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Month/Year of Review: February 2012
Date of Last Review: Sept 2010
PDL Class: Analgesics for Gout
Source Document: Provider Synergies (PS)

Current Preferred Agents:
Allopurinol
Colchicine/probenecid

Current Non-Preferred Agents:
Colcyrs® (colchicine)
Probenecid
Uloric® (febuxostat)

Previous Recommendations:

1. There is moderate-quality evidence that there is no difference in efficacy/effectiveness or in safety between agents.
2. Colchicine is the only agent for gout and Famalial Mediterranean Fever.
3. Febuxostat reduces serum urate below 6mg/dl in a significantly greater proportion of patients with gout and hyperuricemia compared to patients receiving allopurinol but with no difference in gout flares.
4. Recommend inclusion of each chemical entity.
5. Consider PA for febuxostat for intolerance or ineffectiveness of allopurinol.

PA Criteria/QL: Patient must have a covered ICD9 diagnosis.

Background:

Treatment of gout is managed in three stages. Acute gout can be treated with colchicine, nonsteroidal anti-inflammatory drugs (NSAIDS), and intra-articular corticosteroid injections. After treatment of an initial gout attack, uricosuric drugs (probenecid) or xanthine oxidase inhibitors (allopurinol and febuxostat) can be used to lower uric acid to a goal of <6mg/dl. Febuxostat has not been studied in patients with secondary hyperuricemia and has not been shown to improve outcomes. It can be an alternative to allopurinol for patients who fail to achieve serum urate less than 6mg/dl after three months or are intolerant of allopurinol treatment. Pegloticase (Krystexxa), a pegylated uric acid specific enzyme, is the latest FDA approved agent and is indicated only for the management of refractory gout and administered intravenously. In clinical trials, pegloticase 8 mg administered intravenously every two weeks was shown to lower serum uric acid level and significantly improve a course of gout in patients with very severe and refractory disease. Due to the risk of anaphylaxis and infusion reactions, pegloticase should be administered intravenously under the supervision of a healthcare professional and should be billed under the Medical benefit. Its use should be restricted to patients who are refractory to conventional therapies such as oral allopurinol, probenecid and Uloric.

Methods:
A MEDLINE OVID search was conducted using all treatments for acute and chronic gout limited to randomized controlled trials and meta-analysis, English language, and conducted in humans since the literature search conducted for the previous PS review. The Agency for Healthcare Research and Quality (AHRQ), Cochrane Collection, the Department of Veteran Affairs, and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were searched for high quality systematic reviews. The FDA website was searched for new drugs, indications, and safety alerts, and the AHRQ National Guideline Clearinghouse (NGC) was searched for updated and recent evidence-based guidelines.

New Trials:

A total of 41 citations resulted and after review for inclusions, three potentially relevant clinical trials were identified (Appendix 1). A randomized, double-blind study compared low-dose colchicine (1.2mg followed by 0.6mg one hour later) and high-dose colchicines (4.8 mg total over 6 hours) with placebo in gout flares, demonstrating superior safety of low-dose colchicine, without loss of efficacy, compared to high-dose.[1] Rates of response was defined by target joint pain score 24 hours after the first dose were similar for the recommended low-dose treatment group and the non-recommended high-dose group (high-dose vs. placebo, OR 2.64, 95% CI1.06-6.62, p=0.034; low-dose vs. placebo, OR 3.31 95% CI 4.41-7.77, p=0.005).[1] Patients in the high-dose group reported significantly more diarrhea, vomiting, and other adverse events (76.9% diarrhea, 19.2% severe diarrhea, OR 21.3, 95%CI 7.9-56) compared with the low-dose (23% diarrhea, no severe diarrhea, OR 1.9, 95% CI 0.8-4.8) and placebo groups. Another identified trial published the two randomized controlled trials which assessed the efficacy and safety of pegloticase (Krystexxa), the newest medication for treatment of gout.[2]

New drugs:

Pegloticase (Krystexxa) IV-

- Indication: The first pegylated uric acid specific enzyme approved for treatment of chronic gout in adults refractory to conventional therapy. It is not recommended in patients with asymptomatic hyperuricemia.
- Efficacy: The safety and efficacy of pegloticase 8mg every 2 weeks or every 4 weeks were evaluated in adult patients with chronic gout refractory to conventional therapy in two, randomized, placebo-controlled, double-blind, 6-month replicate studies.[2,3] All subjects were defined as having a uric acid level of 8mg/dl or higher, intolerance or failure of response to allopurinol treatment, and at least 1 of the following: 3 or more gouty attacks in the previous 18 months, a tophus or gouty arthritis. The primary endpoint in both trials was the proportion of responders, defined as patients achieving serum uric acid < 6 mg/dL for at least 80% of the time during Month 3 and Month 6.

Treatment Group	N	Number (%) with PUA levels less than 6 mg/dL	95% Confidence Interval*	P-Value#
Study 1 (C0405)	104			
Pegloticase 8 mg biweekly	43	20 (47%)	[32%, 61%]	< 0.001^
Pegloticase 8mg monthly	41	8 (20%)	[7%, 32%]	0.044^
Placebo	20	0 (0%)	--	--
Study 2 (C0406)	108			
Pegloticase 8 mg every 2 weeks	42	16 (33%)	[23%, 53%]	0.001^
Pegloticase 8 mg every 4 weeks	43	21 (49%)	[34%, 64%]	< 0.001^
Placebo	23	0 (0%)	--	--

*Confidence interval is for difference in responder rate between Krystexxa and placebo; ^Compared to placebo; #Composite P-Value (GOUT1 and GOUT2) is < 0.001 compared to placebo.

- Safety: Because of risks of hemolysis and methemoglobinemia, pegloticase is contraindicated in G6PD deficiency. Patients at increased risk of this deficiency (e.g., those of African or Mediterranean ancestry) should be screened prior to initiation of therapy. Patients treated with pegloticase are at risk of anaphylaxis and must be pre-treated with antihistamines and corticosteroids (Black box warning). Risk of anaphylaxis is further increased in those with serum uric acid (SUA) levels above 6 mg/dL. Uric acid (UA) levels should be monitored prior to infusion with consideration of discontining pegloticase if UA levels increase above 6 mg/dL, particularly if two consecutive levels > 6 mg/dL are observed. In clinical trials, the most common serious adverse events (SAEs) noted were anaphylaxis (5%), infusion reactions (e.g., urticaria, dyspnea, chest discomfort, chest pain, erythema, pruritus)(26%), and gout flares in the first three months (77%).

Other adverse events occurring in ≥ 5% were: nausea and vomiting,, contusion or ecchymosis, nasopharyngitis, constipation, and chest pain.

- Dosing: 8mg IV over no less than 2 hours every 2 weeks; premedicate with antihistamines and corticosteroids. Pegloticase must be administered in a healthcare setting by a healthcare professional with appropriate medical therapy available in case there is an anaphylactic or infusion reaction

New FDA Indications:
None

New FDA safety alerts:
None

Other FDA alerts:
In 2010, the FDA stopped the marketing of unapproved single-ingredient oral colchicine.[4] This included all generic products. Colcrys is currently the only FDA-approved single-ingredient oral colchicine product available. Multisource colchicines products have not demonstrated bioequivalence to an innovator product and are not considered generics nor have the multisource products received Food and Drug Administration (FDA) approval.4

New Systematic Reviews:
None identified

Guidelines:
None identified.

Recommendations:
1. Since pegloticase is IV and only administered by a healthcare professional; no further research or review needed.

2. Block pegloticase claims billed by pharmacies.

Appendix 1:

1. Terkeltaub RA, Furst, DE, Bennett K, et al. High versus low dosing of oral colchicines for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicines study. *Arthritis Rheum.* 2010;62(4):1060-1068.

   Objective: Despite widespread use of colchicine, the evidence basis for oral colchicine therapy and dosing in acute gout remains limited. The aim of this trial was to compare low-dose colchicine (abbreviated at 1 hour) and high-dose colchicine (prolonged over 6 hours) with placebo in gout flare, using regimens producing comparable maximum plasma concentrations in healthy volunteers
   Methods: This multicenter, randomized, double-blind, placebo-controlled, parallel-group study compared self-administered low-dose colchicine (1.8 mg total over 1 hour) and high-dose colchicine (4.8 mg total over 6 hours) with placebo. The primary end point was > or = 50% pain reduction at 24 hours without rescue medication.
   Results: There were 184 patients in the intent-to-treat analysis. Responders included 28 of 74 patients (37.8%) in the low-dose group, 17 of 52 patients (32.7%) in the high-dose group, and 9 of 58 patients (15.5%) in the placebo group (P = 0.005 and P = 0.034, respectively, versus placebo). Rescue medication was taken within the first 24 hours by 23 patients (31.1%) in the low-dose group (P = 0.027 versus placebo), 18 patients (34.6%) in the high-dose group (P = 0.103 versus placebo), and 29 patients (50.0%) in the placebo group. The low-dose group had an adverse event (AE) profile similar to that of the placebo group, with an odds ratio (OR) of 1.5 (95% confidence interval [95% CI] 0.7-3.2). High-dose colchicine was associated with significantly more diarrhea, vomiting, and other AEs compared with low-dose colchicine or placebo. With high-dose colchicine, 40 patients (76.9%) had diarrhea (OR 21.3 [95% CI 7.9-56.9]), 10 (19.2%) had severe diarrhea, and 9 (17.3%) had vomiting. With low-dose colchicine, 23.0% of the patients had diarrhea (OR 1.9 [95% CI 0.8-4.8]), none had severe diarrhea, and none had vomiting.
   Conclusion: Low-dose colchicine yielded both maximum plasma concentration and early gout flare efficacy comparable with that of high-dose colchicine, with a safety profile indistinguishable from that of placebo.

2. Wortmann RL, MacDonald PA, Hunt B, Jackson RL. Effect of Prophylaxis on Gout Flares After the Initiation of Urate-Lowering Therapy: Analysis of Data From Three Phase III Trials. *Clinical Therapeutics*. 2010;32(14):2386-2397.

   Objective: The present analysis examined flare rates during the 3 Phase III trials of febuxostat based on mean postbaseline serum urate (sUA) concentrations and duration of prophylaxis. Adverse events (AEs) were assessed by prophylaxis with colchicine or naproxen.
   Methods: This investigator-initiated, post hoc reanalysis of data on gout flares from the 3 randomized, placebo-controlled, Phase III trials evaluated the proportion of patients requiring treatment for gout flares at 4-week intervals based on mean postbaseline sUA concentrations <6.0 and ≥6.0 mg/dL. The 3 trials enrolled males or females aged 18–85 years who had a diagnosis of gout and a baseline sUA concentration ≥8.0 mg/dL. Patients received ULT (febuxostat or allopurinol) or placebo for 6 months or 1 year and flare prophylaxis with colchicine 0.6 mg/d or naproxen 250 mg BID for 8 weeks or 6 months. The prophylactic regimen was chosen at the discretion of the investigator, based on renal function and known intolerance to either drug. Patients with an estimated creatinine clearance <50 mL/min were not to receive naproxen. AEs were summarized based on prophylaxis with colchicine or naproxen.
   Results: The 3 trials enrolled a total of 4101 patients with gout. The majority were white (80.1%), male (94.5%), and obese (body mass index ≥30 kg/m2) (62.8%). The mean duration of gout ranged from 10.9–11.9 years, and the mean baseline sUA concentration ranged from 9.6–9.9 mg/dL. Flare rates increased sharply (up to 40%) at the end of 8 weeks of prophylaxis and then declined gradually, whereas flare rates were consistently low (range, 3%–5%) at the end of 6 months of prophylaxis. Mean postbaseline sUA concentrations were correlated with flare rates; by the end of each study, patients with a mean postbaseline sUA concentration <6.0 mg/dL had fewer flares than did those with a mean postbaseline sUA concentration ≥6.0 mg/dL. There were differences in rates of AEs between prophylaxis groups, but the rates did not increase with increased duration of prophylaxis.
   Conclusion: This analysis of gout flare data from the 3 Phase III trials of febuxostat found that flare prophylaxis for up to 6 months during the initiation of ULT appeared to provide greater benefit than flare prophylaxis for 8 weeks, with no increase in AEs.

3. Sundy JS, Baraf HSB, Yood RA, et al. Efficacy and Tolerability of Pegloticase for the Treatment of Chronic Gout in Patients Refractory to Conventional Treatment. *JAMA: The Journal of the American Medical Association*. 2011;306(7):711 -720.

   Objective To assess the efficacy and tolerability of pegloticase in managing refractory chronic gout.

Design, Setting, and Patients Two replicate, randomized, double-blind, placebo-controlled trials (C0405 and C0406) were conducted between June 2006 and October 2007 at 56 rheumatology practices in the United States, Canada, and Mexico in patients with severe gout, allopurinol intolerance or refractoriness, and serum uric acid concentration of 8.0 mg/dL or greater. A total of 225 patients participated: 109 in trial C0405 and 116 in trial C0406.
Intervention Twelve biweekly intravenous infusions containing either pegloticase 8 mg at each infusion (biweekly treatment group), pegloticase alternating with placebo at successive infusions (monthly treatment group), or placebo (placebo group).
Main Outcome Measure Primary end point was plasma uric acid levels of less than 6.0 mg/dL in months 3 and 6.
Results In trial C0405 the primary end point was reached in 20 of 43 patients in the biweekly group (47%; 95% CI, 31%-62%), 8 of 41 patients in the monthly group (20%; 95% CI, 9%-35%), and in 0 patients treated with placebo (0/20; 95% CI, 0%-17%; $P < .001$ and <.04 for comparisons between biweekly and monthly groups vs placebo, respectively). Among patients treated with pegloticase in trial C0406, 16 of 42 in the biweekly group (38%; 95% CI, 24%-54%) and 21 of 43 in the monthly group (49%; 95% CI, 33%-65%) achieved the primary end point; no placebo-treated patients reached the primary end point (0/23; 95% CI, 0%-15%; $P = .001$ and $< .001$, respectively). When data in the 2 trials were pooled, the primary end point was achieved in 36 of 85 patients in the biweekly group (42%; 95% CI, 32%-54%), 29 of 84 patients in the monthly group (35%; 95% CI, 24%-46%), and 0 of 43 patients in the placebo group (0%; 95% CI, 0%-8%; $P < .001$ for each comparison). Seven deaths (4 in patients receiving pegloticase and 3 in the placebo group) occurred between randomization and closure of the study database (February 15, 2008).
Conclusion Among patients with chronic gout, elevated serum uric acid level, and allopurinol intolerance or refractoriness, the use of pegloticase 8 mg either every 2 weeks or every 4 weeks for 6 months resulted in lower uric acid levels compared with placebo.

References:

1. Terkeltaub RA, Furst DE, Bennett K, et al. High versus low dosing of oral colchicine for early acute gout flare: Twenty-four-hour outcome of the first multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-comparison colchicine study. *Arthritis Rheum.* 2010;62(4):1060-1068.

2. Sundy JS, Baraf HSB, Yood RA, et al. Efficacy and Tolerability of Pegloticase for the Treatment of Chronic Gout in Patients Refractory to Conventional Treatment. *JAMA: The Journal of the American Medical Association*. 2011;306(7):711 -720.

3. Center for Drug Evaluation and Research. Summary Review. application number125293. Available at: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/125293Orig1s000SumR.pdf.

4. FDA news release. Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm227796.htm.