# Therapeutic Class Review
## Anti-gout agents

| MEDICATION* | MARKETER | AVAILABILITY |
|---|---|---|
| Colchicine/probenecid | Various | **Generic**: 0.5 mg/500 mg tablet |
| **Colcrys** (colchicine)† | Takeda | **Brand:** 0.6 mg tablet |
| **Gloperba** (colchicine) § | Romeg Therapeutics | **Brand:** 0.6 mg/5 mL oral solution |
| **Krystexxa** (pegloticase) | Horizon Pharma | **Brand:** 8 mg injection |
| **Mitigare** (colchicine)† | Hikma Americas | **Brand**: 0.6 mg capsule |
| Probenecid | Various | **Generic:** 500 mg tablet |
| **Uloric** (febuxostat) | Takeda | **Brand:** 40 mg, 80 mg tablets |
| **Zyloprim** (allopurinol) | Casper | **Brand/Generic:** 100 mg, 300 mg tablets |
| **Purpose of Review:** To evaluate the safety and efficacy of the anti-gout agents for formulary consideration. | | |

*Brand names are indicated by bolded text; generic-only products are indicated by non-bolded text
†Colcrys and Mitigare are also available as co-licensed products under the brand name of colchicine
§Not yet available commercially

Note: Information on indications, pharmacology, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.


## SUMMARY

**Background**

- Gout is a form of inflammatory arthritis characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain; the episodes are referred to as acute gouty arthritis flares or attacks (*Newberry 2016*).
- The risk of cardiovascular (CV) events, including death, is significantly greater in patients with gout than in those without gout *(Choi et al 2007, Krishnan et al 2008).*
- Colchicine has been used for centuries to treat and prevent gout in adults. It was used before the creation of the Food and Drug Administration (FDA), and therefore was "grandfathered" without receiving FDA approval. In 2006, however, colchicine was formally studied, and Colcrys was officially FDA-approved for gout treatment and prophylaxis, as well as treatment of Familial Mediterranean fever. In 2014, the FDA approved Mitigare, a brand of colchicine, with an approved generic colchicine that followed a few months later. An oral liquid colchicine formulation, Gloperba, was FDA-approved in January 2019 for the prophylaxis of gout flares. Its approval was based on published colchicine studies.
- Zurampic (lesinurad) and Duzallo (lesinurad/allopurinol), FDA-approved for hyperuricemia associated with gout in 2015 and 2017, respectively, were discontinued by the manufacturer on February 1, 2019. Per the manufacturer, discontinuation was due to low utilization, rather than safety or efficacy reasons *(Ironwood Pharmaceuticals 2019).*
- During Uloric's (febuxostat) phase 3 clinical trials, there was a safety signal noted for CV events; however, the results were not found to be statistically significant. Upon approval of febuxostat in 2009, a warning for CV risk was added to the package insert, and the FDA mandated a post-marketing CV safety trial for febuxostat vs allopurinol (*FDA 2019*).
  - The results of this safety clinical trial (discussed in the Clinical Efficacy section below) led to the addition of a boxed warning for CV death and a change to the indication for febuxostat as a second-line therapy after allopurinol (see Indication section below).
  - Additional CV safety trials (in Japan and Europe) are underway to provide additional data regarding the CV risk of febuxostat vs allopurinol *(Katsiki and Borghi 2018).*

**Indication**

**Table 1. FDA-approved indications for anti-gout agents**

| Indications | Allopurinol | Colchicine |
|---|---|---|
| Management of patients with signs and symptoms of primary or secondary gout | ✓ | |
| Prophylaxis and treatment of acute gout flares | | ✓ |
| Chronic management of hyperuricemia in adult patients with gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable | | |
| Treatment of hyperuricemia associated with gout and gouty arthritis | | |
| Treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout | | |
| Treatment of chronic gout in adult patients refractory to conventional therapy | | |

- Various anti-gout agents listed in the table above have additional indications that are unrelated to gout, and will therefore not be a part of this therapeutic class review.

## Pharmacology

- Both allopurinol and febuxostat are xanthine oxidase inhibitors (XOIs) that lower serum uric acid (sUA); however, the mechanism by which they inhibit xanthine oxidase (XO) differs.
  - Allopurinol inhibits XO, the enzyme responsible for the conversion of hypoxanthine to xanthine and then xanthine to uric acid; this leads to a decrease in sUA.
  - Febuxostat lowers sUA levels by occupying a channel in the XO dimer and impairing access to purine base substrates at the active site of XO catalysis.
- The exact mechanism by which colchicine exerts its sUA lower effects is not fully understood. However, it is thought to reduce lactic acid production by leukocytes, which results in a decrease in uric acid deposition. It is also thought to reduce phagocytosis, with abatement of the inflammatory response.
- Pegloticase is a uric acid specific enzyme, which is a recombinant uricase, and achieves its therapeutic effects by catalyzing the oxidation of uric acid to allantoin, thereby lowering sUA.
- Probenecid is a uricosuric and renal tubular blocking agent. It inhibits the tubular reabsorption of urate, thus increasing the urinary excretion of uric acid and decreasing sUA levels.

## Clinical Efficacy

- CARES is a double-blind (DB), multicenter (MC), randomized, noninferiority trial that compared febuxostat 40 to 80 mg orally daily (n = 3098) to allopurinol 200 to 600 mg orally daily (dose adjusted based on renal function; n = 3092) for a median follow-up period of 32 months. Patients in this study were diagnosed with gout and had a history of CV disease (eg, myocardial infarction [MI], hospitalization for unstable angina or transient ischemic attacks [TIA], stroke, peripheral vascular disease [PVD], or diabetes mellitus [DM] with evidence of micro- or macrovascular disease) *(White et al 2018)*.
  - There was a large discontinuation rate of 56.6% during the study, as well as 45.0% of patients lost during the follow-up period.
  - A determination of noninferiority of febuxostat to allopurinol required that the upper bound of the one-sided confidence interval (CI) of the hazard ratio (HR) for the end points be < 1.3.
  - The results of the modified intent-to-treat analysis are listed in Table 2 below.

**Table 2. Results for primary and secondary endpoints in CARES trial**

| | Endpoint | Febuxostat | Allopurinol | HR | p-value |
|---|---|---|---|---|---|
| | | n (%) | HR (95% CI) | | |
| Primary endpoint | Composite of CV death, nonfatal MI, nonfatal stroke, or urgent revascularization due to unstable angina | 335 (10.8) | 321 (10.4) | 1.03 (0.87 to 1.23) | 0.66 |
| Secondary endpoints | CV death | 134 (4.3) | 100 (3.2) | 1.34 (1.03 to 1.73) | 0.03 |
| | Nonfatal MI | 111 (3.6) | 118 (3.8) | 0.93 (0.72 to 1.21) | 0.61 |
| | Nonfatal stroke | 71 (2.3) | 70 (2.3) | 1.01 (0.73 to 1.41) | 0.94 |
| | Urgent revascularization due to unstable angina | 49 (1.6) | 56 (1.8) | 0.86 (0.59 to1.26) | 0.44 |

| | | | | | |
|---|---|---|---|---|---|
| | Composite of CV death, nonfatal MI, or nonfatal stroke | 296 (9.6) | 271 (8.8) | 1.09 (0.92 to 1.28) | 0.33 |
| | Death from any cause | 243 (7.8) | 199 (6.4) | 1.22 (1.01 to 1.47) | 0.04 |

**Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction**

- While no statistically significant difference was found between the treatment groups with respect to the primary end point, there were differences noted between the treatment groups for 2 of the 6 secondary endpoints above.
  - As noted in the table above, the febuxostat group showed statistically significantly higher rates of all-cause mortality (HR 1.22; 95% CI, 1.01 to 1.47) and CV mortality (HR 1.34; 95% CI, 1.03 to 1.73) compared with the allopurinol group.
- Probenecid has been available since the 1950s and allopurinol and colchicine/probenecid have been available since the 1960s. Studies for these agents are therefore mainly limited to trials from the 1960s that were observational in nature. It should also be noted that there is limited literature evaluating the use of colchicine/probenecid.
- Several meta-analyses have been published to support the use of colchicine, febuxostat, and pegloticase in the treatment of gout *(Seth et al 2014, Sundy et al 2011, Tayar et al 2012, Van Echteld et al 2014).*

## Place in Therapy

- The American College of Rheumatology (ACR) is in the process of updating its guidelines for the management of gout (anticipated completion in the early part of 2020). Their 2012 guidelines (Part 1 and 2) for the treatment and prophylaxis of gout, however, make the following key recommendations (*Khanna et al 2012*):
  - An acute gouty arthritis attack should be treated with pharmacologic therapy, initiated within 24 hours of onset.
  - Established urate-lowering therapy (ULT) should be continued, without interruption, during an acute gout attack.
  - Monotherapy with non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids, or colchicine is recommended as first-line agents for an acute gout attack (combination therapy is appropriate in patients experiencing severe pain).
  - XOI therapy with either allopurinol or febuxostat is recommended as the first-line pharmacologic ULT in gout.
    - Probenecid is recommended as an alternative first-line pharmacologic ULT option in the setting of contraindication or intolerance to at least 1 XOI agent.
  - sUA level should be lowered sufficiently to durably improve signs and symptoms of gout, with a target of < 6 mg/dL at a minimum, and often < 5 mg/dL.
  - Combination ULT with 1 XOI and 1 uricosuric agent is appropriate when the sUA target has not been met by therapeutically-appropriate doses of an XOI monotherapy.
  - Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral urate-lowering options.
- Agency for Healthcare Research and Quality (AHRQ): Diagnosis and Management of gout: Current state of evidence *(AHRQ 2017)*
  - Effective treatments for gout attacks include NSAIDs, colchicine, and corticosteroids.
  - ULT, including allopurinol and febuxostat, reduce sUA.
    - Based on the data from systematic reviews, ULT did not reduce the frequency of gout attacks during the initial 6 months of therapy. The increased risk of gout attacks with initiation of ULT was ameliorated with the concomitant use of prophylactic agents (eg, colchicine, NSAIDs).
    - After 12 months of ULT, the frequency of gout attacks was reduced.
- Management of acute and recurrent gout: A clinical practice guideline from the American College of Physicians (ACP) *(Qaseem et al 2016)*
  - The ACP recommends corticosteroids, NSAIDs, or colchicine to treat patients with acute gout.
  - Low-dose colchicine is recommended for treating acute gout.
  - The ACP recommends against initiating long-term ULT in most patients after the first gout attack or in patients with infrequent attacks.
  - Febuxostat and allopurinol are equally effective at decreasing sUA levels.
  - Prophylactic therapy with low-dose colchicine or low-dose NSAIDs helps to reduce the risk for acute gout attacks in patients initiating ULT.

## Safety

- Key warnings/precautions for allopurinol include skin rash, bone marrow suppression, and requirement for adequate fluid intake (to prevent formation of xanthine calculi and to prevent renal precipitation or urates in patients receiving concomitant uricosuric agents). Key adverse effects with allopurinol include skin rash, gout flares, diarrhea, and nausea.
- Contraindications for colchicine include concomitant use with drugs that inhibit cytochrome P450 3A4 (CYP3A4) and P-glycoprotein (P-gp) in patients with renal or hepatic impairment. Colchicine use should be avoided in patients with renal or hepatic impairment. The most common adverse effects with colchicine are gastrointestinal (GI) in nature.
- Febuxostat carries a recently added boxed warning for CV death. Febuxostat is contraindicated in patients who are

concurrently on azathioprine or mercaptopurine therapy. Key adverse effects include liver function abnormalities, nausea, arthralgia, and rash.
- Pegloticase has a boxed warning for anaphylaxis and infusion reactions, as well as Glucose-6-phosphate dehydrogenase (G6PD) deficiency-associated hemolysis and methemoglobinemia. Pegloticase use is contraindicated in patients with G6PD deficiency. The most common adverse effects include gout flare, infusion reactions, and nausea.
- Probenecid is contraindicated in patients < 2 years of age and known blood dyscrasias or kidney stones. The most common adverse effects include central nervous system (CNS), genitourinary, and hematologic adverse effects.

**Dosing**
- Allopurinol
  - Allopurinol is dosed once or twice daily and is titrated at weekly intervals until the target sUA < 6 mg/dL is achieved.
  - The dose of allopurinol should be adjusted according to the patient's renal function.
- Colchicine
  - The dose for colchicine for gout prophylaxis is 0.6 mg orally (with or without food) once or twice daily, with a maximum daily dose of 1.2 mg.
  - For the treatment of gout flares, 1.2 mg should be administered at the first sign of flare, followed by 0.6 mg 1 hour later.
- Febuxostat
  - The recommended dose of febuxostat is 40 or 80 mg orally once daily.
  - No dose adjustments are recommended in patients with mild or moderate renal or hepatic impairment. However, 40 mg orally daily is recommended for patients with severe renal impairment.
- Pegloticase
  - The recommended dose is 8 mg intravenously (IV), administered over ≥ 120 minutes, every 2 weeks.
  - Pre-infusion medications (eg, antihistamines, corticosteroids) are recommended, and the patient should be monitored for anaphylaxis for approximately 1 hour post-infusion. If an infusion reaction occurs, the infusion may be slowed or stopped and restarted at a slower rate, at the discretion of the physician.
- Probenecid
  - The recommended dose of probenecid is 250 mg orally twice daily for 1 week, then 500 mg twice daily.
  - Probenecid should not be started until an acute gouty attack has subsided.
- Probenecid/colchicine
  - The initial dose is 1 tablet orally once daily for 1 week, followed by a maintenance dose of 1 tablet orally twice daily.

**Conclusion**
- Agents such as allopurinol, colchicine, and probenecid have been available for many years; however, the armamentarium of anti-gout agents is not as robust as required to treat this painful form of inflammatory arthritis. Newer agents such as febuxostat, lesinurad, and pegloticase have been approved in the last 2 decades; however, lesinurad was recently removed from the market due to low utilization.
- The CARES CV safety study determined that there were no statistically significant differences between febuxostat and allopurinol for the majority of study endpoints; however, statistically significantly higher rates of all-cause mortality and CV death were demonstrated with febuxostat.
  - Based on the FDA's evaluation of the results of this study, a boxed warning was added to the febuxostat label, which indicates an increased risk of CV death with febuxostat use. Additionally, the FDA required a change to the indication such that febuxostat is limited to use in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.
  - It is important to note that the CARES trial had a large discontinuation rate during the study and the post-treatment follow-up period. It is possible that the large discontinuation rate may have biased the results toward the null hypothesis. Additionally, the patients in this trial had significant comorbidities; the study population may not be representative of the general gout population. Further CV safety studies are underway and may provide additional data to determine the true CV risk of febuxostat vs allopurinol.

## BACKGROUND

- Gout may progress to a chronic and persistent condition, with development of tophi (solid deposits of monosodium urate [MSU] crystals in joints, cartilage, tendons, bursae, bone, and soft tissue), a condition called chronic tophaceous gout *(Newberry 2016).*
- The prevalence of gout among U.S. adults in 2007 to 2008 was 3.9% (8.3 million people) *(Zhu et al 2011).*
  - Both the incidence and prevalence of the disease appear to be increasing since at least the late 1970s in the U.S. (*Becker and Gaffo 2019).*
- Gout tends to occur earlier in life in men than women and is rare in childhood (*Becker and Gaffo 2019*).
- Clinical manifestations include excruciatingly painful acute attacks of gouty arthritis, the formation of tophaceous MSU

crystal deposits in joints and other body tissues, chronic joint damage, renal stone formation, and potential renal insufficiency *(Roddy and Choi 2014).*

- Key risk factors for gout include (*Becker and Gaffo 2019):*
  - Increased longevity and age-associated CV, metabolic, and renal diseases in the population.
  - Use of medications that alter urate balance as an unintended consequence of treatment for these chronic disorders (and to prevent organ rejection among transplant recipients).
  - Increased dietary intake of foods and food additives (such as high-fructose corn syrup) that contribute to the development of obesity and DM.
- A definitive diagnosis should be sought when a gout flare is suspected, both to exclude alternative explanations for the acute event and to ensure that long-term therapy is not prescribed unnecessarily. The diagnosis is most secure when supported by visualization of urate crystals by experienced examiners in a sample of fluid aspirated from an affected joint (or bursa). Ultrasonography of joints and adjacent soft tissues is useful for guiding fluid aspiration and can identify specific abnormalities that are highly sensitive and specific for urate crystal deposition (*Becker and Gaffo 2019).*
- Management for the prevention of recurrent gout flares and damage to joints and other tissues from urate crystal deposition includes pharmacologic therapy, as well as lifestyle modification and other strategies for risk reduction *(Becker and Perez-Ruiz 2019).*
- Long-term success in maintaining subsaturating sUA is accompanied by clinical benefits that include cessation of gout flares, resolution of tophi, and improvement in patient physical function and health-related quality of life *(Becker and Perez-Ruiz 2019).*
- Treatments to prevent recurrent gout flares are strongly indicated in patients with multiple recurrent gout flares annually or with clinical or imaging findings that indicate joint injury (gouty arthropathy) or the development of tophi, as well as in selected patients with renal disease, urolithiasis, or marked hyperuricosuria *(Becker and Perez-Ruiz 2019).*
  - Preventing recurrent gout flares, progressive gouty arthritis, and tophi often requires the long-term use of drugs that reduce sUA either by enhancing renal excretion of uric acid (uricosuric agents) or by decreasing urate synthesis (XOIs) or both.
  - Precise definitions of frequent or disabling flares are not strictly established. Two or more flares annually is often quoted as an indication for ULT. However, a lower threshold for treatment may be considered after discussion with the patient if even infrequent flares are especially prolonged, interfere with vocational or avocational activities, and/or continue to recur over several years.
- The risk of CV events, including death, is significantly greater in patients with gout than in those without gout *(Choi et al 2007, Krishnan et al 2008).*
- Colchicine has been used for centuries to treat and prevent gout in adults. It was used before the creation of the FDA, and therefore was "grandfathered" without receiving FDA approval. In 2006, however, colchicine was formally studied and Colcrys was officially FDA-approved for gout treatment and prophylaxis, as well as treatment of Familial Mediterranean fever. In 2014, the FDA approved Mitigare, a brand of colchicine, with an approved generic colchicine that followed a few months later. An oral liquid colchicine formulation, Gloperba, was FDA-approved in January 2019 for the prophylaxis of gout flares. Its approval was based on published colchicine studies.
- Zurampic (lesinurad) and Duzallo (lesinurad/allopurinol), FDA-approved for hyperuricemia associated with gout in 2015 and 2017, respectively, were discontinued by the manufacturer on February 1, 2019. Per the manufacturer, discontinuation was due to business reasons, rather than safety or efficacy reasons *(Ironwood Pharmaceuticals 2019).*
- During Uloric's (febuxostat) phase 3 clinical trials, there was a safety signal noted for CV events; however, the results were not found to be statistically significant. Upon approval of febuxostat in 2009, a warning for CV risk was added to the package insert, and the FDA mandated a post-marketing CV safety trial for febuxostat (*FDA 2019*).
  - The results of this safety clinical trial lead to the addition of a boxed warning for CV death and a change to the indication for febuxostat as a second-line therapy after allopurinol.
  - Additional CV safety trials (in Japan and Europe) are underway to provide additional data regarding the CV risk of febuxostat vs allopurinol *(Katsiki and Borghi 2018).*

## INDICATIONS

**Table 3. FDA-approved indications for anti-gout agents**

| Indication | Allopurinol | Colchicine | Febuxostat | Pegloticase | Probenecid | Probenecid/ colchicine |
|---|---|---|---|---|---|---|
| Management of patients with signs and symptoms of primary or secondary gout* | ✓ | | | | | |
| Prophylaxis and treatment of acute gout flares† | | ✓ | | | | |
| Chronic management of hyperuricemia in adult patients with | | | ✓§ | | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| gout who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable | | | | | | |
| Treatment of the hyperuricemia associated with gout and gouty arthritis | | | | | ✓ | |
| Treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout | | | | | | ✓ |
| Treatment of chronic gout in adult patients refractory to conventional therapy | | | | ✓§ | | |
| Management of patients with leukemia, lymphoma, and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels† | ✓ | | | | | |
| The management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients‡ | ✓ | | | | | |
| As adjuvant therapy with penicillin or with ampicillin, methicillin, oxacillin, cloxacillin, or nafcillin, for elevation or prolongation of plasma levels by whatever route the antibiotic is given† | | | | | ✓ | |
| Treatment of familial Mediterranean disease† | | ✓ | | | | |

*Signs and symptoms include acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy
†This indication will not be reviewed as part of this therapeutic class review
‡Therapy in such patients should be carefully assessed initially and reassessed periodically to determine in each case that treatment is beneficial and that the benefits outweigh the risks
§Limitation of use: not recommended for the treatment of asymptomatic hyperuricemia

## PHARMACOLOGY

- Both allopurinol and febuxostat are XOIs that lower sUA; however, the way that they inhibit XO differs.
  - Allopurinol is a structural analogue of the natural purine base, hypoxanthine. By inhibiting XO, the enzyme responsible for the conversion of hypoxanthine to xanthine and of xanthine to uric acid, there is a decrease in production of sUA. Allopurinol is metabolized to the corresponding xanthine analogue, oxipurinol (alloxanthine), which also is an inhibitor of XO catabolism, without disrupting the biosynthesis of purines.
  - Febuxostat lowers sUA levels by occupying a channel in the XO dimer and impairing access to purine base substrates at the active site of XO catalysis.
- The exact mechanism by which colchicine exerts its sUA lower effects is not fully understood. However, it is thought to involve the following:
  - A reduction in lactic acid production by leukocytes, which results in a decrease in uric acid deposition.
  - A reduction in phagocytosis, with abatement of the inflammatory response.
    - Colchicine is not an analgesic, though it relieves pain in acute attacks of gout.
- Pegloticase is a uric acid specific enzyme, which is a recombinant uricase, and achieves its therapeutic effects by catalyzing the oxidation of uric acid to allantoin, thereby lowering sUA.
- Probenecid is a uricosuric and renal tubular blocking agent. It inhibits the tubular reabsorption of urate, thus increasing the urinary excretion of uric acid and decreasing sUA levels.

## CLINICAL EFFICACY

**STUDY DESIGN ABBREVIATIONS: AC = active control; CI = confidence interval, DB = double-blind; HR = hazard ratio; MC = multi-center; OL = open-label; OR = odds ratio; PC = placebo-controlled; PG = parallel-group; RCT = randomized controlled trial; RR = relative risk; SB = single-blind; SC = single-center; XO = crossover**

***Search Strategy**: Studies supporting the FDA-approved indications were identified using search terms "allopurinol, colchicine, febuxostat, pegloticase, or probenecid" and "gout" through April 15, 2019. Manufacturer submitted data were also reviewed when available. A comprehensive PubMed literature search was performed for human studies published in English. Assessment of each study's design (eg, randomization, blinding methodology, appropriateness of treatment outcomes, etc.), validity and importance was completed. Review of patient data in groups to which they were randomized (intention to treat analysis), accounting for patient withdrawals, and baseline characteristics was completed.*

**Study 1. White WB et al, *N Engl J Med.* 2018;378:1200-1210**

| **Study Objective:** To determine whether febuxostat was noninferior to allopurinol with regard to major CV events in patients with gout and CV disease. | |
|---|---|
| **Study Design, Follow-up** | **Treatment Groups*** |
| • DB, MC, randomized, noninferiority trial (N = 6190) | • Febuxostat 40 mg to 80 mg per day (n = 3098)<br>• Allopurinol 200 mg to 600 mg per day* (n = 3092)<br><br>*For allopurinol, the dose was adjusted based on renal function and for febuxostat, the dose was adjusted based on sUA<br><br>• Colchicine, an NSAID (with lansoprazole), or prednisone prophylaxis were administered for acute gout attacks |
| **Inclusion Criteria** | **Exclusion Criteria** |
| • Male or female patients (≥ 50 or ≥ 55 years of age, respectively) with diagnosis of gout based on ACR criteria<br>• sUA ≥ 7.0 mg/dL or ≥ 6.0 mg/dL with inadequately controlled gout)<br>• History of CV disease (MI, hospitalization for unstable angina or TIA, stroke, PVD, or DM with evidence of micro- or macrovascular disease) | • Secondary hyperuricemia<br>• History of xanthinuria<br>• Active peptic ulcer disease<br>• ULT or other exclusionary medication < 7 days prior to randomization<br>• History of cancer (other than basal cell carcinoma of the skin) within 5 years prior to the first dose of study medication<br>• MI or stroke within 60 days of screening<br>• Liver transaminases > 2 times upper limit of normal<br>• CLcr < 30 mL/min |
| **Primary Endpoint** | **Secondary Endpoints** |
| • Primary composite end point: first occurrence of CV death, nonfatal MI, nonfatal stroke, or urgent revascularization for unstable angina | • Composite of CV death, nonfatal MI, or nonfatal stroke as well as the individual components of the primary endpoint<br>• Death from any cause, urgent cerebrovascular revascularization, transient ischemic attack, hospitalization for heart failure, arrhythmias not associated with ischemia, and venous thromboembolic events |

- **Results:**
  - Baseline characteristics were balanced between both treatment groups.
  - Patients were followed for up to 85 months, with a median follow-up period of 32 months.
  - Of note, treatment was discontinued in 56.6% of patients, and 45.0% were lost during the follow-up period. The discontinuation rates were similar between both treatment groups (57.3% in the febuxostat group and 55.9% in the allopurinol group), as well as the percentage of patients lost during the follow-up period (45.0% in the febuxostat group and 44.9% in the allopurinol group).
  - A determination of noninferiority of febuxostat to allopurinol required that the upper bound of the one-sided CI of the HR for the end points be < 1.3.
  - The results of the modified intent-to-treat analysis are listed in Table 4 below.

**Table 4. Results for primary and secondary endpoints in CARES trial**

| | Endpoint | Febuxostat | Allopurinol | HR | p-value |
|---|---|---|---|---|---|
| | | n (%) | | HR (95% CI) | |
| Primary endpoint | Composite of CV death, nonfatal MI, nonfatal stroke, or urgent revascularization due to unstable angina | 335 (10.8) | 321 (10.4) | 1.03 (0.87 to 1.23) | 0.66 |

| | | | | | |
|---|---|---|---|---|---|
| Secondary endpoints | CV death | 134 (4.3) | 100 (3.2) | 1.34 (1.03 to 1.73) | 0.03 |
| | Nonfatal MI | 111 (3.6) | 118 (3.8) | 0.93 (0.72 to 1.21) | 0.61 |
| | Nonfatal stroke | 71 (2.3) | 70 (2.3) | 1.01 (0.73 to 1.41) | 0.94 |
| | Urgent revascularization due to unstable angina | 49 (1.6) | 56 (1.8) | 0.86 (0.59 to 1.26) | 0.44 |
| | Composite of CV death, nonfatal MI, or nonfatal stroke | 296 (9.6) | 271 (8.8) | 1.09 (0.92 to 1.28) | 0.33 |
| | Death from any cause | 243 (7.8) | 199 (6.4) | 1.22 (1.01 to 1.47) | 0.04 |

**Abbreviations: CI = confidence interval; CV = cardiovascular; HR = hazard ratio; MI = myocardial infarction**

- While no statistically significant difference was found between the treatment groups with respect to the primary end point, there were statistically significant differences noted between the treatment groups for 2 of the 6 secondary endpoints above.
  - As noted in the table above, febuxostat group showed significantly higher rates of all-cause mortality (HR 1.22; 95% CI, 1.01 to 1.47) and CV mortality (HR 1.34; 95% CI, 1.03 to 1.73) compared with the allopurinol group.
  - Additionally, the rate of CV death was statistically significantly greater in febuxostat-treated patients vs allopurinol-treated patients (HR 1.34; 95% CI, 1.03 to 1.73).
- **Authors' conclusion:**
  - In patients with gout and major CV coexisting conditions, febuxostat was noninferior to allopurinol with respect to rates of adverse CV events. All-cause mortality and CV mortality were higher with febuxostat than with allopurinol.
- **Study Appraisal:**
  - **Study sponsorship:**
    - Takeda Pharmaceuticals
  - **Study rating:**
    - Fair
  - **Study strengths:**
    - This was a reasonably-designed clinical trial with independent reviewers conducting the analyses.
    - The treatment groups were fairly well-balanced.
  - **Study limitations:**
    - This population was fairly ill with multiple comorbidities; this trial population may not be representative of the general population.
    - There was a large discontinuation rate during the trial and during the follow-up period; this may have biased the data toward the null hypothesis.
    - A portion of patients in the febuxostat group were not maximized on their aspirin doses.

**Study 2. Seth et al, *Cochrane Database Syst Rev.* 2014;10:CD006077.**

| **Study Objective: To assess the efficacy and safety of allopurinol compared with placebo and other ULT for treating chronic gout.** | |
|---|---|
| **Study Design** | **Treatment Groups** |
| • Cochrane review, meta-analysis of 11 RCTs (n = 4531) | • Allopurinol<br>• Febuxostat<br>• Colchicine or probenecid<br>• Benzbromarone*<br>• Placebo<br><br>*Not available in the US |
| **Inclusion Criteria** | **Exclusion Criteria** |
| • RCTs and quasi clinical controlled trials involving patients with gout<br>• Adults with a diagnosis of chronic gout<br>• Diagnosis of gout based on ACR criteria or based on the diagnosis by the trial author or treating physician | • Populations that included a mix of people with chronic gout and asymptomatic hyperuricemia, unless results for the chronic gout population could be separated out for analysis |
| **Primary Endpoints** | **Secondary Endpoints** |
| • Frequency of acute gout attacks and the number of participants with an acute gout attack | • Health-related quality of life (HRQoL)<br>• Participant global assessment of treatment success |

| | |
|---|---|
| • Serum urate normalization as measured by percent change in sUA from baseline, absolute change in sUA from baseline (mmol/L or mg/dL) or proportion of participants achieving a target sUA (eg, < 6 mg/dL)<br>• Pain, as measured by visual analogue scale (VAS), numerical rating scale (NRS), Likert scales or qualitative scales<br>• Function (activity limitation), as measured by the Health Assessment Questionnaire for Rheumatoid Arthritis (HAQ-DI), 36-item Short Form (SF-36) Physical Health component or other validated gout specific function measures.<br>• Tophus regression, using physical measurement techniques or ultrasound-guided measurements<br>• Proportion of participant withdrawals due to adverse effects<br>• Proportion of participants with serious adverse effects | • Proportion of participants with adverse effects |

- **Results:**
  - Moderate-quality evidence from 1 trial (57 participants) indicated allopurinol 300 mg daily probably does not reduce the rate of gout attacks (2/26 with allopurinol vs 3/25 with placebo; risk ratio (relative risk) 0.64; 95% CI, 0.12 to 3.52 but increases the proportion of participants achieving a target sUA over 30 days (25/26 with allopurinol vs 0/25 with placebo, RR 49.11, 95% CI, 3.15 to 765.58; number needed to treat for an additional beneficial outcome [NNTB] = 1).
  - In 2 studies (453 participants), there was no significant increase in withdrawals due to adverse effects (6% with allopurinol vs 4% with placebo, RR 1.36; 95% CI, 0.61 to 3.08) or serious adverse effects (2% with allopurinol vs 1% with placebo, RR 1.93; 95% CI, 0.48 to 7.80).
  - One trial reported no difference in pain reduction or tophus regression, but did not report outcome data or measures of variance sufficiently and the differences between groups could not be calculated. Neither trial reported function.
  - Low-quality evidence from 3 trials (1136 participants) indicated there may be no difference in the incidence of acute gout attacks with allopurinol up to 300 mg daily vs febuxostat 80 mg daily over 8 to 24 weeks (21% with allopurinol vs 23% with febuxostat, RR 0.89; 95%CI, 0.71 to 1.1); however more participants may achieve target sUA levels (4 trials; 2618 participants) with febuxostat 80 mg daily vs allopurinol 300 mg daily (38% with allopurinol vs 70% with febuxostat, RR 0.56; 95% CI, 0.48 to 0.65, NNTB with febuxostat = 4).
  - Two trials reported no difference in tophus regression between allopurinol and febuxostat over a 28- to 52-week period; but as the investigators did not provide variance, mean difference between groups could not be calculated.
  - The trials did not report pain reduction or function.
  - Moderate-quality evidence from pooled data from 3 trials (2555 participants) comparing allopurinol up to 300 mg daily vs febuxostat 80 mg daily indicated no difference in the number of withdrawals due to adverse effects (7% with allopurinol vs 8% with febuxostat, RR 0.89; 95% CI, 0.62 to 1.26) or serious adverse effects (4% with allopurinol vs 4% with febuxostat, RR 1.13; 95% CI, 0.71 to 1.82) over a 24- to 52-week period.
- **Author's conclusion:**
  - This review found low- to moderate-quality evidence indicating similar effects on withdrawals due to adverse effects and serious adverse effects and incidence of acute gout attacks when allopurinol (100 to 600 mg daily) was compared with placebo, benzbromarone (100 to 200 mg daily) or febuxostat (80 mg daily). There was moderate-quality evidence of little or no difference in the proportion of participants achieving target sUA when allopurinol was compared with benzbromarone. However, allopurinol seemed more successful than placebo and may be less successful than febuxostat (80 mg daily) in achieving a target sUA level (≤ 6 mg/dL; ≤ 0.36 mmol/L) based on moderate- to low-quality evidence. Single studies reported no difference in pain reduction when allopurinol (300 mg daily) was compared with placebo over 10 days, and no difference in tophus regression when allopurinol (200 to 300 mg daily) was compared with febuxostat (80 mg daily). None of the trials reported on function, HRQoL, or participant global assessment of treatment success, where further research would be useful.
- **Study Appraisal**
  - **Study sponsorship:**
    - Internal: (1) University Hospital Southampton NHS Foundation Trust, UK (2) School of Public Health and Preventative Medicine, Monash University, Australia (3) Division of Rheumatology, University of British Columbia, Vancouver, Canada (4) Institute for Work & Health, Toronto, Canada.
    - External: No sources of support supplied
  - **Study rating:**
    - N/A (MA)
  - **Study limitations:**
    - There were only 2 trials that compared allopurinol to placebo, and these trials were so different that the efficacy

data couldn't be pooled for analysis.
- Some trials had a variable duration of follow up.
- Some trials had small sample sizes.
- Three studies used low-dose allopurinol 100 to 300 mg daily (depending on renal function) compared with a reasonable dose of febuxostat 80 mg daily.
- One study was at high risk of performance and detection bias, while a few other studies had an unclear risk of performance and detection bias.

**Study 3. Van Echteld et al, *Cochrane Database Syst Rev.* 2014;8:CD006190.**

| **Study Objective: To evaluate the benefits and harms of colchicine for the treatment of acute gout.** | |
|---|---|
| **Study Design** | **Treatment Groups** |
| • Cochrane review, meta-analysis of 2 RCTs (n = 124) | • Low dose colchicine (1.8 mg) per day<br>• High dose colchicine (0.5 mg every 2 hours until relief in 1 study and 4.8 mg total in another study)<br>• Placebo |
| • Inclusion Criteria | • Exclusion Criteria |
| • RCTs and quasi clinical controlled trials investigating the benefits and harms of colchicine in acute gout<br>• Adults with a diagnosis of acute gout (author defined or presence of monosodium crystals in joint aspirate, or patients fulfilling the ACR, Rome, or New York criteria for gout) | • Populations that included a mix of people with acute gout and other musculoskeletal pain, unless results for the acute gout population could be separated out for analysis |
| **Primary Endpoints** | |
| • Benefits: Defined as ≥ 50% decrease in pain<br>• Harms: Defined as study participation withdrawal due to adverse effects<br>• Reduction of inflammation (joint swelling/erythema/tenderness)<br>• Function of target joint (movement)<br>• Patient global assessment of treatment success<br>• HRQoL<br>• Total number and types of adverse effects and serious adverse effects | |

- **Results:**
  - Based upon pooled data from 2 trials (124 participants), there was low-quality evidence that a greater proportion of people receiving high-dose colchicine experienced a ≥ 50% decrease in pain from baseline up to 32 to 36 hours compared with placebo (35/74 in the high-dose colchicine group vs 12/50 in the placebo group (RR 2.16; 95% CI, 1.28 to 3.65), with an NNTB of 4 (95% CI, 3 to 12). However, the total number of adverse effects (diarrhea, vomiting, or nausea) was greater in those who received high-dose colchicine vs placebo (62/74 in the high-dose colchicine group vs 11/50 in the placebo group [RR 3.81; 95% CI, 2.28 to 6.38]), with a number needed to treat to harm (NNTH) of 2 (95% CI, 2 to 5).
  - Only 1 trial included reduction of inflammation as part of a composite measure comprising pain, tenderness, swelling, and erythema, each graded on a 4-point scale (none 0 to severe 3) to derive a maximum score for any one joint of 12. They reported the proportion of people who achieved a 50% reduction in this composite score. Based upon 1 trial (n = 43), there was low-quality evidence that more people in the high-dose colchicine group had a 50% or greater decrease in composite score from baseline up to 32 to 36 hours compared to the placebo group (11/22 in the high-dose colchicine group vs 1/21 in the placebo group [RR 10.50; 95% CI, 1.48 to 74.38] and 45% absolute difference). Based upon data from 1 trial (n = 103), there was low-quality evidence that low-dose colchicine was more efficacious than placebo with respect to the proportion of people who achieved a 50% or greater decrease in pain from baseline up to 32 to 36 hours (low-dose colchicine 31/74 vs placebo 5/29 [RR 2.43; 95% CI, 1.05 to 5.64]), with an NNTB of 5 (95% CI, 2 to 20).
  - There were no additional harms in terms of adverse effects (diarrhea, nausea or vomiting) with low-dose colchicine compared to placebo (19/74 and 6/29 respectively [RR 1.24; 95% CI, 0.55 to 2.79]). Based upon data from 1 trial (126 participants), there was low-quality evidence that there are no additional benefits in terms of the proportion of people achieving 50% or greater decrease in pain from baseline up to 32 to 36 hours with high-dose colchicine compared to low-dose (19/52 and 31/74 respectively [RR 0.87, 95% CI, 0.56 to 1.36]). However, there were statistically significantly more adverse effects in those who received high-dose colchicine (40/52 vs 19/74 in the low-dose group [RR 3.00; 95% CI, 1.98 to 4.54]), with an NNTH of 2 (95% CI, 2 to 3).
  - No trials reported function of the target joint, patient-reported global assessment of treatment success, HRQoL, or withdrawals due to adverse effects. No studies were identified comparing colchicine to NSAIDs or other active treatments such as glucocorticoids (by any route).
- **Author's conclusion**:

- Based upon only 2 published trials, there is low-quality evidence that low-dose colchicine is likely to be an effective treatment for acute gout. The evidence was downgraded because of a possible risk of selection and reporting biases and imprecision. Both high- and low-dose colchicine improve pain when compared to placebo. While there is some uncertainty around the effect estimates, compared with placebo, high-dose but not low-dose colchicine appears to result in a statistically significantly greater number of adverse effects. Therefore low-dose colchicine may be the preferred treatment option. There are no trials about the effect of colchicine in populations with comorbidities or in comparison with other commonly used treatments, such as NSAIDs and glucocorticoids.

- **Study Appraisal**
  - **Study sponsorship:**
    - Internal: Cochrane Musculoskeletal Group, Australian Editorial Base, Australia
    - External: No sources of support supplied
  - **Study rating:**
    - N/A (MA)
  - **Study limitations:**
    - Potential for selection bias in 1 trial
    - Risk of selective reporting in another trial
    - Both trials had small sample sizes
    - Data were only available for pain, inflammation, and adverse effects

**Study 4. Tayar et al, *Cochrane Database Syst Rev.* 2012;11:CD008653.**

| **Study Objective: To evaluate the benefits and harms of febuxostat for chronic gout** | |
|---|---|
| **Study Design** | **Treatment Groups** |
| • Cochrane review, meta-analysis of 4 RCTs and 2 OLTs (n = 3978) | • Febuxostat 40 mg, 80 mg, 120 mg, 240 mg<br>• Allopurinol (varying doses)<br>• Placebo |
| **Inclusion Criteria** | **Exclusion Criteria** |
| • RCTs and quasi controlled trials in patients with gout<br>• Adults with a diagnosis of chronic gout<br>• Patients 16 years of age meeting the preliminary ACR criteria for acute arthritis of primary gout or given a diagnosis of gout as described by the authors | • Populations that included a mix of people with chronic gout and asymptomatic hyperuricemia, unless results for the chronic gout population could be separated out for analysis |
| **Primary Endpoints** | **Secondary Endpoints** |
| • Frequency of gout flares<br>• Change in sUA and percent change in sUA from baseline at final visit<br>• Harms: As assessed by the incidence of patients with adverse effects (total and serious adverse effects, liver function test abnormalities, skin reactions, CV events, hypertension, and diarrhea) and withdrawal rates (and specific reasons for withdrawals) | • Tophus burden as measured by size measurement of individual tophus (regression of tophi), including disappearance of tophi and velocity of tophus regression<br>• HRQoL, assessed by SF-36<br>• Pain (assessed via VAS, NRS, or qualitative scale)<br>• Musculoskeletal function<br>• Patient global and physician global assessment<br>• Joint imaging |

- **Results:**
  - Patients taking febuxostat 120 mg and 240 mg reported more frequent gout flares than in the placebo group at 4 to 28 weeks (RR 1.7; 95% CI, 1.3 to 2.3, and RR 2.6; 95% CI, 1.8 to 3.7 respectively). No statistically significant differences were observed at 40 mg and 80 mg.
  - Compared to placebo, patients on febuxostat 40 mg were 40.1 times more likely to achieve sUA levels < 6.0 mg/dL at 4 weeks (95% CI, 2.5 to 639), with an absolute treatment benefit of 56% (95% CI, 37% to 71%). For febuxostat 80 mg and 120 mg, patients were 68.9 and 80.7 times more likely to achieve sUA levels < 6.0 mg/dL at their final visit compared to placebo (95% CI, 13.8 to 343.9; 95% CI, 16.0 to 405.5), respectively; with an absolute treatment benefit of 75% and 87% (95% CI, 68 to 80% and 81 to 91%), respectively.
  - Total discontinuation rates were significantly higher in the febuxostat 80 mg group compared to placebo (RR 1.4; 95% CI, 1.0 to 2.0, absolute risk increase 11%; 95% CI, 3 to 19%). No other differences were observed. When comparing allopurinol to febuxostat at 24 to 52 weeks, the number of gout flares was not significantly different between the 2 groups, except for febuxostat 240 mg (RR 2.3; 95% CI, 1.7 to 3.0). Patients on febuxostat 40 mg showed no statistically significant differences in benefits or harms. Patients on febuxostat 80 mg and 120 mg were 1.8 and 2.2 times more likely to achieve sUA levels < 6.0 mg/dL at their final visit (95% CI, 1.6 to 2.2, 95% CI, 1.9 to 2.5) with an absolute treatment benefit of 29% and 44% (95% CI, 25% to 33%, 95% CI, 38% to 50%), respectively, at 24 to 52 weeks. Total discontinuation rates were higher for febuxostat 80 mg and 120 mg compared to allopurinol (RR 1.5; 95% CI, 1.2 to 1.8, absolute risk increase 11%; 95% CI, 6% to 16%; and RR 2.6; 95% CI, 2.0 to 3.3, absolute risk

increase 20%; 95% CI, 3% to 14%, respectively).
  - Discontinuations due to adverse effects were similar across groups. Total adverse effects were lower for febuxostat 80 mg and 120 mg compared with allopurinol (RR 0.93; 95% CI, 0.87 to 0.99, absolute risk increase 6%; 95% CI, 0.7% to 11%; and RR 0.90; 95% CI, 0.84 to 0.96, absolute risk increase 8%; 95% CI, 3% to 13%, respectively). No other relevant differences were noted. After 3 years of follow-up there were no statistically significant differences regarding effectiveness and harms between febuxostat 80 mg or 120 mg and allopurinol groups (adverse effect rate per 100 patient-years 227, 216, and 246, respectively).
- **Author's conclusion:**
  - Although the incidence of gout flares requiring treatment may be increased in patients taking febuxostat compared to placebo or allopurinol during early treatment, no such increase in gout flares was observed in the long-term follow-up study when compared to allopurinol. Febuxostat at any dose was shown to be beneficial in achieving sUA levels < 6.0 mg/dL and reducing sUA levels in the period from baseline to final visit when compared to placebo and to allopurinol. However, the grade of evidence ranged from low to high, which indicates that further research is needed.
- **Study Appraisal**
  - **Study sponsorship:**
    - Internal: The University of Texas M.D. Anderson Cancer Center, not specified.
    - External: No sources of support supplied
  - **Study rating:**
    - N/A (MA)
  - **Study limitations:**
    - All febuxostat studies were funded by the manufacturer, TAP Pharmaceuticals, owned by Takeda Global Growth & Development Center.
    - Selective reporting: Some trials failed to report pre-specified secondary outcomes.

**Study 5. Sundy et al. *JAMA*. 2011;306:711.**

| **Study Objective: To assess the efficacy and tolerability of pegloticase in managing refractory chronic gout.** | |
|---|---|
| **Study Design, Follow-up** | **Treatment Groups** |
| • Two 6-month, replicate, DB, PC, RCTs | • Pegloticase 8 mg IV every 2 weeks (biweekly treatment group) (Trial C0405 n = 43, Trial C0406 n = 42)<br>• Pegloticase 8 mg IV alternating with placebo (monthly treatment group) (Trial C0405 n = 41, Trial C0406 n = 43)<br>• Placebo (Trial C0405 n = 20, Trial C0406 n = 23) |
| **Inclusion Criteria** | **Exclusion Criteria** |
| • Refractory gout:<br>○ Baseline sUA of 8.0 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 | • G6PD deficiency<br>• Prior treatment with a uricase-containing agent<br>• Pregnancy<br>• Unstable angina<br>• Uncontrolled hypertension (> 150/95 mm Hg) or cardiac arrhythmia<br>• Uncompensated congestive heart failure, renal dialysis, or solid organ transplant |
| **Primary Endpoint** | **Secondary Endpoints** |
| • Proportion of sUA responders (sUA < 6.0 mg/dL) in each pegloticase treatment group vs the placebo group | • Tophus resolution<br>• Reductions in the proportion of patients with gout flare and in the number of flares per patient during months 1 to 3 and 4 to 6 of the trial<br>• Reductions in tender joint count (TJC) and swollen joint count (SJC)<br>• Patient-reported changes in pain, physical function, and quality of life (QOL), measured, respectively, by the Health Assessment Questionnaire (HAQ) pain scale |

- **Results:**
  - sUA normalized within 24 hours of the first infusion in all patients receiving pegloticase, but afterward, some patients lost the urate-lowering response whereas others maintained UA < 6.0 mg/dL throughout the trial. The proportion of sUA responders (defined as an sUA < 6.0 mg/dL for ≥ 80% of the time during months 3 and 6) in both pegloticase treatment groups was significantly greater than for the placebo group in the pooled analysis ($p < 0.001$ for both) and

in the individual trials.
  - When analyzed separately by dose, patients treated with biweekly pegloticase experienced response rates of 47% (20/43; 95% CI, 31% to 62%) and 38% (16/42; 95% CI, 24% to 54%) in the 2 trials. Patients treated with monthly pegloticase reported response rates of 20% (8/41; 95% CI, 9% to 35%) and 49% (21/43; 95% CI, 33% to 65%) in the 2 trials. Response rates were 0% in both placebo groups (95% CI, 0% to 17% and 0% to 15% in the 2 trials).
  - Forty percent of patients in the biweekly pegloticase group and 21% in the monthly group had a complete response (CR) for 1 or more tophi by the final visit compared with 7% of patients receiving placebo (p = 0.002 and p = 0.20, respectively). During months 1 to 3, both the incidence of gout flares (proportion of patients suffering at least 1 flare) and the number of flares per patient were higher for pegloticase-treated patients compared with the placebo group. However, with continued treatment during months 4 to 6, significant reductions were seen in the proportion of patients with gout flare in the biweekly treatment group vs the placebo group. Flares per patient were also numerically fewer during this period with biweekly pegloticase treatment compared with placebo treatment, but the difference was not significant.
  - There were also reductions in TJC and SJC in patients treated with pegloticase compared with the respective values in placebo recipients, but only differences in TJC were statistically significant.
  - Both pegloticase dosing groups reported significant improvements in physical function and QOL compared with placebo. VAS were significantly reduced with biweekly pegloticase vs placebo. Treatment with biweekly pegloticase was also associated with significant changes from baseline in HAQ-DI scores and SF-36 Physical Component Summary scores that met or exceeded the minimum clinically important differences established for the respective instrument in inflammatory arthritides.
- **Authors' Conclusion:**
  - Among patients with chronic gout, elevated sUA 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 sUA levels compared with placebo.
- **Study Appraisal**
  - **Study sponsorship:**
    - Internal: Savient Pharmaceuticals
    - External: None reported
  - **Study rating:**
    - N/A (MA)
  - **Study limitations:**
    - Study sponsorship by manufacturer

## CLINICAL GUIDELINES

- **Agency for Healthcare Research and Quality (AHRQ): Diagnosis and Management of gout: Current state of evidence** *(AHRQ 2017)*
  - See Appendix B for an explanation regarding the levels of evidence.
  - Effective treatments for gout attacks include NSAIDs, colchicine, and corticosteroids (high strength of evidence).
  - ULT, including allopurinol and febuxostat, reduce sUA (high strength of evidence).
    - Based on the data from systematic reviews, ULT did not reduce the frequency of gout attacks during the initial 6 months of therapy (high strength of evidence). The increased risk of gout attacks with initiation of ULT was ameliorated with the concomitant use of prophylactic agents (eg, colchicine, NSAIDs) (high strength of evidence).
    - After 12 months of ULT, the frequency of gout attacks was reduced (moderate strength of evidence).
- **Management of acute and recurrent gout: A clinical practice guideline from the American College of Physicians (ACP)***(Qaseem et al 2016)*
  - See Appendix A for an explanation regarding the levels of evidence.
  - The ACP recommends corticosteroids, NSAIDs, or colchicine to treat patients with acute gout (strength: strong recommendation, high-quality evidence).
    - Corticosteroids should be considered first-line in patients without contraindications, as they are generally safer and a low-cost treatment option.
    - Moderate-quality evidence shows no difference between the different NSAIDs.
  - Low-dose colchicine is recommended for treating acute gout (strength: strong recommendation, moderate-quality evidence).
    - Moderate-quality evidence suggests that lower doses of colchicine (1.2 mg followed by 0.6 mg 1 hour later) are as effective as higher doses at reducing pain and associated with fewer GI adverse effects.
  - The ACP recommends against initiating long-term ULT in most patients after the first gout attack or in patients with infrequent attacks (strength: recommendation, moderate-quality evidence).
    - In cases of recurrent gout (≥ 2 episodes per year) or problematic gout (eg, gout associated with tophi, chronic renal disease, or urolithiasis), shared decision making with the patient is warranted to review possible harms and benefits of ULT.

- It is recommended that physicians discuss benefits, harms, costs, and individual preferences with patients before initiating ULT, including concomitant prophylaxis, in patients with recurrent gout attacks (strength: recommendation, moderate-quality evidence).
  - Upon resolution of acute gout, some patients have no or a few attacks over many years, whereas others have more frequent or recurrent attacks.
  - Febuxostat and allopurinol are equally effective at decreasing sUA levels.
  - Prophylactic therapy with low-dose colchicine or low-dose NSAIDs helps to reduce the risk for acute gout attacks in patients initiating ULT.

- **American College of Rheumatology: Guidelines for the management of gout. Part 1: Systematic nonpharmacologic and pharmacologic therapeutic approaches to hyperuricemia** (*Khanna et al 2012*)
  - Per the ACR Web site, the 2012 gout guidelines are being revised and are anticipated to be completed in early 2020.
  - See Appendix C for an explanation regarding the levels of evidence.
  - Indications for pharmacologic ULT include:
    - Any patient with established diagnosis of gouty arthritis and:
      - Tophus/tophi by clinical exam or imaging study
      - Frequent attacks of acute gouty arthritis (≥ 2 attacks/year)
      - Chronic kidney disease stage 2 or worse
      - Past urolithiasis
  - Recommendations for treating sUA target:
    - The minimum sUA target is < 6 mg/dL
    - sUA lowering < 5 mg/dL may be needed to improve gout signs and symptoms
    - If sUA target is achieved, the following is recommended for the long-term management of gout:
      - Continue gout attack prophylaxis if there are ongoing gout symptoms and/or signs (≥ 1 tophus on physical exam).
      - After palpable tophi and all acute and chronic gouty arthritis gout symptoms have been resolved, continue all measures (including ULT) needed to maintain sUA < 6 mg/dL indefinitely.
    - If sUA target is not achieved, the following is recommended:
      - Increase intensity of ULT and reevaluate sUA.
      - When sUA target is achieved, recommendations for long-term management of gout should be followed.
  - XOI therapy with either allopurinol or febuxostat is recommended as the first-line pharmacologic ULT in gout.
    - Allopurinol
      - Starting dosage should be no greater than 100 mg/day for any patient. Patients with stage 4 or worse chronic kidney disease should be started on 50 mg/day.
      - The maintenance dose should be gradually titrated upward every 2 to 5 weeks to appropriate maximum dose in order to treat chosen sUA target.
      - Dose can be increased to > 300 mg/day, even in patients with renal impairment, provided adequate patient education and monitoring for drug toxicity is present.
      - Prior to initiation, consider HLA-B*5801 screening in selected patients.
  - Probenecid is recommended as an alternative first-line ULT option in the setting of contraindication or intolerance to ≥ 1 XOI agent.
  - sUA should be lowered sufficiently to durably improve signs and symptoms of gout, with a target < 6 mg/dL at a minimum, and often < 5 mg/dL.
  - Combination oral ULT with 1 XOI and 1 uricosuric agent is appropriate when the sUA target has not been met by appropriate dosing of a XOI.
  - Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral ULT options.
  - For refractory gout, the recommendations are as follows:
    - An attempt should be made to maximize the XOI dose.
    - Febuxostat can be substituted for allopurinol or vice versa in the event of drug intolerance and adverse events, and such a substitution should be considered after initial failure of upward dose titration of 1 XOI.
    - Effective therapeutic options include addition of a uricosuric agent (eg, probenecid) to an XOI drug or vice versa.
    - Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, conventional and appropriately-dosed ULT. It is not recommended as a first-line ULT agent for any case scenarios.
    - There is a lack of consensus on the appropriate duration of pegloticase therapy relative to intended and achieved decrease in symptoms and signs of gout, including decrease in tophus size.

- **American College of Rheumatology: Guidelines for the Management of Gout. Part 2: Therapy and Anti-inflammatory Prophylaxis of Acute Gouty Arthritis** (*Khanna et al 2012*)
  - Per the ACR Web site, the 2012 gout guidelines are being revised and are anticipated to be completed in early 2020.
  - See Appendix C for an explanation regarding the levels of evidence.
  - An acute gouty arthritis attack should be treated with pharmacologic therapy, initiated within 24 hours of onset.
  - Established ULT should be continued, without interruption, during an acute attack of gout.

- Monotherapy with an NSAID (with proton pump inhibitor where indicated), corticosteroids, or colchicine is recommended as first-line agents for an acute gout attack.
  - Low-dose colchicine or low-dose NSAIDs are recommended first-line.
  - If colchicine or NSAIDs are not tolerated, contraindicated, or ineffective, then second-line options, such as low dose prednisone or prednisolone (≤ 10 mg/day), can be utilized.
  - If the patient is experiencing severe pain, particularly for a polyarticular attack or an attack affecting multiple large joints, initial combination therapy is an appropriate option.
- If there is an inadequate outcome, switching to an alternate monotherapy or add-on combination therapy is appropriate.
- If there is a successful outcome, consider indications for ULT or adjustment of ongoing ULT (see Part 1 of guidelines).

**SAFETY**

- **Contraindications**
  - Allopurinol
    - Patients who have developed a severe reaction to allopurinol should not be restarted on allopurinol
  - Colchicine
    - Concomitant colchicine and drugs that inhibit CYP3A4 and P-gp should be avoided in patients with renal or hepatic impairment
    - Colchicine should be avoided in patients with both renal and hepatic impairment
  - Febuxostat
    - Concomitant azathioprine or mercaptopurine therapy
  - Pegloticase
    - G6PD deficiency
  - Probenecid
    - Children < 2 years of age
    - Known blood dyscrasias or uric acid kidney stones
    - Should not be started until an acute gouty attack has subsided
- **Key warnings/precautions**
  - Allopurinol
    - Allopurinol should be discontinued at the first appearance of skin rash or other signs which may indicate an allergic reaction.
    - There may be an increased risk of hypersensitivity reactions to allopurinol in patients with decreased renal function receiving concomitant thiazides. Caution should be exercised if administering this combination.
    - Dose adjustments may be required when administering allopurinol with mercaptopurine or azathioprine.
    - A few cases of reversible clinical hepatotoxicity, and in some patients, asymptomatic rises in serum alkaline phosphatase or serum transaminase have been observed.
    - Caution should be exercised when partaking in activities that require alertness, as allopurinol may cause drowsiness.
    - A fluid intake sufficient to yield a daily urinary output of ≥ 2 liters and the maintenance of a neutral or slightly alkalinized urine are recommended to prevent the possible formation of xanthine calculi and to prevent renal precipitation or urates in patients receiving concomitant uricosuric agents.
    - Bone marrow suppression has been reported 6 weeks to 6 years after allopurinol initiation.
  - Colchicine
    - Fatal overdoses have been reported with colchicine in adults and children.
    - Blood dyscrasias have been reported at therapeutic colchicine doses.
    - Life threatening and fatal drug interactions have been reported with concomitant use of colchicine and P-gp or strong CYP3A4 inhibitors.
    - Neuromuscular toxicity: Myotoxicity including rhabdomyolysis may occur; especially in combination with other drugs known to cause this effect (eg, statins, fibrates).
  - Febuxostat
    - **Boxed warning**: CV death
      - Gout patients with established CV disease treated with febuxostat had a higher rate of CV death compared to those treated with allopurinol in a CV outcome study.
      - The risks and benefits of febuxostat should be considered when deciding to prescribe or continue patients on this medication. Febuxostat should only be used in patients who have an inadequate response to a maximally titrated dose of allopurinol, who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable.
    - Gout flare: An increase in gout flares is frequently observed during initiation of anti-hyperuricemic agents including febuxostat. If a gout flare occurs during treatment, febuxostat need not be discontinued. Gout flare prophylaxis may be beneficial for up to 6 months.
    - Hepatic effects: Post-marketing reports of hepatic failure, sometimes fatal, have occurred. Causality cannot be excluded. Febuxostat should not be restarted if liver injury is confirmed and no alternate etiology can be found.

- Serious skin reactions: Postmarketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms (DRESS), and toxic epidermal necrolysis (TENS) have been reported in patients taking febuxostat. Febuxostat should be discontinued if serious skin reactions are suspected.

- Pegloticase
  - **Boxed warning:** Anaphylaxis and infusion reactions; G6PD deficiency-associated hemolysis and methemoglobinemia
    - Anaphylaxis reactions have been reported during and after pegloticase administration. Anaphylaxis may occur with any infusion and generally manifests within 2 hours of the infusion; however, delayed-type hypersensitivity reactions have been reported.
    - Pegloticase should be administered in a healthcare setting by a healthcare provider(s) prepared to manage anaphylaxis and infusion reactions. Patients should be closely monitored for an appropriate period of time post infusion.
    - sUA levels should be monitored prior to infusions; treatment may be discontinued if sUA levels increase above 6 mg/dL particularly when 2 consecutive levels > 6 mg/dL are observed.
    - Patients should be screened for G6PD deficiency prior to pegloticase initiation. Hemolysis and methimoglobinemia have been reported with pegloticase in this patient population. Pegloticase should not be administered to patients with G6PD deficiency.
  - Infusion reactions
  - Gout flares: Gout flare prophylaxis is recommended for at least the first 6 months of therapy.
  - Congestive heart failure (CHF): CHF exacerbation may occur; patients should be monitored closely post infusion.
- Probenecid
  - Maintenance doses of colchicine or NSAIDs generally should be given prophylactically when probenecid is begun, due to increased risk of gout flares.
  - Increase in plasma concentration of methotrexate is possible when used concurrently with probenecid; concomitant use should be avoided if possible and if not, then methotrexate dose should be reduced.
  - Severe allergic reactions and anaphylactic reactions are possible.
  - Use with caution in patients with peptic ulcer disease.

- **Key adverse effects**
  - Allopurinol
    - Skin rash (may be severe and fatal), incidence = 1% to 3%
    - Acute gout attacks following initiation of allopurinol
    - Diarrhea
    - Nausea
    - Increase in alkaline phosphatase
  - Colchicine
    - The most common adverse effects reported are diarrhea, nausea, vomiting, and abdominal pain.
  - Febuxostat
    - Adverse effects that occurred in ≥ 1% of patients treated with febuxostat and at least 0.5% greater than noted in patients receiving placebo include:

**Table 5. Adverse reactions for febuxostat compared to placebo and allopurinol***

| Adverse reactions | Placebo | Febuxostat | | Allopurinol* |
|---|---|---|---|---|
| | n = 134 | 40 mg n = 757 | 80 mg n = 1279 | n = 1277 |
| Liver function abnormality | 0.7% | 6.6% | 4.6% | 4.2% |
| Nausea | 0.7% | 1.1% | 1.3% | 0.8% |
| Arthralgia | 0% | 1.1% | 0.7% | 0.7% |
| Rash | 0.7% | 0.5% | 1.6% | 1.6% |

*Of the patients who received allopurinol, 10 received 100 mg, 145 received 200 mg, and 1122 received 300 mg, based on level of renal impairment.

    - The most common adverse effect leading to discontinuation form therapy was liver function abnormalities in 1.8% of patients on febuxostat 40 mg, 1.2% on febuxostat 80 mg, and 0.9% on allopurinol.
  - Pegloticase
    - Adverse effects that occurred in ≥ 5% of patients in clinical trials include:
      - Gout flare (77% with pegloticase vs 81% with placebo)
      - Infusion reaction (26% with pegloticase vs 5% with placebo)
      - Nausea (12% with pegloticase vs 2% with placebo)
      - Contusion or ecchymosis (11% with pegloticase vs 5% with placebo)
      - Chest pain (6% with pegloticase vs 2% with placebo)

- Anaphylaxis (5% with pegloticase vs 0 with placebo)
  - Probenecid
    - CNS: Headache, dizziness
    - Acute symptoms of gout
    - GI: hepatic necrosis, vomiting, anorexia
    - Genitourinary: Nephrotic syndrome, uric acid stones, renal colic, costovertebral pain, urinary frequency
    - Hematologic: Aplastic anemia, leukopenia, hemolytic anemia, anemia
    - Integumentary: Dermatitis, alopecia, flushing

- **Drug Interactions**

**Table 6. Key drug interactions for anti-gout agents**

| Precipitant Drug | Object Drug | | Description |
|---|---|---|---|
| Allopurinol | Ampicillin, amoxicillin | ↔ | Risk of skin rash with allopurinol coadminstration as compared with either drug alone |
| Allopurinol | Azathioprine, mercaptopurine | ↑ | Increase in levels of azathioprine and mercaptopurine, as these drugs are metabolized by XO. A Reduction of azathioprine and mercaptopurine dose of one-third to one-fourth of usual dose is required. |
| Colchicine | Cyclosporine | ↑ | Significant increase in colchicine plasma levels. Fatal colchicine toxicity has been reported with cyclosporine. |
| Colchicine | Macrolides and related antibiotics | ↑ | Significant increase in colchicine plasma levels. Fatal colchicine toxicity has been reported with clarithromycin, a strong CYP3A4 inhibitor. |
| Colchicine | Nefazodone | ↑ | Significant increase in colchicine plasma levels |
| Colchicine | Protease inhibitors | ↑ | Significant increase in colchicine plasma levels |
| Colchicine | Verapamil, diltiazem | ↑ | Significant increase in colchicine plasma levels; neuromuscular toxicity seen with verapamil and diltiazem interactions |
| Febuxostat | Azathioprine, mercaptopurine | ↑ | Increase in levels of azathioprine and mercaptopurine, as these drugs are metabolized by XO; use with azathioprine and mercaptopurine is contraindicated. |
| Probenecid | Methotrexate | ↑ | Increase in methotrexate levels |
| Probenecid | NSAIDs | ↑ | Increase toxicity of NSAID possible |

## DOSAGE AND ADMINISTRATION

- Allopurinol
  - The dose should be is based on signs/symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)
  - The initial dose recommended is 100 mg/day orally as a single or divided dose with increases at weekly intervals by 100 mg until sUA < 6 mg/dL
  - Maintenance dosing
    - Mild gout: 200 to 300 mg/day as a single or divided dose
    - Moderate-severe gout: 400 mg to 600 mg/day as a single or divided dose
    - Maximum dose = 800 mg/day
- Colchicine
  - For gout prophylaxis, the recommended dose is 0.6 mg orally (with or without food) once or twice daily. The maximum daily dose 1.2 mg.
  - For the treatment of gout flares, 1.2 mg should be administered at the first sign of flare, followed by 0.6 mg 1 hour later.
- Febuxostat
  - The recommended dose is 40 or 80 mg orally once daily. More specifically, the recommended starting dose is 40 mg once daily; for patients who do not achieve a sUA of < 6 mg/dL after 2 weeks, the dose should be increased to 80 mg once daily.
  - No dose adjustments are recommended in patients with mild or moderate renal or hepatic impairment. However, 40 mg orally daily is recommended for patients with severe renal impairment.
  - Febuxostat can be taken with or without food or antacid use.
- Pegloticase
  - The recommended dose is 8 mg IV, administered over ≥ 120 minutes, every 2 weeks.
  - Pre-infusion medications (eg, antihistamines, corticosteroids) are recommended.
    - If an infusion reaction occurs, the infusion may be slowed or stopped and restarted at a slower rate, at the

discretion of the physician.
    - Patients should be monitored for anaphylaxis for approximately 1 hour post-infusion.
- Probenecid
    - The recommended dose is 250 mg orally twice daily for 1 week, then 500 mg twice daily.
    - Probenecid should not be started until an acute gouty attack has subsided.
- Probenecid/colchicine
    - The initial dose is 1 tablet orally once daily for 1 week, followed by a maintenance dose of 1 tablet orally twice daily.
    - Probenecid/colchicine should not be started until an acute gouty attack has subsided.

## SPECIFIC POPULATIONS

- **Geriatrics**
    - Allopurinol, probenecid
        - Safety and effectiveness have not been established in this patient population.
    - Colchicine
        - Due to the increased incidence of renal impairment in elderly patients (and other comorbidities), a lower dose should be considered.
    - Febuxostat, pegloticase
        - No dosage adjustments are necessary in elderly patients.
- **Pediatrics**
    - Allopurinol, colchicine, febuxostat, pegloticase, probenecid
        - Safety and effectiveness have not been established in this patient population.
- **Renal dysfunction**
    - Allopurinol
        - Patients with decreased renal function should receive lower doses of allopurinol.
    - Colchicine
        - Dose reduction or alternatives should be considered for the prophylaxis of gout flares in patients with renal impairment.
        - Colchicine is not effectively removed by hemodialysis. Patients on hemodialysis should be monitored carefully for colchicine toxicity.
    - Febuxostat
        - No dosage adjustments are necessary for mild to moderate renal impairment; however, for patients with severe renal impairment (CLcr 15 to 29 mL/min), a lower dose is recommended.
    - Pegloticase
        - No dosage adjustments are required for patients with renal impairment.
    - Probenecid
        - Probenecid may not be beneficial in patients with chronic renal insufficiency, particularly in patients with a CLcr ≤ 30 mL/minute.
- **Hepatic dysfunction**
    - Allopurinol, pegloticase
        - The safety and effectiveness have not been established in this patient population.
    - Colchicine
        - Dose reduction or alternatives should be considered for the prophylaxis of gout flares in patients with hepatic impairment.
    - Febuxostat
        - No dosage adjustments are necessary for mild to moderate hepatic impairment (Child-Pugh Class A or B). No studies have been conducted in patients with severe hepatic impairment (Child-Pugh Class C).
- **Pregnancy and nursing**
    - Allopurinol, febuxostat, pegloticase
        - The safety and effectiveness have not been established in this patient population.
    - Colchicine, probenecid
        - Both colchicine and probenecid cross the placental barrier. As with other drugs, its use requires that the anticipated benefit would outweigh the potential hazards.

## IMPORTANT PRODUCT AVAILABILITY AND STORAGE REQUIREMENTS

- Pegloticase must be stored in its original carton and maintained under refrigeration between 36° to 46°F at all times. The vial should not be shaken or frozen, and it should be protected from light.

## APPENDICES

**Appendix A. ACP guideline grading system** *(Qaseem et al 2016)*

**Table 7. ACP grading system**

| Quality of evidence | Strength of recommendation | |
|---|---|---|
| | **Benefits clearly outweigh risks and burdens or risks and burden clearly outweigh benefits** | **Benefits finely balanced with risks and burdens** |
| **High** | Strong | Weak |
| **Moderate** | Strong | Weak |
| **Low** | Strong | Weak |

**Appendix B. AHRQ Strength of evidence scale** (*AHRQ 2017)*

**Table 8. Strength of evidence scale**

| Quality of evidence | Description |
|---|---|
| **High** | High confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. |
| **Moderate** | Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. |
| **Low** | Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. |
| **Insufficient** | Evidence either is unavailable or does not permit a conclusion. |

**Appendix C. ACR grading system** *(Khanna et al 2012*)

**Table 9. ACR Evidence grades for recommendations**

| Levels | Description |
|---|---|
| **Level A** | Supported by multiple randomized clinical trials or meta-analyses |
| **Level B** | Derived from a single randomized trial or nonrandomized studies |
| **Level C** | Consensus opinion of experts, case studies, or standard of care |

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