

Therapeutic Class Overview

Anti-gout agents

INTRODUCTION

- Gout is a form of inflammatory arthritis characterized by acute intermittent episodes of synovitis with joint swelling and pain; the episodes are referred to as acute gouty arthritis flares or attacks (*Newberry 2016*). The inflammation is induced by the deposition of monosodium urate (MSU) crystals in synovial fluid and other tissues. MSU crystal formation and deposition can occur during a state of hyperuricemia, which is typically defined as a serum uric acid (sUA) level > 6.8 mg/dL (*Neogi 2011*).
- Hyperuricemia can be caused by impaired renal excretion or overproduction of serum urate and/or overconsumption of purine-rich foods that are metabolized to urate. Humans lack the enzyme uricase and therefore cannot convert urate to the soluble allantoin (excreted in the urine) as the end product of purine metabolism. Hyperuricemia is a necessary but not sufficient precondition for the development of urate crystal deposition disease and should be distinguished from gout, the clinical syndrome. Most hyperuricemic individuals never experience a clinical event resulting from urate deposition (*Becker 2018*).
- Long-term success in achieving and maintaining sub-saturating sUA levels is associated with clinical benefits that include cessation of acute gout flares, resolution of tophi, and improvement in patient physical function and health-related quality of life (QOL) (*Becker 2018*).
- Lowering sUA levels can be achieved by decreasing uric acid production via xanthine oxidase inhibitors (XOIs) or by increasing excretion via uricosuric agents (*Becker 2018*).
 - The 2 XOIs available are Zyloprim (allopurinol) and Uloric (febuxostat). While both agents function as XOIs, they differ in their mechanism of action. Allopurinol acts as a purine analogue, while febuxostat occupies a channel in the xanthine oxidase (XO) dimer, impairing access to purine base substrates.
 - Probenecid is a uricosuric and renal tubular blocking agent. It inhibits the tubular reabsorption of urate, thus increasing the urinary excretion of uric acid.
 - Zurampic (lesinurad) is a uricosuric which inhibits uric acid transporter 1 (URAT1) and organic anion transporter 4 (OAT4), and is used in combination with an XOI for the treatment of hyperuricemia associated with gout.
 - Colchicine is the agent of choice for acute gout attacks, but it can also be used prophylactically. The exact mechanism of action of colchicine in gout is not completely known, however, it is effective for pain associated with an acute gout attack.
 - Pegloticase is a pegylated uricase, which stimulates the breakdown of uric acid. It is reserved for refractory cases of gout and is administered via intravenous (IV) infusion every 2 weeks.
- Combination products such as Duzallo (lesinurad/allopurinol) and probenecid/colchicine are also available and are included in this class review.
- Non-steroidal anti-inflammatory drugs (NSAIDs) are utilized as an alternative to colchicine for prophylaxis during the initiation of urate-lowering therapies (*Becker 2018*). However, NSAIDs will not be included as part of this class review.
- Medispan class: Antigout Agent; Uric Acid Transporter 1 (URAT1) Inhibitor; Uricosuric agent; Xanthine Oxidase Inhibitor; Enzyme; Enzyme, Urate-Oxidase

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Colcrys (colchicine)†	✓
Duzallo (lesinurad/allopurinol)	-
Krystexxa (pegloticase)	-
Mitigare (colchicine)†	✓
probenecid	✓
probenecid/colchicine	✓
Uloric (febuxostat)	-

Data as of April 25, 2018 DB/JD

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Drug	Generic Availability
Zurampic (lesinurad)	-
Zyloprim (allopurinol)	✓

†Colcrys and Mitigare are both branded colchicine products; both have authorized generics available.

(Drugs @FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018)

INDICATIONS

Table 2. Food and Drug Administration Approved Indications

Indication	Colcrys (colchicine)	Duzallo (lesinurad/allopurinol)	Krystexxa (pegloticase)	Mitigare (colchicine)	probenecid	probenecid/colchicine	Uloric (febuxostat)	Zurampic (lesinurad)	Zyloprim (allopurinol)
Treatment and prophylaxis of gout flares in adults	✓			✓ ‡					
Chronic management of hyperuricemia in patients with gout							✓		
Treatment of chronic gout in adult patients refractory to conventional therapy			✓						
Treatment of hyperuricemia associated with gout		✓ *			✓			✓ **	
Management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy)									✓
Treatment of gouty arthritis when complicated by frequent, recurrent acute attacks of gout						✓			

*Duzallo is recommended for patients who have not achieved target sUA levels with a medically appropriate dose of allopurinol alone.

**Zurampic is recommended for patients who have not achieved target sUA levels with a XO1 alone.

‡Mitigare is indicated for prophylaxis of gout flares only (not FDA-approved for the treatment of gout flares).

(Prescribing information: Colcrys 2015, Duzallo 2017, Krystexxa 2016, Mitigare 2014, probenecid 2016, probenecid/colchicine 2016, Uloric 2018, Zurampic 2016, Zyloprim 2009).

- Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- Probenecid has been available since the 1950s and allopurinol and colchicine/probenecid have been available since the 1960s. Studies for these agents are therefore mainly limited to trials from the 1960s that were observational in nature. It should also be noted that there is limited literature evaluating the use of colchicine/probenecid.
- Colchicine was in use prior to the creation of the Food and Drug Administration (FDA), and therefore was “grandfathered” without receiving FDA approval. In 2006, however, colchicine was formally studied and officially approved under the brand name Colcrys. Mitigare, another brand of colchicine, was FDA-approved a few years later.

- A meta-analysis of 11 randomized controlled trials (RCTs) (n = 1258) was conducted in 2014 to assess the safety and efficacy of allopurinol (*Seth et al 2014*).
 - Moderate-quality evidence from 1 trial (n = 57) indicated that allopurinol 300 mg daily probably does not reduce the rate of gout attacks, but increases the proportion of participants achieving target sUA over 30 days.
 - In 2 studies (n = 453), there was no significant increase in withdrawals due to adverse effects (AEs) or serious AEs.
 - Low-quality evidence from 3 trials (n = 1136) indicated there may be no difference in the incidence of acute gout attacks with allopurinol up to 300 mg daily vs febuxostat 80 mg daily over 8 to 24 weeks (21% with allopurinol vs 23% with febuxostat, relative risk [RR] 0.89, 95% confidence interval [CI], 0.71 to 1.1); however more participants may achieve target sUA levels with febuxostat 80 mg daily vs allopurinol 300 mg daily (38% with allopurinol vs 70% with febuxostat, RR 0.56, 95% CI, 0.48 to 0.65).
- Colchicine's benefits and risks were examined in a meta-analysis conducted in 2014 (n = 124) (*Van Echteld et al 2014*).
 - Based upon pooled data from 2 trials, there was low-quality evidence that a greater proportion of patients receiving high-dose colchicine experienced a ≥ 50% decrease in pain from baseline up to 32 to 36 hours compared with placebo.
 - Only 1 trial included reduction of inflammation as part of a composite measure comprising pain, tenderness, swelling and erythema, each graded on a 4-point scale (none 0 to severe 3) to derive a maximum score for any 1 joint of 12. They reported the proportion of patients who achieved a 50% reduction in this composite score. Based upon 1 trial (n = 43), there was low-quality evidence that more patients in the high-dose colchicine group had a 50% or greater decrease in composite score from baseline up to 32 to 36 hours than patients in the placebo group.
- In a meta-analysis conducted in 2012, 6 febuxostat studies (n = 3978), were examined to determine the benefits and risks of febuxostat at multiple doses (*Tayar et al 2012*).
 - Patients taking febuxostat 120 mg and 240 mg reported more frequent gout flares vs placebo at 4 to 28 weeks (RR 1.7; 95% CI, 1.3 to 2.3, and RR 2.6; 95% CI, 1.8 to 3.7, respectively). No statistically significant differences were observed at febuxostat 40 mg and 80 mg. Compared to placebo, patients on febuxostat 40 mg were 40.1 times more likely to achieve sUA levels < 6.0 mg/dL at 4 weeks (95% CI, 2.5 to 639), with an absolute treatment benefit of 56% (95% CI, 37% to 71%). For febuxostat 80 mg and 120 mg, patients were 68.9 and 80.7 times more likely to achieve sUA levels < 6.0 mg/dL at their final visit compared to placebo (95% CI, 13.8 to 343.9; 95% CI, 16.0 to 405.5, respectively).
 - When comparing allopurinol to febuxostat at 24 to 52 weeks, the number of gout flares was not significantly different between the 2 groups, except for febuxostat 240 mg (RR 2.3; 95% CI, 1.7 to 3.0). Patients on febuxostat 40 mg showed no statistically significant differences in benefits or AEs. Patients on febuxostat 80 mg and 120 mg were 1.8 and 2.2 times more likely to achieve sUA levels < 6.0 mg/dL at their final visit, respectively, at 24 to 52 weeks.
- The combination of lesinurad with XOIs has been demonstrated to result in additive sUA lowering beyond that of XOIs alone. The Combining Lesinurad with Allopurinol in Inadequate Responders trials (CLEAR 1 and CLEAR 2) were replicate phase 3, 12-month, multicenter (MC), placebo-controlled (PC), double-blind (DB), RCTs (n = 603 and n = 610, respectively) assessing the efficacy and safety of lesinurad 200 mg and 400 mg once daily in combination with a patient's current stable dose of allopurinol (≥ 300 mg daily or ≥ 200 mg daily for those with moderate renal impairment) compared to placebo plus allopurinol. The primary endpoint was the proportion of patients achieving an sUA level < 6.0 mg/dL at month 6 (*Bardin et al 2016, Saag et al 2017*).
 - Results for CLEAR 1 showed that 54.2% and 59.2% of the lesinurad 200 mg and 400 mg daily plus allopurinol-treated groups, respectively, achieved the target sUA level compared to 27.9% of the placebo plus allopurinol-treated group at month 6 (both p < 0.0001 vs placebo + allopurinol).
 - Results for CLEAR 2 similarly showed that 55.4% and 66.5% of the lesinurad 200 mg and 400 mg daily plus allopurinol-treated groups, respectively, achieved the target sUA level compared to 23.3% of the placebo plus allopurinol-treated group at month 6 (both p < 0.0001 vs placebo + allopurinol).
 - The majority of gout patients inadequately responding to allopurinol alone who were treated with lesinurad plus allopurinol achieved a target sUA level by month 1 and this was maintained throughout both 12-month studies.
 - Key secondary endpoints [frequency of gout flares requiring treatment during months 6 to 12 and complete resolution of ≥ 1 target tophi by month 12 (in patients with target tophi at baseline)] were not met, possibly due to the low gout flare rates and a low number of patients with target tophi at baseline.
 - An increase in serum creatinine (sCr) (1.5 x baseline) was more prevalent in the lesinurad 400 mg group. These sCr increases were transient and reversible.

- The Combination Treatment Study in Subjects with Tophaceous Gout with Lesinurad and Febuxostat (CRYSTAL) was a third pivotal phase 3, 12-month, MC, PC, DB, RCT (n = 324) evaluating the efficacy and safety of lesinurad 200 mg and 400 mg once daily in combination with febuxostat 80 mg compared to placebo plus febuxostat in treatment-naïve and treatment-experienced patients with tophaceous gout and elevated sUA levels (*Dalbeth et al 2017*).
 - Lesinurad 200 mg or 400 mg once daily in combination with febuxostat significantly increased the proportion of patients achieving sUA target (< 5.0 mg/dL) at all monthly visits from months 1 to 12, except for the lesinurad 200 mg + febuxostat group at month 6, compared to febuxostat alone in patients with tophaceous gout.
 - Although treatment with lesinurad + febuxostat resulted in a greater area of tophus resolution compared to febuxostat alone and an increase in the proportion of patients with complete resolution of ≥ 1 target tophi, these endpoints were not statistically significant.
- The FDA approval of pegloticase was based on two 6-month, replicate, MC, DB, PC, RCTs. Adult patients with chronic gout refractory to conventional therapy who were randomized to receive pegloticase 8 mg IV every 2 weeks, every 4 weeks, or placebo. The primary endpoint in both trials was the proportion of patients who achieved sUA < 6 mg/dL for at least 80% of the time during month 3 and month 6 (*Sundy et al 2011*).
 - sUA normalized within 24 hours of the first infusion in all patients receiving pegloticase, but afterward, some patients lost the urate-lowering response, whereas others maintained sUA < 6.0 mg/dL throughout the trial. Data showed that a greater proportion of patients treated with pegloticase every 2 weeks achieved urate lowering to below 6 mg/dL than patients receiving placebo. In trial 1, when pegloticase was dosed at 8 mg every 2 weeks, 47% of patients responded with sUA in the target range. When pegloticase was dosed at 8 mg every 4 weeks, 20% responded vs none in the placebo group. In trial 2, when pegloticase was dosed at 8 mg every 2 weeks, 38% of patients responded. With pegloticase 8 mg every 4 weeks, 49% of patients responded, while none of the placebo patients responded.
 - Forty percent of patients in the biweekly pegloticase group and 21% in the monthly group had a complete response for ≥ 1 tophi by the final visit compared with 7% of patients receiving placebo (p = 0.002 and p = 0.20, respectively). Both pegloticase dosing groups reported significant improvements in physical function and QOL compared with placebo.

CLINICAL GUIDELINES

- The American College of Physicians (ACP) published guidelines in 2016 for the management of acute and recurrent gout (*Qaseem et al 2017*).
 - Corticosteroids, NSAIDs, or colchicine (low-dose preferred) are recommended to treat patients with acute gout.
 - ACP recommends against initiating long-term urate-lowering therapy in most patients after a first gout attack or in patients with infrequent attacks.
 - Febuxostat (40 mg/day) and allopurinol (300 mg/day) are equally effective at decreasing sUA levels.
 - Data on the most appropriate duration of urate-lowering therapy are insufficient. However, moderate to high quality evidence suggests that urate-lowering therapy reduces the risk for acute gout attacks after 1 year, but not within the first 6 months of treatment.
- In 2012, the American College of Rheumatology (ACR) published guidelines for the management of gout. Some key points include:
 - An XOI, ie, allopurinol or febuxostat, is recommended as the first-line pharmacologic urate-lowering therapy.
 - Probenecid is recommended as an alternative first-line pharmacologic urate-lowering therapy option in the setting of contraindication or intolerance to at least 1 XOI agent.
 - sUA level should be lowered sufficiently to durably improve signs and symptoms of gout, with a target of < 6 mg/dL at a minimum, and often < 5 mg/dL.
 - Combination oral urate-lowering with 1 XOI and 1 uricosuric agent is appropriate when the sUA target has not been met by therapeutically-appropriate doses of an XOI monotherapy.
 - If sUA target is not achieved, a uricosuric agent (titrated to maximum appropriate dose) can be added.
 - If sUA target still has not been achieved, then pegloticase can be considered. Pegloticase is appropriate for patients with severe gout disease burden and refractoriness to, or intolerance of, appropriately dosed oral urate-lowering options.
- A 2016 update to the European League Against Rheumatism (EULAR) 2006 guidelines for the management of gout makes the following key recommendations (*Richette et al 2016*):
 - Recommended first-line options for acute flares are colchicine (within 12 hours of flare onset) at a loading dose of 1 mg followed 1 hour later by 0.5 mg on day 1 and/or an NSAID (plus proton pump inhibitor if appropriate), oral

corticosteroid, or articular aspiration and injectable corticosteroids. Colchicine and NSAIDs should be avoided in patients with severe renal impairment.

- In patients with normal renal function, allopurinol is recommended for first-line urate-lowering therapy, starting at a low dose (100 mg/day) and increasing by 100 mg increments every 2 to 4 weeks if required, to reach the sUA target. If the sUA target cannot be reached by an appropriate dose of allopurinol, allopurinol should be switched to febuxostat or a uricosuric or combined with a uricosuric. Febuxostat or a uricosuric are also indicated if allopurinol cannot be tolerated.
- In patients with crystal-proven, severe debilitating chronic tophaceous gout and poor QOL, in whom the sUA target cannot be reached with any other available drug at the maximal dosage (including combinations), pegloticase is indicated.

SAFETY SUMMARY

• Contraindications

- Colchicine is contraindicated in patients with renal or hepatic impairment who are taking a P-glycoprotein or strong cytochrome P450 (CYP) 3A4 inhibitor, due to the potential for life-threatening and fatal colchicine toxicity.
- Febuxostat is contraindicated in patients being treated with azathioprine or mercaptopurine.
- Lesinurad is contraindicated in patients with severe renal impairment (creatinine clearance [Cl_{cr}] < 30 mL/min), end-stage renal disease, kidney transplant recipients, or patients on dialysis. Lesinurad should also be avoided in patients with tumor lysis syndrome or Lesch-Nyhan syndrome.
- Pegloticase is contraindicated in patients with G6PD deficiency, due to risk of hemolysis and methemoglobinemia.
- Probenecid is contraindicated in patients with known blood dyscrasias or uric acid kidney stones.

• Boxed Warnings

- Lesinurad-containing products
 - Acute renal failure has occurred with lesinurad, especially when lesinurad was given alone.
 - Lesinurad should be used in combination with an XOI.
- Pegloticase
 - Anaphylaxis may occur with any infusion, and generally manifests within 2 hours of the infusion. However, delayed-type hypersensitivity reactions have also been reported. Patients should be pre-medicated with anti-histamines and corticosteroids.

• Warnings

- With the majority of these agents (except for colchicine), gout prophylaxis should be continued at the initiation of therapy, due to risk of gout flares.
- The febuxostat product information carries a warning about cardiovascular events based on pre-approval clinical trials that showed a higher rate of cardiovascular deaths, non-fatal myocardial infarctions, and non-fatal strokes compared to allopurinol (*FDA 2017*).
 - The FDA issued a drug safety communication alerting the public that the preliminary results from a required safety clinical trial show an increased risk of cardiac-related death with febuxostat compared to allopurinol.
 - The preliminary results show that overall, febuxostat did not increase the risk of cardiac-related death compared to allopurinol. However, when the outcomes were evaluated separately, febuxostat showed an increased risk of cardiac-related deaths and death from all causes.
- The FDA approved a new warning for skin reactions that was added to the febuxostat product information in February 2018. Post marketing reports of serious skin and hypersensitivity reactions, including Stevens-Johnson Syndrome, drug reaction with eosinophilia and systemic symptoms, and toxic epidermal necrolysis have been reported in patients taking febuxostat. Anaphylaxis and severe allergic reactions have been reported with allopurinol (especially in patients with renal failure), pegloticase (boxed warning), and probenecid.
- Caution should be used in patients with hepatic impairment when taking allopurinol or febuxostat.
- Caution should also be used when administering allopurinol and lesinurad in patients with renal insufficiency.
- Bone marrow suppression has been reported after allopurinol initiation, and blood dyscrasias have been reported at therapeutic doses of colchicine.

• Adverse Effects

- Liver function abnormalities may be seen with allopurinol, febuxostat, and probenecid.
- Rash has been noted with allopurinol and febuxostat.
- Nausea, vomiting, gout flares, and headache are AEs that have been observed with most of the agents in this review.

• Drug Interactions

- Allopurinol and febuxostat inhibit XO, which can cause an increase in azathioprine and mercaptopurine levels when given concomitantly. The dose of azathioprine or mercaptopurine will require reduction when used concomitantly with allopurinol. Concomitant use of either of these agents with febuxostat is contraindicated.
- Increased colchicine levels can be seen when used with strong CYP 3A4 inhibitors.
- When administered with probenecid, an increase in methotrexate and NSAID levels may be seen.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Colcrys (colchicine)	Tablets	Oral	<u>Prophylaxis</u> : Once or twice daily <u>Treatment</u> : 2 tablets at first sign of gout flare, followed by 1 tablet 1 hour later	Dosage adjustment of prophylactic dose recommended in patients with severe renal or hepatic failure
Duzallo (lesinurad/allopurinol)	Tablets	Oral	Once daily	Should be taken with food and water; should not be initiated or continued in patients with a CLcr < 45 mL/min; not recommended in patients with severe hepatic impairment
Krystexxa (pegloticase)	Injection	IV	Every 2 weeks	Should not be administered via IV push or bolus; premedication is recommended
Mitigare (colchicine)	Capsules	Oral	Once or twice daily	Dose adjustments should be considered in patients with severe renal and/or hepatic impairment
probenecid	Tablets	Oral	Twice daily	Should not be started until acute gouty attack has subsided; dose adjustments may be necessary in patients with renal impairment
probenecid/colchicine	Tablets	Oral	Once daily for 1 week, then twice daily	Should not be started until acute gouty attack has subsided; dose adjustments may be necessary in patients with renal impairment
Uloric (febuxostat)	Tablets	Oral	Once daily	Dose should be limited in patients with severe renal impairment
Zurampic (lesinurad)	Tablets	Oral	Once daily	Should be taken in combination with an XOI; should not be initiated or continued in patients with a CLcr < 45 mL/min; not recommended in patients with severe hepatic impairment
Zyloprim (allopurinol)	Tablets	Oral	In divided doses for doses > 300 mg	Dose should be adjusted in patients with renal failure; better tolerated when taken following meals

See the current prescribing information for full details

CONCLUSION

- Gout is a form of inflammatory arthritis characterized by acute intermittent episodes of synovitis presenting with joint swelling and pain; the episodes are referred to as acute gouty arthritis flares or attacks (*Newberry 2016*). The inflammation is induced by the deposition of MSU crystals in synovial fluid and other tissues. MSU crystal formation and deposition can occur during a state of hyperuricemia, which is typically defined as an sUA level > 6.8 mg/dL (*Neogi 2011*).
- Lowering sUA levels can be achieved by decreasing uric acid production via XOIs (ie, allopurinol or febuxostat) or by increasing excretion with agents such as probenecid and lesinurad (*Becker 2018*).
- XOIs are the preferred treatment for lowering sUA, while colchicine is the preferred treatment for acute gout attacks.
- With the majority of these agents, gout prophylaxis should be continued at the initiation of therapy, due to risk of gout flares.
- The FDA recently issued a drug safety communication alerting the public that preliminary results from a required safety clinical trial show an increased risk of cardiac-related death with febuxostat compared to allopurinol. Overall, febuxostat did not increase the risk of cardiac-related death compared to allopurinol. However, when the outcomes were evaluated separately, febuxostat showed an increased risk of cardiac-related deaths and death from all causes (*FDA 2017*).
- Lesinurad and pegloticase carry boxed warnings for acute renal failure and anaphylaxis, respectively.
- Caution should be used when prescribing anti-gout medications, as several agents in this class have a number of potential drug-drug interactions.
- Pegloticase, the only IV anti-gout agent, should be utilized only in advanced, tophaceous, and symptomatic gout cases that are refractory to other anti-gout medications (*Becker 2018*).

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Publication Date: May 2, 2018