



Antihyperuricemics Therapeutic Class Review (TCR)

January 27, 2022

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MANAGEMENTSM

FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
allopurinol* (Zyloprim®) ¹	generic, Casper	<ul style="list-style-type: none"> ▪ Management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy) ▪ Management of patients with leukemia, lymphoma, and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels ▪ 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
colchicine tablet [†] (Colcris®) ²	generic, Takeda	<ul style="list-style-type: none"> ▪ Treatment and prevention of gout flares in adults ▪ Management of familial Mediterranean fever in adults and children ages ≥ 4 years
colchicine solution [†] (Gloperba®) ³	Avion	<ul style="list-style-type: none"> ▪ Prophylaxis of gout flares in adults
colchicine capsule [†] (Mitigare®) ⁴	generic, Hikma	<ul style="list-style-type: none"> ▪ Prophylaxis of gout flares in adults[‡]
febuxostat* (Uloric®) ⁵	generic, Takeda	<ul style="list-style-type: none"> ▪ Chronic management of hyperuricemia in adult patients with gout who have an inadequate response to maximally titrated dose, who are intolerant to, or for whom treatment with allopurinol is not advisable.
pegloticase* (Krystexxa®) ⁶	Horizon	<ul style="list-style-type: none"> ▪ Treatment of chronic gout in adult patients refractory to conventional therapy[§]
probenecid ⁷	generic	<ul style="list-style-type: none"> ▪ Treatment of hyperuricemia associated with chronic gout or gouty arthritis
probenecid/colchicine ⁸	generic	<ul style="list-style-type: none"> ▪ Treatment of chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout

* Allopurinol, febuxostat, and pegloticase are not recommended for the treatment of asymptomatic hyperuricemia.

† Colchicine capsule (Mitigare), colchicine solution (Gloperba), and colchicine tablet (Colcris) were FDA-approved via the 505(b)(2) pathway, in which approval relied, at least in part, on data not developed by the applicant.^{9,10,11}

‡ The safety and effectiveness of colchicine capsules (Mitigare) for acute treatment of gout flares during prophylaxis have not been studied.

§ Gout refractory to conventional therapy occurs when a patient fails to normalize serum uric acid and whose signs and symptoms are not controlled with xanthine oxidase inhibitors at maximum dose, as medically appropriate, or for whom these drugs are contraindicated.

|| Probenecid is also FDA-approved for adjunctive therapy with penicillin G, amoxicillin, ampicillin, or cefoxitin and azithromycin for the treatment of uncomplicated gonorrhea; adjunctive therapy with cefoxitin followed by doxycycline, with or without metronidazole, for pelvic inflammatory disease; adjunctive therapy with penicillin G for neurosyphilis; and adjunct to antibiotic (e.g., penicillin) to increase and/or prolong antibiotic serum concentrations. Indications for adjunctive therapy to antibiotics will not be addressed in this review.

OVERVIEW

Hyperuricemia (serum uric acid > 6.8 mg/dL) can occur due to either an overproduction of uric acid, an underexcretion of uric acid, or a combination of the 2 mechanisms.^{12,13} Most often, hyperuricemia is due to a reduction in fractional clearance of urate rather than an over production of urate. Primary hyperuricemia may be caused by under excretion of uric acid or overproduction of urate that results from diseases such as Lesch-Nyhan syndrome (a genetic disorder characterized by uric acid

overproduction, motor dysfunction, and cognitive and behavioral disturbances) resulting in salvaged purines from rapid cell turnover; or inflammatory disorders, including lympho-myeloproliferative disorders and severe exfoliative psoriasis; and cytotoxic drugs. Secondary hyperuricemia may be due to renal impairment; hypertension; lead nephropathy; hypothyroidism; and drugs including low dose aspirin, diuretics, ethanol, and cyclosporine.^{14,15,16} Hyperuricemia is the most important risk factor for developing gout.

Gout is the crystal deposition of monosodium urate associated with elevated levels of uric acid.^{17,18} Crystals are deposited in joints, tendons, and surrounding tissues. Acute attacks of gout are painful and, in approximately over half of all cases, the metatarsophalangeal joint of the great toe is the first joint to be affected. Over time, deposition of urate masses in joints creates tophi. Treatment of gout is managed in 3 stages: acute treatment, prophylaxis to prevent acute flares, and lowering excess stores of urate to prevent flares of gouty arthritis and prevent tissue deposition of urate crystals. Acute gouty arthritis can be treated with colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), and intra-articular corticosteroid injections.

After an initial gout attack, the choice of urate-lowering medications includes uricosuric drugs (colchicine, probenecid) or xanthine oxidase inhibitors (allopurinol, febuxostat).^{19,20} Probenecid promotes uric acid excretion by inhibiting the tubular reabsorption of filtered and secreted urate. Some patients with gout can experience an increased incidence of uric acid stones due to increased uric acid renal clearance. This condition could lead to renal calculi or colic, hematuria, or costovertebral pain. Urine should be kept alkaline to increase the solubility of uric acid and decrease the risk of developing nephrolithiasis. Probenecid can increase the number of acute gouty attacks occurring in the first 6 to 12 months of therapy.

The xanthine oxidase inhibitors, allopurinol and febuxostat, inhibit uric acid production.^{21,22} With allopurinol, serum urate concentrations begin to decrease within 1 to 2 days; however, significant reductions may not be immediately apparent due to the dissolution of uric acid deposits. Normal serum urate levels are usually obtained within 1 to 3 weeks. If allopurinol is discontinued, uric acid concentrations may return to pretreatment levels, which usually occur 7 to 10 days after allopurinol discontinuation. No studies with febuxostat have been conducted in patients with secondary hyperuricemia (including patients being treated for Lesch-Nyhan syndrome, malignant disease, or in organ transplant recipients); therefore, febuxostat is not recommended for use in these patients. Febuxostat offers an alternative to allopurinol for patients who fail to achieve serum urate levels < 6 mg/dL after 3 months of therapy or who are intolerant to allopurinol; however, febuxostat may have a greater risk for cardiovascular (CV) adverse events as compared to allopurinol.

In most patients, dose titration of oral urate-lowering agents can adequately achieve target uric acid levels. However, it has been noted that approximately 3% of patients do not respond to oral urate-lowering medications because of refractoriness, contraindications, or intolerance. Pegloticase (Krystexxa) provides an effective alternative therapy to conventional oral urate-lowering medications for patients who cannot take oral urate-lowering medications.²³

In 2012, the American College of Rheumatology (ACR) published their first set of guidelines for the management of gout.^{24,25} In 2020, these guidelines were updated.²⁶ The most notable difference in the new guidelines is the strong recommendation of allopurinol as the preferred first-line urate-lowering therapy (ULT) for all patients, including patients with moderate-to-severe chronic kidney disease (CKD), due to new CV safety concerns with febuxostat, combined with other non-clinical considerations. The

ACR advises treatment for an acute gouty arthritis attack to begin early after symptom onset in order to provide optimal care. Furthermore, the guidelines also recommend continuation of established ULT without interruption during an acute gout attack, if applicable, although this is a conditional recommendation. The ACR guidelines state oral NSAIDs, systemic corticosteroids, or oral colchicine are all appropriate first-line therapies, but specific anti-inflammatory medications should be based on individual patient factors. The ACR guidelines do not advocate any NSAID over another as first-line therapy; however, they do recommend, if appropriate, the continuation of the initial NSAID regimen at full dose until the acute attack completely resolves. Oral colchicine is also suggested as an appropriate treatment option for acute gout; Low-dose colchicine is strongly recommended as an appropriate treatment option for acute gout over high-dose colchicine, due to similar efficacy and lower risk of adverse events. The ACR guidelines state oral corticosteroids are appropriate for all cases of gout, with parenteral glucocorticoids favored as alternative agents when oral dosing is not feasible. Topical ice is a conditional recommendation as an adjuvant treatment for patients during a gout flare. Anti-inflammatory prophylaxis is also recommended for all patients who have started ULT due to an increased frequency of gout attacks during early therapy. Continuation of concomitant anti-inflammatory prophylaxis for at least 3 to 6 months after starting ULT is strongly recommended, especially if the patient continues to have flares. The ACR recommends colchicine, NSAIDs, prednisone, or prednisolone as first-line anti-inflammatory prophylaxis, but no one agent is recommended over another in the current guidelines.

The ACR recommends that the goal of ULT is to reach a target serum urate level < 6 mg/dL; the guidelines strongly recommend a treat-to-target strategy that revolves around ULT dose titration and subsequent serum measurement to achieve target serum urate.²⁷ The ACR no longer recommends other specific thresholds due to absence of supporting evidence. The guidelines also suggest medications that induce hyperuricemia should be discontinued, if possible, but state that a medication should only be discontinued when the benefits for improving gout clearly outweigh the risks of stopping the medication. Patients with an established gouty arthritis diagnosis who have tophus/tophi or frequent acute gout attacks (≥ 2 attacks per year) should receive ULT (strong recommendation) according to the ACR guidelines; however, moderate to severe CKD or past history of urolithiasis only received a conditional recommendation to receive ULT. ULT may be started during an acute attack (conditional recommendation) as long as effective anti-inflammatory therapy has been initiated. The ACR recommends the xanthine oxidase inhibitor, allopurinol, as the first-line pharmacologic approach over all other ULTs (strong recommendation). When the serum urate target has not been met with initial therapy, the ACR suggests providers use a treat-to-target strategy over a fixed-dose strategy, and that the specific dose titration should be left to the provider and patient based on customized factors, such as patient comorbidities and patient preferences. Due to the uncommon use of uricosuric agents, such as probenecid, the ACR did not formally vote on their place in therapy and continue to state that probenecid is useful as add-on therapy in patients who are only partially responsive to a xanthine oxidase inhibitor. The ACR advocates pegloticase as an appropriate pharmacologic option in patients with severe gout who are refractory or have intolerance to appropriately dosed oral ULT; pegloticase is recommended as a third-line therapy.

In 2017, the American College of Physicians (ACP) released clinical guidelines for the management of acute and recurrent gout.²⁸ The ACP recommends corticosteroids, NSAIDs, or colchicine (low-dose; 1.2 mg followed by 0.6 mg 1 hour later; Grade: strong recommendation, moderate-quality evidence) for the treatment of acute gout (Grade: strong, high-quality evidence) as they are effective for the

reduction of pain. Corticosteroids should be considered as first-line therapy since they are generally safer, low-cost, and have been shown to be as effective as NSAIDs, with fewer side effects, when treating gout. There is no evidence to show one NSAID is more efficacious than another when treating gout (moderate-quality evidence). The ACP recommends against starting long-term (≥ 12 months) ULT in most patients after an initial gout attack or in patients with infrequent attacks (< 2 attacks per year) (Grade: strong recommendation, moderate-quality evidence). Patients with ≥ 2 attacks per year or those with problematic gout (e.g., tophi, chronic renal disease, urolithiasis) should consider the benefits and risks of the medication along with cost before starting therapy. Allopurinol (300 mg daily) and febuxostat (40 mg daily) are equally efficacious at decreasing serum urate levels and evidence shows therapy reduces the risk for acute gout attacks after 1 year; however, therapy does not reduce the risk within the first 6 months. Prophylactic low-dose colchicine or NSAID therapy reduces the risk for acute attacks when starting ULT (high quality evidence); continuing therapy for > 8 weeks was more effective than shorter durations (moderate-quality evidence). The guidelines did not address pegloticase, claiming the medication would not likely be prescribed by primary care prescribers.

Joint 2018 guidelines from the American College of Foot and Ankle Surgeons and the American Association of Nurse Practitioners recommend NSAIDs as the first-line treatment for acute gout.²⁹ In addition, long-term medications, such as allopurinol, are necessary for the treatment of recurrent gout, and when used, allopurinol should be titrated to a uric acid level of < 6 mg/dL.

In addition to the prevention and treatment of gout flares, colchicine tablet (Colcrys) is also FDA-approved as an orphan drug for the treatment of familial Mediterranean fever (FMF). FMF is an autosomal recessive disorder characterized by recurrent episodes of painful inflammation in the abdomen, chest, or joints.³⁰ These episodes are often accompanied by fever and sometimes a rash. The first episode usually occurs in childhood or adolescence but, in some cases, the initial attack occurs much later in life. Typically, episodes last 48 to 96 hours, with peak intensity occurring in the first 12 hours, and can vary in severity. The length of time between attacks is also variable. Without treatment to help prevent attacks and complications, a buildup of amyloid in the body's organs and tissues may occur, which can lead to kidney failure. FMF primarily affects populations originating in the Mediterranean region, particularly people of Armenian, Arabic, Turkish, and Jewish ancestry. The disorder affects 1 in 250 people to 1 in 2,600 people in these populations. Mutations in the Mediterranean fever (*MEFV*) gene cause FMF. The *MEFV* gene provides instructions for making a protein called pyrin, which is found in white blood cells. Pyrin is involved in the immune system, helping to regulate inflammation. When inflammation and resolution of the offending stimulus has been accomplished, the body stops the inflammatory response to prevent damage to its own cells and tissues. Mutations in the *MEFV* gene reduce the activity of the pyrin protein, which disrupts control of the inflammation process. An inappropriate or prolonged inflammatory response can result and is usually accompanied by fever and pain in the abdomen, chest, or joints. The European League Against Rheumatism (EULAR) recommendations state that colchicine (in single or divided doses) should be initiated as soon as clinical diagnosis is made.³¹

Rasburicase (Elitek®), a recombinant injectable urate oxidase, is approved for use in preventing complications of hyperuricemia during tumor lysis syndrome, but it is not included in this review.³²

PHARMACOLOGY^{33,34,35,36,37,38}

Drug Mechanism of Action	Mechanism of Action
allopurinol	<ul style="list-style-type: none"> ▪ Xanthine oxidase inhibitor that blocks the conversion of hypoxanthine to xanthine and of xanthine to uric acid, thereby decreasing the production of uric acid ▪ Unlike uricosuric agents that increase the urinary excretion of uric acid, allopurinol interferes with purine catabolism; as a result, concentrations of uric acid in the blood and urine are lowered ▪ Oxypurinol, an allopurinol metabolite, also inhibits xanthine oxidase and is the agent responsible for the pharmacologic effects of allopurinol; even though hypoxanthine and xanthine serum concentrations increase, their renal clearance is at least 10 times that of uric acid
colchicine tablet (Colcrys) colchicine solution (Gloperba) colchicine capsule (Mitigare)	<ul style="list-style-type: none"> ▪ Colchicine binds to proteins in microtubules of neutrophils and inhibits the migration of neutrophils into the area of inflammation, thereby interfering with the inflammatory response to urate crystal deposition; although colchicine does not inhibit phagocytosis of uric acid crystals, it does appear to prevent the release of an inflammatory glycoprotein from phagocytes ▪ Colchicine arrests metaphase due to 2 separate antimetabolic effects: disruption of mitotic spindle formation and disruption of sol-gel formation; these actions also may contribute to its antigout properties; toxic effects of colchicine are related to its antimetabolic activity within proliferating tissues such as the skin, hair, and bone marrow ▪ The mechanism of action of colchicine (Colcrys) in patients with FMF has not been fully established; however, evidence suggests that colchicine may interfere with the intracellular processes present in neutrophils and monocytes that mediate activation of interleukin-1 beta ▪ Colchicine inhibits β-tubulin polymerization into microtubules which disrupts cytoskeletal functions and prevents neutrophil activation, degranulation, and migration which is thought to mediate some symptoms of gout
febuxostat (Uloric)	<ul style="list-style-type: none"> ▪ Xanthine oxidase inhibitor that blocks the conversion of hypoxanthine to xanthine and of xanthine to uric acid, thereby decreasing the production of uric acid ▪ Febuxostat is not anticipated to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations
pegloticase (Krystexxa)	<ul style="list-style-type: none"> ▪ Pegloticase is a uric acid specific enzyme which is pegylated and acts by catalyzing the oxidation of uric acid to allantoin which lowers serum uric acid
probenecid	<ul style="list-style-type: none"> ▪ Probenecid competitively inhibits active reabsorption of urate at the proximal renal tubule. It increases the urinary excretion of uric acid and lowers serum urate concentrations; probenecid may decrease or prevent urate deposition, tophi formation, and chronic joint changes; promote resolution of existing urate deposits; and, after several months of therapy, reduce the frequency of acute attacks of gout by lowering serum concentrations of uric acid below its solubility limits

The mechanisms of effect for combination products within this class, probenecid/colchicine, is described above based on its individual components.

PHARMACOKINETICS^{39,40,41,42,43,44}

Drug	Absorption (%)	Half-Life (hours)	Metabolism	Excretion (%)
allopurinol	90	1-2; oxypurinol 15	Oxypurinol	Renal: 80 Feces: 20
colchicine tablet (Colcrys)	45	26.6-31.2	3 metabolites	Fecal and urinary excretion
colchicine solution (Gloperba)	45	25-37	3 metabolites	Fecal and urinary excretion
colchicine capsule (Mitigare)	45	21.7-49.9	3 metabolites	Fecal and urinary excretion
febuxostat (Uloric)	>49	5-8	4 active metabolites	Renal: 49 Feces: 45
pegloticase (Krystexxa)	100	nr	nr	nr
probenecid	Complete absorption	3-12 hrs; dose dependent	Active metabolites	Hepatic and renal (5-11 unchanged)

Pharmacokinetic data are not available for colchicine/probenecid combination product.

CONTRAINDICATIONS/WARNINGS^{45,46,47,48,49,50,51}

allopurinol (Zyloprim)

Allopurinol is contraindicated in patients with a history of a severe reaction to allopurinol; do not rechallenge patients.

A few cases of reversible clinical hepatotoxicity have been noted in patients taking allopurinol; in some patients, asymptomatic rises in serum alkaline phosphatase (ALP) or serum transaminase have been observed.

Allopurinol should be discontinued at the first appearance of a skin rash or other signs of an allergic reaction. In some cases, skin rash may be followed by a more severe hypersensitivity reaction such as exfoliative, urticarial, and purpuric lesions, as well as Stevens-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS) syndrome, drug hypersensitivity syndrome (DHS), and/or generalized vasculitis, irreversible hepatotoxicity, or death. Hypersensitivity reactions may be increased in patients with renal impairment and receiving thiazides. Use allopurinol with caution and observe patients closely in this patient population. The HLA-B*5801 allele is a genetic risk marker for severe skin reactions indicative of hypersensitivity to allopurinol.

Due to the occasional occurrence of drowsiness, patients should be aware to use caution when engaging in activities where alertness is imperative.

There is an increased risk of myelosuppression with concomitant use of allopurinol with mercaptopurine or azathioprine. Concurrent use with these agents should be avoided, if possible. See the Drug Interaction section of this review for more information. Rarely, a patient may develop varying degrees of bone marrow depression while receiving allopurinol alone.

Allopurinol can prolong the half-life of select coumarin anticoagulants. The prothrombin time should be reassessed periodically in patients receiving concomitant coumarin anticoagulants.

During early use of allopurinol, an increase in acute gout attacks have been observed. Prophylactic maintenance doses of colchicine are recommended as a result.

colchicine (Colcrys, Gloperba, Mitigare)

Life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses in patients treated concurrently with a P-glycoprotein (P-gp) or strong CYP3A4 inhibitors (cyclosporine, clarithromycin, and all protease inhibitors, except fosamprenavir). If treatment with a P-gp or strong CYP3A4 inhibitor cannot be avoided in patients with normal renal and hepatic function, dose reduction and/or therapy interruption and monitoring for colchicine toxicity is warranted. Use of colchicine in conjunction with a P-gp or strong CYP3A4 inhibitor is contraindicated in patients with renal or hepatic impairment. See the Drug Interaction section of this review for more information.

Fatal overdoses, both accidental and intentional, have been reported in adults and children who have ingested colchicine. Colchicine should be kept out of reach of children.

Blood dyscrasias including myelosuppression, leukopenia, granulocytopenia, thrombocytopenia, pancytopenia, and aplastic anemia have been reported with therapeutic doses of colchicine. Colchicine should be used cautiously in patients with pre-existing bone marrow suppression. Prolonged administration of colchicine has been associated with bone marrow suppression including blood dyscrasias, such as agranulocytosis, thrombocytopenia, or aplastic anemia. Patients with dental disease should use colchicine with caution. If possible, dental work should be performed prior to initiating colchicine therapy or deferred until blood counts return to normal.

Colchicine-induced neuromuscular toxicity and rhabdomyolysis have been reported with chronic treatment in therapeutic doses. Patients with renal dysfunction and elderly patients, even those with normal renal and hepatic function, are at increased risk for neuromuscular toxicity. Concurrent use of atorvastatin, simvastatin, pravastatin, fluvastatin, gemfibrozil, fenofibrate, or fenofibric acid (themselves associated with myotoxicity) or cyclosporine may potentiate myopathy development. Once colchicine is stopped, the symptoms generally resolve within 1 week to several months.

Elderly or debilitated patients should use colchicine with caution due to their susceptibility to cumulative toxicity.

Patients with both renal and hepatic impairment should not be prescribed colchicine.

Colchicine should not be used as an analgesic medication.

febuxostat (Uloric)

Febuxostat is contraindicated in patients being treated with azathioprine or mercaptopurine.

In a CV outcome study (CARES), gout patients with established CV disease treated with febuxostat had a higher rate of CV death compared to patients treated with allopurinol. The study concluded febuxostat was similar to allopurinol in terms of nonfatal MI, nonfatal stroke, and unstable angina with urgent coronary revascularization; however, there was a significant increase in CV deaths in febuxostat patients (134 [1.5 per 100 patient years]) compared to patients treated with allopurinol (100 [1.1 per 100 patient years]; hazard ratio [HR], 1.34, 95% confidence interval [CI], 1.03 to 1.73). Sudden cardiac

death was the most common cause of adjudicated CV deaths in febuxostat treated patients (2.7%) compared to allopurinol treated patients (1.8%). Due to these reasons, febuxostat should only be used in patients who have inadequate response to allopurinol despite a maximum titrated dose, patients who are intolerant to allopurinol, or for whom treatment with allopurinol is not advisable. Following these results, the FDA updated their prior safety communication investigating these risks, originally issued in 2017, and required updated labeling for febuxostat, including the addition of CARES data and a boxed warning for CV death.⁵² Prescribers should consider the risks and benefit of febuxostat use and monitor for signs and symptoms of MI and stroke. Prescribers should also consider prescribing low-dose aspirin for patients with a history of CV disease.

After initiation of febuxostat, an increase in gout flares is often observed. A reduction in serum uric acid levels occurs which results in the mobilization of urate from tissue deposits and causes gout flares. In order to prevent gout flares when febuxostat is initiated, concurrent prophylactic treatment with a NSAID or colchicine is recommended for up to 6 months. There is no need for febuxostat to be discontinued if a gout flare occurs during therapy; however, the gout flare should be monitored concurrently.

Fatal and non-fatal reports of hepatic failure have been reported in patients taking febuxostat. Transaminase elevations > 3 times the upper limit of normal (ULN) have been observed in febuxostat-treated patients. However, transaminase elevations have not had any dose-effect relationship noted. Liver function tests should be performed before initiating therapy to establish a baseline. Patients who report symptoms of liver injury should have their hepatic function tested and, if abnormal tests result, febuxostat therapy should be interrupted and an investigation into the probable cause for liver injury should be performed. If no other explanation exists for the liver test abnormalities, these patients should not be restarted on febuxostat therapy. Patients who have serum alanine aminotransferase (ALT) > 3 times the reference range and total bilirubin level twice the reference range without other causes are at risk for severe drug-induced hepatic injury and should not restart febuxostat therapy. Patients who have smaller elevations in serum ALT or bilirubin levels and probable alternative causes for liver test abnormalities can use febuxostat with caution.

Serious skin and hypersensitivity reactions, including Steven-Johnson Syndrome, DRESS, and toxic epidermal necrolysis (TEN) have been reported. If serious skin reactions are suspected, the medication should be discontinued. Many of these patients had reported previous similar skin reactions with allopurinol; febuxostat should be used with caution in these patients.

pegloticase (Krystexxa)

Pegloticase is contraindicated in patients with a glucose-6-phosphate dehydrogenase (G6PD) deficiency because it increases the risk of hemolysis and methemoglobinemia. Patients who are at a higher risk for a G6PD deficiency (patients of Mediterranean, Southern Asian, or African ancestry) should be screened for G6PD deficiency before initiating pegloticase.

The label for pegloticase also includes a boxed warning of anaphylactic and infusion reactions, instructing the drug be administered to patients in a healthcare setting in order to manage these events if they occur. Anaphylaxis has been reported in 6.5% of the patients using pegloticase and can occur with any infusion and will usually present within the first 2 hours of the infusion. However, patients should be monitored for an appropriate amount of time after the infusion as delayed type hypersensitivity reactions have occurred. In addition, patients should undergo pre-treatment with oral

antihistamines and intravenous (IV) corticosteroids and/or acetaminophen prior to pegloticase administration. Infusion reactions have been reported more frequently in patients using pegloticase (26% to 41%) compared to placebo (5%). The reactions occurred despite pre-treatment with antihistamines and corticosteroids. Most infusion reactions (approximately 91%) occurred during the time of infusion. Pegloticase should be infused over at least 120 minutes and therapy should be slowed or stopped and restarted at a slower rate if infusion reactions occur. Anaphylaxis and infusion reaction risk is higher in patients with uric acid levels > 6 mg/dL, especially when 2 consecutive levels > 6 mg/dL exist. Patients' serum uric acid levels should be monitored prior to infusions and discontinuation of therapy may be warranted if levels increase > 6 mg/dL. For these reasons, pegloticase should be administered in a healthcare setting equipped to manage anaphylaxis and infusion reactions.

The combination of oral ULT and pegloticase may blunt the increase of serum uric acid levels. Before starting pegloticase, it is recommended that oral urate-lowering medications be discontinued and not restarted during pegloticase therapy.

Patients may experience an increase in gout flares when initiating pegloticase because of mobilization of urate from tissue deposits which alters serum uric acid levels. Unless contraindicated or an intolerance exists, NSAIDs or colchicine is recommended starting at least 1 week before beginning pegloticase and for 6 months thereafter. There is no need to discontinue pegloticase in the event of a gout flare.

Pegloticase has not been studied formally in patients with congestive heart failure. However, caution should be exercised since some patients experienced exacerbations of congestive heart failure during clinical trials.

There are no controlled trials demonstrating the safety and efficacy of re-treatment with pegloticase after stopping therapy for > 4 weeks. Patients receiving re-treatment may be at a higher risk for anaphylaxis and infusion reactions due to the immunogenicity of pegloticase. Patients receiving re-treatment should be monitored closely.

probenecid

Probenecid is contraindicated in an acute attack of gouty arthritis and should be initiated after the attack has subsided. Probenecid is also contraindicated in patients with blood dyscrasias, uric acid kidney stones, coadministration with salicylates, and hypersensitivity to probenecid. Children < 2 years of age should not receive probenecid.

Probenecid contains a sulfonamide side chain. Therefore, caution should be used when prescribing probenecid in patients with a known history of sulfonamide hypersensitivity; however, probenecid does not contain the N4 aromatic amine or the N1-substituent that is present in sulfonamide antibiotics and thought to be responsible for hypersensitivity-type adverse reactions.

The use of probenecid to increase serum penicillin concentrations is not recommended for patients with renal impairment. Probenecid should not be given to patients with renal failure or renal disease associated with moderate-to-severe renal impairment (glomerular filtration rate < 50 mL/min). Probenecid is completely ineffective when the CrCl is < 30 mL/min.

The use of small or large doses of salicylates is contraindicated in patients. Use of acetaminophen is preferred.

Probenecid should be used with caution in patients with peptic ulcer disease because of a possible increase in gastrointestinal (GI) adverse reactions.

Renal colic, hematuria, costovertebral pain, and the formation of uric acid stones may occur in gouty patients. Alkalinization of the urine and liberal intake of fluids may help prevent these occurrences. Patients should be monitored closely.

probenecid/colchicine

Individual contraindications and warnings associated with colchicine and probenecid are also applicable to probenecid/colchicine.

Exacerbation of gout after probenecid/colchicine therapy may occur; additional colchicine may be needed.

Anaphylaxis and rare serious reactions can occur with probenecid/colchicine. The appearance of hypersensitivity reactions should warrant immediate discontinuation of therapy.

DRUG INTERACTIONS^{53,54,55,56,57,58}

allopurinol (Zyloprim)

Allopurinol prolongs the half-life of the anticoagulant, dicumarol; therefore, monitoring prothrombin times and international normalized ratio (INR) levels when allopurinol and oral anticoagulants are administered concurrently is warranted.

Monitor cyclosporine levels and adjust cyclosporine dose appropriately, if used concurrently with allopurinol, due to a potential increase in cyclosporine levels.

By inhibiting xanthine oxidase, allopurinol inhibits the conversion of mercaptopurine, 6-MP, to its inactive metabolites. As a result, the myelosuppressive effects and other side effects of 6-MP may be enhanced. In patients taking 300 mg to 600 mg of allopurinol daily, the dose of 6-MP should be reduced to approximately one-third to one-fourth the usual dose; subsequent dose adjustments should be made based on therapeutic response and appearance of toxic effects. Similarly, concomitant use of 300 mg to 600 mg of allopurinol daily will require an azathioprine dose reduction to one-third to one-fourth the usual dose; close hematologic monitoring is required. Subsequent dosage adjustments should be made based on therapeutic response and appearance of toxic effects.

Enhanced bone marrow suppression has been reported with concomitant use of allopurinol and cytotoxic drugs (e.g., cyclophosphamide, doxorubicin, bleomycin, procarbazine) in patients with neoplastic disease, except leukemia.

Patients with renal impairment who receive allopurinol and thiazide diuretics are at an increased risk of hypersensitivity reactions.⁵⁹ Renal function should be monitored in patients taking allopurinol and thiazide diuretics; dose adjustments may be warranted.

An increased frequency of skin rash has been reported in patients receiving concomitant amoxicillin or ampicillin, although the cause of the association has not been established.

The plasma half-life of chlorpropamide may be prolonged by allopurinol due to competing excretion via the renal tubule; the risk of hypoglycemia may be increased when used concomitantly.

The concomitant administration of uricosuric drugs and allopurinol has been linked with a decrease in the excretion of oxypurines and an increase in urinary uric acid excretion.

colchicine (Colcrys, Gloperba, Mitigare)

Colchicine is a substrate of the efflux transporter P-gp. The CYP3A4 enzyme is the main cytochrome P450 enzyme, of those tested, involved in the metabolism of colchicine. Increased concentrations of colchicine are likely if colchicine is administered with drugs that inhibit P-gp, most of which also inhibit CYP3A4 (e.g., clarithromycin). Concomitant use of colchicine with CYP3A4 and/or P-gp inhibitors should be avoided due to potential for serious and life-threatening toxicity; if co-administration is needed, the dose of colchicine should be adjusted by either reducing the daily dose or reducing the dosing frequency. Fatal drug interactions have been reported.

For concurrent therapy with strong CYP450 3A4 inhibitors (e.g., atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin), colchicine requires a dose reduction due to significantly higher colchicine levels. For gout flare treatment, colchicine should be reduced by half to 0.6 mg for 1 dose then 0.3 mg given 1 hour later. Do not repeat colchicine gout flare treatment for at least 3 days. For the prophylaxis of gout flares, patients should receive an adjusted dose of 0.3 mg once daily if the intended dose was 0.6 mg twice daily, and 0.3 mg once every other day if the original intended dose was 0.6 mg once daily. For FMF, the maximum daily dose of colchicine is reduced to 0.6 mg per day.

Higher colchicine levels have been observed with moderate CYP450 3A4 inhibitors; therefore, dose reduction of colchicine is recommended. For concurrent use with moderate CYP450 3A4 inhibitors (e.g., amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil), colchicine should be given at the usual dose (1.2 mg) when treating gout flare, but the treatment should not be repeated for at least 3 days. For the prophylaxis of gout flares, the intended daily colchicine dose should be cut in half. For FMF, the colchicine maximum dose is 1.2 mg per day for adults.

Concurrent administration with a P-gp inhibitor, such as cyclosporine and ranolazine, warrants a dose reduction, as significantly higher colchicine plasma levels are expected. In such cases, colchicine is given as 0.6 mg for 1 dose for the treatment of gout flares. Do not repeat for at least 3 days. For the prophylaxis of gout flares, the adjusted dose is 0.3 mg daily when the original dose was 0.6 mg twice daily and the adjusted dose is 0.3 mg once daily every other day when the original dose was 0.6 mg once daily. For FMF, the colchicine dose is reduced to 0.6 mg per day.

Pharmacokinetic and/or pharmacodynamic interactions have been reported when atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, fibrates, gemfibrozil, or digoxin is used concurrently with colchicine. The combinations have resulted in myopathy and rhabdomyolysis (including a fatality). Therefore, the potential benefits and risks of the combination therapy should be weighed. Patients should be monitored carefully for any signs or symptoms of muscle pain, tenderness, or weakness, especially during early therapy. Monitoring creatine phosphokinase (CPK) will not necessarily prevent severe myopathy occurrence.

Treatment of gout flares is not recommended for patients receiving prophylactic therapy with colchicine and CYP3A4 inhibitors.

febuxostat (Uloric)

Febuxostat has been shown to alter the metabolism of theophylline in humans based on a drug interaction study in healthy subjects. Caution should be used when administering the drugs together.

There are no drug interaction studies that evaluate concomitant use of febuxostat and other drugs that are metabolized by xanthine oxidase, such as azathioprine and mercaptopurine. The plasma levels of these drugs may be increased due to febuxostat's inhibitory effects on xanthine oxidase, resulting in toxicity of these substrates.

pegloticase (Krystexxa)

No clinical studies have been conducted with pegloticase and other drugs to determine drug interactions. There may be potential for binding with other pegylated products since anti-pegloticase antibodies appear to bind to the pegylated portions of drugs.

probenecid

Probenecid inhibits the renal tubular secretion of many drugs, including acyclovir, valacyclovir, famciclovir, penicillins, sulbactam, tazobactam, gatifloxacin, nitrofurantoin, zidovudine, zalcitabine, dapsone, rifampin, sulfonamides, sulfonyleureas, captopril, methotrexate, aminosaliclates, ertapenem, meropenem, dyphylline, doripenem, ciprofloxacin, ganciclovir, imipenem/cilastatin, tenofovir, and most cephalosporins. A higher systemic exposure and longer half-life may occur which could lead to toxic levels of these agents.

Probenecid and methotrexate used concurrently is not recommended because the combination can increase the risk of uric acid neuropathy.

Probenecid has been shown to decrease the tubular secretion of cidofovir and may decrease cidofovir-induced nephrotoxicity. Concomitant use of probenecid is recommended and beneficial during cidofovir therapy; however, clinicians should be aware that cidofovir serum concentrations also increase. Clinicians should be alert to increased cidofovir adverse reactions, especially in patients with compromised renal function.

Coadministration of probenecid and salicylates is contraindicated. The uricosuric actions of probenecid are inhibited by salicylates even though the plasma concentration of salicylates is not influenced by probenecid.

Probenecid can decrease the renal clearance of NSAIDs, especially indomethacin, ketoprofen, ketorolac, and naproxen, increasing the possibility of adverse effects. Concurrent use of ketorolac and probenecid is contraindicated since the clearance of ketorolac is significantly decreased, resulting in a doubled elimination half-life of ketorolac.

Probenecid dose adjustments may be needed with concurrent use of ethacrynic acid, diazoxide, ethanol, ethambutol, thiazide diuretics, pyrazinamide, and triamterene as hyperuricemia may occur. Additionally, probenecid may interfere with the pharmacologic effects of penicillamine.

Probenecid can interfere with the natriuresis and plasma renin activity of diuretics such as bumetanide, furosemide, and indapamide. In addition, the effects of probenecid can be antagonized by these diuretics as they can increase the levels of serum uric acid.

Concurrent use of probenecid and allopurinol may have additive antihyperuricemic effects. When used together, the serum urate concentration decreases more than if either agent were used alone and an increase in the urinary excretion of uric acid may be expected.

Probenecid may inhibit the metabolism of benzodiazepines, such as lorazepam. Concurrent therapy has shown a 50% decrease in lorazepam clearance and an increase in elimination half-life.

Concurrent use of probenecid and pegloticase may increase the risk of anaphylaxis and infusion reactions of pegloticase. Oral ULT should be stopped prior to beginning pegloticase therapy and withheld throughout treatment.

Concurrent use of probenecid and citalopram may result in an increased exposure to citalopram and lead to an increased risk for QT interval prolongation.

probenecid/colchicine

Drug interactions associated with colchicine and probenecid are also applicable to probenecid/colchicine.

ADVERSE EFFECTS^{60,61,62,63,64,65,66}

Drug	Arthralgia	Rash	Diarrhea	Nausea	LFT Elevations
allopurinol (Zyloprim)	< 1	< 1-3	< 1	< 1	< 1
colchicine tablet (Colcrys)	nr	reported	23-77	4-17	reported
colchicine solution (Gloperba)	nr	reported	reported	reported	reported
colchicine capsule (Mitigare)	nr	reported	reported	reported	reported
febuxostat (Uloric)	0.7-1.1	0.5-1.6		1.1-1.3	4.6-6.6
allopurinol	0.7	1.6	reported	0.8	4.2
placebo	0	0.7		0.7	0.7
pegloticase (Krystexxa)	nr	reported	nr	12	nr
probenecid	nr	reported	nr	reported	nr
probenecid/colchicine	nr	reported	reported	reported	reported

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. nr = not reported.

The most common adverse events associated with pegloticase use include immunogenicity (42% to 92%), gout flares (41% to 81%), infusion reactions (26% to 41%), nausea (12%), contusion or ecchymosis (11%), nasopharyngitis (7%), anaphylactic reaction (4.8% to 6.5%), constipation (6%), chest pain (6%), and vomiting (5%). Congestive heart failure has been reported in 2 patients using pegloticase during clinical trials and 4 patients had exacerbations of pre-existing congestive heart failure. Asthenia, malaise, and peripheral swelling have also been reported.

Due to changing serum uric acid levels resulting in the mobilization of urate from tissue deposits, an increase in gout flares may occur after starting uric lowering medications, including pegloticase, febuxostat, and allopurinol. Colchicine or NSAIDs are recommended upon initiation of gout flare prophylaxis with uric acid lowering therapy. Prophylactic therapy may be beneficial for up to 6 months.

SPECIAL POPULATIONS^{67,68,69,70,71,72,73}

Pediatrics

Safety and effectiveness of febuxostat (Uloric) and pegloticase (Krystexxa) in pediatric patients have not been established. Allopurinol (Zyloprim) is rarely indicated for use in pediatrics with the exception of children with hyperuricemia secondary to malignancy or other rare inborn errors of purine metabolism. Probenecid is contraindicated in children < 2 years of age. Colchicine tablet (Colcrys) is indicated in the management of FMF for children ages \geq 4 years. For the treatment and prevention of gout flares, safety and effectiveness of colchicine (Colcrys, Gloperba, Mitigare) have not been established in pediatric patients; colchicine is therefore not recommended in this population.

Pregnancy

Labeling for colchicine tablets (Colcrys) and colchicine solution (Gloperba) complies with the Pregnancy and Lactation Labeling Rule (PLLR) and advises that no risks for adverse maternal or fetal outcomes have been identified with the product in published literature. There are insufficient data to inform of a drug-associated risk with allopurinol, febuxostat, pegloticase, or probenecid in pregnant women.

Renal Insufficiency

Allopurinol requires dose adjustment in renal insufficiency. In addition, for patients with extreme renal impairment (CrCl < 3 mL/min), the interval between doses may need to be lengthened. Some patients with pre-existing renal disease or poor urate clearance have shown a rise in blood urea nitrogen (BUN) when using allopurinol. Renal failure associated with allopurinol in patients with hyperuricemia secondary to neoplastic diseases and gouty nephropathy has also been observed. Patients with renal impairment should be observed and a dosage decrease or medication cessation may be warranted.

Clearance of colchicine is decreased in patients with impaired renal function, and the drug is not effectively removed by dialysis. No dose adjustment of colchicine tablet (Colcrys) is required in patients with mild (CrCl 50 to 80 mL/min) or moderate (CrCl 30 to 50 mL/min) impairment for treatment or prophylaxis of gout flares; however, patients should be monitored closely for adverse effects. Dosage reductions and/or a lengthened interval between doses is required in patients with severe renal impairment (CrCl < 30 mL/min) who are receiving treatment or prophylaxis for gout flares, as outlined in the *Dosages* section of this review. In addition, treatment of gout flares with colchicine is not recommended in patients with renal impairment who are receiving colchicine for prophylaxis.

For patients with FMF and renal insufficiency, the dose of colchicine (Colcrys) should be reduced in patients with CrCl < 30 mL/min or end-stage renal disease, including patients on dialysis. Patients with mild-to-moderate impairment should be monitored closely, as dosage reductions may be necessary.

The labeling for colchicine capsules (Mitigare) and colchicine solution (Gloperba) recommends that dose reduction or alternatives be considered for the prophylaxis of gout flares in patients with severe renal impairment.

No dose adjustment for febuxostat is necessary in patients with mild or moderate renal impairment (CrCl 30 to 89 mL/min). Patients with severe renal impairment (CrCl, 15 to 29 mL/min) should be limited to 40 mg once daily. The use of febuxostat has not been studied in patients with end-stage renal disease who are also on dialysis.

Probenecid should not be used in patients with estimated CrCl of < 50 mL/min. Probenecid can be used without dosage adjustment in patients with an estimated CrCl of ≥ 50 mL/min.

No dose adjustment is needed for patients with renal failure when using pegloticase.

Hepatic Insufficiency

No dose adjustment for allopurinol is necessary in patients with hepatic impairment.

For treatment or prevention of gout flares in patients with mild-to-moderate hepatic impairment, no dose adjustment for colchicine tablet (Colcrys) is required but patients should be closely monitored. In patients with severe impairment, a dose reduction should be considered. For the treatment of gout flares, no dosage reduction is needed, but the treatment course should be repeated no more than once every 2 weeks. Treatment of gout flares with colchicine is not recommended in patients with hepatic impairment who are receiving colchicine for prophylaxis. Monitoring should be performed in patients with FMF and mild-to-moderate hepatic impairment; dose reductions should be considered in patients with severe hepatic impairment.

The labeling for colchicine capsules (Mitigare) and colchicine solution (Gloperba) recommends that a dose reduction or alternatives be considered in patients with severe hepatic impairment.

No dose adjustment for febuxostat is necessary in patients with mild or moderate hepatic impairment (Child-Pugh Class A or B). Caution should be taken in patients with severe hepatic impairment (Child-Pugh Class C) as there are no sufficient data in this patient population.

DOSAGES^{74,75,76,77,78,79,80}

Drug	Initial Dose	Titration	Dose Adjustments/ Comments	Availability
allopurinol (Zyloprim)	100 mg daily Maximum recommended dose is 800 mg daily, in divided doses Children 6 to 10 years: 300 mg daily Children < 6 years: 150 mg daily	To reduce the possibility of flare-up of acute gouty attacks start at 100 mg daily, increased by 100 mg weekly until serum urate ≤ 6 mg/dL Maximum daily dose is 800 mg Mild cases of gout: ▪ 200–300 mg per day Moderate-to-severe tophaceous gout: ▪ 400–600 mg per day, in divided doses	Renal Impairment CrCl 10-20 mL/min: 200 mg daily CrCl < 10 mL/min: 100 mg/day CrCl < 3 mL/min: interval between dosing may also need to be lengthened	100 mg, 300 mg (generic only) tablet
colchicine tablet (Colcrys)	Gout Flare Treatment: 1.2 mg at the first sign of a flare, then 0.6 mg 1 hour later Maximum dose is 1.8 mg over 1 hour	--	Gout Flare Treatment: Renal (CrCl < 30 mL/min) or Severe Hepatic Insufficiency: do not repeat treatment for 2 weeks; consider alternative therapy for patients requiring repeated courses Hemodialysis: 0.6 mg once and do not repeat more than once every 2 weeks Drug Interactions: See table	0.6 mg tablet Administer orally without regard to meals
	Gout Flare Prevention: 0.6 mg once or twice daily in adults and adolescents (> 16 years) Maximum daily dosage is 1.2 mg		Gout Flare Prevention: Renal (CrCl < 30mL/min): 0.3 mg daily; monitor dose increases closely Hemodialysis: 0.3 mg twice weekly with close monitoring Severe Hepatic Impairment: consider dose reduction and monitor for adverse effects Drug Interactions: See table	
	FMF: Adults and children > 12 years: 1.2-2.4 mg per day Ages 6 to 12 years: 0.9 to 1.8 mg per day Ages 4 to 6 years: 0.3 to 1.8 mg per day		FMF: Give total daily dose in 1 or 2 divided doses Increase or decrease the dose as indicated and as tolerated in increments of 0.3 mg/day, not to exceed the maximum recommended daily dose	

Dosages (continued)

Drug	Initial Dose	Titration	Dose Adjustments	Availability
colchicine solution (Gloperba)	0.6 mg (5 mL) orally once or twice daily Maximum daily dose is 1.2 mg (10 mL)	--	Renal and Hepatic Insufficiency: Dose reduction or alternatives should be considered in patients with severe renal or severe hepatic impairment	solution 0.6 mg/5 mL, ready-to-use Administer orally without regard to meals
colchicine capsule (Mitigare)	0.6 mg once or twice daily Maximum daily dose is 1.2 mg	--	Renal and Hepatic Insufficiency: Dose reduction or alternatives should be considered in patients with severe renal or hepatic impairment	0.6 mg capsule Administer orally without regard to meals
febuxostat (Uloric)	40 mg daily	If serum uric acid > 6 mg/dL after 2 weeks, increase to 80 mg daily	Can be taken without regard to food or antacid use	40 mg, 80 mg tablets
pegloticase (Krystexxa)	8 mg administered as an IV infusion every 2 weeks	--	--	8 mg/mL in a 2 mL single-use vial Store in refrigerator; do not freeze or shake; protect from light
probenecid	250 mg twice daily for 1 week, then 500 mg twice daily	Dose may be increased by 500 mg increments per day every 4 weeks Maximum dose is 2 gm per day	Administer with food or antacids to minimize GI adverse effects	500 mg tablet
probenecid/ colchicine	1 tablet daily for 1 week, then 1 tablet twice daily	If tolerated and if symptoms are not controlled or the 24-hour uric acid excretion is not > 700 mg, increase by 1 tablet/day every 4 weeks; most patients do not need > 4 tablets daily; continue for 6 months once serum uric acid concentrations are within normal limits; thereafter, dose may be decreased by 1 tablet/day every 6 months	Do not initiate combination therapy until an acute gout attack has been resolved If a patient is controlled on therapy and an acute attack occurs, the maintenance dosage may be continued	0.5 mg/500 mg tablet

Pegloticase should be administered in a healthcare setting IV over at least 120 minutes by gravity feed, syringe-type pump, or infusion pump. Pegloticase should not be administered as an IV push or bolus. In order to minimize the risk of anaphylaxis and infusion reactions patients should be treated with pre-infusion medications (e.g., antihistamines, corticosteroids) and monitored for an appropriate period, approximately 1 hour after completion of infusion. If an infusion reaction occurs during administration the infusion may be slowed, or stopped and restarted at a slower rate, per physician discretion. The risk of anaphylaxis and infusion reactions is higher in patients who have lost therapeutic response; patient serum uric acid levels should be monitored prior to infusion and discontinuation should be considered if levels increase to > 6 mg/dL, especially when 2 consecutive levels > 6 mg/dL are observed. It is recommended that before starting pegloticase patients stop oral urate-lowering medications and not start therapy with oral urate-lowering medications while on pegloticase.

Additional Dosing Notes: Colchicine

Treatment of gout flares is not recommended in patients with renal and/or hepatic impairment who are taking colchicine for prophylaxis. The safety and efficacy of repeat treatment for gout flares have not been evaluated for colchicine. Treatment of gout flares is not recommended for patients receiving prophylactic therapy with colchicine and CYP3A4 inhibitors.

If patients are taking or have recently completed treatment with drugs listed in the table below within the prior 14 days, the dose of colchicine should be reduced as listed.

Drug Interactions with Colchicine	Recommended Dose for Gout Flares	Recommended Dose for Management of FMF
Strong CYP 3A4 Inhibitors: atazanavir, clarithromycin, darunavir/ritonavir, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, tipranavir/ritonavir	Treatment of Gout Flares: 0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later Dose to be repeated no earlier than 3 days	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
	Prevention of Gout Flares: 0.3 mg daily or every other day	
Moderate CYP 3A4 Inhibitors: amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil	Treatment of Gout Flares: 1.2 mg (2 tablets) x 1 dose; dose to be repeated no earlier than 3 days	Maximum daily dose of 1.2 mg (may be given as 0.6 mg twice a day)
	Prevention of Gout Flares: 0.3 mg twice daily or 0.6 mg once daily or 0.3 mg once daily	
P-gp Inhibitors: cyclosporine, ranolazine	Treatment of Gout Flares: 0.6 mg (1 tablet) x 1 dose; dose to be repeated no earlier than 3 days	Maximum daily dose of 0.6 mg (may be given as 0.3 mg twice a day)
	Prevention of Gout Flares: 0.3 mg daily or every other day	

CLINICAL TRIALS

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this class. Studies included for analysis in the review were published in English, performed with human participants, and randomly allocated participants to comparison groups. In addition, studies must contain clearly stated, predetermined outcome measure(s) of known or probable clinical importance, use data analysis techniques consistent with the study question, and include follow-up (endpoint assessment) of at least 80% of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Current literature is lacking in the evaluation of colchicine and probenecid as the combination.

febuxostat (Uloric) and allopurinol

In a 52-week randomized, double-blind FACT trial in patients (n=762) with serum urate concentrations of at least 8 mg/dL, patients were randomly assigned to receive either febuxostat 80 mg or 120 mg or allopurinol 300 mg per day.⁸¹ Prophylaxis against gout flares with naproxen or colchicine was provided during weeks 1 through 8. The primary endpoint, a serum urate concentration of < 6 mg/dL at the last 3 monthly measurements, was reached in 53% of patients receiving febuxostat 80 mg, 62% of patients on febuxostat 120 mg, and 21% of those receiving allopurinol (p<0.001 for the comparison of each febuxostat group with the allopurinol group). Although the incidence of gout flares diminished with continued treatment, the overall incidence during weeks 9 through 52 was similar in all groups: 64% of patients receiving 80 mg of febuxostat, 70% of those receiving 120 mg of febuxostat, and 64% of those receiving allopurinol (p=0.99 for 80 mg of febuxostat versus allopurinol; p=0.23 for 120 mg of febuxostat versus allopurinol). More patients in the high-dose febuxostat group than in the allopurinol group (p=0.003) or the low-dose febuxostat group discontinued the study. Four of the 507 patients in the 2 febuxostat groups (0.8%) and none of the 253 patients in the allopurinol group died; all deaths were from causes that the investigators (while still blinded to treatment) judged to be unrelated to the study drugs (p=0.31 for the comparison between the combined febuxostat groups and the allopurinol group). The study compared moderate-dose allopurinol to high-dose febuxostat.

Febuxostat 80 mg, 120 mg, or 240 mg once daily showed significantly greater urate-lowering efficacy than allopurinol 100 mg (adjusted for renal impairment) or 300 mg once daily in a 28-week, randomized, double-blind, placebo-controlled trial (APEX) in patients (n=1,072) with gout and hyperuricemia.⁸² Patients had gout with normal to impaired renal function (serum creatinine level > 1.5 to ≤ 2.0 mg/dL). The primary endpoint, achievement of serum urate levels < 6 mg/dL for the last 3 months, occurred more frequently with febuxostat (80 mg [48%], 120 mg [65%], and 240 mg [69%], all p-values ≤0.05) than with allopurinol (22%) or placebo (0%). A significantly (p<0.05) higher percentage of subjects with impaired renal function treated with febuxostat 80 mg (4 of 9 [44%]), 120 mg (5 of 11 [45%]), and 240 mg (3 of 5 [60%]) achieved the primary endpoint compared with those treated with 100 mg of allopurinol (0 of 10 [0%]). Adverse events were similar across groups, although diarrhea and dizziness were more frequent in the febuxostat 240 mg group. The primary reasons for withdrawal

were similar across groups except for gout flares, which were more frequent with febuxostat than with allopurinol. The study compared moderate-dose allopurinol to high-dose febuxostat.

In a phase 3, randomized, double-blind study, febuxostat 40 mg and 80 mg daily and allopurinol 300 mg daily (200 mg daily for renal impairment) were compared for safety and efficacy over 6 months in 2,226 patients with gout.⁸³ Prophylaxis for gout flares was colchicine 0.6 mg daily or naproxen 250 mg twice daily plus lansoprazole 15 mg daily. Prophylaxis for gout flares with naproxen was not administered to patients with CrCl < 50 mL/min. Primary outcome parameters were the proportion of all subjects with serum uric acid levels < 6 mg/dL and the proportion of subjects with mild (CrCl 60 to 89 mL/min) to moderate (CrCl 30 to 59 mL/min) renal impairment with serum uric acid levels < 6 mg/dL. Sixty-five percent of patients had renal impairment. A total of 418 patients prematurely discontinued treatment, 120 within the first month of treatment. The proportions of patients achieving serum uric acid < 6 mg/dL were 45.2% of febuxostat 40 mg group, 67.1% of febuxostat 80 mg group, and 42.1% of allopurinol group. Urate lowering efficacy of febuxostat 40 mg was non-inferior to allopurinol; the difference in the response rates between the 2 groups was not significant. The urate lowering response rate with febuxostat 80 mg compared with either febuxostat 40 mg (21.9%) or allopurinol (24.9%) was significant ($p < 0.001$). The urate lowering response rate in the febuxostat 80 mg group (72%) with renal impairment was greater than that observed in the febuxostat 40 mg (49.7%) and allopurinol groups (42.3%; $p \leq 0.001$ for each comparison). For patients with renal impairment, the urate lowering response rate was greater for febuxostat 40 mg than allopurinol ($p = 0.021$). Adverse events and discontinuation rates were similar among the groups.

A multicenter, double-blind, noninferiority trial was conducted over a median of 32 months to assess CV outcomes associated with febuxostat or allopurinol in patients ($n = 6,190$) with gout and CV disease.⁸⁴ The trial had a prespecified noninferiority margin of 1.3 for the hazard ratio (HR) for the primary end point of composite of CV death, nonfatal MI, nonfatal stroke, or stable angina with urgent revascularization. In the modified intent-to-treat analysis, a primary end point was achieved in 335 (10.8%) of the febuxostat patients and 321 patients (10.4%) in the allopurinol group (HR, 1.03; upper limit of the 1-sided 98.5% CI, 1.23; $p = 0.002$ for noninferiority). Cardiovascular and all-cause mortality were higher in the febuxostat treated patients compared to the allopurinol treated patients (HR for death [any cause], 1.22 [95% CI, 1.01 to 1.47]; HR for CV death, 1.34 [95% CI, 1.03 to 1.73]). The results in primary end point, all-cause mortality, and CV mortality in the analysis of events during treatment were similar to the results in the modified intent-to-treat analysis. The study concluded that in patients with gout and major CV coexisting conditions, febuxostat was noninferior to allopurinol when assessing rates of adverse CV events.

colchicine plus allopurinol

A double-blind, placebo-controlled trial evaluated the use of colchicine to prevent acute gout flares during initiation of allopurinol in 43 patients with chronic gouty arthritis.⁸⁵ Patients starting allopurinol for crystal-proven chronic gouty arthritis were randomized to colchicine 0.6 mg twice daily ($n = 21$) or placebo ($n = 22$). Allopurinol was initiated at 100 mg daily and titrated in 100 mg increments at 2 to 3 week intervals to achieve serum uric acid levels < 6.5 mg/dL. For patients with renal impairment (CrCl 20 to 50 mL/min), allopurinol dose was escalated in 50 mg increments. All patients achieved serum uric acid < 6.5 mg/dL. Patients were followed for acute gout flares for 3 months after attainment of serum uric acid concentrations < 6.5 mg/dL. Patients treated with colchicine experienced fewer total flares (0.52 versus 2.91, $p = 0.008$), fewer flares from 0 to 3 months (0.57 versus 1.91, $p = 0.022$), fewer flares

from 3 to 6 months (0 versus 1.05, $p=0.033$), less severe flares as reported on visual analog scale (3.64 versus 5.08, $p=0.018$), and fewer recurrent gout flares ($p=0.001$). Colchicine was well tolerated. Administration frequency of colchicine was reduced from twice daily to once daily in 62% of patients compared to placebo (36%, $p=0.094$). Discontinuation rates were similar. Colchicine prophylaxis during initiation of allopurinol for chronic gouty arthritis reduces the frequency and severity of acute flares and reduces the likelihood of recurrent flares.

colchicine (Colcrys)

The efficacy of a low dosage regimen of oral colchicine (1.2 mg followed by 0.6 mg 1 hour later) for treatment of gout flares was assessed in a multicenter, randomized, double-blind, placebo-controlled, parallel group, 1 week, dose comparison study.^{86,87} Patients meeting American College of Rheumatology (ACR) criteria for gout were randomly assigned to 3 groups: high-dose colchicine ($n=52$) (1.2 mg, then 0.6 mg hourly \times 6 hours [4.8 mg total]); low-dose colchicine ($n=74$) (1.2 mg, then 0.6 mg in 1 hour [1.8 mg total] followed by 5 placebo doses hourly); or placebo ($n=58$) (2 capsules, then 1 capsule hourly \times 6 hours). Patients took the first dose within 12 hours of the onset of the flare and recorded pain intensity and adverse events over 72 hours. The efficacy of colchicine was measured based on response to treatment in the target joint, using patient self-assessment of pain at 24 hours following the time of first dose as recorded in the diary. A responder was one who achieved at least a 50% reduction in pain score at the 24-hour post-dose assessment relative to the pre-treatment score and did not use rescue medication prior to the actual time of 24-hour post-dose assessment. Rates of response were similar for the recommended low-dose treatment group (37.8%; $p=0.005$ versus placebo) and the non-recommended high-dose group (32.7%; $p=0.034$ versus placebo), but were higher as compared to the placebo group (15.5%). Rescue medication within the first 24 hours was taken by 31.1% in the low-dose group ($p=0.027$ versus placebo), 34.6% in the high-dose group ($p=0.103$ versus placebo), and 50% in the placebo group. Adverse event profile was similar in the low-dose group and placebo. Patients in the high-dose colchicine group reported significantly more diarrhea, vomiting, and other adverse events compared with the low-dose and placebo groups. Diarrhea was reported in 76.9% of patients in the high-dose group with 19.2% reporting severe diarrhea (odds ratio [OR], 21.3; 95% CI, 7.9 to 56.9). In the low-dose group, 23% of patients reported diarrhea (OR, 1.9; 95% CI, 0.8 to 4.8) with no reports of severe diarrhea. The manufacturer of Colcrys funded the study.

The evidence for the efficacy of colchicine in patients with FMF is derived from 3 randomized, placebo-controlled studies with a total of 48 adult patients.⁸⁸ Patients who were compliant had a reduced rate of attacks compared to placebo. However, data are incomplete for 1 of the studies. Noncompliance was reported in about one-third of patients. Open-label experience with colchicine in adults and children with FMF is consistent with the randomized, controlled trial experience and was utilized to support information on the safety profile of colchicine and for dosing recommendations.

pegloticase (Krystexxa)

Two replicate, double-blinded, randomized, placebo-controlled trials were conducted for 6 months in 225 patients throughout 56 rheumatology clinics in the United States, Mexico, and Canada for the purposes of assessing the efficacy and tolerability of pegloticase in the management of refractory chronic gout.⁸⁹ Patients were 18 years or older and had severe gout, allopurinol intolerance or refractoriness, serum uric acid concentrations of 8 mg/dL or more, and at least 1 of the following conditions: 3 or more self-reported gout flares within the last 18 months, at least 1 tophi, and gouty

arthropathy. Patients who were receiving urate-lowering medications at the onset of screening were required to undergo a 1 week washout. Prophylactic gout therapy was started 1 week before the pegloticase infusion and continued throughout the study. Patients also received pre-treatment with medications to protect against infusion reactions. Patients were randomized into 3 study groups in a 2:2:1 ratio: pegloticase biweekly, pegloticase monthly, or placebo, respectively. In the pooled analysis, the portion of uric acid responders (defined as plasma uric acid < 6 mg/dL for ≥ 80% of the time during months 3 and 6) in the pegloticase groups was significantly greater than placebo ($p < 0.001$). When examining response rates by dose, the pegloticase biweekly group had response rates of 47% (20/43; 95% CI) and 38% (16/42; 95% CI) in the 2 trials. Patients treated with monthly pegloticase had a response rate of 20% (8/41; 95% CI) and 49% (21/43; 95% CI). The response rates in the placebo groups were 0% (95% CI). The study also found that non-responder patients had uric acid levels < 6 mg/dL through week 10, but then remained above the target level thereafter, suggesting an emergence of decreased urate-lowering efficacy early in treatment. The study also found that 41% of the biweekly pegloticase, 21% of the monthly pegloticase, and 7% of the placebo patients experienced a complete response to at least 1 tophi ($p=0.002$ and $p=0.2$, respectively). Immunogenicity occurred in 134 of the 150 patients treated with pegloticase, indicated by the presence of pegloticase antibodies (95% CI). In addition, 2% (1 of 52) of pegloticase-treated patients with a pegloticase antibody titer exceeding 1:2430 at any time maintained a urate-lowering response to therapy. In contrast, 63% (52 of 82) of pegloticase-treated patients who remained in the study for 2 months or longer and who never had a pegloticase antibody titer greater than 1:2430 maintained their urate-lowering responses. Overall, the study concluded that pegloticase provided significant improvements in patient quality of life, physical function, and pain levels due to its ability to reduce uric acid levels compared to placebo.

META-ANALYSIS

A systematic review evaluated the efficacy and safety of colchicine for the relief of the signs and symptoms of acute gout. Randomized controlled clinical trials were gathered from numerous databases. One randomized controlled trial with 43 patients that compared colchicine to placebo for the acute treatment of gout was identified. The results favored the use of colchicine over placebo with an absolute reduction of 34% for pain and 30% reduction in clinical symptoms, such as tenderness on palpation, swelling, redness, and pain. The number-needed-to-treat with colchicine versus placebo to reduce pain was 3 and the number-needed-to-treat to reduce clinical symptoms was 2. All patients experienced GI adverse effects, namely diarrhea and/or vomiting. No studies comparing colchicine to NSAIDs or corticosteroids were identified. Due to the high likelihood of adverse effects, the systematic review concluded that colchicine should be used as second-line therapy when NSAIDs or corticosteroids are contraindicated or ineffective.

A meta-analysis was performed on urate-lowering medications (allopurinol, febuxostat, pegloticase, rasburicase, probenecid, benzbromarone [unavailable in U.S.], sulphinyprazole [unavailable in U.S.], losartan, fenofibrate, and sodium-glucose linked transporter 2 [SGLT2] inhibitors) to determine if ULT has differences in CV outcomes.⁹⁰ A total of 35 studies were included for review. Several trials did not report CV events; 6 were not randomized controlled trials, 4 reported no events in either intervention group, 4 had 40 events in the febuxostat group ($n=3,631$) and 5 in the allopurinol group ($n=1,154$). The overall pooled analysis did not show a significant difference between febuxostat and allopurinol (relative risk [RR], 1.69; 95% CI, 0.54 to 5.34; $p=0.37$). When comparing shorter studies (< 52 weeks) to longer ones, no statistical differences were noted. However, in febuxostat and allopurinol long-term

studies, results approached significance for more CV events in patients treated with febuxostat. When comparing urate-lowering treatment to placebo (8 studies; n=2,221), no significant differences in all-cause mortality were noted (any ULT versus placebo: RR, 1.45; 95% CI, 0.35 to 5.77; p=0.6). The authors concluded that data do not suggest CV event differences with ULT for the treatment of gout. However, even though the trials had few events despite high-risk patients, the trials may have been too short to show a CV reduction via controlling inflammatory attacks and lowering uric acid.

A meta-analysis was conducted comparing the clinical benefits of febuxostat and allopurinol in patients with gout or asymptomatic hyperuricemia (n=13,539; 13 studies).⁹¹ Compared to allopurinol, febuxostat was not associated with an increased risk of cardiac-related mortality in the overall study population (OR, 0.72; 95% CI, 0.24 to 2.13; p=0.55). Patients receiving febuxostat had significantly fewer adverse skin reactions than patients receiving allopurinol (OR, 0.5; 95% CI, 0.3 to 0.85; p=0.01).

SUMMARY

Probenecid promotes uric acid excretion by inhibiting the tubular reabsorption of filtered and secreted urate, thereby increasing urate excretion. Xanthine oxidase inhibitors, allopurinol and febuxostat, inhibit uric acid production. Febuxostat (Uloric) reduces serum urate levels < 6 mg/dL in a significantly greater proportion of patients with gout and hyperuricemia compared to allopurinol; however, the incidence of gout flares, a clinical outcome, does not appear lower with febuxostat compared to allopurinol. Pegloticase (Krystexxa) provides an effective alternative therapy to conventional oral urate-lowering medications for those patients who are refractory to or cannot take oral urate-lowering medications.

Colchicine tablet (Colcrys) was the first FDA-approved colchicine product. Colchicine has significant drug interactions and frequent GI adverse effects. It is approved at a lower dosage for the treatment and prevention of gout flares than previously described. Colcrys has approval as an orphan drug for the treatment of familial Mediterranean fever (FMF). Capsule and oral solution formulations of colchicine (Mitigare and Gloperba, respectively) are available but are only indicated for the prophylaxis of gout flares for adults. Mitigare does not appear to provide any additional benefit over the tablet formulation. Gloperba may provide benefit in patients who have difficulty swallowing tablets and capsules.

According to the American College of Rheumatology (ACR) 2020 guidelines, acute gouty arthritis can be treated with oral colchicine, nonsteroidal anti-inflammatory drugs (NSAIDs), oral corticosteroids, and intra-articular or intramuscular corticosteroid injections. Recommended medications should be started within early onset of the gout flare in order to provide optimal care. They also recommend colchicine, NSAIDs, prednisone, or prednisolone as first-line therapy for gout prophylaxis, although no one product is recommended over another. After an initial gout attack, ACR strongly recommends the xanthine oxidase inhibitor, allopurinol, for initial urate-lowering therapy (ULT) due to lower risk of cardiovascular adverse events and non-clinical considerations. Probenecid was not voted on in the updated guidelines, but the panel indicated it was an option for patients that had a suboptimal response to a xanthine oxidase inhibitor. The guidelines recommend pegloticase (Krystexxa) as a third-line therapy option.

The 2017 American College of Physician (ACP) guidelines recommend corticosteroids, NSAIDs, or colchicine for the treatment of acute gout, with corticosteroids being first-line therapy. The ACP does not recommend long-term ULT in most patients after an initial gout attack or when gout attacks are

infrequent. The guidelines state allopurinol and febuxostat are equally effective at decreasing serum urate levels and prophylactic low-dose colchicine or NSAIDs reduce the risk for acute attacks when initiating ULT. The guidelines did not address pegloticase.

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