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Pharmacotherapy Update

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Pegloticase: A New Treatment for Gout

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Indications: Pegloticase (Krystexxa™; Savient Pharmaceuticals) is a PEGylated uric acid specific enzyme indicated for the treatment of chronic gout in adult patients who no longer respond to conventional therapy. It is an intravenous (IV) medication reserved for patients who remain symptomatic and fail to achieve normal serum uric acid levels despite treatment with maximum doses of xanthine oxidase inhibitors. It can also be used when xanthine oxidase therapy is contraindicated. Pegloticase is not recommended for the treatment of asymptomatic hyperuricemia.

Mechanism of Action: Pegloticase lowers uric acid levels by catalyzing the oxidation of uric acid to allantoin, a highly soluble inert metabolite which is readily eliminated, primarily through renal excretion. It does not inhibit the formation of uric acid.

Clinical Studies: Two multicenter, double-blind, placebo-controlled studies randomized patients to receive pegloticase 8 mg IV every 2 weeks or every 4 weeks or placebo in a 2:2:1 ratio. Approximately 71% of patients had baseline tophi. Patients were given nonsteroidal anti-inflammatory drugs (NSAIDs) or colchicine as prophylaxis for gout flares at least 1 week prior to pegloticase therapy. Inclusion criteria were as follows: patients with a baseline uric acid level ≥ 8 mg/dL, symptomatic gout with at least three gout flares in the previous 18 months or at least one episode of gout typhus or gouty arthritis and either a contraindication or treatment resistance to allopurinol (failure to achieve uric acid level < 6 mg/dL after at least 3 months of therapy at the maximum tolerated dose). The primary endpoint of both trials was the proportion of patients who achieved a plasma uric acid level < 6 mg/dL. A secondary endpoint included improved effects on tophi defined as a 100% resolution of a single target tophus, no new tophi appearing, and no single tophi progressing. A greater proportion of patients receiving pegloticase every 2 weeks achieved a uric acid level lower than 6 mg/dL than those receiving placebo ($p<0.001$). Although significantly more patients receiving the drug every 4 weeks attained a plasma uric acid level < 6 mg/dL than those receiving placebo ($p< 0.044$), this less frequent dosage regimen was associated with an increased incidence of anaphylaxis and infusion-related reactions. Furthermore, only the 2-week regimen achieved statistical significance for the secondary endpoint of tophi resolution compared to placebo ($p=0.001$).

Adverse Effects: The most common adverse reactions observed during the clinical trials which evaluated pegloticase included gout flare, infusion-related reactions, nausea, contusion or

ecchymosis, nasopharyngitis, constipation, chest pain, anaphylaxis, and vomiting (See Table 1). Gout flares may occur due to mobilization of uric acid from tissue deposits. To prevent pegloticase-induced gout flares, the manufacturer recommends prophylaxis with an NSAID or colchicine, beginning at least 1 week prior to initiating therapy and continuing for at least 6 months. Pegloticase should be used with caution in patients with congestive heart failure, since there have been reports of drug-induced heart failure exacerbations.

Table 1: Adverse Reactions in ≥ 5% of Patients Treated with Pegloticase versus Placebo

Adverse Reaction	Pegloticase (Krystexxa™) N=85 N (%)	Placebo N=43 N (%)
Gout Flare	65 (77%)	35 (81%)
Infusion Reaction	22 (26%)	2 (5%)
Nausea	10 (12%)	1 (2%)
Contusion or Ecchymosis*	9 (11%)	2 (5%)
Nasopharyngitis	6 (7%)	1 (2%)
Constipation	5 (6%)	2 (5%)
Chest Pain	5 (6%)	1 (2%)
Anaphylaxis	4 (5%)	0 (0%)
Vomiting	4 (5%)	1 (2%)

Adapted from: Krsytexxa™ package insert. East Brunswick, NJ: Savient Pharmaceuticals, Inc.; 2010 September.
*Most did not occur on the day of infusion and could be related to other factors

Contraindications: Pegloticase is contraindicated in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency due to the risk of hemolysis and methemoglobinemia. Patients of African and Mediterranean ancestry have a higher incidence of G6PD deficiency and should be tested for this condition prior to initiation of therapy.

Black Box Warning and REMS: Pegloticase carries a black box warning and a Risk Evaluation and Mitigation Strategy (REMS) concerning the occurrence of anaphylaxis, infusion-related reactions, and the contraindication of use in patients with G6PD deficiency. The risk of anaphylaxis is higher in patients treated with pegloticase whose uric acid level increases to > 6 mg/dL, especially in cases when two consecutive > 6 mg/dL levels are observed. Due to these concerns, the following precautions should be taken:

- Patients at higher risk for G6PD deficiency (e.g., African or Mediterranean ancestry) should be screened prior to initiating therapy
- Pegloticase should only be administered in a healthcare setting by healthcare providers
- Patients should be pre-treated with antihistamines and corticosteroids prior to each dose
- Patients should be closely monitored for anaphylaxis after each dose. Serum uric acid level should be measured prior to infusions; if levels increase to > 6 mg/dL, discontinuation of treatment should be considered especially if two consecutive levels > 6 mg/dL are observed

Pregnancy and Lactation: Pegloticase is classified as a pregnancy-risk category C. There are currently no data from animal reproductive studies or well-controlled studies in pregnant women. It is unknown whether pegloticase therapy will cause fetal harm in pregnant women or affect reproductive capacity. Although lactation studies have not confirmed that the drug is excreted in the breast milk, the manufacturer does not recommend its use in nursing mothers due to the potential risks to the breastfed infant.

Drug Interactions: There have been no studies conducted to examine potential drug interactions with pegloticase. Anti-pegloticase antibodies bind to the PEG portion of pegloticase and may also bind with other pegylated products. However, the impact of these antibodies on other pegylated products is unknown.

Dose and Administration: The recommended dose of pegloticase is 8 mg diluted in 250 mL of 0.9% sodium chloride. The final diluted solution is stable for 4 hours refrigerated or at room temperature. The manufacturer recommends that the pegloticase infusion be refrigerated, protected from light, and used within 4 hours of dilution. The infusion should be warmed to room temperature prior to administration however artificial heating (e.g., hot water, microwave) should never be used. An antihistamine and a corticosteroid need to be given prior to the pegloticase dose which should be infused over at least 2 hours. Patients should be monitored for approximately 1 hour after administration. The dose is repeated every 2 weeks. The optimal duration of therapy for pegloticase has not been determined.

Availability: Pegloticase (Krystexxa™) which is supplied as a single-use 8 mg/mL (2 mL) vial has an average wholesale price (AWP) of $2,760 per vial. This product is currently not on the Cleveland Clinic Formulary however it will be reviewed for formulary addition by the CCHS Medical Staff Pharmacy and Therapeutics Committee in June 2011.

References Provided Upon Request

Formulary Update

The CCHS Medical Staff P&T Committee met on Monday, April 4, 2011, and the Cleveland Clinic Local P&T Committee met on April 5, 2011, and the following decisions were made:

Additions:

Adults:

1. **Denosumab (Xgeva®):** It is FDA-approved for the prevention of skeletal-related events in patients with bone metastases from solid tumors. The dosing for this indication is 120 mg SQ every 4 weeks which differs from the dosing for denosumab (Prolia™) for the treatment of osteoporosis in postmenopausal females which is 60 mg SQ as a one time dose every 6 months. The use of Xgeva® is **restricted** to the **outpatient** setting only and will mainly be used in the Taussig Cancer Center.
2. **Eribulin (Halven®):** It is FDA-approved for the treatment of patients with metastatic breast cancer who have previously received at least two chemotherapeutic regimens for the treatment of metastatic disease. The recommended dose of eribulin is 1.4 mg/m^2 administered intravenously over 2 to 5 minutes on Days 1 and 8 of a 21-day cycle. Dosage adjustments are recommended for hepatic and renal impairment. This drug is not a known vessicant or irritant. Use of eribulin will mainly be in the Taussig Cancer Center.
3. **Capsaicin 8% Patch (Qutenza®):** It is FDA-approved for the management of neuropathic pain associated with postherpatic neuralgia (PHN). The prescription strength capsaicin 8% patch is 100-300 times more potent than any of the over-the-counter capsaicin products; therefore, special application and removal procedures are recommended for Qutenza®. Only physicians or health care professionals under the close supervision of a physician are to administer Qutenza®. Topical anesthetic is applied before the capsaicin 8% patch; up to four patches can be applied at one time. The capsaicin 8% patch is applied for 60 minutes then gently removed. Next, the supplied Cleansing Gel is applied and removed with a dry wipe after 1 minute. Only nitrile gloves should be used when handling the capsaicin 8% patch and when cleaning the treatment areas. Acute pain occurring during and after the procedure can be treated with local cooling and/or analgesics. The manufacturer of Qutenza® recommends that the patches should not be bent or folded during storage in order to maintain patch integrity. Qutenza® is **restricted** to the **outpatient** setting only.
4. **IncobotulinumtoxinA (Xeomin®):** It is FDA-approved for adults with cervical dystonia, to decrease the severity of abnormal head position and neck pain in both botulinum toxin-naïve and previously treated patients and for blepharospasm in adults previously treated with OnabotulinumtoxinA (Botox®). The use of Xeomin® is **restricted** to the Departments of Neurology and Ophthalmology for **outpatient** use only. OnabotulinumtoxinA (Botox®), AbobotulinumtoxinA (Dysport™), and RimabotulinumtoxinB (Myobloc®) remain on the Formulary with restrictions to **outpatient** use only.
5. **Polidocanol (Asclera®):** It is FDA-approved for use as a sclerosing agent indicated to treat uncomplicated spider veins (varicose veins ≤ 1 mm in diameter) and uncomplicated reticular veins (varicose veins 1 to 3 mm in diameter) in the lower extremity. Its use will mainly be by the Departments of Dermatology and Vascular Medicine.
6. **Methyl-aminoevulinate (Metvixia®):** It is FDA-approved in combination with the Aktilite® CL123 lamp (i.e., a narrowband, red light illumination source) for treatment of thin and moderately thick, non-hyperkeratotic, non-pigmented actinic keratoses of the face and scalp in immunocompetent patients when used in conjunction with lesion preparation in the physician's office when other therapies are considered medically less appropriate. Metvixia® cream is contraindicated in patients with allergies to peanut and/or almond oil. Its use is **restricted** to the Department of Dermatology for **outpatient** use only.

Children's Hospital/Pediatrics:

1. **Lidocaine cream (LMX®):** Due to a quicker onset of action (30 minutes) compared to other topical anesthetic creams such as lidocaine/prilocaine cream (EMLA®) (60 minutes), LMX® was added as an alternative to EMLA®. As a result, EMLA® is being removed from the Children's Hospital/Pediatric Formulary.
2. **Vasolex® ointment:** Alternative for Xenaderm® ointment. This conversion has already been completed for adults.

Change in Formulary Restriction;

1. **Methylnaltrexone (Relistor®):** Currently, methylnaltrexone is on the Formulary restricted to the Department of Hematology and Medical Oncology and Palliative Care Medicine and now the restriction will be expanded to include use by practitioners involved with Pain Management/Pain Medicine.

Not Added:

Adults:

1. **Intravenous ibuprofen (Caldolor®):** Should not be ordered, stocked, or dispensed. The Committee determined that there is no advantage over other formulary agents.
2. **Exenatide (Byetta®):** Should not be ordered, stocked, or dispensed (not even for continuation of therapy from home). The Committee determined that this agent is not needed for inpatients; patients can be managed on other formulary agents.
3. **Liraglutide (Victoza®):** Should not be ordered, stocked, or dispensed (not even for continuation of therapy from home). The Committee determined that this agent is not needed for inpatients; patients can be managed on other formulary agents.

Children's Hospital/Pediatrics:

1. **Lidocaine/tetracaine topical patch (Synera®):** Should not be ordered, stocked, or dispensed. Lidocaine cream (LMX®) will be used as the Formulary alternative.

Therapeutic Interchange:

Adults:

1. **Pantoprazole (generic; Protonix®):** The CCHS Medical Staff P&T Committee agreed to change the preferred proton pump inhibitor (PPI) for all Cleveland Clinic Health System (CCHS) to an all pantoprazole product line (e.g., injection, oral suspension, and tablets). Overall the cost savings for the health system for this change in PPI product line will be ~$390,000 per year. Further communication will be sent regarding the implementation date for the new therapeutic interchange to pantoprazole, until then, please continue to adhere to our current PPI therapeutic interchange.

Drug Use Policy:

1. **Hypertonic Saline:** The CCHS Medical Staff P&T Committee agreed to limit the standard concentrations of intravenous hypertonic saline to 2% (peripheral), 3% (central) and 23.4% (central). This policy change will be effective May 3, 2011.