# Antihyperuricemics
# Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS[1,2]

| Drug | Manufacturer | Indication(s) |
|---|---|---|
| allopurinol (Zyloprim® )[3] | generic, Prometheus | ▪ Management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)<br>▪ Management of patients with leukemia, lymphoma, and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels<br>▪ 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 (Colcrys®)[4] | generic, Takeda | ▪ Gout flares – treatment and prevention in adults<br>▪ Management of Familial Mediterranean Fever in adults and children ages 4 years and older |
| colchicine capsule (Mitigare™)[5] | generic, Himka | Prophylaxis of gout flares in adults |
| febuxostat (Uloric®)[6] | Takeda | ▪ Chronic management of hyperuricemia in patients with gout |
| pegloticase (Krystexxa®)[7] | Crealta | ▪ Treatment of chronic gout in adult patients refractory to conventional therapy |
| probenecid | generic | ▪ Treatment of hyperuricemia associated with chronic gout or secondary to other causes |
| probenecid – colchicine[8] | generic | ▪ Treatment of chronic gouty arthritis when complicated by frequent, recurrent, acute attacks of gout |

Probenecid is also FDA-approved for the adjunctive therapy with penicillin G, amoxicillin, cefoxitin, or ampicillin for treatment of uncomplicated gonorrhea; adjunctive therapy with cefoxitin for pelvic inflammatory disease; and adjunctive therapy with amoxicillin for arthritis caused by Lyme disease. Indications for adjunctive therapy to antibiotics will not be addressed in this review.

Allopurinol, febuxostat, and pegloticase are not recommended for the treatment of asymptomatic hyperuricemia. The safety and effectiveness of colchicine capsules (Mitigare) for acute treatment of gout flares during prophylaxis has not been studied.

## OVERVIEW[9]

Hyperuricemia (serum uric acid > 6.8 mg/dL) can occur due to either an overproduction of uric acid, an under excretion of uric acid, or a combination of the 2 mechanisms.[10] Most often, hyperuricemia is due to a reduction in fractional clearance of urate rather than an over production of urate. Urate under excretion can occur as a result of both primary and secondary hyperuricemia. Secondary hyperuricemia may be due to renal impairment; hypertension; lead nephropathy; hypothyroidism; and drugs including low dose aspirin, diuretics, ethanol, and cyclosporine.[11,12] Urate over production may occur due to primary hyperuricemia, Lesch-Nyhan syndrome (a genetic disorder characterized by uric acid overproduction, motor dysfunction, and cognitive and behavioral disturbances), and as a result of salvaged purines from rapid cell turnover or inflammatory disorders, including lympho-myeloproliferative disorders and severe exfoliative psoriasis, and cytotoxic drugs. 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. Crystals are deposited in joints, tendons, and surrounding tissues. Acute attacks of gout are painful


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and, in over approximately 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 include uricosuric drugs (colchicine, probenecid) or xanthine oxidase inhibitors (allopurinol, febuxostat). 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. 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 less than 6 mg/dL after 3 months of therapy or who are intolerant of allopurinol; however, febuxostat may have a greater risk for cardiovascular adverse events as compared to allopurinol.

In addition to the prevention and treatment of gout flares, colchicine (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. 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 12 to 72 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 1,000 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.


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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 provides an effective alternative therapy to conventional oral urate-lowering medications for those patients who cannot take oral urate-lowering medications.[13]

In 2006, the European League Against Rheumatism (EULAR) published evidence-based recommendations for the treatment of gout that addressed the symptomatic control of acute gout, urate lowering therapy, and prophylaxis of acute attacks.[14] The recommended drugs for acute gout attacks were oral NSAIDs, oral colchicine, or joint aspiration and injection of a corticosteroid. Patients with recurrent acute attacks, arthropathy, tophi, or radiographic changes of gout should be prescribed urate lowering therapy. They emphasize the importance of patient education, lifestyle modification (weight loss if obese; reduced alcohol consumption; low animal purine diet) as important factors in gout management. Allopurinol is recommended as an effective long term urate lowering therapy. If allopurinol toxicity occurs, options include other xanthine oxidase inhibitors, allopurinol desensitization, or a uricosuric agent. If the patient's gout is associated with diuretic use, the diuretic should be discontinued, if possible. Colchicine 0.5 mg to 1 mg daily or an NSAID with gastroprotection are recommended for prophylaxis against acute attacks. Febuxostat and pegloticase were not available at the time the guidelines were developed. However in separate 2008 review, febuxostat was noted only to be used in those patients intolerant of allopurinol.[15]

In 2012, the American College of Rheumatology (ACR) published their first set of guidelines for the management of gout.[16,17] The ACR advises treatment for an acute gouty arthritis attack to begin within 24 hours of onset in order to provide optimal care. Furthermore, the guidelines also recommend continuation of established urate-lowering therapy without interruption during an acute gout attack, if applicable. When choosing a pharmacologic agent, the severity of pain and the number of joints affected should be assessed. For mild to moderate pain, particularly for an attack involving 1 or a few small joints or 1 to 2 larger joints, the ACR guidelines state oral NSAIDs, systemic corticosteroids, or oral colchicine are appropriate monotherapy options. For severe pain, particularly for those having an acute polyarticular attack or an attack involving multiple large joints, initial combination pharmacologic therapy is appropriate. Acceptable combination therapies include full doses of either colchicine and NSAIDs; oral corticosteroids and colchicine; or intra-articular steroids with all other modalities. 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 suggested as an appropriate treatment option for acute gout if the onset of the attack is no more than 36 hours prior to initiation of treatment. The ACR guidelines state oral corticosteroids are appropriate for all cases of gout; however, prescribers should consider the extent and number of joints involved when selecting corticosteroids as initial therapy. Additionally, the ACR recommends the option of intra-articular corticosteroids when 1 or 2 large joints are involved. If the patient does not respond to initial monotherapy, the ACR promotes switching to an alternative monotherapy or adding a second recommended agent for combination therapy. Anti-inflammatory prophylaxis is also recommended for all patients for whom urate-lowering therapy was started due to the increased frequency of gout attacks during early therapy. The ACR recommends low-dose oral colchicine as first-line therapy for gout attack prophylaxis. Despite having lower evidence, the ACR also suggests low-dose NSAIDs with proton pump inhibitors or other effective peptic ulcer disease suppression therapy as a first-line option. Low-dose prednisone or prednisolone is


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appropriate when the patient has a contraindication, intolerance, or refractoriness to colchicine and NSAIDs; the use of high-dose prednisone or prednisolone, in most cases, is considered inappropriate. Anti-inflammatory prophylaxis should continue if there is evidence of disease activity.

The ACR recommends the goal of urate-lowering therapy is to reach a target serum urate level below 6 mg/dL; in some instances, a level below 5 mg/dL is needed to improve gout signs and symptoms. The guidelines also suggest medications that induce hyperuricemia should be discontinued, if possible. Patients with an established gouty arthritis diagnosis who have tophus/tophi, frequent acute gout attacks (≥2 attacks per year), chronic kidney disease (CKD) stage 2 or worse, or past urolithiasis are indicated to receive urate-lowering therapy according to the ACR guidelines. Urate-lowering therapy may be started during an acute attack as long as effective anti-inflammatory therapy has been initiated. The ACR recommends a xanthine oxidase inhibitor, allopurinol or febuxostat, as a first-line pharmacologic approach. The ACR guidelines do not prefer 1 agent over the other but did note the lack of published safety data for febuxostat in CKD stage 4 or worse. Probenecid is recommended as an alternative first-line therapy when there is a contraindication or intolerance to at least 1 xanthine oxidase inhibitor. Probenecid is not recommended as a first-line urate-lowering agent in patients with a creatinine clearance (CrCL) < 50 mL/min, history of urolithiasis, or uric acid overproduction. When the serum urate target has not been met with initial therapy, the ACR suggests an upward dose titration of a xanthine oxidase inhibitor to the maximum approved dose, if appropriate. If this upward titration does not achieve the target serum urate level or is not tolerated, then substitution of another xanthine oxidase inhibitor is appropriate. The ACR guidelines also note that probenecid is helpful in refractory disease. Specifically, the ACR recommends oral urate-lowering therapy combined with a uricosuric agent. The ACR only advocates pegloticase as an appropriate pharmacologic option in patients with severe gout who are refractory or have intolerance to appropriately dosed oral urate-lowering therapy; pegloticase is recommended as a third-line therapy only.

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.


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## PHARMACOLOGY[18,19]

| Drug Mechanism of Action | Mechanism of Action |
|---|---|
| allopurinol | ▪ Xanthine oxidase inhibitor which blocks the conversion of hypoxanthine to xanthine and of xanthine to uric acid, thereby decreasing the production of uric acid<br>▪ Unlike uricosuric agents which 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)[20]<br><br>colchicine capsule (Mitigare)[21] | ▪ 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<br>▪ Colchicine arrests metaphase due to 2 separate antimitotic 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 antimitotic activity within proliferating tissues such as the skin, hair, and bone marrow<br>▪ 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<br>▪ 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)[22] | ▪ Xanthine oxidase inhibitor which blocks the conversion of hypoxanthine to xanthine and of xanthine to uric acid, thereby decreasing the production of uric acid<br>▪ Febuxostat is not anticipated to inhibit other enzymes involved in purine and pyrimidine synthesis and metabolism at therapeutic concentrations |
| pegloticase (Krystexxa)[23] | ▪ 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 | ▪ 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<br>▪ Antibiotic therapy adjunct — At the proximal and distal renal tubules probenecid is a competitive inhibitor of the secretion of weak organic acids, including penicillins, and some of the cephalosporin antibiotics. As a result, it increases blood concentrations of these antibiotics (penicillin concentrations may increase two to fourfold), extends their duration of action, and increases their elimination half-life |
| probenecid – colchicine | ▪ Colchicine relieves the pain of acute attacks by inhibiting leukocyte migration<br>▪ Probenecid is a uricosuric agent that inhibits the tubular reabsorption of uric acid |


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## PHARMACOKINETICS[24,25]

| Drug | Absorption (%) | Half-Life (hours) | Metabolism | Excretion (%) |
|---|---|---|---|---|
| allopurinol | 80-90 | 1-2; oxypurinol 15 (range 12 to 30) | Oxypurinol | Renal: 80<br>Feces: 20 |
| colchicine tablet (Colcrys)[26] | 45 | 26.6-31.2 | 3 metabolites | Fecal and urinary excretion |
| colchicine capsule (Mitigare)[27] | 45 | 21.7-49.9 | 3 metabolites | Fecal and urinary excretion |
| febuxostat (Uloric)[28] | > 49 | 5-8 | 4 active metabolites | Renal: 49<br>Feces: 45 |
| pegloticase (Krystexxa)[29] | 100 | nr | nr | nr |
| probenecid | Complete absorption | 3-12 hrs; dose dependent | Active metabolites | Hepatic and renal (5-10% unchanged) |

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

## CONTRAINDICATIONS/WARNINGS[30,31,32,33,34,35,36]

### allopurinol

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, 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.

Due to the occasional occurrence of drowsiness, patients should be alerted 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.

### colchicine

Life-threatening and fatal colchicine toxicity has been reported with colchicine taken in therapeutic doses in these patient treated concurrently with a P-glycoprotein (P-gp) or strong CYP3A4 inhibitors


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(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

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

After initiation of febuxostat, an increase in gout flares is often observed. A reduction in serum uric acid levels occur 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.

Compared to allopurinol, randomized controlled trials have shown that febuxostat has a higher rate of cardiovascular thromboembolic events [cardiovascular deaths, non-fatal myocardial infarctions (MI), and non-fatal strokes]. However, no causal relationship with febuxostat has been established. Prescribers should monitor for signs and symptoms of MI and stroke.

Fatal and non-fatal reports of hepatic failure have been reported in patients taking febuxostat. Transaminase elevations greater than 3 times the upper limit of normal (ULN) have been observed in febuxostat-treated patients. The transaminase elevations have not had any dose-effect relationship noted. Liver function tests should be performed before initiating therapy to establish a baseline.


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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) greater than 3 times the refence 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.

## pegloticase

Patients with a glucose-6-phosphate dehydrogenase (G6PD) deficiency should not use pegloticase because it increases the risk of hemolysis and methemoglobinemia. Patients who are at a higher risk for a G6PD deficiency (patients of Mediterranean or African ancestry) should be screened for G6PD deficiency before initiating pegloticase.

Upon FDA approval in 2010, pegloticase was subject to a Risk Evaluation and Mitigation Strategies (REMS) program to warn providers who prescribe, administer, and dispense pegloticase about the risk of anaphylaxis and infusion reactions associated with concurrent pegloticase and oral urate-lowering therapy, and the contraindicated use of pegloticase in patients with glucose 6-phosphate dehydrogenase (G6PD) deficiency. However, on April 11, 2016, the FDA determined that the REMS communication plan met its goals and therefore the REMS requirement was eliminated for this agent.[37]

The label for pegloticase continues to include a boxed warning of anaphylactic and infusion reactions, which instructs that the drug should 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. 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 above 6 mg/dL, especially when 2 consecutive levels above 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 above 6 mg/dL.

The combination of oral urate-lowering therapy 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 are recommended starting at least 1 week before beginning


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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 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 more than 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 and probenecid/colchicine

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 younger than 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. Alkalization of the urine and liberal intake of fluids may help prevent these occurrences. Patients should be monitored closely.

## DRUG INTERACTIONS[38,39,40,41,42,43,44]

### allopurinol

Allopurinol prolongs the half-life of the anticoagulant, dicumarol; therefore, monitoring prothrombin times and 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 for an 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 will be


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enhanced. Allopurinol should be avoided in patients receiving mercaptopurine. If this is not possible, 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 allopurinol should be avoided whenever possible as it can result in increased risk of azathioprine toxicity (bone marrow suppression, leukopenia, and pancytopenia). If use of both products is necessary, the dose of azathioprine should be reduced to one-third to one-fourth the usual dose and close hematologic monitoring is required.

Patients with renal impairment who receive allopurinol and thiazide diuretics are at an increased risk of hypersensitivity reactions.[45]

## colchicine (Colcrys)

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. Fatal drug interactions have been reported.

For concurrent therapy with strong CYP450 3A4 inhibitors, including atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and 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 (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 to 1.2 mg per day for adults.

Dose reduction is warranted as significantly higher colchicine plasma levels are expected with concurrent administration with a P-gp inhibitor, such as cyclosporine and ranolazine. In this scenario, 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.

Pharmacokinetics and/or pharmacodynamic interactions have been reported when atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, fibrates, gemfibrozil, or digoxin are 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,


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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 CYP 3A4 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.

Drug interaction studies have not been conducted to examine febuxostat with other drugs that are metabolized by xanthine oxidase. Inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of these drugs leading to toxicity.

## 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 portion of the drug.

## probenecid

Probenecid inhibits the renal tubular secretion of many drugs including: acyclovir, valacyclovir, famciclovir, penicillins, sulbactam, tazobactam, gatifloxacin, nitrofurantoin, zidovudine, zalcitabine, dapsone, pantothenic acid, rifampin, sulfonamides, sulfonylureas, captopril, methotrexate, aminosalicylates, ertapenem, meropenem, dyphylline, doripenem, ciprofloxacin, clofibrate, ganciclovir, imipenem/cilastatin, and most cephalosporins. 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.

Probenecid and salicylates used concurrently 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, mecamylamine, and triamterene as hyperuricemia may occur. Additionally, probenecid may interfere with the pharmacologic effects of penicillamine.


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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.

The anticoagulant effects of heparin may be increased by concomitant administration of probenecid.

Concurrent use of probenecid and allopurinol may have additive antihyperuricemic effects. When used together, the serum urate concentration decreases more than if either agent was 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 urate-lowering therapy should be stopped prior to pegloticase therapy beginning 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.

## ADVERSE EFFECTS[46,47]

| Drug | Arthralgia | Rash | Diarrhea | Nausea | LFT Elevations |
|---|---|---|---|---|---|
| allopurinol[48] | < 1 | 1-3 | > 1 | > 1 | > 1 |
| colchicine tablet (Colcrys)[49] | nr | reported | 23-77 | 4-17 | reported |
| colchicine capsule (Mitigare)[50] | nr | reported | reported | reported | reported |
| febuxostat (Uloric)[51]<br>allopurinol<br>placebo | 0.7-1.1<br>0.7<br>0 | 0.5-1.6<br>1.6<br>0.7 | nr | 1.1-1.3<br>0.8<br>0.7 | 4.6-6.6<br>4.2<br>0.7 |
| pegloticase (Krystexxa)[52] | nr | reported | nr | 12 | nr |
| probenecid | nr | nr | 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.

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 is recommended upon initiation of gout flare prophylaxis with uric acid lowering therapy.


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## SPECIAL POPULATIONS[53,54,55,56,57,58,59,60]

### Pediatrics

Safety and effectiveness of allopurinol (Zyloprim), febuxostat (Uloric), and pegloticase (Krystexxa) in pediatric patients have not been established. Probenecid is contraindicated in children younger than 2 years of age. Colchicine (Colcrys) is indicated in the management of FMF for children ages 4 years and older. For the treatment and prevention of gout flares, safety and effectiveness of colchicine have not been established in pediatric patients; colchicine is therefore, not recommended in this population.

### Pregnancy

All products in this review, except for probenecid, are Pregnancy Category C. Probenecid is Pregnancy Category B.

### Renal Insufficiency

Allopurinol requires dose adjustment in renal insufficiency. For patients with a CrCL of 10 to 20 mL/min, a daily dose of 200 mg is recommended and for patients with a CrCL < 10 mL/min, a daily dose of 100 mg is recommended. In patients with extreme renal impairment (CrCL < 3 mL/min), the interval between doses may need to be lengthened.

In the presence of renal impairment (CrCL < 30 mL/min), colchicine dosing for treatment of gout flares should be repeated no more than once every 2 weeks. For patients undergoing dialysis, the total recommended colchicine dose for the treatment of gout flares should be reduced to 0.6 mg for 1 dose and should not be repeated more than once every 2 weeks. Patients with severe renal impairment should receive colchicine 0.3 mg daily for the prevention of gout flares. For patients undergoing dialysis and receiving colchicine for the prevention of gout flares, the starting dose of colchicine should be 0.3 mg given twice weekly with close monitoring. No dosage adjustment is necessary for colchicine in patients with CrCL > 30 mL/min; however, monitoring for adverse effects should be performed. 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, dosage of colchicine should be reduced for patients with CrCL < 30 mL/min or end-stage renal disease to 0.3 mg daily with a dose increase carefully monitored for adverse effects. For patients undergoing hemodialysis, the total recommended starting dose of colchicine should be 0.3 mg daily.

No dose adjustment for febuxostat is necessary in patients with mild or moderate renal impairment (CrCL 30-89 mL/min). Caution should be taken in patients with severe renal impairment (CrCL < 30 mL/min) as there is no sufficient data in this patient population. 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.

### Hepatic Insufficiency

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


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For treatment or prevention of gout flares in patients with mild to moderate hepatic impairment, no dose adjustment for colchicine is required but patients should be closely monitored. However, in patients with severe hepatic impairment, the colchicine dose does not need to be adjusted but should be considered. A 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 and dose reductions should 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 is no sufficient data in this patient population.

## DOSAGES[61,62]

| Drug | Initial Dose | Titration | Dose Adjustments | Availability |
|---|---|---|---|---|
| allopurinol[63] | 100 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<br>Maximum daily dose is 800 mg<br>Mild cases of gout:<br>▪ 200–300 mg per day<br>Moderate to severe tophaceous gout:<br>▪ 400–600 mg per day | CrCL 10-20 mL/min: 200 mg daily<br><br>CrCL < 10 mL/min: 100 mg/day<br><br>CrCL < 3 mL/min: interval between dosing may also need lengthened | 100, 300 mg tablets |
| febuxostat (Uloric)[64] | 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, 80 mg tablets |
| pegloticase (Krystexxa)[65] | 8 mg administered as an intravenous 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<br>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 greater than 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<br><br>If a patient is controlled on therapy and an acute attack occurs, the maintenance dosage may be continued | 0.5 mg/500 mg tablet |


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### *Dosages (continued)*

| Drug | Initial Dose | Titration | Dose Adjustments | Availability |
|---|---|---|---|---|
| colchicine tablet (Colcrys)[66] | **Gout Flare Treatment:** 1.2 mg at the first sign of a flare, then 0.6 mg 1 hour later<br>Maximum dose is 1.8 mg over 1 hour | -- | **Gout Flare Treatment:**<br>Renal (CrCL < 30 mL/min) or **Severe Hepatic Insufficiency**: do not repeat treatment for 2 weeks<br>**Hemodialysis:** 0.6 mg once and do not repeat for 2 weeks<br>**Drug Interactions:**<br>See table | 0.6 mg tablet<br><br>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:**<br>Renal (CrCL < 30mL/min): 0.3 mg daily; monitor dose increases closely<br>**Hemodialysis:** 0.3 mg twice weekly with close monitoring<br>**Severe Hepatic Impairment:** consider dose reduction and monitor for adverse effects<br>**Drug Interactions:**<br>See table | |
| | FMF:<br>Adults and children > 12 years:<br>1.2-2.4 mg per day<br>Ages 6 to12 years:<br>0.9-1.8 mg per day<br>Ages 4 to 6 years:<br>0.3-1.8 mg per day | FMF:<br>Give total daily dose in 1 or 2 divided doses<br>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 | FMF:<br>Renal Insufficiency<br>If CrCl of 30 to 80 mL/min dose reduction may be necessary<br>If CrCL < 30 mL/min including dialysis: 0.3 mg daily and monitor for adverse effects when increasing dose<br>Severe Hepatic Impairment: consider dose reduction and monitor for adverse effects<br>Drug Interactions:<br>see table | |
| colchicine capsule (Mitigare)[67] | 0.6 mg once or twice daily; maximum daily dose is 1.2 mg | | Renal and hepatic insufficiency:<br>Dose reduction or alternatives should be considered in patients with severe renal or hepatic impairment | 0.6 mg capsule<br><br>Administer orally without regard to meals |

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 has not been evaluated for colchicine.


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Pegloticase should be administered in a healthcare setting intravenously 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 above 6 mg/dL, especially when 2 consecutive levels above 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 patients are on pegloticase.

## colchicine drug interactions and dosage adjustments[68]

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 below.

| Drug Interactions with colchicine | Recommended dose for Gout Flares | Recommended dose for management of FMF |
|---|---|---|
| Strong CYP 3A4 Inhibitors:<br>atazanavir, clarithromycin, darunavir/ritonavir, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin, tipranavir/ritonavir | **Treatment of Gout Flares:**<br>0.6 mg (1 tablet) x 1 dose, followed by 0.3 mg (half tablet) 1 hour later<br>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:**<br>0.3 mg daily or every other day | |
| Moderate CYP 3A4 Inhibitors:<br>amprenavir, aprepitant, diltiazem, erythromycin, fluconazole, fosamprenavir, grapefruit juice, verapamil | **Treatment of Gout Flares:**<br>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:**<br>0.3 mg twice daily or 0.6 mg once daily or 0.3 mg once daily | |
| P-gp Inhibitors:<br>cyclosporine, ranolazine | **Treatment of Gout Flares:**<br>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:**<br>0.3 mg daily or every other day | |

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


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## 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.[69] 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 of 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.[70] 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 [44%] of 9), 120 mg (5 [45%] of 11), and 240 mg (3 [60%] of 5) achieved the primary endpoint compared with those treated with 100 mg of allopurinol (0 [0%] of 10). Adverse events were similar across groups, although diarrhea and dizziness were more frequent in the febuxostat 240 mg group. The primary reasons for withdrawal


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were similar across groups except for gout flares, which were more frequent with febuxostat than with allopurinol. The study compared moderate dose of 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.[71] 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 (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≤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.

## 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.[72] 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 20-50 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.[73,74] 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 × 6 hours [4.8 mg total]); low-dose colchicine (n=74) (1.2 mg, then 0.6 mg


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in 1 hour [1.8 mg total] followed by 5 placebo doses hourly); or placebo (n=58) (2 capsules, then 1 capsule hourly × 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 21.3, 95% CI, 7.9 to 56.9). In the low dose group, 23% of patients reported diarrhea (odds ratio 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.[75] 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.[76] 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 were 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


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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). Two percent (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) 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 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 gastrointestinal 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.

## 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) reduced 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.

Colchicine tablet (Colcrys) is the first FDA-approved colchicine product. Colchicine has significant drug interactions and frequent gastrointestinal adverse effects; however, Colcrys is approved at a lower dosage for the treatment and prevention of gout flares than previously described. Colcrys is approved as an orphan drug for the treatment of FMF. A newer capsule formulation of colchicine (Mitigare) is now available but is only indicated for the prophylaxis of gout flares for adults and does not appear to provide any additional benefit over the tablet formulation.

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.

According to the ACR 2012 guidelines, acute gouty arthritis can be treated with oral colchicine, NSAIDs, corticosteroids, or intra-articular corticosteroid injections, or a combination of products, and should be started within 24 hours of onset in order to provide optimal care. They also recommend low-dose oral colchicine as first-line therapy for gout attack prophylaxis or low-dose NSAIDs with a proton pump inhibitor despite having a lower level of evidence. If low-dose oral colchicine and NSAID therapy can


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not be used, then low-dose prednisone or prednisolone can be used as second-line therapy. After an initial gout attack, the choice of urate-lowering medications is probenecid, colchicine/probenecid combination, or xanthine oxidase inhibitors. However, the ACR 2012 guidelines consider xanthine oxidase inhibitors as first-line therapy and probenecid as an alternative first-line agent. The guidelines recommend pegloticase (Krystexxa) as a third-line therapy option only.

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