective weakening of muscles. Overall, the class has potent neuromuscular blocking activity, long duration of action, and few side effects.

All botulinum toxins are a serotype that are synthesized as a 150 kDa neurotoxin polypeptide chain with low intrinsic activity. A set of neurotoxins associated proteins (NAPs), which protect the neurotoxin from proteases. Toxin moiety is consistent in the formulations, the difference is in the nontoxic accessory proteins (NAPs) bonded to the 150-kD active neurotoxin that ultimately inhibits acetylcholine release. Xeomin® is the only botulinum toxin which only contains the 150-kD neurotoxin and is free of the NAPs. This is proposed to have a lower rate of antibody production however the overall clinical occurrence and significance is not clear. The class has broad utilization across many FDA approved and non-FDA approved clinical uses.

**PHARMACOKINETICS:** It is not possible to detect botulinum toxin in the peripheral blood following intramuscular injection at recommended doses.

**SPECIAL POPULATIONS:**

| | **Botox®** | **Xeomin®** |
|---|---|---|
| **Pregnancy** | Category C – no adequate and well-controlled studies | No adequate studies. It was reported to be embryotoxic in rats and increased abortion in rabbits at higher doses. |
| **Lactation** | Unknown if excreted into human milk, caution should be exercised | Unknown if excreted into human milk, caution should be exercised |
| **Pediatrics** | Prophylaxis of chronic migraine, axillary hyperhidrosis, spasticity– not recommended below age 18.<br>Cervical dystonia – not recommended below age 16.<br>Blepharospasm and strabismus – not recommended below age 12. | Safety and efficacy not established in patients less than 18 for lower limb spasticity, cervical dystonia, blepharospasm.<br>Chronic sialorrhea – approved for ages 6 and over. |
| **Geriatrics** | Insufficient studies in patients over 65 years old so clinical experience has not been identified. Recommendations are to start at lowest dose. | Insufficient studies in patients over 65 years old so clinical experience has not been identified. Recommendations are to start at lowest dose. |
| **Hepatic Impairment** | No data | No data |
| **Renal Impairment** | No data | No data |

**CLINICAL STUDIES:**

| Indication | | Xeomin<br>incobotulinumtoxinA | Botox<br>onabotulinumtoxinA | Conclusion |
|---|---|---|---|---|
| **GU** | | | | |
| **Overactive bladder (OAB)** | FDA approval: | No | Yes | |
| | Evidence summary: | **Study 1:**<br>**Correction of overactive bladder (OAB) with botulinum toxin type A (BTX-A)[1]**<br>Design: Retrospective, open label<br>90 patients mean age 39-86, 59 women and 31 males<br>Methods: Both groups underwent general anesthesia and underwent injection of 200 units of incobotulinumtoxinA (intravesical in the detrusor and suburothelial)<br>Outcomes summary:<br>• Duration of overactive bladder was 5.72 years and 68.9% had neurological pathology with predominant involvement of lumbar or cervical spine.<br>• Functional volume of the bladder increased by 1.51 times ($p<0.05$) in Group 1 and by 1.42 times ($p<0.05$) in Group 2 one month after BTX-A injection in both groups.<br>• Maximum detrusor pressure when filling the bladder decreased by 95.2% ($p<0.05$) in Group 1 and 90.6% ($p<0.05$) in Group 2.<br>Author's conclusions: Results consistent with other studies. The use of BTX-A in patients with overactive bladder promotes reduction of clinical symptoms and is safe and effective.<br>**Study 2:**<br>**ntravesical injection of highly purified botulinum toxin for the treatment of neurogenic detrusor overactivity (NDO)[3]**<br>Design: Retrospective, case series | **Study 1:**<br>**OnabotulinumtoxinA is a well-tolerated and effective treatment for refractory overactive bladder (OAB) in real-world practice[2]**<br>Design: Large, prospective, observational, non-randomized multinational study, 504 patients<br>Methods: Number of patients 504 aged ≥ 18 years Range (49.4-77.4), with overactive bladder inadequately managed with one or more anticholinergic received onabotulinumtoxinA per their physician's normal clinical practice. To be included patients had to be botulinum toxin naïve, patients with history of use within the past 18 month were excluded.<br>Outcomes Summary:<br>● Reductions in urinary incontinence (UI) episodes/day were observed as early as week 1 (mean ± SD change from baseline, −2.4 ± 3.4, $p < 0.001$ versus baseline.<br>● This improvement from baseline was sustained until the primary time point of week 12 (−3.0 ± 3.9, $p < 0.001$ versus baseline). This translated into reductions in urinary incontinence episodes/day of −46.9 ± 64.8% at week 1 and − 61.3 ± 58.6% at week 12 ($p < 0.001$ versus baseline for both time points).<br>● Treatment Benefit Scale (TBS) data were available for 347 patients. A positive treatment response on the TBS at | ● Evolving evidence for the use of incobotulinumtoxinA for OAB does demonstrate a potential treatment role.<br>● Studies varied in overall analysis in the trials evaluated, hence the ability to compare outcomes between studies that included onabotulinumtoxinA versus incobotulinumtoxinA is not possible.<br>● OnabotulinumtoxinA has more evidence and FDA approval for overactive bladder, however there is supportive evidence independently indicating no clear difference in safety or efficacy for treatment of overactive bladder with incobotulinumtoxinA.<br>● Dosing within the trials when reported was 200 units.<br>● There is no data on switching patients between onabotulinumtoxinA and incobotulinumtoxinA in overactive bladder, but there is data in cervical dystonia for switching. This would have to be extrapolated with provider input for a switch from onabotulinumtoxinA to incobotulinumtoxinA. |

| Indication | | Xeomin incobotulinumtoxinA | Botox onabotulinumtoxinA | Conclusion |
|---|---|---|---|---|
| | | Methods: Patients with NDO confirmed on urodynamics (UDS) were identified and reported urgency incontinence (UI) in those who received intravesical incobotulinumtoxinA injection for neurogenic bladder between November 2013 and May 2017. Parameters studied were daytime frequency, daily incontinence episodes, daily pad use, clean intermittent catheterization (CIC) volumes, symptom scores (UDI6, IIQ7, PGII), and complications.<br>Outcomes Summary: CIC Patients: Daily pads no change, Number of incontinence episodes per day from 2 to 0, hours to CIC increased from 4 to 6, UDI6 decreased, patients requiring pads went from 3 to 0<br>Voiding patients: Daily pads increased from 7.5 to 12, daily frequency decreased from 11 to 4, number of incontinence episodes decreased from 2.5 to 1<br>Author's Conclusions: Quality of life scores improved, patients reported global impression of improvement following treatment, larger scale studies needed | week 12 was seen in 87.6% of these patients.<br>● The mean number of incontinence products (total of pads/liners and diaper pants) used over the prior month decreased from baseline (74.3) to week 12 (32.1, p = 0.001) and remained constant over the remainder of the study out to week 52 (27.2, p = 0.001).<br>Author's Conclusions: UI frequency improved in addition to other urinary symptoms including urgency. The improvement in urinary symptoms was accompanied by an improvement in Quality of Life (QoL) measured by TBS. The data adds to the evidence that onabotulinumtoxinA can improve urinary symptoms and QoL in most patients with OAB symptoms. For cost savings for patients, the reduction in oral medications and incontinence product usage may provide additional benefits. The low rates of urinary retention and urinary tract infection seen in this study suggest that onabotulinumtoxinA treatment may be better tolerated in clinical practice than previously indicated. | |
| | Evidence Summary: | **Comparator Trial Study: IncobotulinumtoxinA versus onabotulinumtoxinA intradetrusor injections in patients with neurogenic detrusor overactivity incontinence (NDOI): a double-blind, randomized, non-inferiority trial[4]**<br>Design: Prospective, national, multicenter, phase III, double-blind, 85 patients enrolled with 58 completing the study (28 received incobotulinumtoxinA and 29 received onabotulinumtoxinA)<br>Methods: Sixty-four patients with spinal cord injury (SCI) or multiple sclerosis were randomized to receive 30 intradetrusor injections of Incobot/A or OnabotA 200 units; 28 patients in incobotulinumtoxinA group and 29 in onabotulinumtoxinA group completed the study. Primary outcome measure was the non-inferior variation from baseline in daily urinary incontinence (UI) episodes (week 12), with a non-inferiority margin of one episode/day. Secondary outcomes measures were changes in Incontinence- Quality of Life questionnaire | | |

| Indication | | Xeomin incobotulinumtoxinA | Botox onabotulinumtoxinA | Conclusion |
|---|---|---|---|---|
| | | (I-QOL), Visual Analog Scale Score (VAS) (bother of symptoms on Quality of Life), urodynamic parameters, occurrence of adverse effects and related costs (week 12).<br>Outcomes Summary:<br>● Mean episodes/day of UI, I-QoL and VAS score differences not different between the groups, urodynamics after 12 weeks similar between the groups.<br>● Mean value of difference of UI episode/day at 12 weeks between groups was -0.2 (95% two-sided CI: -1; 0.7). Using ANCOVA analysis was -0.4 with a higher limit of one-sided 95% CI of 0.2 UI episodes/day which was lower for non-inferiority margin of 1 UI episode difference per day.<br>● Mean total scores of VAS and I-QoL did not show significant differences between groups. Urodynamics detrusor overactivity lower with incobotulinumtoxinA (-9.2; 95% two-sided CI: -16; -2.4; p=0.02), no difference in maximum cytometric capacity (MCC) were similar. Other symptoms of daily pads and average catheterization were not different.<br>Author's Conclusions: IncobotulinumtoxinA is not inferior to onabotulinumtoxinA in patients with NDOI resistant to conventional pharmacologic therapy. | | |
| | | | | |
| **GI** | | | | |
| **Esophageal Applications** | FDA approval: | No | No | |
| | Evidence summary: | **Study 1: Treatment of gastrointestinal (GI) sphincters spasms with botulinum toxin A[5]**<br>Design: Review article<br>Methods: Review of data on the use of botulinum toxin A in treatment of GI related conditions. Data bases were searched for primary literature and the following key words: anus; physiopathology; autonomic nervous system diseases; biliary diseases; botulinum toxin; therapeutic use; chronic constipation; enteric nervous system; esophageal achalasia; esophageal diseases; exocytosis; fissure-in-ano; gastric emptying; gastrointestinal motility; membrane fusion; membrane proteins; neuromuscular agents; obesity; pain; spasm.<br>Outcomes Summary:<br>● Cricopharyngeal Dysphagia: the majority of patients reported improved swallowing function: approximately 75% in combined analysis. Complications were infrequent and included transient vocal fold paresis, temporary worsening of dysphagia, neck cellulitis, and aspiration pneumonia.<br>● Achalasia: In general, 75%–100% of patients show an initial response but more sustained improvement (beyond 6 months) is seen in about two-thirds. For unclear reasons, it appears that patients older than 50 years of age respond at a higher rate (82% vs. 43% in younger patients). Similarly, patients with so-called vigorous achalasia (with the esophagus retaining some contractile ability) respond at a higher rate (100% vs. 52% with classic achalasia).<br>● Anal Fissure: Botulinum toxin (BT) injection is efficacious in the treatment of chronic anal fissures. With greater than 60% response rates noted at two months with | ● The studies evaluated cannot be directly compared as they have different designs and outcomes.<br>● There are no head-to-head evaluations of onabotulinumtoxinA and incobotulinumtoxinA for esophageal applications.<br>● Both onabotulinumtoxinA and incobotulinumtoxinA are not FDA approved for esophageal applications.<br>● Based on cost-effectiveness, available switch studies, and both products not being FDA approved for esophageal applications, incobotulinumtoxinA is a prudent choice when selecting a botulinum toxin for the treatment of esophageal indications.<br>● Per the American College of Gastroenterology (ACG) guidelines, pharmacologic therapy is the least effective option for achalasia and botulinum toxin injection is only recommended as first-line therapy for patients |

| Indication | | Xeomin incobotulinumtoxinA | Botox onabotulinumtoxinA | Conclusion |
|---|---|---|---|---|
| | | further response to re-treatment, BT can be considered a viable treatment option when more conservative treatment fails. In elderly patients, in who rates of fecal incontinence after surgery may be increased, BT can be considered first-line treatment. Surgery is still the most durable treatment option, but the risks of fecal incontinence must be weighed carefully against the benefits of the procedure.<br>Author's Conclusions:<br>● BT use for treatment of spastic gastrointestinal tract (GIT) disorders has gained widespread acceptance over the last 15 years, especially in the treatment of chronic anal fissures and achalasia. Its administration is generally safe and relatively non-invasive compared to many of the alternatives. However, its short-term duration of action in disorders that affect patients long-term is its most significant negative. Repeated administrations with are generally necessary, with noted loss of efficacy.<br>● The use of BT in many GIT disorders, although exciting, has not reached a level supported by clinical evidence. Further trials are needed with corresponding research to elucidate the pathophysiology of the spastic GIT disorders.<br>**Study 2: Pharmacotherapy for the management of achalasia: Status, challenges and future directions[6]**<br>Design: Review Article<br>Methods:<br>● In one study, patients received two injections spaced 1 cm apart in each of four quadrants for a total of eight injections equaling 100 units of botulinum toxin (BT) A. The response rate was 89.65% at 30 d and 55.17% at one year but fell to 13.79% at 2 years.<br>● In another study involving seven patients, 100 units of BT (A) was injected in eight aliquots, with four injections each at the LES and approximately 4 cm above the lower esophageal sphincter (LES), respectively. At follow up, only 28.6% of patients were in remission.<br>Outcomes Summary:<br>BT injection is considered effective in the short term but has a high rate of relapse requiring a need for reinjection. For example, one meta-analysis evaluated nine studies with a total of 315 patients and found that the rate of symptomatic improvement at one month to be 78.7%, but gradually decreased to 70% at 3 months, 53.3% at 6 months and 40.6% at 1 year. Furthermore, at least a second treatment was required in 46.6% of patients. Generally speaking, there is almost universal symptom relapse by two years, although some studies have shown continued efficacy in up to 34% of patients at two years [35]. The efficacy of BT with repeat injections decreases and is thought to be secondary to antibody formation.<br>Authors Conclusion:<br>BT injection into the LES is the most commonly used initial therapy in patients with achalasia. Although lauded for its remarkably safety profile and short time efficacy, issues with need for repeat injection and decreased efficacy over time have relegated it to use in patients unable to undergo more long-lasting procedures such as myotomy and as a form of salvage therapy. However, the large body of ongoing research into BT may provide a stronger role for BT injection as a form | that are unfit for definitive therapies (i. e. pneumatic dilation , laparoscopic Heller myotomy , or Per-Oral Endoscopic Myotomy POEM) as compared with other less-effective pharmacological therapies.[15] |

| Indication | | Xeomin incobotulinumtoxinA | Botox onabotulinumtoxinA | Conclusion |
|---|---|---|---|---|
| | | of minimally invasive, cost effective and efficacious form of therapy for patients with achalasia. Further research in achalasia models is needed to investigate the role of different BT | | |
| **Anal Fissure** | FDA approval: | No | No | |
| | Evidence summary: | **Study 1: The treatment of chronic anal fissures with fissure excision and botulinum toxin type A injection**[7]<br>Design: single-center randomized study<br>Methods: The study included 80 patients randomized by random number generation in 2 groups. Forty patients underwent fissure excision in combination with injections of botulinum toxin type A into the internal sphincter (main group) and 40 – in combination with pneumatic balloon dilatation of the anal sphincter (control group).<br>Outcomes Summary: There were no statistically significant differences in the intensity of pain after defecation and during the day between the groups, p=0.45 and p=0.39, respectively. The groups were comparable in the complications rate such as perianal skin hematomas (p=0.84), external hemorrhoid thrombosis (p=0.1), urinary retention (p=0.46), long-term non-healing wounds (p=0.76). Transitory weakening of the anal sphincter was significantly more often in the control group. On day 30, the transitory anal incontinence in the main group were observed in 6 (21%), in the control group – in 18 (75%) patients (p=0.0002). On day 60, the weakness of the anal sphincter remained in the main group in 3 (10.7%), in the control group – in 10 (41%) patients (p=0.02).<br>Author's Conclusions: botulinum toxin type A and pneumatic balloon dilatation have equal effectiveness in the treatment of chronic anal | **Study 1: Therapeutic properties of botulinum toxin on chronic anal fissure treatment and the patient factors role**[8]<br>Design: case series prospective study<br>Methods: Patients (n=106) who suffer from chronic anal fissure were treated by botulinum toxin injections. All patients were treated by 30 units of botulinum toxin. Physical examinations were conducted every week for 2 months. They were evaluated for bleeding, pain, hematoma, thrombosis, infection, incontinence, and healing of the fissure. At the end of the follow-up period, the fissure healing rate and its relation to age, gender, prior topical therapy, duration of symptoms, and the position of the fissure were assessed.<br>Outcomes Summary: At 8 weeks the study was concluded, the healing rate was 84.9% (90 patients responded to injections). Healing rate was higher in females and in patients who experienced a shorter duration of symptoms before injection. The mean healing time was 4.68 weeks. In addition, patients with one fissure (anterior or posterior) demonstrated higher healing rate and shorter healing time compared to patients with two fissures (anterior and posterior).<br>Author's Conclusions: This study demonstrated that botulinum toxin injection is safe and effective for the treatment of chronic anal fissures, with a low complication rate. In | ● The studies evaluated cannot be directly compared as they have different designs and outcomes.<br>● There are no head-to-head evaluations of onabotulinumtoxinA and incobotulinumtoxinA for anal fissures.<br>● Both onabotulinumtoxinA and incobotulinumtoxinA are not FDA approved for anal fissure<br>● Based on cost-effectiveness, available switch studies, and both products not being FDA approved for anal fissure, incobotulinumtoxinA is a prudent choice when selecting a botulinum toxin for the treatment of anal fissures.<br>● Per ACG guidelines, local application of calcium channel blockers (CCB) is the pharmacological therapy of choice and botulinum toxin A can be considered when CCB fail. Furthermore, evidence suggests surgical treatment (lateral internal sphincterotomy) is the therapy of choice in chronic anal fissures.[15] |

| Indication | | Xeomin incobotulinumtoxinA | Botox onabotulinumtoxinA | Conclusion |
|---|---|---|---|---|
| | | fissure. The use of botulinum toxin type A can reduce the incidence of transitory weakening of the anal sphincter function in patients with chronic anal fissure. | addition, the healing rate was higher in females, patients with shorter duration of symptoms, and those with one fissure. | |

**COMPARATIVE EFFICACY:**

**Overactive bladder**

OnabotulinumtoxinA has FDA approval for this indication, while incobotulinumtoxinA does not have FDA approval. The most recent studies to date for this indication include retrospective case series for the use of incobotulinumtoxinA. There is one comparison trial between onabotulinumtoxinA and incobotulinumtoxinA for overactive bladder, which was prospective, double-blind. It is important to note that these studies had different inclusion and exclusion criteria in addition to different measures in efficacy and outcome. For this reason, it is not possible to compare the studies, each one must be evaluated individually.

For the case series of incobotulinumtoxinA that was reported by Grishin[7] OAB with and without imperative incontinence were included. The study found a statistical difference in functional volume of the bladder in both groups compared to baseline and a reduction in urinations per day. Assessments were made with both patient report and cystometry readings. The authors concluded the result is similar to other studies with onabotulinumtoxinA however the outcome measurements were not the same in the Hamid et al trial[10] which evaluated onabotulinumtoxinA in clinical practice. The Hamid trial was a larger trial and did show statistical reductions in urinary incontinence/day.

The retrospective case series of incobotulinumtoxin for OAB reported by Asafu-Aduei et al[8] was also a small study that looked at reduction in daily pad use, frequency, incontinence episodes, and CIC (chronic intermittent catheterization) volumes. Reductions were noted but it was not possible to determine statistical significance based on outcome measures and small sample size.

The one comparison study was a prospective, double-blind, non-inferiority study of 85 patients comparing incobotulinumtoxinA and onabotulinumtoxinA in patients with neurogenic detrusor overactivity incontinence (NDOI). Patients included had SCI or MS and were refractory to pharmacologic therapy and CIC. The study demonstrated non-inferiority of incobotulinumtoxinA and onabotulinumtoxinA in episodes of urinary incontinence and no significant differences in the Incontinence Quality of Life Score (I-QoL).

*Overall take-aways:*

- Evolving evidence for the use of incobotulinumtoxinA for OAB does demonstrate a potential treatment role.
- Studies varied in overall analysis in the trials evaluated, hence the ability to compare outcomes between studies that included onabotulinumtoxinA versus incobotulinumtoxinA is not possible.
- OnabotulinumtoxinA has more evidence and FDA approval for OAB, however there is supportive evidence independently indicating no clear difference in safety or efficacy for treatment of OAB with incobotulinumtoxinA.
- Dosing within the trials when reported was 200 units.
- *There is no data on switching patients between onabotulinumtoxinA and incobotulinumtoxinA in OAB, but there is data in cervical dystonia for switching.* This would have to be extrapolated with provider input for a switch from onabotulinumtoxinA to incobotulinumtoxinA.

**WARNING AND PRECAUTIONS:** (Consistent in botulinum toxin A class unless otherwise specified)

Spread of toxin effects; swallowing and breathing difficulties can lead to death. Seek immediate medical attention if respiratory, speech or swallowing difficulties occur

- Potential serious adverse reactions after injections for unapproved uses
- Concomitant neuromuscular disorder may exacerbate clinical effects of treatment
- Use with caution in patients with compromised respiratory function
- Corneal exposure and ulceration due to reduced blinking may occur with treatment of blepharospasm
- Retrobulbar hemorrhages and compromised retinal circulation may occur with treatment of strabismus
- Bronchitis and upper respiratory tract infections in patients treated for spasticity
- Urinary tract infections in patients treated for OAB
- Urinary retention: Post-void residual urine volume should be monitored in patients treated for OAB or adult detrusor overactivity associated with a neurologic condition who do not catheterize routinely, particularly patients with multiple sclerosis or diabetes mellitus.

**CONTRAINDICATIONS:** (Consistent for all botulinum toxin A agents unless specified)

- Infection at proposed injection sites
- Known allergy to cow's milk protein (abobotulinumtoxinA only)
- Potential for immunogenicity from therapeutic proteins (abobotulinumtoxinA only)
- Intradetrusor injections: urinary tract infection or urinary retention

**ADVERSE REACTIONS:**

Incidence of adverse reactions is similar between agents and varies with site of injection.

IncobotulinumtoxinA

- Chronic Sialorrhea (≥4% of patients): tooth extraction, dry mouth, diarrhea, and hypertension
- Upper Limb Spasticity in Adults (≥2% of patients): seizure, nasopharyngitis, dry mouth, and upper respiratory tract infection
- Upper Limb Spasticity in Pediatric Patients (≥3% of patients): nasopharyngitis and bronchitis
- Cervical Dystonia (≥5% of patients): dysphagia, neck pain, muscle weakness, injection site pain, and musculoskeletal pain
  Blepharospasm (≥10% of patients): eyelid ptosis, dry eye, visual impairment, and dry mouth

OnabotulinumtoxinA

- OAB: urinary tract infection, dysuria, urinary retention
- Adult Detrusor Overactivity associated with a neurologic condition: urinary tract infection, urinary retention
- Pediatric Detrusor Overactivity associated with a neurologic condition: urinary tract infection, leukocyturia, bacteriuria
- Chronic Migraine: neck pain, headache
- Adult Spasticity: pain in extremity
- Pediatric Spasticity: upper respiratory tract infection
- Cervical Dystonia: dysphagia, upper respiratory infection, neck pain, headache, increased cough, flu syndrome, back pain, rhinitis
- Axillary Hyperhidrosis: injection site pain and hemorrhage, non-axillary sweating, pharyngitis, flu syndrome

**CLINICALLY SIGNIFICANT DRUG INTERACTIONS:**

| Interacting Drug | Effect |
|---|---|
| Aminoglycosides | Neuromuscular transmission inhibition may be potentiated as an additive effect |
| Anticholinergic agents | Botulinum toxin A may potentiate systemic anticholinergic effects (example is blurred vision) |
| Muscle relaxants | Excessive weakness may be exaggerated |

**DOSING AND ADMINISTRATION:**

All three botulinum toxin A agents carry a warning that they are not dose interchangeable. **However, incobotulinumtoxinA (Xeomin) and onabotulinumtoxinA (Botox) have been dosed at an equipotent 1:1.**

**OnabotulinumtoxinA (Botox)**

- Overactive Bladder: Recommended total dose 100 Units, as 0.5 mL (5 Units) injections across 20 sites into the detrusor
- Adult Detrusor Overactivity associated with a Neurologic Condition: Recommended total dose 200 Units, as 1 mL (~6.7 Units) injections across 30 sites into the detrusor
- Chronic Migraine: Recommended total dose 155 Units, as 0.1 mL (5 Units) injections per each site divided across 7 head/neck muscles
- Adult Upper Limb Spasticity: Recommended total dose up to 400 Units divided among affected muscles

**IncobotulinumtoxinA (Xeomin)**

- Chronic Sialorrhea: total dose is 100 Units per treatment session consisting of 30 Units per parotid gland and 20 Units per submandibular gland, no sooner than every 16 weeks
- Upper Limb Spasticity in Adults: the recommended total dose is up to 400 Units, divided among affected muscles
- Upper Limb Spasticity in Pediatric Patients, excluding spasticity caused by cerebral palsy: the recommended total dose is 8 Units/kg (maximum 200 Units) per single upper limb or 16 Units/kg (maximum 400 U) in both upper limbs, divided among affected muscles
- Cervical Dystonia: the recommended initial total dose is 120 Units per treatment session
- Blepharospasm: the recommended initial total dose is 50 Units (25 Units per eye)

**RECOMMENDED MONITORING:**

- No specific laboratory or radiological monitoring required
- Monitoring is specific on indication and is related to improvement in symptoms

**UTILIZATION:**

| Row Labels | Colon and Rectal Surgery | Gastroenterology | General Surgery | Urology | % of usage |
|---|---|---|---|---|---|
| **Achalasia** | | **10** | | | |
| 100 | | 10 | | | |
| **Anal Fissure** | **15** | | | | |
| 100 | 15 | | | | |
| **Esophageal cancer** | | | **5** | | |
| 100 | | | 5 | | |
| **Esophageal stricture** | | | **1** | | |
| 100 | | | 1 | | |
| **Overactive bladder** | | | | **51** | **58%** |
| **100** | | | | 29 | |
| 150 | | | | 1 | |
| **200** | | | | 19 | |
| 300 | | | | 2 | |
| **Urinary incontinence due to detrusor overactivity** | | | | **6** | |
| 100 | | | | 3 | |
| 200 | | | | 2 | |
| 300 | | | | 1 | |
| **Grand Total** | **15** | **10** | **6** | **57** | |
| **% of usage** | 17% | 11% | 7% | **65%** | |

**PHARMACOECONOMICS/COST:**

| Product | 50 Units | 100 Units | 200 Units | 300 Units | 500 Units | Single Dose Vial | Lyophilized Powder |
|---|---|---|---|---|---|---|---|
| IncobotulinumtoxinA | X | X | X | | | X | X |
| OnabotulinumtoxinA | | X | X | | | X | X |

| | J Code | Cost per unit (Feb 2023) | Utilization (2022) | Cost | Cost Savings per dose | Annual cost savings |
|---|---|---|---|---|---|---|
| Botox® onabotulinumtoxinA | J0585 | $6.34/unit | 110 administered doses | $69,740 | $158 per 100 units | (Estimated 50% conversion of Botox doses to Xeomin) **$8,681.20** |
| Xeomin® incobotulinumtoxinA | J0588 | $4.76/unit | n/a | Estimated cost of 50% conversion = $26,189 | | |

**CONCLUSION & RECOMMENDATION:**
IncobotulinumtoxinA (Xeomin®) is the prudent product of choice when indicated for blepharospasm, cervical dystonia, esophageal applications, and anal fissure. While the FDA has not approved botulinum toxin A for esophageal applications and anal fissure, restrictions should be in place to utilize incobotulinumtoxinA (Xeomin®) as the primary cost-effective option when prescribers require botulinum therapy and it is payer authorized for these indications.

OnabotulinumtoxinA has more evidence and FDA approval for overactive bladder, however there is supportive evidence independently indicating no clear difference in safety or efficacy for treatment of overactive bladder with incobotulinumtoxinA. There is no data on switching patients between onabotulinumtoxinA and incobotulinumtoxinA in overactive bladder.

IncobotulinumtoxinA as compared to onabotulinumtoxinA on a cost per unit basis favors incobotulinumtoxinA as the more cost-effective option, however it has a lower reimbursement rate per unit. Overall literature supports clinical equivalency between the agents. In addition, operational efficiency and storage benefits lie with incobotulinumtoxinA which does not require refrigeration.

**It is recommended to designate incobotulinumtoxinA (Xeomin) as the preferred botulinum toxin A agent when it can be successfully utilized for FDA approved or payer approved off-label indications. BotulinumtoxinA (Botox) will remain on formulary for situations when the preferred agent cannot be utilized due to payer restrictions, etc.**

**FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)**

| Medication Management Step | Identified Risk | Steps for Prevention |
|---|---|---|
| **Selection & Procurement** | | |
| Therapeutic interchange? | N/A | Limit formulary agents |
| Special Ordering Requirements? | Generic and Brand | |
| **Storage** | | |
| LASA* separation of stock? | Yes | Separate by brand name, Botox and is refrigerated and Xeomin is room temperature |
| Special storage (e.g., refrigeration, protect from light, controlled substance)? | Yes | Botox refrigerate |
| Pharmacist/Technician Education? | Yes | Ensure brand name differences as generic names can be confused |
| **Ordering & Prescribing** | | |
| Restriction to particular specialty, indication, or particular patient population? | Yes | |
| Dosing Issues (e.g., renal, hepatic dosage adjustment, max dose warnings)? | Unknown | |
| Drug Interactions? | Yes | See product package insert for complete list |
| Pregnancy? | Category C | |
| Absolute Contraindications? | Yes | Hypersensitivity to selected product and infection at injection site |
| Requires Order Set, Protocol, concomitant therapy with another drug? | No | |
| LASA* nomenclature issues? | N/A | |
| Prescriber education? | Yes | Socialize restriction criteria |
| **Processing, Preparing, & Dispensing** | | |
| High-risk drug double check? | N/A | |
| Drug Interaction check in place? | Yes | Per Package Insert |
| LASA* computer warnings? | Yes | If multiple botulinumtoxin products in inventory |
| Administration Notes for MAR (e.g., handling precautions, surrounding food or other drugs)? | N/A | Administered by prescriber |
| Packaging/Labeling (e.g., prepacking)? | N/A | |
| Dispensing (e.g., auxiliary labeling, light protection, refrigeration)? | Yes | See Storage |

| | | |
|---|---|---|
| Documentation required (e.g., double check, worksheet)? | N/A | |
| Pharmacist/Technician Education? | N/A | |
| **Administration** | | |
| Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information? | N/A | |
| Special delivery system (e.g., pump)? | Yes | Do not tube |
| Documentation required? (e. g. double check) | N/A | |
| Nurse education? | N/A | |
| **Monitoring** | | |
| Interactions, adverse effects, efficacy, changes in renal function, or similar? | N/A | |
| Follow-up laboratory tests? | N/A | |
| Education? | N/A | |
| **Operational Impact** | | |
| Unique procurement process? (e.g., orphan medication) | N/A | |
| Unique equipment required? | N/A | |
| Complex preparation process required | N/A | |

**FORMULARY UPDATE**

**THERAPEUTIC CLASS:** Interleukin-5 Receptor Antagonists; Eosinophilic Monoclonal Antibodies

**SEE SEPARATE HANDOUT**

**FORMULARY REVIEW**

**GENERIC NAME:** Pegloticase

**PROPRIETARY NAME:** *Krystexxa®*

**INDICATIONS:**

| **FDA Approved** |
|---|
| Treatment of chronic gout in adult patients refractory to conventional therapy |

**THERAPEUTIC CATEGORY:** PEGylated uric acid specific enzyme

**PHARMACOKINETICS:**

| | **Pegloticase (Krystexxa)** |
|---|---|
| **Absorption** | N/A |
| **Excretion** | Urine |
| **t ½ (hr)** | ~14 days |

**SPECIAL POPULATIONS:**

| | **Pegloticase (Krystexxa)** |
|---|---|
| **Pregnancy** | Adverse events have been observed in some animal reproduction studies |
| **Lactation** | It is not known if pegloticase is excreted in breast milk |
| **Pediatrics** | The safety and effectiveness of pegloticase in pediatric patients < 18 years of age have not been established |
| **Geriatrics** | No overall differences in safety or effectiveness were observed between older and younger patients, but greater sensitivity of some older individuals cannot be ruled out. No dose adjustment is needed for patients ≥ 65 |
| **Hepatic Impairment** | There are no dosage adjustments provided in the manufacturer's labeling (has not been studied) |
| **Renal Impairment** | No dose adjustment is required |

**CLINICAL STUDIES:**

| **A Randomized, Double-Blind, Placebo-Controlled, Multicenter, Efficacy and Safety Study of Methotrexate to Increase Response Rates in Patients With Uncontrolled Gout Receiving KRYSTEXXA (Pegloticase) (MIRROR RCT)** | |
|---|---|
| **METHODS** | |
| **Study Design** | Randomized, double-blind, placebo-controlled, multicenter |
| **Patient Enrollment Inclusion** | ● Willing and able to give informed consent<br>● Willing and able to comply with the prescribed treatment protocol and evaluations for the duration of the study<br>● Adult men or women ≥18 years of age<br>● Uncontrolled gout, defined as meeting the following criteria: hyperuricemia during the screening period defined as sUA ≥7 mg/dL, failure to maintain normalization of sUA with xanthine oxidase inhibitors at the maximum medically appropriate dose, or with a contraindication to xanthine oxidase inhibitor therapy based on medical record review or subject interview, and symptoms of gout including at least 1 of the following: presence of at least one tophus, recurrent flares defined as 2 or more flares in the past 12 months prior to screening, presence of chronic gouty arthritis<br>● Willing to discontinue any oral urate lowering therapy for at least 7 days prior to MTX dosing at Week -6 and remain off when receiving pegloticase infusions<br>● Women of childbearing potential must have negative serum/urine pregnancy tests during screening and week -6; subjects must agree to use 2 reliable forms of contraception during the study<br>● Men who are not vasectomized must agree to use appropriate contraception so as to not impregnate a female partner of reproductive potential during the study, beginning with the initiation of MTX at Week -6 and continuing and for at least 3 months after the last dose of MTX or placebo for MTX<br>● Able to tolerate MTX 15 mg orally for 2 weeks prior to randomization |

**Patient Enrollment Exclusion**

- Weight > 160 kg
- Any serious acute or bacterial infection (< 2 weeks prior)
- Severe chronic or recurrent bacterial infections
- Current or chronic treatment with systemic immunosuppressive agents
- History of HBV, HCV, or HIV
- Glucose-6-phosphate dehydrogenase deficiency (tested at the Screening Visit)
- Chronic renal impairment defined as eGFR < 40 mL/min/1.73 $m^2$ or currently on dialysis
- Non-compensated congestive heart failure or hospitalization for congestive heart failure within 3 months of the Screening Visit, uncontrolled arrhythmia, treatment for acute coronary syndrome (myocardial infarction or unstable angina), or uncontrolled blood pressure (>160/100 mmHg) prior to Randomization at Week -4
- Pregnant, planning to become pregnant, breastfeeding, planning to impregnate a female partner, or not on an effective form of birth control, as determined by the Investigator
- Prior treatment with pegloticase, another recombinant uricase (rasburicase), or concomitant therapy with a polyethylene glycol-conjugated drug
- Known allergy to pegylated products or history of anaphylactic reaction to a recombinant protein or porcine product
- Contraindication to MTX treatment or MTX treatment considered inappropriate.
- Known intolerance to MTX
- Receipt of an investigational drug within 4 weeks or 5 half-lives, whichever is longer, prior to MTX administration at Week -6 or plans to take an investigational drug during the study
- Liver transaminase levels (aspartate aminotransferase [AST] or alanine aminotransferase [ALT]) > upper limit of normal (ULN) or albumin < the lower limit of normal (LLN) at the Screening Visit)
- Chronic liver disease
- White blood cell count < 4,000/µL, hematocrit < 32 percent, or platelet count < 75,000/µL
- Currently receiving systemic or radiologic treatment for ongoing cancer
- History of malignancy within 5 years other than non-melanoma skin cancer or in situ carcinoma of the cervix
- Diagnosis of osteomyelitis
- Known history of hypoxanthine-guanine phosphoribosyl-transferase deficiency, such as Lesch-Nyhan and Kelley-Seegmiller syndrome
- Unsuitable candidate for the study, based on the opinion of the Investigator (e.g., cognitive impairment), such that participation might create undue risk to the subject or interfere with the subject's ability to comply with the protocol requirements or complete the study
- Alcohol use in excess of 3 alcoholic beverages per week
- A known intolerance to all protocol standard gout flare prophylaxis regimens (i.e. subject must be able to tolerate at least one: colchicine and/or non-steroidal anti-inflammatory drugs and/or low dose prednisone ≤10 mg/day)
- Current pulmonary fibrosis, bronchiectasis or interstitial pneumonitis. If deemed necessary by the Investigator, a chest X-ray may be performed during Screening

**Baseline Characteristics**

| | **Pegloticase + MTX (n=100)** | **Pegloticase + Placebo (n=52)** |
|---|---|---|
| **Mean Age (years)** | 55.6 (± 12.74) | 53 (± 12.12) |
| **Sex (male)** | 91 (91%) | 44 (84.6%) |
| **Ethnicity** | | |
| Hispanic or Latino | 19 (19%) | 9 (17.3%) |
| Not Hispanic or Latino | 81 (81%) | 42 (80.8%) |
| Unknown or Not Reported | 0 (0%) | 1 (1.9%) |
| **Race/Ethnicity** | | |
| American Indian or Alaska Native | 0 (0%) | 0 (0%) |
| Asian | 8 (8%) | 6 (11.5%) |
| Black or African American | 16 (16%) | 6 (11.5%) |
| Native Hawaiian or Other Pacific Islander | 4 (4%) | 1 (1.9%) |
| White | 69 (69%) | 36 (69.2 %) |
| Other, Not Specified | 3 (3%) | 2 (3.8%) |

| | | | |
|---|---|---|---|
| | Missing | 0 (0%) | 1 (1.9%) |
| **Treatment Plan** | Patients who were able to tolerate two weeks on oral methotrexate 15 mg were then randomized to receive four additional weeks on either methotrexate 15 mg or matching placebo prior to initiating pegloticase therapy in a 2:1 ratio. Once randomized, participants received IV pegloticase 8 mg every 2 weeks for a total of 26 infusions from Day 1 through the Week 50 Visit, in addition to oral MTX 15 mg or matching placebo. | | |
| **RESULTS** | | | |
| **Primary Endpoint** | | | |

| | **Pegloticase + MTX (n = 100)** | **Pegloticase + Placebo (n = 52)** | **p-value** | **95% Confidence Interval** |
|---|---|---|---|---|
| **Serum uric acid (sUA) responders (sUA < 6 mg/dL) during month 6 (%)** | 71 (61.1-79.6) | 38.5 (25.3-53) | <0.0001 | 16.3-48.3 |

**Secondary Endpoint**

| | **Pegloticase + MTX (n = 100)** | **Pegloticase + Placebo (n = 52)** | **p-value** | **Difference (95% Confidence Interval)** |
|---|---|---|---|---|
| **Serum uric acid (sUA) responders (sUA < 6 mg/dL) during month 12, no (%)** | 60 (60) | 16 (31) | 0.0003 | 29 (13-45) |

**Adverse Events**

| **Adverse Reactions Occurring in 5% or More of Patients in Either the Pegloticase Co-administered with Methotrexate or Pegloticase Alone Treatment Period** | | |
|---|---|---|
| **Adverse Reaction** | **Pegloticase + MTX (96)** | **Pegloticase + Placebo (49)** |
| **Gout flare** | 64 (67%) | 35 (71%) |
| **Arthralgia** | 13 (14%) | 5 (10%) |
| **COVID-19** | 9 (9%) | 3 (6%) |
| **Nausea** | 5 (5%) | 2 (4%) |
| **Fatigue** | 5 (5%) | 2 (4%) |
| **Infusion Reaction** | 4 (4%) | 15 (31%) |
| **Pain in extremity** | 1 (1%) | 3 (6%) |
| **Hypertension** | 1 (1%) | 3 (6%) |
| **Vomiting** | 0 | 4 (8%) |

| | |
|---|---|
| **Limitations** | ● This trial has yet to be finalized and published<br>● Extensive exclusion criteria prevent application to these populations |
| | |
| **Reducing Immunogenicity of Pegloticase With Concomitant Use of Mycophenolate Mofetil in Patients With Refractory Gout: A Phase II, Randomized, Double-Blind, Placebo-Controlled Trial** | |
| **METHODS** | |
| **Study Design** | Phase II, Randomized, Double-Blind, Placebo-Controlled Trial |
| **Patient Enrollment Inclusion** | ● Age > 18 years<br>● Fulfillment of the 2015 American College of Rheumatology/European Alliance of Associations for Rheumatology criteria for gout |

<table>
<tr><td></td><td>
<ul>
<li>Presence of chronic refractory gout, defined as signs and symptoms inadequately controlled with urate-lowering therapy (e.g. xanthine oxidase inhibitors or uricosuric agents) at a medically appropriate dose or contraindication to these drugs</li>
<li>Hyperuricemia (i.e., sUA >6 mg/dL at the screening visit)</li>
<li>No previous treatment with pegloticase or other uricase therapies</li>
</ul>
</td></tr>
<tr><td>Patient Enrollment Exclusion</td><td>
<ul>
<li>Weight >160 kg</li>
<li>Infection in the prior 2 weeks</li>
<li>Immunocompromised status</li>
</ul>
</td></tr>
<tr><td>Baseline Characteristics</td><td>
<table>
<tr><th></th><th>MMF + Pegloticase (n=22)</th><th>Placebo + Pegloticase (n=10)</th></tr>
<tr><td>Sex, no (%) male</td><td>19 (86)</td><td>9 (90)</td></tr>
<tr><td>Age, years</td><td>55.0 ± 9.4</td><td>55.5 ± 10.7</td></tr>
<tr><td>2015 ACR/EULAR criteria points</td><td>13.5 ± 2.8</td><td>13.8 ± 2.7</td></tr>
<tr><td>Gout flare history<br>Flare within last year, no (%)<br>Number of flares in the last year, median (IQR)</td><td><br>15 (68)<br>1 (0-2)</td><td><br>5 (50)<br>1 (0-1)</td></tr>
<tr><td>Age at diagnosis, years</td><td>40.9 ± 14.7</td><td>42.1 ± 12.6</td></tr>
<tr><td>Duration of gout, years</td><td>13.3 ± 9.8</td><td>13.4 ± 7.4</td></tr>
<tr><td>PROMIS items<br>Pain intensity T score<br>Physical function T score</td><td><br>50. 8 ± 11.3<br>37.5 ± 7.8</td><td><br>45 ± 12.4<br>33.8 ± 6.4</td></tr>
<tr><td>Pain score</td><td>4.5 ± 4.0</td><td>2.8 ± 3.3</td></tr>
<tr><td>Gout impact score</td><td>45.7 ± 7.5</td><td>46.4 ± 7.1</td></tr>
<tr><td>Oral urate-lowering medication, no (%)<br>Allopurinol<br>Febuxostat</td><td><br>13 (59)<br>4 (18)</td><td><br>6 (60)<br>1 (10)</td></tr>
<tr><td>Acute gout therapy, no (%)<br>Colchicine<br>NSAIDs<br>Corticosteroids</td><td><br>9 (41)<br>16 (73)<br>4 (18)</td><td><br>5 (50)<br>5 (50)<br>2 (20)</td></tr>
<tr><td>No. of alcoholic drinks/day, no (%)<br>0<br>1-2<br>>2</td><td><br>11 (50)<br>7 (32)<br>4 (18)</td><td><br>3 (30)<br>4 (40)<br>3 (30)</td></tr>
<tr><td>Serum urate level, mg/dL</td><td>8.9 ± 1.8</td><td>9.8 ± 1.3</td></tr>
<tr><td>Serum urate level, no (%)<br>≤6 mg/dL<br>>6 mg/dL</td><td><br>2 (9)<br>20 (91)</td><td><br>0 (0)<br>10 (100)</td></tr>
<tr><td>CKD eGFR, mean ± SD#</td><td>81.3 ± 29.3</td><td>78.2 ± 18.4</td></tr>
<tr><td>45-59 ml/minute/1.73 $m^2$, no (%)<br>60-90 ml/minute/1.73 $m^2$, no (%)<br>>90 ml/minute/1.73 $m^2$, no (%)</td><td>4 (18)<br>12 (55)<br>6 (27)</td><td>2 (20)<br>5 (50)<br>3 (30)</td></tr>
<tr><td>Presence of tophi, no (%)</td><td>19 (86)</td><td>9 (90)</td></tr>
<tr><td>BMI, no (%)<br>25 to <30<br>30 to <45<br>>45</td><td><br>3 (14)<br>18 (82)<br>1 (4)</td><td><br>1 (10)<br>7 (70)<br>2 (20)</td></tr>
</table>
</td></tr>
</table>

| | | | |
|---|---|---|---|
| **Comorbidity, no (%)** | | | |
| Diabetes mellitus/metabolic syndrome | 3 (14) | 2 (20) | |
| CVA/PVD/heart disease | 8 (36) | 6 (60) | |
| Systemic hypertension | 18 (82) | 7 (70) | |
| Dyslipidemia | 8 (36) | 4 (40) | |
| Kidney Stones | 4 (18) | 5 (50) | |

| | |
|---|---|
| **Treatment Plan** | Participants from 5 large practices were randomized in a 3:1 ratio by site to receive either MMF or placebo initiated 2 weeks before the administration of pegloticase. Pegloticase was administered at a dose of 8 mg intravenously (IV) every 2 weeks for a total of 12 infusions. MMF or placebo was continued for the first 12 weeks of the 24-week duration of pegloticase therapy. All participants then received pegloticase alone for the remaining 12 weeks. |
| **RESULTS** | |
| **Primary Endpoint** | |

| **Primary Outcome** | **MMF + pegloticase, % (95% CI) (no.) (n=22)** | **Placebo + pegloticase, % (95% CI) (no.) (n=10)** | **Difference between groups, % (95% CI)** | **p-value** |
|---|---|---|---|---|
| **Serum urate ≤ 6 mg/dL up to week 12** | 86 (65, 97) (19) | 40 (12, 74) (4) | 46 (13 ,80) | 0.01 |

**Adverse Events**

| **Adverse Event** | **MMF + pegloticase (n=22)** | **Placebo + pegloticase (n=10)** |
|---|---|---|
| **Any AE, no (%)** | 15 (68) | 7(70) |
| **Any SAE, no (%)** | 2(9) | 1(10) |
| **Discontinuation from treatment due to AE, no (%)** | 1(5) | 3(30) |
| **Most commonly reported AEs, no (%) of patients [total number of events]** | | |
| Cardiac | 2 (9) [2] | 1 (10) [1] |
| Gastrointestinal | 4 (18) [4] | 1 (10) [1] |
| Infections | 2 (9) [2] | 0 (0) [0] |
| Musculoskeletal | 9 (41) [19] | 1 (10) [2] |
| Respiratory | 4 (18) [4] | 0 (0) [0] |
| Skin | 2 (9) [2] | 1 (10) [1] |
| Other | 9 (41) [11] | 5 (50) [5] |

| | |
|---|---|
| **Limitations** | ● Small sample size<br>● Adverse event results were not tested for statistical significance |
| | |
| **Efficacy and Tolerability of Pegloticase for the Treatment of Chronic Gout in Patients Refractory to Conventional Treatment: Two Randomized Controlled Trials** | |
| **METHODS** | |
| **Study Design** | Two replicate, randomized, double-blind, placebo-controlled trials |
| **Patient Enrollment Inclusion** | ● Patients > 18 years and older<br>● Met the following criteria for refractory gout: a baseline sUA of 8 mg/dL or greater and at least 1 of the following: 3 or more self-reported gout flares during the previous 18 months; 1 or more tophi; and gouty arthropathy, defined clinically or radiographically as joint damage due to gout<br>● Contraindication to treatment with allopurinol or history of failure to normalize UA despite 3 or more months of treatment with the maximum medically appropriate allopurinol dose (determined by the treating physician) |
| **Patient Enrollment Exclusion** | ● Glucose-6-phosphate dehydrogenase deficiency<br>● Prior treatment with a uricase-containing agent |

- Pregnancy
- Unstable angina
- Uncontrolled hypertension (>150/90 mmHg) or cardiac arrhythmia
- Uncompensated congestive heart failure
- Renal dialysis
- Solid organ transplant

**Baseline Characteristics**

| TRIAL C0405 | | | |
|---|---|---|---|
| | **Pegloticase Biweekly (n=43)** | **Pegloticase Monthly (n=41)** | **Placebo (n=20)** |
| **Demographics** | | | |
| Age, mean (SD), y | 58.2 (15) | 55.1 (13) | 57.2 (13) |
| Male sex, no (%) | 30 (69.8) | 35 (85.4) | 15 (75) |
| White race/ethnicity, no (%) | 32 (74.4) | 32 (78) | 14 (70) |
| BMI, mean (SD) | 34.85 (8) | 33.68 (8) | 33.3 (6) |
| **Gout characteristics** | | | |
| Duration, mean (SD), y | 16 (14) | 16 (11) | 12 (9) |
| Acute flares in prior 18 mo, no (quartiles) | 43 (4, 8, 10) | 40 (4, 7.5, 12) | 20 (4.5, 8, 12) |
| Baseline tophi, no (%) | 29 (67.4) | 31 (76.5) | 14 (70) |
| Chronic synovitis or arthropathy, no (%) | 27 (62.8) | 23 (56.1) | 13 (65) |
| Serum uric acid, mean (SD), mg/dL | 9.8 (1.6) | 10.4 (1.8) | 9.4 (1.6) |
| **Comorbid conditions, no (%)** | | | |
| ≥ 1 of these CV conditions or risk factors | 36 (84) | 36 (88) | 17 (85) |
| Hypertension | 30 (70 | 30 (73) | 15 (75) |
| Dyslipidemia | 24 (56) | 21 (51) | 13 (65) |
| Diabetes mellitus | 13 (30) | 8 (20) | 5 (25) |
| Cardiac arrhythmia | 10 (23) | 5 (12) | 6 (30) |
| Coronary artery disease | 9 (21) | 10 (24) | 6 (30) |
| Cardiac failure/left ventricular dysfunction | 8 (19) | 4 (10) | 4 (20) |
| Peripheral vascular disease | 3 (7) | 2 (5) | 2 (10) |
| Cerebrovascular disease | 3 (7) | 2 (5) | 0 |
| **Obesity (BMI ≥ 30)** | 29 (67) | 27 (66) | 14 (70) |
| **Chronic kidney disease** | 12 (28) | 13 (32) | 6 (30) |
| **Sleep apnea syndrome** | 6 (14) | 5 (12) | 3 (15) |
| **Venous thromboembolic disease** | 1 (2) | 1 (2) | 1 (5) |

| TRIAL C0406 | | | |
|---|---|---|---|
| | **Pegloticase Biweekly (n=42)** | **Pegloticase Monthly (n=43)** | **Placebo (n=23)** |
| **Demographics** | | | |
| Age, mean (SD), y | 54.3 (16) | 53.9 (14) | 53.8 (11) |
| Male sex, no (%) | 38 (91.5) | 34 (79.1) | 21 (91.3) |
| White race/ethnicity, no (%) | 22 (52.4) | 27 (62.8) | 16 (69.6) |
| BMI, mean (SD) | 31 (6) | 32 (8) | 31 (8) |
| **Gout characteristics** | | | |
| Duration, mean (SD), y | 15 (11) | 16 (9) | 15 (10) |
| Acute flares in prior 18 mo, no (quartiles) | 41 (4, 6, 10) | 43 (4, 7, 10) | 23 (3, 5, 10) |
| Baseline tophi, no (%) | 33 (78.6) | 33 (78.6) | 15 (65.2) |
| Chronic synovitis or arthropathy, no (%) | 23 (54.8) | 23 (54.8) | 13 (56.5) |
| Serum uric acid, mean (SD), mg/dL | 9.5 (1.7) | 9.5 (1.7) | 9.8 (1.6) |
| **Comorbid conditions, no (%)** | | | |
| ≥ 1 of these CV conditions or risk factors | 36 (86) | 35 (81) | 18 (78) |
| Hypertension | 32 (76) | 30 (70) | 16 (70) |
| Dyslipidemia | 18 (43) | 20 (47) | 7 (30) |
| Diabetes mellitus | 11 (26) | 10 (23) | 3 (13) |

| | | | | |
|---|---|---|---|---|
| | Cardiac arrhythmia | 10 (24) | 4 (9) | 1 (4) |
| | Coronary artery disease | 5 (12) | 6 (14) | 3 (13) |
| | Cardiac failure/left ventricular dysfunction | 4 (10) | 4 (9) | 2 (9) |
| | Peripheral vascular disease | 4 (10) | 4 (9) | 1 (4) |
| | Cerebrovascular disease | 1 (2) | 1 (2) | 1 (4) |
| | **Obesity (BMI ≥ 30)** | 21 (50) | 28 (65) | 10 (43) |
| | **Chronic kidney disease** | 14 (33) | 12 (29) | 3 (13) |
| | **Sleep apnea syndrome** | 2 (5) | 4 (9) | 3 (13) |
| | **Venous thromboembolic disease** | 2 (5) | 1 (2) | 1 (4) |
| **Treatment Plan** | Starting at week 1, patients received 2-hour IV infusions of 250-mL 0.9% sodium chloride containing either pegloticase 8 mg at each infusion (biweekly treatment group), pegloticase 8 mg alternating with placebo (every-4-week or monthly treatment group), or placebo (placebo group). Participants receiving urate-lowering medication at screening underwent a 1-week washout. | | | |
| **RESULTS** | | | | |
| **Primary Endpoint** | | | | |

| **Primary Outcome: No. responders/No. treated (%) [95% CI]** | **Pegloticase Biweekly** | **Pegloticase Monthly** | **Placebo** |
|---|---|---|---|
| **Pooled results**<br>P-value | 36/85 (42) [32 to 54]<br><0.001 | 29/84 (35) [24 to 46]<br><0.001 | 0/43 (0) [0 to 8] |
| **Trial C0405**<br>P-value | 20/43 (47) [31 to 62]<br><0.001 | 8/41 (20) [9 to 35]<br>0.04 | 0/20 (0) [0 to 17] |
| **Trial C0406**<br>P-value | 16/42 (38) [24 to 54]<br>0.001 | 21/43 (49) [33 to 65]<br><0.001 | 0/23 (0) [0 to 15] |

**Adverse Events**

| Adverse Event, no (%) | Pegloticase Biweekly (n=85) | Pegloticase Monthly (n=84) | Placebo (n=43) |
|---|---|---|---|
| **Any AE** | 80 (94) | 84 (100) | 41 (95) |
| **Any SAE** | 20 (24) | 19 (23) | 5 (12) |
| **Death** | 2 (2) | 1 (1) | 0 |
| **Discontinuation owing to AE** | 15 (18) | 16 (19) | 1 (2) |
| **Most commonly reported** | | | |
| Gout flare | 65 (76) | 71 (85) | 35 (81) |
| Infusion reaction | 22 (26) | 35 (42) | 2 (5) |
| Headache | 8 (9) | 9 (11) | 4 (9) |
| Nausea | 10 (12) | 6 (7) | 1 (2) |
| Back pain | 3 (4) | 7 (8) | 2 (5) |
| Nasopharyngitis | 6 (7) | 4 (5) | 1 (2) |
| Dyspnea | 4 (5) | 5 (6) | 2 (5) |
| Vomiting | 4 (5) | 5 (6) | 1 (2) |
| Chest pain | 5 (6) | 4 (5) | 1 (2) |
| Pruritus | 3 (4) | 5 (6) | 0 |
| Contusion | 7 (8) | 0 | 1 (2) |
| Pyrexia | 2 (2) | 5 (6) | 1 (2) |
| Constipation | 5 (6) | 2 (2) | 2 (5) |
| Blood pressure increased | 0 | 6 (7) | 0 |
| **Adjudicated CV events** | | | |
| **APTC events** | 2 (2) | 1 (1) | 0 |
| CV death | 2 (2) | 0 | 0 |
| Nonfatal MI | 0 | 1 (1) | 0 |
| **Non-APTC events** | 3 (2) | 6 (7) | 0 |
| CHF | 1 (1) | 1 (1) | 0 |
| Arrhythmia | 0 | 1 (1) | 0 |
| DVT | 0 | 1 (1) | 0 |
| TIA | 0 | 1 (1) | 0 |
| Unstable angina | 0 | 1 (1) | 0 |
| Coronary revascularization | 0 | 1 (1) | 0 |

**Limitations**

- Short trial length limits knowing the impact of treatment beyond 6-months
- Adverse event results were not tested for statistical significance

**COMPARATIVE EFFICACY:**

There are currently no other treatments indicated for the treatment of gout refractory to conventional therapy. Other agents are considered first line for the treatment and prevention of gout and should be utilized prior to consideration of pegloticase, if there are no contraindications. Guidelines from the American College of Rheumatology strongly suggest treatment with allopurinol as the preferred first-line agent, and conditionally recommend switching to a second xanthine oxidase inhibitor (XOI), such as febuxostat, over adding a uricosuric agent, such as lesinurad and probenecid, in patients with a poor response to allopurinol. Furthermore, guidelines strongly recommend switching to pegloticase over continuing current urate-lowering therapy for patients with gout for whom XOI treatment, uricosurics, and other interventions have failed to achieve the serum urate target, and who continue to have frequent gout flares (≥2 flares/year) OR who have non-resolving subcutaneous tophi. Current guidelines do not reflect the recent FDA-approval of pegloticase in combination with weekly methotrexate.

**WARNING AND PRECAUTIONS:**

- Hypersensitivity/anaphylactoid reactions: anaphylaxis and infusion reactions have been reported during and after administration
- Gout flare may occur following initiation of uric acid lowering therapy
- G6PD deficiency associated hemolysis and methemoglobinemia
- Heart failure exacerbation may occur
- Discontinue use of oral antihyperuricemic agents prior to and do not initiate during the course of pegloticase therapy
- Potential for immunogenicity, patients who reinitiate therapy after discontinuing treatment for >4 weeks may be at increased risk for anaphylaxis and infusion reactions

**BLACK BOX WARNINGS:**

- **Anaphylaxis and infusion reactions:** have been reported to occur during and after administration. May occur with any infusion, including a first infusion, and generally manifest within 2 hours of the infusion; however, delayed hypersensitivity reactions have also been reported. Pegloticase should be administered in a healthcare setting by healthcare providers prepared to manage anaphylactic reactions. Premedicate with antihistamines and corticosteroids.
- **G6PD deficiency-associated hemolysis and methemoglobinemia:** screen patients at risk for G6PD deficiency prior to starting pegloticase, treatment is contraindicated in patients with G6PD deficiency

**CONTRAINDICATIONS:**

- Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Patients with history of serious hypersensitivity reactions, including anaphylaxis, to pegloticase or any of its components

**ADVERSE REACTIONS:**

| Adverse Reactions | Intervention Group (N=85) % | Placebo or Standard of Care Group (N=43) % |
|---|---|---|
| Anti-pegloticase antibodies | 92 | 28 |
| Gout flare | 77 | 81 |
| Infusion reaction | 26 | 5 |
| Nausea | 12 | 2 |
| Contusion or Ecchymosis | 11 | 5 |
| Nasopharyngitis | 7 | 2 |
| Constipation | 6 | 5 |
| Chest Pain | 6 | 2 |
| Anaphylaxis | 5 | 0 |
| Vomiting | 5 | 2 |

**CLINICALLY SIGNIFICANT DRUG INTERACTIONS:**

| Interacting Drug | Effect |
|---|---|
| Methotrexate | Co-administration of methotrexate with pegloticase may increase pegloticase concentration compared to pegloticase alone |
| PEGylated products | Pegloticase may diminish the therapeutic effect of PEGylated drug products |
| Allopurinol/febuxostat/ probenecid | May blunt increase in serum urate that would signal an increased risk of anaphylaxis and infusion reactions |
| Pegvaliase | PEGylated drug produced may enhance the adverse/toxic effect of pegvaliase |

**DOSING AND ADMINISTRATION:** 8 mg IV every 2 weeks

**RECOMMENDED MONITORING:**

- The risk of infusion reactions, including anaphylaxis, is higher in patients who have lost therapeutic response
- Monitor serum uric acid levels prior to each infusion and discontinue treatment if levels increase to above 6 mg/dL, particularly when 2 consecutive levels above 6 mg/dL are observed

**PHARMACOECONOMICS/COST:**

| Product (Drug, Strength, Form) | NDC | Size | Cardinal Specialty | Cost/Year |
|---|---|---|---|---|
| Krystexxa 8 mg/mL | 75987-0080-10 | 1 x 1mL | **$26,665.22** | $693,295.72 |

**Medication specific billing codes:**

| | | | |
|---|---|---|---|
| J2057 | Pegloticase injection | 1 mg | $3143.504 |

**Reimbursement Rates from Major Commercial Payers:**

| Payer | Reimbursement (1 mg) | Reimbursement (8 mg) | Net Gain or Loss |
|---|---|---|---|
| **BCBSTN** | $3,203 | $25,623 | -$1,043 |
| **Cigna** | $3,610 | $28,883 | +$2,217 |
| **Medicare** | $2,854 | $22,830 | -$3,836* |

*In 2019, Medicare margin was negative at $723 per dose.

**CONCLUSION & RECOMMENDATION:**
Gout treatment options were previously reviewed in a class review prepared by CHI in March of 2019. The review determined Krystexxa (pegloticase) should be non-formulary because it must be given intravenously, is associated with potentially severe side effects, and is prohibitively expensive. Since 2019, primary data has demonstrated increased efficacy and tolerability of pegloticase when combined with methotrexate or mycophenolate mofetil. In 2022, the FDA approved pegloticase in combination with weekly methotrexate based on the MIRROR RCT clinical trial results. There was a decreased incidence of infusion reactions when used concomitantly with methotrexate.

Guidelines from the American College of Rheumatology strongly recommend switching to pegloticase over continuing current urate-lowering therapy for patients with gout for whom xanthine oxidase inhibitor treatment, uricosurics, and other interventions have failed to achieve the serum urate target, and who continue to have frequent gout flares (≥2 flares/year) OR who have non-resolving subcutaneous tophi. Current guidelines were updated in 2020 and do not reflect the recent FDA-approval of pegloticase in combination with weekly methotrexate.

Drs. Bragg and Garcia-Rosell (Rheumatology) asked that CHI Memorial reconsider adding Krystexxa to the outpatient infusion center formulary in order to keep CHI Memorial patients within CHI Memorial. Erlanger and 12 Stone infusion are two local infusion centers that offer Krystexxa infusions.

Increased efficacy and safety have been demonstrated but cost is significant. Based on trial baseline characteristics (age), patients benefiting from pegloticase include Medicare and non-Medicare beneficiaries; therefore, reimbursement data from major third party payers was reviewed and reimbursement rates vary. Medicare & Blue Cross comprise over 80% of our patient volume for the OP Infusion Center, so assuming this pattern holds, over 80% of the patients who use Krystexxa would incur a loss.

**It is recommended to maintain the non-formulary status of Krystexxa since there are two local infusion centers who can offer it to our patients, plus this would prevent a financial loss.**

**FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)**

| Medication Management Step | Identified Risk | Steps for Prevention |
|---|---|---|
| **Selection** | | |
| Therapeutic interchange? | No | N/A |
| Special Ordering Requirements? | No | N/A |
| **Storage** | | |
| LASA* separation of stock? | No | N/A |
| Special storage (e.g. refrigeration, protect from light, controlled substance)? | Yes | Vials must be protected from light and kept under refrigeration between 2°C to 8°C |
| Pharmacist/Technician Education? | Yes | Do not shake or freeze |
| **Ordering & Prescribing** | | |
| Restriction to particular specialty, indication, or particular patient population? | Yes | Restrict to patients refractory to conventional gout therapy |
| Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)? | No | N/A |
| Drug Interactions? | Yes | EHR alerts are recommended |

| Medication Management Step | Identified Risk | Steps for Prevention |
|---|---|---|
| Pregnancy? | Possibly | Adverse events have been observed in some animal reproduction studies |
| Absolute Contraindications? | Yes | Patients should be screened prior to use for G6PD deficiency or history of anaphylaxis |
| Requires Order Set, Protocol, concomitant therapy with another drug? | Yes | Due to risk of infusion related reactions, this drug should be administered with an antihistamine and corticosteroid 30 minutes prior to each infusion |
| LASA* nomenclature issues? | No | N/A |
| Prescriber education? | No | N/A |
| **Processing, Preparing, & Dispensing** | | |
| High-risk drug double check? | No | N/A |
| Drug Interaction check in place? | No | N/A |
| LASA* computer warnings? | No | N/A |
| Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)? | Yes | Should be infused over no less than 120 minutes; in the event of an infusion reaction, the infusion should be slowed, or stopped and restarted at a slower rate |
| Packaging/Labeling (e.g. prepacking)? | No | N/A |
| Dispensing (e.g. auxiliary labeling, light protection, refrigeration)? | Yes | Diluted solutions should be stored under refrigeration, not frozen, protected from light, and used within 4 hours of dilution |
| Documentation required (e.g. double check, worksheet)? | Yes | Patients should have documentation of screening for a G6PD deficiency prior to use |
| Pharmacist/Technician Education? | No | N/A |
| **Administration** | | |
| Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information? | Yes | Must be diluted prior to use. Do not administer as an IV push or bolus. Visually inspect for particulate matter and discoloration before administration. Invert the infusion bag several times to mix; do not shake. |
| Special delivery system (e.g. pump)? | No | N/A |
| Documentation required? (e. g. double check) | No | N/A |
| Nurse education? | No | N/A |
| **Monitoring** | | |
| Interactions, adverse effects, efficacy, changes in renal function, or similar? | Yes | Patients should be monitored for infusion reactions, including anaphylaxis, during and 1 hr after administration |
| Follow-up laboratory tests? | Yes | Monitor serum uric acid levels prior to each infusion |
| Education? | No | N/A |
| **Operational Impact** | | |
| Unique procurement process? (e.g. orphan medication) | No | N/A |
| Unique equipment required? | No | N/A |
| Complex preparation process required | No | N/A |

CHI Memorial

*Imagine better health.℠*

February 9, 2023

Drs. Bragg & Garcia-Rosell,

This letter is to provide you with information regarding an update on the CHI Memorial formulary status of a medication.

The P&T committee voted at today's meeting for Krystexxa (pegloticase) to be non-formulary.

Based on trial baseline characteristics (age), patients benefiting from pegloticase include Medicare and non-Medicare beneficiaries; therefore, reimbursement data from our major third party payers was reviewed and reimbursement rates vary.

Medicare & Blue Cross comprise over 80% of our patient volume for the outpatient infusion. Reimbursement from each causes a loss to incur per patient: ~$3800 loss with Medicare and ~$1000 loss with BCBS. 80% of the patients who use Krystexxa would incur a loss.

Erlanger Hospital and Twelve Stone Health Partners Infusion Center are two local infusion centers that offer Krystexxa and it is the recommendation of the committee to refer patients qualifying for Krystexxa to either of these infusion centers.

CHI Memorial strives to provide high quality and cost effective care to our patients and this formulary decision is aligned with that goal.

Sincerely,

Nathan Chamberlain, MD
Chairman, P&T Committee

Rachel Kile, Pharm.D., BCPS
Pharmacy Clinical Manager

**FORMULARY REVIEW**

**GENERIC NAME:** Amino acids with electrolytes in dextrose with calcium

**PROPRIETARY NAME:** Clinimix E 5/15; Clinimix E 8/14

**INDICATIONS:**

| **FDA Approved** |
|---|
| • IV nutrition - source of calories and protein and electrolytes for patients requiring parenteral nutrition when oral or enteral nutrition is not possible, insufficient, or contraindicated.<br>• Treatment of negative nitrogen balance in patients requiring parenteral nutrition. |

**THERAPEUTIC CATEGORY:** Intravenous nutritional therapy

**CLINICAL STUDIES:**

**Harrison S, Kopczynska M, Leahy G, et al. Hybrid model of compounded and multichamber bag parenteral nutrition for adults with chronic intestinal failure. J Parenter Enteral Nutr. 2022;46:1632‐1638**

| | |
|---|---|
| **Study Design** | This was a cross-sectional evaluation conducted on September 1, 2021. All HPN-dependent adults cared for at a national United Kingdom reference center for IF were reviewed and their PN regimen classified as compounded PN, compounded electrolytes, hybrid regimen, or MCB/terminal sterilized fluids. Hybrid regimen was defined as a combination of licensed standardized MCBs and customized compounded PN. |
| **Inclusion Criteria** | All patients receiving compounded PN regimen at the time of the study were included. |
| **Exclusion Criteria** | Patients who were already on hybrid or MCB regimens were excluded from the study. Moreover, patients receiving compounded fluid and electrolytes were excluded from the study because matching these prescriptions to a hybrid regimen would involve using multiple terminal sterilized fluid bags per patient, increasing the number of central venous catheter connections required.<br>Reviewed for hybrid PN regimen-The following were excluded.<br>• Those infusing < 1000 ml/day or >3100 ml/day<br>• Those with no calcium or phosphate within their compounded aqueous regimen<br>• Those receiving < 20 mmol or >80 mmol of potassium in their current customized PN bag<br>Certain comorbidities were felt by the MDT to preclude matching to a hybrid regimen were as follows:<br>• Patients with diabetes requiring insulin.<br>• Patients with congestive cardiac failure are likely to be less tolerant of intraday variance in fluids and electrolytes.<br>• Patients with significant renal impairment (eGFR < 30 ml/min), where caution in any changes to electrolytes including potassium, calcium, and phosphate would be required. |
| **Baseline Characteristics** | TABLE 1 Patient demographics, clinical characteristics, and differences between cohort of patients suitable and not suitable for switch to hybrid regimen |

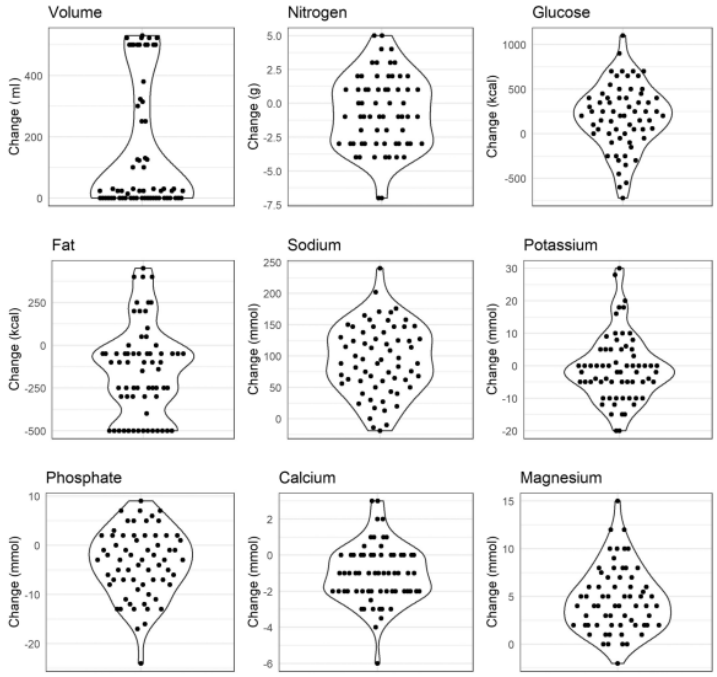
| Patient characteristics | | Total[a] (*n* = 180) | Suitable for hybrid[b] No (*n* = 115) | Yes (*n* = 65) | *P* value |
|---|---|---|---|---|---|
| Mechanism of IF | SBS | 93 | 64 (68.8) | 29 (31.2) | 0.039* |
| | Fistulas | 31 | 20 (64.5) | 11 (35.5) | |
| | Dysmotility | 41 | 27 (65.9) | 14 (34.1) | |
| | Mechanical obstruction | 9 | 2 (22.2) | 7 (77.8) | |
| | Mucosal disease | 6 | 2 (33.3) | 4 (66.7) | |
| Nature of the disease | Active malignant cancer | 7 | 2 (28.6) | 5 (71.4) | 0.214 |
| | Benign disease | 173 | 113 (65.3) | 60 (34.7) | |
| Severity of IF | PN1 | 21 | 14 (66.7) | 7 (33.3) | 0.002* |
| | PN2 | 82 | 46 (56.1) | 36 (43.9) | |
| | PN3 | 60 | 38 (63.3) | 22 (36.7) | |
| | PN4 | 17 | 17 (100.0) | 0 (0) | |
| Average daily volume (ml) | Mean (SD) | 1974.8 (856.8) | 2116.4 (945.2) | 1724.3 (601.7) | 0.003* |
| Average daily energy (kcal/kg) | Mean (SD) | 19.4 (10.7) | 19.3 (11.5) | 19.5 (9.2) | 0.931 |
| Total number of infusions per week | Mean (SD) | 5.8 (1.5) | 6.0 (1.5) | 5.4 (1.5) | 0.022* |
| Total duration of HPN (years) | Mean (SD) | 5.8 (5.3) | 6.0 (5.5) | 5.3 (5.0) | 0.370 |

Abbreviations: HPN, home parenteral nutrition; IF, intestinal failure; PN, parenteral nutrition; SBS, short bowel syndrome.

[a]Values are number or mean (SD).

[b]Values are number (proportion of each characteristics subcategory) or mean (SD).

*P*-values ≤ 0.05 are significant.

| | |
|---|---|
| **Outcome Measures** | Primary Endpoint: Patient suitability for a hybrid PN regimen<br><br>Secondary Endpoints:<br><br>● Proposed changes in prescription between the original and alternative hybrid regimen per week<br>● Potential Cost Savings |
| **Treatment Plan** | The HPN prescriptions of 255 HPN‐dependent patients were reviewed; of these, 217 patients were receiving a customized compounded HPN regimen, 36 were already receiving MCB PN, and 2 were already receiving a hybrid HPN regimen. Of the remaining 217 patients receiving compounded HPN, 37 were receiving compounded fluid and electrolytes. |
| **Results** | |
| **Outcome Summary** | The HPN prescriptions of 255 HPN‐dependent patients were reviewed; of these, 217 patients were receiving a customized compounded HPN regimen, 36 were already receiving MCB PN, and 2 were already receiving a hybrid HPN regimen. Of the remaining 217 patients receiving compounded HPN, 37 were receiving compounded fluid and electrolytes. |
| **Secondary Endpoints** | Distribution of parenteral nutrition constituent changes between one compounded bag and one hybrid multichamber bag for the group.<br>  <br><br>FIGURE 1 Distribution of parenteral nutrition constituent changes between one compounded bag and one hybrid multichamber bag. The violin plot outlines illustrate kernel probability density, that is, the width of the shaded area represents the proportion of the data located there. Each dot represents a change in a constituent for one patient<br><br>Cost Savings<br>● Within England, the cost of PN is based on the national HPN framework and PN bags are banded and priced based on complexity and number of ingredients required for compounded bags. The average cost for a Band A (compounded HPN bag with ≥8 ingredients) is £133.85 compared with Band E (MCB), which costs £94.85 as per the national framework for HPN within England. The potential cost saved in our patient population was calculated as the difference between the average cost for the Band A and B and E PN bag multiplied with the number of Band A bags switched to Band E bags**.** |

**WARNING AND PRECAUTIONS:**

- Pulmonary Embolism due to Pulmonary Vascular Precipitates: if signs of pulmonary distress occur, stop the infusion and initiate a medical evaluation.
- Precipitation with Ceftriaxone: do not administer ceftriaxone simultaneously with CLINIMIX E via a Y-site.
- Hypersensitivity Reactions: monitor for signs and symptoms and discontinue infusion if reactions occur.
- Risk of Infections, Refeeding Complications, and Hyperglycemia or Hyperosmolar Hyperglycemic State: monitor for signs and symptoms; monitor laboratory parameters.
- Vein Damage and Thrombosis: solutions with osmolarity of ≥ 900 mOsm/L must be infused through a central catheter.
- Hepatobiliary Disorders: monitor liver function parameters and ammonia levels.
- Aluminum Toxicity: increased risk in patients with impaired kidney function, including preterm infants.
- Parenteral Nutrition Associated Liver Disease: increased risk in patients who receive parenteral nutrition for extended periods of time, especially preterm infants; monitor liver function tests, if abnormalities occur consider discontinuation or dosage reduction.
- Electrolyte Imbalance and Fluid Overload: patients with cardiac insufficiency or kidney disease may require adjustment of fluid, protein and electrolyte content.

**ADVERSE REACTIONS:**

- Diuresis
- Extravasation
- Glycosuria
- Hyperglycemia
- Hyperosmolar coma

**CONTRAINDICATIONS:**

- Neonates (28 days of age or younger) receiving concomitant treatment with ceftriaxone, even if separate infusion lines are used, due to the risk of fatal ceftriaxone calcium salt precipitation in the neonate's bloodstream
- Patients with known hypersensitivity to one or more amino acids or dextrose
- Patients with inborn errors of amino acid metabolism due to risk of severe metabolic and neurologic complications
- Patients with pulmonary edema or acidosis due to low cardiac output.

**CLINICALLY SIGNIFICANT DRUG INTERACTIONS:**

- Drugs that can cause hyperkalemia: Clinimix E should be administered with caution in patients treated with agents or products that can cause hyperkalemia or increase the risk of hyperkalemia, such as potassium sparing diuretics (amiloride, spironolactone, triamterene), with ACE inhibitors, angiotensin II receptor antagonists, or the immunosuppressants tacrolimus and cyclosporine.
- Ceftriaxone must not be administered simultaneously with calcium-containing intravenous solutions such as Clinimix E via a Y-site

**DOSING AND ADMINISTRATION:**

Clinimix E will be chosen for central IV nutrition for everyone EXCEPT:

- Critically Ill-patients with life threatening conditions that require pressor and/or mechanical support of vital organ functions
- AKI or CRRT patients
- CKD patients will be assessed individually with Nephrology input
- Home TPN patients- see above study for possible additional exploration of savings. For ease of transition, will exclude home TPN. Area providers do not currently use Clinimix for home patients at this time.
- Patients with electrolytes extremely out of range i.e. Potassium < 3 or > 5 or Phosphorus <2 or > 4.5
- Patients with fluid restriction requirements that exceed Clinimix capability of providing adequate nutrition

If the patient does not meet criteria above, the pharmacist will choose a Clinimix E product based on the following criteria:

- Fluid needs will be assessed
- Daily protein and calories requirements will be assessed per ASPEN guidelines
- Electrolytes will be assessed
- Individual orders will be based on the maximum amount of protein and calories needed for the volume that the patient can tolerate
- Individual product dosing tables provided by the manufacturer will be used-(see attached)

Other Clinimix E considerations:

- Dextrose infusion rates will be evaluated and will not exceed 2 mg/kg/min upon initiation and advanced slowly to prevent refeeding
- Lipids will be hung separately and will be limited to 20 grams IV daily for the first 7 days of Clinimix E and increased to 50 grams daily thereafter
- Lipids will not exceed 1 g/kg/day
- Pharmacy will add MVI (or substitution) to Clinimix E on MWF only due to ongoing shortage of MVI
- Trace elements will be added to Clinimix E daily
- If needed, pharmacist will utilize the electrolyte protocol for bolus dosing
- If Clinimix E provides maximum fluid required, maintenance IV fluids may be discontinued per policy
- Monitoring and daily order requirements of Clinimix E will not deviate from existing protocols

**RECOMMENDED MONITORING:**

- Monitor fluid and electrolyte status
- Serum osmolarity
- Blood glucose
- Liver and kidney function
- Blood count and coagulation parameters throughout treatment
- In situations of severely elevated electrolyte levels, stop Clinimix E until levels have been corrected.
- Daily input and output
- Daily weight

**PHARMACOECONOMICS/COST:**

Similar to the study above, TPN patient populations from October 2021 through April 2022 at CHI Memorial Glenwood and Hixson were assessed. For the 7 month period, the number of total TPN patients was 126. To quantify the estimated number of patients who would qualify for Clinimix E, the 126 patients were assessed for the following exclusions: critically ill, home TPN, renal patients (AKI, CKD and CRRT). 52 patients were identified as potential candidates for Clinimix E (41% of TPN candidates).

| Product | Average cost per bag | Total number of TPN days (1 day = 1 TPN bag) | Total Annual cost of therapy (n=52) |
|---|---|---|---|
| Custom TPN | $188 | 473 | $152,441.14 |

| Product | Product cost (per item) | Total cost of therapy for 1 day (based on equal use of all 4 Clinimix E products) | Estimated annual cost of therapy (based on historical TPN use for select patient population) |
|---|---|---|---|
| Clinimix E 8/14 1L | $56.75 | $107.53 | $87,193.21 |
| Clinimix E 8/14 2L | $109.02 | | |
| Clinimix E 5/15 1L | $40.50 | | |
| Clinimix E 5/15 2L | $77.24 | | |
| Clinolipid 20% 100 ml bag (daily) | $25.46 | | |
| Multivitamin 10 ml (3x/week) | $8.01 | | |
| TRALEMENT 1 ml (daily) | $18.11 | | |

| Total Annual cost of custom TPN therapy (n=52) | Estimated annual cost of Clinimix E therapy (based on historical TPN use for select patient population) | Estimated annual cost savings |
|---|---|---|
| $152,441.14 | $87,193.21 | **$65,247.94** |

**CONCLUSION & RECOMMENDATION:**
Clinimix E is a standardized, commercially available parenteral nutrition product available as multichamber bag parenteral nutrition (MCB-PN). Compared to custom TPN, it requires fewer compounding steps before administration, has reduced infection rates, and comparable nutrition efficacy. Several local and regional hospitals have successfully incorporated use of Clinimix products into their parenteral nutrition protocols. There are considerations for patients with fluid restrictions due to volume delivered, and these cases should be discussed on a per patient basis with Nephrology. Adoption of Clinimix products to formulary would allow for substantial annual cost savings for the hospital.

**It is recommended to:**

- **Approve Clinimix products to formulary**
- **Approve Consult to Pharmacist for TPN management to allow the pharmacist to use guidelines, existing TPN policy, and clinical judgment to determine if the patient shall be initiated on a Clinimix product or a custom TPN**
- **Do not allow blanket requests by prescribers such as "No Clinimix for any of my patients"**
- **Update the TPN order set to add Clinimix as an option**

**FAILURE, MODE AND EFFECTS ANALYSIS (FMEA)**

| Medication Management Step | Identified Risk | Steps for Prevention |
|---|---|---|
| **Selection & Procurement** | | |
| Therapeutic interchange? | Yes | |
| Special Ordering Requirements? | Yes | Must meet ASPEN guidelines for provision of parenteral nutrition |
| **Storage** | | |
| LASA* separation of stock? | Clinimix E/Custom TPN | Separate stock, educate pharmacy staff |
| Special storage (e.g. refrigeration, protect from light, controlled substance)? | Once removed from the protective overwrap, mixed (peel seal activated) or unmixed (peel seal intact), CLINIMIX E solutions may be stored under refrigeration for up to 9 days.<br><br>Use promptly after mixing. Any storage with additives should be under refrigeration and limited to a brief period of time, less than 24 hours. After removal from refrigeration, use promptly and complete the infusion within 24 hours. Any remaining mixture must be discarded | Educate pharmacy and nursing staff regarding proper storage |
| Pharmacist/Technician Education? | | |
| **Ordering & Prescribing** | | |
| Restriction to particular specialty, indication, or particular patient population? | Restricted to patients that meet ASPEN guidelines for IV parenteral nutrition | Pharmacy Education |
| Dosing Issues (e.g. renal, hepatic dosage adjustment, max dose warnings)? | Dosing based on disease state, nutritional, fluid and electrolyte status | Pharmacy Education |
| Drug Interactions? | Ceftriaxone, Electrolyte containing medications, medications that can cause wasting of electrolytes and/or retention of electrolytes, specifically potassium | Include warnings upon order entry notifying interaction |
| Pregnancy? | Caution, insufficient data<br>There are no adequate or well-controlled studies in pregnant women with CLINIMIX | Pharmacy education |

| | | |
|---|---|---|
| | E. Additionally, animal reproduction studies have not been conducted with amino acids and electrolytes and dextrose. It is not known whether CLINIMIX E can cause fetal harm when administered to a pregnant woman | |
| Absolute Contraindications? | • Neonates (28 days of age or younger) receiving concomitant treatment with ceftriaxone, even if separate infusion lines are used, due to the risk of fatal ceftriaxone calcium salt precipitation in the neonate's bloodstream<br>• Patients with known hypersensitivity to one or more amino acids or dextrose • Patients with inborn errors of amino acid metabolism due to risk of severe metabolic and neurologic complications. • Patients with pulmonary edema or acidosis due to low cardiac output. | Staff education |
| Requires Order Set, Protocol, concomitant therapy with another drug? | Requires TPN Policy and TPN Order Set | Staff Education on updates |
| LASA* nomenclature issues? | Confusion with custom central TPN and also custom peripheral TPN | Education needed regarding each delivery system and appropriate dosing and administration of each |
| Prescriber education? | Addition of Clinimix will require notification and education of prescribers. | Pharmacist and Physician education needed on new process changes |
| **Processing, Preparing, & Dispensing** | | |
| High-risk drug double check? | Yes | Requires double checks on both order entry and compounding. |
| Drug Interaction check in place? | Drug interaction checks in EMR | |
| LASA* computer warnings? | Yes | EPIC changes-Pharmacy staff education |
| Administration Notes for MAR (e.g. handling precautions, surrounding food or other drugs)? | Yes, see above storage concerns. | Pharmacy and Nursing Staff education |
| Packaging/Labeling (e.g. prepacking)? | Yes, special labeling required | Pharmacy staff education |
| Dispensing (e.g. auxiliary labeling, light protection, refrigeration)? | Central line admin only, high risk | Pharmacy staff education |
| Documentation required (e.g. double check, worksheet)? | Yes<br>Nursing double check TPN labels at admin<br>Pharmacy double checks as above | Nurse and pharmacy education |
| Pharmacist/Technician Education? | Mixing instructions, stability | Pharmacy staff education |
| **Administration** | | |
| Handling precautions, high-risk double check, administration with/without food, interactions, incompatibilities, or other administration information? | Yes | Staff Education |
| Special delivery system (e.g. pump)? | Yes | Staff Education |
| Documentation required? (e. g. double check) | Yes | Staff Education |
| Nurse education? | LASA, Administration changes | Staff Education |
| **Monitoring** | | |
| Interactions, adverse effects, efficacy, changes in renal function, or similar? | See above drug interactions. Pharmacist will closely evaluate daily for tolerance, fluid status, electrolyte status and clinical status. | Staff education |
| Follow-up laboratory tests? | Yes, daily labs and weights required | |

# 5/15

**Baxter**

Clinimix E

AMINO ACIDS WITH ELECTROLYTES IN DEXTROSE WITH CALCIUM INJECTION

| Rate mL/hr | 24 hour volume (mL) | Grams of Amino Acids | kcal from Amino Acids | Grams of Dextrose | kcal from Dextrose | Total kcal | mEq/d Na+ provided | mEq/d K+ provided | mEq/d Mg++ provided | mEq/d Ca++ provided | mMol/d PO4- provided | mEq/d Acetate provided | mEq/d Chloride provided |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 | 720 | 36 | 144 | 108 | 367 | 511 | 25 | 22 | 4 | 3 | 11 | 58 | 28 |
| 35 | 840 | 42 | 168 | 126 | 428 | 596 | 29 | 25 | 4 | 4 | 13 | 67 | 33 |
| 40 | 960 | 48 | 192 | 144 | 490 | 682 | 34 | 29 | 5 | 4 | 14 | 77 | 37 |
| 42 | 1000 | 50 | 200 | 150 | 510 | 710 | 35 | 30 | 5 | 5 | 15 | 80 | 39 |
| 45 | 1080 | 54 | 216 | 162 | 551 | 767 | 38 | 32 | 5 | 5 | 16 | 86 | 42 |
| 50 | 1200 | 60 | 240 | 180 | 612 | 852 | 42 | 36 | 6 | 5 | 18 | 96 | 47 |
| 55 | 1320 | 66 | 264 | 198 | 673 | 937 | 46 | 40 | 7 | 6 | 20 | 106 | 51 |
| 60 | 1440 | 72 | 288 | 216 | 734 | 1022 | 50 | 43 | 7 | 6 | 22 | 115 | 56 |
| 63 | 1500 | 75 | 300 | 225 | 765 | 1065 | 53 | 45 | 8 | 7 | 23 | 120 | 59 |
| 65 | 1560 | 78 | 312 | 234 | 796 | 1108 | 55 | 47 | 8 | 7 | 23 | 125 | 61 |
| 70 | 1680 | 84 | 336 | 252 | 857 | 1193 | 59 | 50 | 8 | 8 | 25 | 134 | 66 |
| 75 | 1800 | 90 | 360 | 270 | 918 | 1278 | 63 | 54 | 9 | 8 | 27 | 144 | 70 |
| 80 | 1920 | 96 | 384 | 288 | 979 | 1363 | 67 | 58 | 10 | 9 | 29 | 154 | 75 |
| 82 | 2000 | 100 | 400 | 300 | 1020 | 1420 | 70 | 60 | 10 | 9 | 30 | 160 | 78 |
| 85 | 2040 | 102 | 408 | 306 | 1040 | 1448 | 71 | 61 | 10 | 9 | 31 | 163 | 80 |
| 90 | 2160 | 108 | 432 | 324 | 1102 | 1534 | 76 | 65 | 11 | 10 | 32 | 173 | 84 |
| 95 | 2280 | 114 | 456 | 342 | 1163 | 1619 | 80 | 68 | 11 | 10 | 34 | 182 | 89 |
| 100 | 2400 | 120 | 480 | 360 | 1224 | 1704 | 84 | 72 | 12 | 11 | 36 | 192 | 94 |
| 105 | 2520 | 126 | 504 | 378 | 1285 | 1789 | 88 | 76 | 13 | 11 | 38 | 202 | 98 |
| 110 | 2640 | 132 | 528 | 396 | 1346 | 1874 | 92 | 79 | 13 | 12 | 40 | 211 | 103 |
| 115 | 2760 | 138 | 552 | 414 | 1408 | 1960 | 97 | 83 | 14 | 12 | 41 | 221 | 108 |
| 120 | 2880 | 144 | 576 | 432 | 1469 | 2045 | 101 | 86 | 14 | 13 | 43 | 230 | 112 |
| 125 | 3000 | 150 | 600 | 450 | 1530 | 2130 | 105 | 90 | 15 | 14 | 45 | 240 | 117 |

# 8/14

**Baxter**
Clinimix E
AMINO ACIDS WITH ELECTROLYTES IN DEXTROSE WITH CALCIUM INJECTION

| Rate mL/hr | 24 hour volume (mL) | Grams of Amino Acids | kcal from Amino Acids | Grams of Dextrose | kcal from Dextrose | Total kcal | mEq/d Na+ provided | mEq/d K+ provided | mEq/d Mg++ provided | mEq/d Ca++ provided | mMol/d PO4- provided | mEq/d Acetate provided | mEq/d Chloride provided |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 30 | 720 | 58 | 230 | 101 | 343 | 574 | 25 | 22 | 4 | 3 | 11 | 60 | 55 |
| 35 | 840 | 67 | 269 | 118 | 401 | 669 | 29 | 25 | 4 | 4 | 13 | 70 | 64 |
| 40 | 960 | 77 | 307 | 134 | 458 | 765 | 34 | 29 | 5 | 4 | 14 | 80 | 73 |
| 42 | 1000 | 80 | 320 | 140 | 477 | 798 | 35 | 30 | 5 | 5 | 15 | 83 | 76 |
| 45 | 1080 | 86 | 346 | 151 | 515 | 861 | 38 | 32 | 5 | 5 | 16 | 90 | 82 |
| 50 | 1200 | 96 | 384 | 168 | 572 | 956 | 42 | 36 | 6 | 5 | 18 | 100 | 91 |
| 55 | 1320 | 106 | 422 | 185 | 630 | 1052 | 46 | 40 | 7 | 6 | 20 | 110 | 100 |
| 60 | 1440 | 115 | 461 | 202 | 687 | 1148 | 50 | 43 | 7 | 6 | 21 | 120 | 109 |
| 63 | 1500 | 120 | 480 | 210 | 716 | 1196 | 53 | 45 | 8 | 7 | 23 | 125 | 114 |
| 65 | 1560 | 125 | 499 | 218 | 744 | 1243 | 55 | 47 | 8 | 7 | 23 | 129 | 119 |
| 70 | 1680 | 134 | 538 | 235 | 801 | 1339 | 59 | 50 | 8. | 8 | 25 | 139 | 128 |
| 75 | 1800 | 144 | 576 | 252 | 859 | 1435 | 63 | 54 | 9 | 8 | 27 | 149 | 137 |
| 80 | 1920 | 154 | 614 | 269 | 916 | 1530 | 67 | 58 | 10 | 9 | 29 | 159 | 146 |
| 82 | 1999 | 160 | 640 | 280 | 954 | 1593 | 70 | 60 | 10 | 9 | 30 | 166 | 152 |
| 85 | 2040 | 163 | 653 | 286 | 973 | 1626 | 71 | 61 | 10 | 9 | 31 | 169 | 155 |
| 90 | 2160 | 173 | 691 | 302 | 1030 | 1722 | 76 | 65 | 11 | 10 | 32 | 179 | 164 |
| 95 | 2280 | 182 | 730 | 319 | 1088 | 1817 | 80 | 68 | 11 | 10. | 34 | 189 | 173 |
| 100 | 2400 | 192 | 768 | 336 | 1145 | 1913 | 84 | 72 | 12 | 11 | 36 | 199 | 182 |
| 105 | 2520 | 202 | 806 | 353 | 1202 | 2008 | 88 | 76 | 13 | 11 | 38 | 209 | 192 |
| 110 | 2640 | 211 | 845 | 370 | 1259 | 2104 | 92 | 79 | 13 | 12 | 40 | 219 | 201 |
| 115 | 2760 | 220 | 883 | 386 | 1317 | 2200 | 97 | 83 | 14 | 12 | 41 | 229 | 210 |
| 120 | 2880 | 230 | 922 | 403 | 1374 | 2295 | 101 | 86 | 14 | 13 | 43 | 239 | 219 |
| 125 | 3000 | 240 | 960 | 420 | 1431 | 2391 | 105 | 90 | 15 | 14 | 45 | 249 | 228 |

**Low-dose pantoprazole for management of gastrointestinal bleeding**

**BACKGROUND:**

Pantoprazole is a proton pump inhibitor (PPI) indicated to treat conditions such as gastroesophageal reflux syndrome (GERD) and peptic ulcer disease (PUD). It is also used as adjunct therapy to endoscopy and is effective pharmacotherapy in high-risk patients with peptic ulcer bleeding.[1] In vitro studies have shown that coagulation and stable platelet aggregation do not occur at pH levels less than 6, which is why acid suppression drugs are used to control re-bleeding episodes.[2] It is also known that PPIs are superior to placebo and histamine-2 receptor antagonists (H2RAs) in gastric acid suppression[2] explaining why they remain the standard of care in patients with gastrointestinal (GI) bleeds. Though it is certain that PPIs are the drug of choice in reducing re-bleeding rates after endoscopy, the debate lingers as to what the proper dosing regimen is for PPIs in patients with acute upper GI hemorrhages.

Current treatment of GI bleeds after endoscopy is pantoprazole 80 mg bolus followed by 8 mg/hour continuous infusion for 72 hours,[1,3-5] which is also the current therapy utilized at CHI Memorial. However, studies show that a lower dose of pantoprazole 40 mg IV given every 12 hours was as effective as a high dose regimen in reducing the risk of recurrent bleeding.[3-4]

The overuse of PPIs can lead to harm. Several retrospective studies have shown that hospitalized patients are over twice as likely to develop *Clostridium difficile* infections if prescribed proton pump inhibitors.[9] The Food and Drug Administration (FDA) also recommends that patients should use the lowest dose and shortest duration of PPI therapy to reduce risk of *C. difficile* infection (CDI).[10] Duration of therapy has been identified as contributing to CDI with a higher incidence occurring when PPI use exceeds 2 days. In fact, up to 60% of patients receive acid-suppressive agents for stress ulcer prophylaxis in a non-ICU setting in which the risk for clinically important bleeding is less than 0.2%.[11]

In addition to CDI, proton pump inhibitors can increase the risk for hospital acquired pneumonia (HAP). A large, hospital-based pharmacoepidemiologic cohort showed that acid suppressive medication use was associated with a 30% increased odds of HAP.[12] PPIs have been used in clinical practice for over 2 decades and are generally believed to have an excellent safety profile[13], which may explain the increased utilization of acid-suppressive medication in the inpatient setting despite the absence of an accepted indication in a majority of these patients.[12]

Lastly, pantoprazole infusions are also incompatible with many IV medications. This leads to the need for a dedicated IV line just for the pantoprazole infusion and another for all other medications. A bolus regimen allows for better ease of administration for nurses and does not tie up an IV site. Pantoprazole regimens require 5 vials to be individually reconstituted with normal saline, then withdrawn and injected into the normal saline bag. This is a labor intensive process for pharmacy technicians.

**LITERATURE:**

**Table 1. Study Table: Literature supporting low-dose, intermittent pantoprazole**

| Study | Standard Regimen | Study Regimen | Outcomes |
|---|---|---|---|
| Sachar H, Vaidya K, et al Meta-analysis | 80 mg bolus pantoprazole + cont. infusion of 192 mg/day x 3 days | Intermittent bolus pantoprazole IV or PO | Intermittent PPI therapy was noninferior to current GDMT (IV bolus plus continuous infusion) in patients with endoscopically treated high-risk bleeding ulcers |
| Leung T, Kedzior S, et al | IV esomeprazole or pantoprazole 40 mg twice daily | Continuous infusion PPI | A 2-hospital policy change favoring intermittent over continuous PPI therapy for UGIB was not associated with increased risk of rebleeding |
| Yao-Chun H, Chin-Lin P, et al | 80 mg bolus pantoprazole + cont. infusion of 192 mg a day x 3 days | Pantoprazole 40 mg IV Q 6 hours x 3 days | Endoscopic hemostasis appeared similar at both doses |
| Chih-Hung W, et al Meta-Analysis | 80 mg bolus omeprazole or pantoprazole + cont. infusion 8 mg/hr x 72 hrs | Omeprazole 20 mg/day IV x 3 days<br>Omeprazole 40 mg PO Q 12 hrs. x 3 days<br>Pantoprazole 80 mg IV bolus + 40 mg IV Q 12 hrs. x 3 days | High-dose PPIs are not superior to non-high-dose PPIs in reducing the rates of re-bleeding, surgical intervention or mortality after endoscopic treatment |

| | | | |
|---|---|---|---|
| | | Pantoprazole 80 mg PO Q 12 hrs. x 3 days | |
| Songür Y, Balkarli A, et al. | 80 mg bolus esomeprazole + cont. infusion of 8 mg/hr x 72 hrs | 40 mg IV esomeprazole BID for 3 days | No significant differences were observed between a 3 day PPI infusion therapy and twice daily IV PPI |
| Yüksel I, Ataseven H, et al. | 80 mg bolus pantoprazole + cont. infusion 8 mg/hr x 72 hrs | Pantoprazole 40 mg IV bolus Q 12 hrs | No difference in duration of stay or need for transfusion and surgery in either group. Prevalence of re-bleeding was similar in both groups |
| Andriulli A, et al. | 80 mg bolus pantoprazole + cont. infusion 8 mg/hr x 72 hrs | Pantoprazole 40 mg IV bolus followed by placebo/saline infusion x 72 hrs | Patients with bleeding peptic ulcers with successful endoscopic hemostasis with high-dose PPI regimen had no advantage with respect to rates of re-bleeding, LOS or death |
| Liang C, Lee J, et al. | 80 mg bolus pantoprazole + cont. infusion 8 mg/hr x 72 hrs | 80 mg IV pantoprazole bolus Q 24 hours | IV non-high-dose pantoprazole is equally effective as high dose pantoprazole when treating low risk patients with bleeding ulcers |

**UTILIZATION:**

A utilization report from November 1 through December 31, 2022 was run to identify patients who received a pantoprazole continuous infusion. The report identified 133 patients over the 2 month period.

**PHARMACOECONOMICS/COST:**

**Table 2: Cost analysis of high-dose pantoprazole regimen (2 months)**

| Patients (n) | 80 mg boluses *(assuming 75% of pts received a bolus dose)* (n) | 200 mg drip (bags) (n) | Total cost of 80 mg bolus $4.46 (n=100) | Total cost for drips $10.82/bag (n=362) | Total Cost (n=100) |
|---|---|---|---|---|---|
| 133 | 100 | 362 | $446.00 | $3,916.84 | $4,362.84 |

**Table 3: Cost analysis for pantoprazole intermittent bolus regimen (2 months)**

| Patients (n) | # vials(six 40 mg vials for 3 days of therapy) | Total cost ($2.23/dose) |
|---|---|---|
| 133 | 798 | $1,779.54 |

**Table 4: Cost savings per patient course**

| Cost of therapy per patient | Pantoprazole 80 mg bolus, then continuous gtt x 3 days | Pantoprazole 40 mg IV BID x 3 days |
|---|---|---|
| **# of 40 mg pantoprazole vials** | 17 | 6 |
| **# of NS 10 ml vials for reconstitution** | 2 | 6 |
| **Cost of 40 mg vials ($1.83)** | $31.11 | $13.38 |
| **Cost of NS 10 ml vial ($0.40)** | $0.80 | $2.40 |
| **Cost of NS 500 mL bag** | $5.01 | N/A |
| **Total cost** | **$36.92** | **$13.38** |
| **Cost savings per patient switching from bolus + gtt → IV BID intermittent bolus regimen** | **$23.54** | |

**Table 5: Estimated annual cost savings** (assuming 75% of patients initiated on a pantoprazole drip received an 80 mg bolus dose)

| | |
|---|---|
| **Cost of high-dose pantoprazole regimen (2 months)** | $4,362.84 |
| **Cost of intermittent bolus regimen (2 months)** | $1,779.54 |
| **Cost savings (2 months)** | $2,583.30 |
| **Estimated annual cost savings** | **$15,499.80** |

**CONCLUSION:** After a comprehensive literature search, we found that there is no difference in outcomes following endoscopy in patients who have received high-dose PPI versus low-dose PPI. To reduce the risk of infection and patient harm, the adoption of a low-dose intermittent PPI regimen may be preferred.
Additionally, instead of the high dose pantoprazole regimen, if patients were initiated on 40 mg IV bolus every 12 hours, the maximum cost of therapy for one patient over 3 days would be $13.38 compared to a patient on the standard high-dose PPI regimen which would be roughly $37.00. By initiating a low-dose PPI regimen the cost savings are over $20.00 per patient. If we extrapolate the total patients from our collected data and apply it to the proposed regimen, the estimated cost savings would be over $2,500 in a 2 month period which equates to approximately $15,500 annual cost savings, not including pharmacy technician labor expenses. The values used for this approximation are the maximum dosages allowed by our potential protocol and the savings could theoretically be more than the estimated amount.

**RECOMMENDATION:**
It is recommended that the high dose pantoprazole regimen (80 mg IV x1, followed by 8 mg/hr for up to 72 hrs) be eliminated in lieu of the intermittent low dose bolus regimen (40 mg IV every 12 hours for up to 72 hours).

- For GI bleeds, a one-time bolus dose of pantoprazole 40 mg IV may be administered in the emergency department (ED), followed by an immediate GI consult
    - Pantoprazole 40 mg IV bolus dose may be administered a second time if endoscopy will not occur within 12 hours after initial dose
- Pantoprazole 40 mg IV Q 12 hours should be administered for up to 72 hours after endoscopy
- Patients should be continued on oral PPI therapy (pantoprazole 40 mg PO Q 24 hours)
    - Patients can be transitioned to oral therapy before 72 hours, if applicable
    - No more than 3 days of an IV PPI should be used after endoscopy unless extenuating circumstances (NPO, etc.)

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## DRUG SHORTAGE MANAGEMENT

**BACKGROUND/RATIONALE:**

The medications included in this summary are currently experiencing, or have recently experienced, a critical drug shortage and require Pharmacy & Therapeutics Committee review.

**MEDICATION #1: Injectable lorazepam (Ativan)**

**Summary:** The injectable lorazepam supply has recovered. This summer, the P&T Committee emergently approved the below restrictions for injectable lorazepam use. The restrictions were implemented to ensure appropriate utilization in the long-term, in addition to mitigating utilization in the short term during the critical shortage. During the December 2022 P&T Committee meeting, the committee voted to maintain the below formulary restrictions, with the additions/modifications in **bold**.

- Pharmacists may automatically substitute orders for injectable lorazepam to oral lorazepam in a 1:1 ratio if the patient can take oral/NG/FT medications, unless indicated for seizure or alcohol withdrawal
- IV lorazepam is permanently formulary restricted for the treatment of only acute seizures, alcohol withdrawal **(unable to take oral medications)**, chemotherapy-induced nausea and/or vomiting, **ICU agitation (unable to take oral medications)**
- Lorazepam infusions are permanently non-formulary (due to availability of safer alternatives for agitation such as propofol, dexmedetomidine, ketamine and risk of propylene glycol toxicity)
- Benzodiazepine equivalents: Lorazepam 1 mg = Midazolam **2 mg** = Diazepam 5 mg

**Discussion/Recommendation:** Lorazepam IV push at 0.5 mg IV x1 dose has been requested to be added back to the MCT IP CAR CORONARY CTA PRE MEDICATION ORDERS order set. The oral tablet replaced the IV route during the acute shortage. During last month's Non-Invasive Cardiology Committee, the Imaging Cardiologists stated they were unaware that the Cardiac CT staff didn't have access to the IV route or that they were still using PO. There was a unanimous vote to recommend to the P&T Committee that Cardiac Imaging move back to the original protocol.

Dr. Mandawat researched this request and determined that the use of IV lorazepam for this purpose is a standard protocol across the country for acute management of anxiety due to bradycardia caused by beta blocker administration 60-90 minutes prior to the study. Cardiac motion is a barrier to imaging. The use of the oral tablet is leading to throughput issues because the administered beta blocker used for the test is wearing off prior to the onset of action of oral lorazepam.

It is recommended to update the order set and replace the oral tablet with the IV push formulation.

**Medications for COVID-19: Update**

| Emergency Use Authorization (EUA) Medications | | |
|---|---|---|
| | **Current Process** | **Recommended Action** |
| **Tocilizumab (Actemra)** | Pharmacist automatic therapeutic interchange to either product based on product availability | Maintain current process |
| **Baricitinib (Olumiant)** | | |
| **Bamlanivimab/etesevimab** | Federal government (HHS) manages supply and determines which product will be shipped to each state. State of TN then allocates mAb to select sites. Use of agent determined by activity against current variant(s) of concern (VOC). | Maintain current process |
| **Casirivimab/imdevimab (Regen-COV)** | | |
| **Sotrovimab** | | |
| **Bebtelovimab** | | |
| **Nirmatrelvir and ritonavir (Paxlovid)*** | Formulary (stocked by retail pharmacy)<br>Allow continuation of the patient's own home supply upon hospital admission, if ordered to continue by the admitting physician.<br>Federal government (HHS) manages supply and determines which product will be shipped to each state. State of TN then allocates products to select sites. | Maintain current process |
| **Molnupiravir** | Non-formulary.<br>Federal government (HHS) manages supply and determines which product will be shipped to each state. State of TN then allocates products to select sites. | Maintain non-formulary status |

*Per the PAXLOVID fact sheet: “Should a patient require hospitalization due to severe or critical COVID-19 after starting treatment with PAXLOVID, the patient should complete the full 5-day treatment course per the healthcare provider’s discretion.”

| COVID-19 Vaccines | | |
|---|---|---|
| | **Current Process** | **Recommended Action** |
| **Pfizer-BioNTech COVID-19 Vaccine** | Formulary for inpatient use | Non-formulary |
| **Pfizer-BioNTech COVID-19 Bivalent BOOSTER Vaccine** | Formulary for inpatient use | Non-formulary |
| **Moderna COVID-19 Vaccine** | Non-formulary | Maintain current process |
| **Janssen (J&J) COVID-19 Vaccine** | Non-formulary | Maintain current process |

**Use/Restriction Criteria Approved by COVID-19 Medications Subcommittee**

**Remdesivir Criteria: Inpatients** (updated 2/1/22)**:** 5 (FIVE) day course of IV remdesivir (200 mg IV x 1 dose, followed by 100 mg IV daily x 4 days) or until hospital discharge, whichever comes first.

Inclusion criteria:
- COVID-19 (+)
- ≤5 days since symptom onset or positive test (whichever comes first)

Exclusion criteria:
- No greater than 5L of supplemental oxygen to maintain an O2 Sat of 92%
- ALT > 5x ULN
- If the provider determines the patient has end stage comorbidities, it is reasonable to withhold remdesivir and the palliative care screening tool is available to assist with decision making regarding therapy initiation.

-Renal function must be tested prior to starting remdesivir. Remdesivir should be used with caution in patients with an eGFR <30 mL/min (dose has not been studied & the infusion may cause further injury)

*-If patient does not meet the specified criteria but you feel your patient may benefit from remdesivir, ID approval must be obtained.*

**Ritonavir-boosted nirmatrelvir (Paxlovid) Criteria: Inpatients** (updated 2/9/23)**:**

Inclusion criteria:
- Diagnosis of COVID-19 with mild to moderate symptoms
- <= 5 (FIVE) days since symptom onset or positive test (whichever comes first)
- High risk of progressing to severe COVID-19

Exclusion criteria:
- Hospitalized due to COVID-19
- eGFR < 30mL/min (dosage adjustment required for eGFR < 60mL/min)
- Severe Hepatic Impairment (Child-Pugh Class C)
- High risk for serious toxicity due to drug interactions unmanageable via therapy modification

**Remdesivir Criteria: Incidental COVID+ (symptomatic) while admitted for non-COVID diagnosis** (updated 4/12/22)**:**
**(SOTROVIMAB preferred, when available/effective against VOC)**

3 (THREE) day course of IV remdesivir (200 mg IV x 1 dose, followed by 100 mg IV daily x 2 days) or until hospital discharge, whichever comes first.

Inclusion criteria:
- COVID-19 (+) with mild to moderate symptoms
- ≤7 (SEVEN) days since symptom onset or positive test (whichever comes first)
- High risk of progressing to severe COVID-19
- Patient is not a candidate for sotrovimab or ritonavir-boosted nirmatrelvir due to specific patient factors and/or drug availability

Exclusion criteria:
- Hospitalized due to COVID-19
- ALT > 5x ULN
- If the provider determines the patient has end stage comorbidities, it is reasonable to withhold remdesivir and the palliative care screening tool is available to assist with decision making regarding therapy initiation.

-Renal function must be tested prior to starting remdesivir. Remdesivir should be used with caution in patients with an eGFR <30 mL/min (dose has not been studied & the infusion may cause further injury)

***-If patient does not meet the specified criteria but you feel your patient may benefit from remdesivir, ID approval must be obtained.***

**Sotrovimab Criteria (approved 4/12/22):**
**Update [4/5/2022] Sotrovimab is no longer authorized to treat COVID-19 in any U.S. region due to increases in the proportion of COVID-19 cases caused by the Omicron BA.2 sub-variant**

Inclusion criteria:

- COVID-19 (+) with mild to moderate symptoms
- <= 10 (TEN) days since symptom onset or positive test (whichever comes first)
- High risk of progressing to severe COVID-19

Exclusion criteria:

- Hospitalized due to COVID-19

**Bebtelovimab Criteria (approved 4/12/22):**
**Update [11/30/2022] Bebtelovimab is not currently authorized for emergency use in the U.S. because it is not expected to neutralize Omicron sub-variants BQ.1 and BQ.1.1.**

Inclusion criteria:

- COVID-19 (+) with mild to moderate symptoms
- <=7 (SEVEN) days since symptom onset or positive test (whichever comes first)
- ONLY if none of the preferred therapies are available, feasible to deliver, or clinically appropriate (e.g., due to drug-drug interactions, concerns related to renal or hepatic function)

Exclusion criteria:

- Hospitalized due to COVID-19

## "Once" Medication Orders

**Operational Problem:**
"Once" medication orders that are documented as "Not Given" remain active on the MAR and Pyxis.

This has led to medication errors, where the medication dose for the Once order has been removed from Pyxis, and given to the patient, rather than the ordered PRN dose.

This has also led to the medication being given days later without a new order being obtained from the provider.

Upon investigation, the only MAR Actions that will "consume" the Due time (and thus make the order inactive) include "Given", "Return to Cabinet", "Override Pull", and "Done". None of these MAR Actions would make logical sense in nursing workflow, where the dose should merely be documented as "Not Given (along with the appropriate Not Given Reason)", and the order should become inactive.

**Proposed Solution:**
The proposed solution is to:
1) Change the system definition setting for the "Not Given" MAR Action, s*o that it consumes the Due time.* Then, when a Once dose is documented as "Not Given", the order would become inactive on the MAR and in Pyxis.

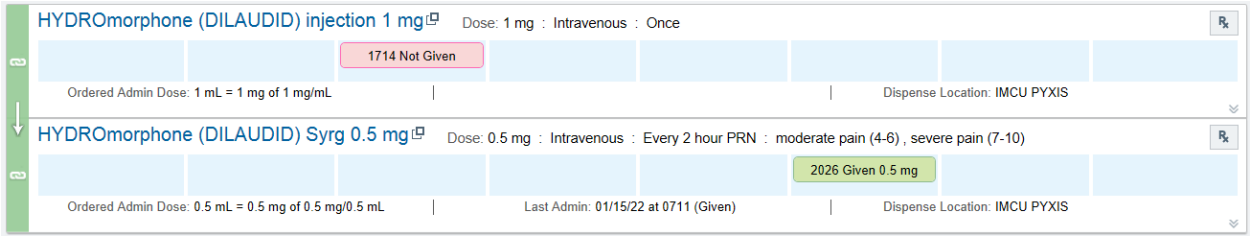
2) Change Once orders to auto-discontinue after 12 hours.

**Alternative Workflows:**
1) Obtaining a provider order to discontinue the Once order, if it does not meet parameters to be Given.
2) Providing nursing education to document the Due time as "Return to Cabinet" rather than "Not Given" so that the order will be "completed"

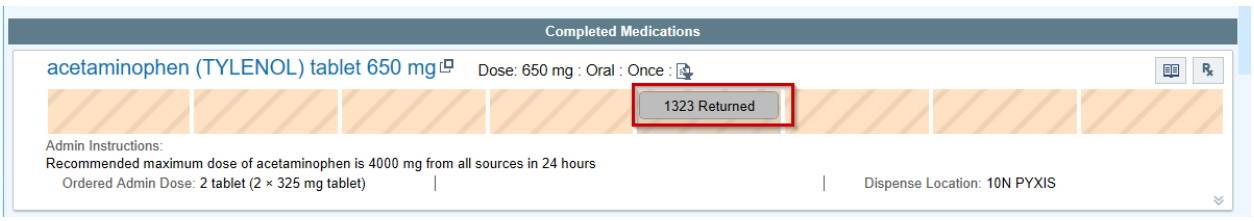
**Reason Workflow is Not Acceptable:**
Relying on nursing education as a solution to a patient safety issue is not acceptable. Any time a staff member has to remember to do something outside of a normal common-sense workflow, the chances are that it will not occur the majority of the time. We need a solution that makes logical sense to our bedside nurses.

**User Impact:**
Nursing staff that document administration of medications on the MAR: inpatient, ED, perioperative

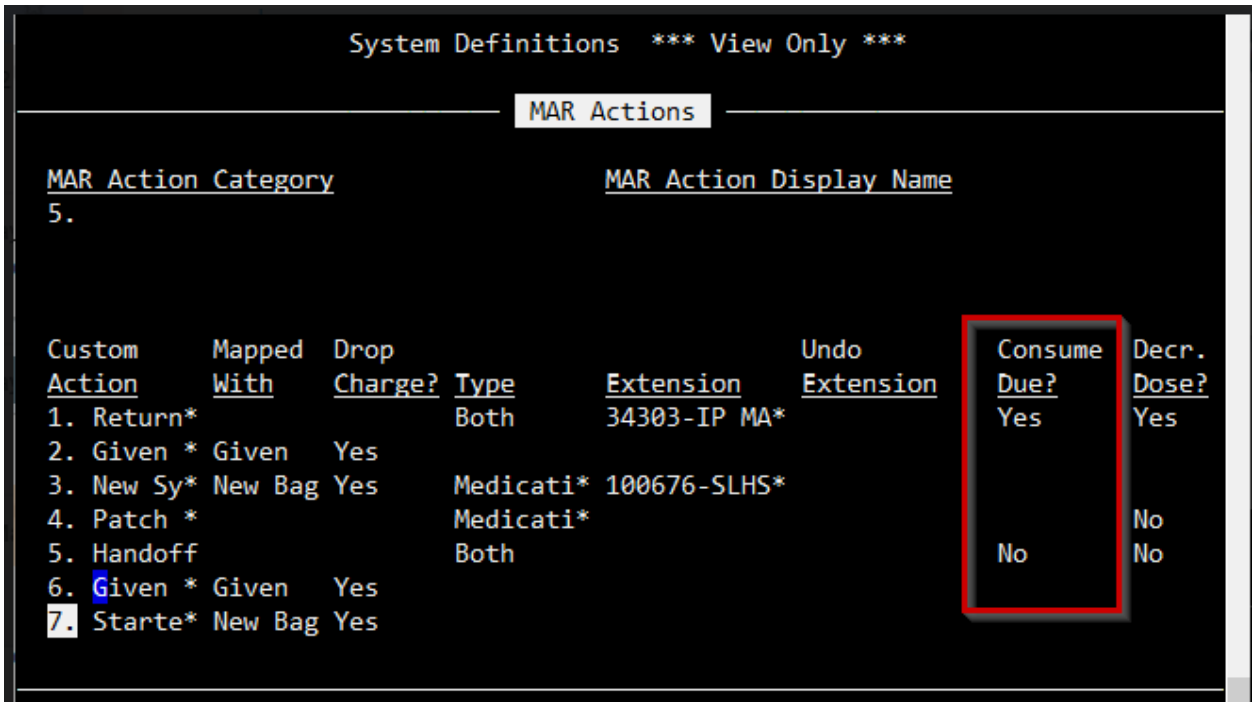
**Screenshots:**
"Once" order documented as "Not Given". The order remained active following documentation.




"Once" order documented as "Return to Cabinet". The order changed to a Completed status.



System Definitions that control if MAR Actions “Consume Due?”




**Discussion:**

- **How long should medication orders with the frequency of “once” remain active/available for administration on the MAR if not documented as “not given”? 12 hours, 24 hours?**

## POLICY

| Title: **MEDICATION ADMINISTRATION – TIMELINESS OF SCHEDULED MEDICATIONS** | | | |
|---|---|---|---|
| | | Page **1** of **5** | |
| Policy Number: MM-05455 | | Date Last reviewed/Revised: 2/23 | Valid Until: 2/26 |
| **Campus**: ☒ CHI Memorial Glenwood ☒ CHI Memorial Hixson ☒ CHI Memorial Georgia *Check all that apply* | | | |
| Department(s) Affected: All Departments | | Review Period: every 3 years | |

**OUTCOME:**
Timely administration of patient medication to support the delivery of scheduled medications in a timely manner to provide safe and effective patient care, and to maintain therapeutic blood levels over a period of time.

**POLICY:**
Centers for Medicare & Medicaid Services (CMS) and the Institute for Safe Medication Practices (ISMP) support the timely administration of patient medication in order to optimize pharmacotherapy.
The purpose of this policy is to:

a. Group medications according to time-critical dosing
b. Offer time based dosing guidelines

**Medications Not Eligible for Scheduled Dosing Times**

I. Definition: Medications which are not eligible for scheduled dosing times are medications which require exact or precise timing of administration, based on diagnosis type, treatment requirements, or therapeutic goals. These medications are NOT administered according to a standard repeated cycle of frequency.
II. Examples
    a. Stat and Now doses (immediate)
    b. First time or loading doses
    c. One-time doses
    d. Doses specifically timed for procedures
    e. On-call doses
    f. Time-sequenced doses or concomitant medications (chemotherapy and rescue agents, n-acetylcysteine and iodinated contrast media)
    g. Investigational medications (administration time defined by the clinical research)
    h. PRN medications
III. Procedure: Medications not eligible for scheduled dosing times should be administered in a timely manner, considering reasonable preparation and delivery times. This applies to administration of these medications hospital-wide.

**Medications Eligible for Scheduled Dosing Times (Scheduled Medications)**

**I.** **Definition:** Scheduled medications include medications where maintenance doses are administered according to a standard, repeated cycle of frequency. Surgical and intra-procedural areas are not subject to following scheduled dosing times.
**II.** **Examples:** Daily, BID, TID, q4h, q12h, weekly, etc.
**III.** **Time-Critical Scheduled Medications**
    **A.** **Definition:** Time-critical scheduled medications are those where early or delayed administration of greater than 30 minutes from the scheduled administration time may cause

harm or have a significant, negative impact on the intended therapeutic or pharmacological effect.

**B. Examples of scheduled medications that are always time-critical, hospital-wide:**

a. Antibiotics: Vancomycin, Tobramycin, Gentamicin, and Amikacin. Although scheduled dosing times are used for antibiotic doses on MAR, actual administration times may vary depending on lab collection times in regard to therapeutic drug levels for these antibiotics.

b. Anticoagulants: Therapeutic doses of oral and injectable anticoagulants. This excludes warfarin and prophylactic doses of injectable anticoagulants (enoxaparin 40 mg, fondaparinux 2.5 mg)

c. Insulins: Rapid-, short-, or ultra-short-acting insulins are considered time-critical in relation to meal consumption time. Although scheduled dosing times are used for insulin doses on MAR, actual administration time should be based on meal delivery time and actual consumption of the meal.

**C. Procedure:**

a. Time-critical scheduled medications will be designated on the MAR with the Product Instructions "Time-Critical Med".

b. Medication Due time will turn red and be considered overdue 30 minutes after the scheduled administration time.

c. Time-critical scheduled medications will be administered:

1. At the exact time indicated when necessary, or
2. Within 30 minutes before or 30 minutes after the scheduled administration time, for a total administration time window of 1 hour

**IV. Non-Time-Critical Scheduled Medications**

**A. Definition:** Non-time-critical scheduled medications are those where early or delayed administration within a range of 1 hour from the scheduled administration time should not cause harm or have a significant, negative impact on the intended therapeutic or pharmacological effect.

**B. Procedure:**

a. Medication Due time will turn red and be considered overdue 60 minutes after the scheduled administration time.

b. Non-time-critical scheduled medications will be administered within 60 minutes before or 60 minutes after the scheduled administration time, for a total administration time window of 2 hours.

**V. Use of Professional Judgment:** Staff are expected to use their professional judgment in organizing and prioritizing patient care work-loads to assure that medications are delivered in a safe and timely manner. In exercising such judgment staff must take into account the following:

**A.** Complex nature and variability among medications; the indications for which they are prescribed; the clinical situations in which they are administered; and the needs of the patients receiving them

**B.** Prioritization of additional activities that may be required, in the case of particular drugs, such as vital sign assessment or the collection and review of blood work, to ensure safe and timely medication administration.

## VI. Standard Scheduled Administration Times

A. **Standard administration schedules** will be adhered to based on the prescribed dosing frequency whenever possible. See Standard Scheduled Administration Times chart below.

B. **First Doses**
   a. New medication orders will be scheduled according to standard scheduled administration times.
   b. The ordering provider has the option to include a first dose "now" or to have it scheduled by the system according to standard dosing times. The pharmacist will use clinical judgment at verification to determine whether additional dosing adjustments may be needed.

C. **Subsequent doses** should be given according to standard scheduled administration time guidelines.
   a. In most instances, the standard dosing schedule will begin with the second dose. However, the pharmacist may use clinical judgment to modify the standard schedule for the first 1-3 doses.
   b. The ordering provider also has the option to "Adjust Schedule" to change standard scheduled dosing times.

D. **Exceptions**
   a. Exceptions to the standard scheduled administration times will be allowed if the physician orders the medication to be given at a specific time, or in a unique patient situation
   b. Exceptions to standard scheduled administration times may be appropriate to stagger numerous IV piggyback medications, or to keep a time-critical chronic medication on the same schedule used prior to admission.
   c. Nursing may request changes to standard scheduled administration times if:
      1. Schedule adjustments are needed for IV cardiac medications
      2. Schedule adjustments are needed for IV antibiotics

**Standard Scheduled Administration Times**

| Ordered Frequency | Scheduled Dosing Times |
|---|---|
| Daily | 0900 |
| Every morning before breakfast | 0730 |
| Daily with breakfast | 0800 |
| Daily before lunch | 1130 |
| Daily with lunch | 1200 |
| Every evening before dinner | 1630 |
| Daily with dinner | 1700 |
| Every night | 2100 |
| 2 times daily | 0900, 2100 |
| 2 times daily (RT) | 0800, 2000 |
| Every 12 hours scheduled | 0900, 2100 |
| 2 times daily diuretic | 0900, 1700 |
| 2 times daily before meals | 0730, 1630 |
| 2 times daily with breakfast and lunch | 0800, 1200 |
| 2 times daily with breakfast and dinner | 0800, 1700 |
| 3 times daily | 0900, 1500, 2100 |
| 3 times daily (RT) | 0800, 1400, 2000 |

| | |
|---|---|
| 3 times daily before meals | 0730, 1130, 1630 |
| 3 times daily with meals | 0800, 1200, 1700 |
| 3 times daily after meals | 0900, 1300, 1800 |
| Every 8 hours scheduled | 0500, 1300, 2100 |
| Every 8 hours (RT) | 0000, 0800, 1600 |
| Every 8 hours while awake (RT) | 0800, 1600 |
| 4 times daily | 0900, 1300, 1700, 2100 |
| 4 times daily (before meals and nightly) | 0730, 1130, 1630, 2100 |
| 4 times daily (with meals and nightly) | 0800, 1200, 1700, 2100 |
| 4 times daily (after meals and nightly) | 0900, 1300, 1800, 2100 |
| Every 6 hours scheduled | 0000, 0600, 1200, 1800 |
| Every 6 hours (RT) | 0200, 0800, 1400, 2000 |
| Every 6 hours while awake (RT) | 0800, 1400, 2000 |
| 5 times daily | 0100, 0900, 1300, 1700, 2100 |
| Every 4 hours scheduled | 0100, 0500, 0900, 1300, 1700, 2100 |
| Every 4 hours scheduled (RT) | 0000, 0400, 0800, 1200, 1600, 2000 |
| Every 4 hours while awake | 0900, 1300, 1700, 2100 |
| Every 4 hours while awake (RT) | 0800, 1200, 1600, 2000 |
| Every 3 hours | 0300, 0600, 0900, 1200, 1500, 1800, 2100, 0000 |
| Every 3 hours while awake | 0800, 1100, 1400, 1700, 2000, 2300 |
| Every 3 hours while awake (RT) | 0700, 1000, 1300, 1600, 1900, 2200 |
| Every 2 hours | 0200, 0400, 0600, 0800, 1000, 1200, 1400, 1600, 1800, 2000, 2200, 0000 |
| Every 2 hours while awake | 0800, 1000, 1200, 1400, 1600, 1800, 2000, 2200 |

## VII. Early/Late/Missed Administrations

**A.** Time-critical and non-time-critical medications may be given early or late, or may be omitted in some clinical situations. Notify physician if medication is withheld due to a change in patient status.

**B.** Staff administering medications should always reference past administration times on the MAR. This helps to avoid early administration of a medication that was previously administered late, resulting in a dosing interval that is too short.

**C.** **Overdue medications** will show as overdue on Patient List, the Work List, and the Brain. The Due time will be highlighted red on the MAR until documented.

**D.** **Early/Late Administration**

a. Any early or late medication administration is to be documented at the time the medication was actually given.

b. The appropriate Off Schedule Reason must be documented on the MAR (i.e. No IV Access/Loss of IV Access, NPO, Patient not available at scheduled time, etc.).

c. Nurse or RT will review MAR to ensure that future scheduled due times are appropriate.

**E.** **Missed Administrations**

a. Any missed medication dose is to be documented using the appropriate MAR Action (i.e. Not Given, Hold, Recheck, etc.). This includes medications due while the MAR is on hold (i.e. patient in surgery) that appear as "Auto Held" on the MAR.

b. The Reason for the missed dose must be documented on the MAR.

**F. Schedule Adjustment**

a. If a medication dose has been late/missed for any reason, the nurse (in collaboration with the pharmacist and/or physician) will decide whether the late/missed dose should be rescheduled. This decision will be based on the type of medication that is involved, how it is being used, and the patient's condition.
   1. If the late/missed medication is a non-time-critical medication, the nurse may use his/her own judgment regarding rescheduling of doses
   2. If the late/missed medication is a time-critical medication, the nurse must notify the pharmacist and/or physician regarding rescheduling of doses

b. Adherence to standard scheduled administration times is recommended whenever possible when rescheduling a medication dose.

c. The rescheduled dose may be documented as an "Off Schedule" dose on the MAR.

**G. Adverse Outcomes**

a. When an adverse outcome is anticipated or has occurred due to a late/missed medication dose, the following will be completed:
   1. Provider notification
   2. Patient notification
   3. Occurrence report

b. Data from occurrence reports should be used to identify the causes of early/late/missed medication administration, to revise the list of time-critical drugs as appropriate, and to make system-based changes to facilitate timely order review, dispensing, and administration of medications.

c. A non-punitive policy and just culture algorithms should be used to evaluate cases of late/missed medication administration. The goal is to remedy the processes and environmental conditions that contributed to untimely administration.

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**Key Contact:** Pharmacy/Nursing Committee
**Approved/Reviewed by:** Director of Pharmacy, Pharmacy & Therapeutics Committee
**Joint Commission Standard:** Medication Management (MM)
**References:** Centers for Medicare & Medicaid Services (CMS) and the Institute for Safe Medication Practices (ISMP)
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