
Therapeutic Class Overview Agents for Gout

Therapeutic Class Overview/Summary:

Gout is a complex inflammatory disease that occurs in response to the presence of monosodium urate monohydrate crystals in the joints, bones and soft tissues.^{1,2} The disease consists of four clinical phases.³ The first phase is asymptomatic hyperuricemia. Although hyperuricemia is a necessary predisposing factor, the presence of high serum urate levels alone does not automatically lead to gout.^{1,3} One study reported that 78% of the men in the trial with serum urate levels greater than 9 mg/dL did not develop gout over a five year period.⁴ 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.¹ Humans, lack the enzyme uricase and therefore cannot convert urate to the soluble allantoin as the end product of purine metabolism.² The deposition of monosodium urate monohydrate crystals into the joints and other areas of the body begin when serum urate levels are greater than 6.8 mg/dL. This concentration is the saturation point of urate in biological fluids and it is at this concentration where monosodium urate monohydrate crystals begin to precipitate. As mentioned previously the presence of hyperuricemia does not automatically lead to gout. Other factors, when combined with hyperuricemia that contribute to monosodium urate monohydrate deposition and the development of gout include trauma or irritation of joints, lower temperatures which favor crystal deposition and previously diseased joints.⁴

The second phase is characterized by intermittent acute gout attacks.³ These attacks are due to the abrupt release of monosodium urate monohydrate crystals into the joint space where they initiate an acute inflammatory reaction characterized by painful inflammatory arthritis.⁴ These attacks typically resolve spontaneously over a period of seven to 10 days.² The time interval separating these acute attacks is the third phase of the disease and is known as the intercritical gout period.⁵ The time period separating acute gout attacks during this period vary widely between a few days to several years. Overtime, if the disease is left untreated it evolves into chronic tophaceous gout. This phase of the disease is characterized by the deposition of solid monosodium urate monohydrate crystal aggregates known as tophi in a variety of locations including joints, bursae and tendons.⁵ In addition deposits of monosodium urate monohydrate crystals in the renal tubules can also lead to renal calculi and nephropathy.³

Treatment of gout consists of rapid relief of pain and disability caused by acute gout attacks and the reduction of serum urate levels. This reduction prevents further acute attacks and the progression of the disease to tophaceous gout.² Although acute attacks can be treated with anti-inflammatory medications, the underlying cause of the disease can only be treated by lowering serum urate levels.⁴

In addition to the treatment of gout the agents included in this review are also indicated for a number of other indications. These include hyperuricemia due to chemotherapy, Familial Mediterranean Fever, increasing of penicillin levels, and treatment of calcium oxalate calculi. These indications will not be discussed in detail as they are outside the scope of this review.⁶⁻¹³ These agents also have different mechanisms of actions by which they exert their effects. Colchicine is believed to exert a positive effect in gout by preventing the activation, degranulation and migration of neutrophils, implicated in the pathogenesis of gout symptoms. The mechanism by which colchicine acts in patients with Familial Mediterranean Fever has not been fully established; however, there is evidence suggesting that colchicine interferes with the assembly of the inflammasome complex found in neutrophils and monocytes that mediate the activation of interleukin-1 β .^{7,8} Allopurinol and febuxostat are both xanthine oxidase inhibitors. These agents causes a decrease in urate levels through the inhibition of xanthine oxidase, the enzyme responsible for the conversion of hypoxanthine to xanthine and then finally to uric acid.^{6,9} A major difference between these two agents is that allopurinol is a purine analogue where febuxostat is not.¹⁴ Another major difference is that febuxostat is mainly metabolized in the liver and thus does not require renal dosing in mild-moderate renally impaired patients.^{6,9} Pegloticase is a recombinant uricase, a uric acid-specific enzyme, which catalyzes the oxidation of uric acid to allantoin, thereby lowering serum uric

acid. Allantoin is an inert and water soluble purine metabolite which is readily eliminated, primarily via renal excretion.¹⁰ Probenecid is a uricosuric agent that exerts its effects on serum urate by inhibiting the reabsorption of uric acid at the proximal tubule which leads to uric acid excretion and a decrease in overall serum urate levels.^{11,15} Probenecid is also available with colchicine as a combination product.¹² Lesinurad inhibits urate transporter-1 (URAT1) and organic ion transporter-4 (OAT4) thereby reducing renal reabsorption and increasing excretion of urate and thus lowering serum uric acid (sUA) concentrations.¹³

Table 1. Current Medications Available in the Therapeutic Class⁶⁻¹³

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
Single Entity Agent			
Allopurinol (Zyloprim ^{®*})	Management of patients with signs and symptoms of primary or secondary gout (acute attacks, tophi, joint destruction, uric acid lithiasis, and/or nephropathy); management of patients with leukemia, lymphoma and malignancies who are receiving cancer therapy which causes elevations of serum and urinary uric acid levels; management of patients with recurrent calcium oxalate calculi whose daily uric acid excretion exceeds 800 mg/day in male patients and 750 mg/day in female patients	Tablet: 100 mg 300 mg	✓
Colchicine (Colcrys ^{®*} , Mitigare ^{®*})	Prophylaxis of gout flares; treatment of gout flares; treatment of Familial Mediterranean Fever	Capsule: 0.6 mg Tablet: 0.6 mg	✓
Febuxostat (Uloric [®])	Chronic management of hyperuricemia in patients with gout	Tablet: 40 mg 80 mg	-
Lesinurad (Zurampic [®])	In combination with a xanthine oxidase inhibitor for the treatment of hyperuricemia associated with gout in patients who have not achieved target serum uric acid levels with a xanthine oxidase inhibitor alone	Tablet: 200 mg	-
Pegloticase (Krystexxa [®])	Treatment of chronic gout in adult patients refractory to conventional therapy	Vial 8 mg/mL Must be administered in a health care facility.	-
Probenecid*	Treatment of hyperuricemia associated with gout and gouty arthritis; adjuvant therapy with penicillin or with ampicillin,	Tablet: 500 mg	✓

Generic (Trade Name)	Food and Drug Administration-Approved Indications	Dosage Form/Strength	Generic Availability
	methicillin, oxacillin, cloxacillin, or nafcillin, for elevation and prolongation of plasma levels by whatever route the antibiotic is given		
Combination Products			
Colchicine/probenecid*	Treatment of chronic gouty arthritis when complicated by frequent, recurrent acute attacks of gout	Tablet: 0.5 mg/0.5 g	✓

*Generic available in at least one dosage form or strength.

Evidence-based Medicine

- Regarding Familial Mediterranean Fever, studies that have examined the use of colchicine for this disease state are limited. It should be noted, that approval of brand colchicine for Familial Mediterranean Fever treatment was not based on new clinical studies but rather on previously published literature. These studies as well as others confirmed that the agent is efficacious in both reducing the number of attacks and in aborting acute attacks.^{7,24,25,55}
- Efficacy of colchicine for the treatment and prevention of gout and increased uric acid levels is well documented.²⁸⁻³⁰
- The efficacy and safety of pegloticase was evaluated in two identical randomized placebo-controlled studies. The studies were six months in duration and included adult patients with symptomatic gout and at least three gout flares in the previous 18 months or the presence of at least one gout tophus or gouty arthritis. Moreover, patients were included if they had a self-reported contraindication to allopurinol or a medical history of failure to normalize uric acid with at least three months of allopurinol treatment. Patients in both studies were treated with either pegloticase 8 mg every two weeks, every four weeks or placebo. The primary endpoint in both studies was the proportion of patients who achieved plasma uric acid (PUA) levels less than 6 mg/dL for at least 80% of the time during months 3 and 6. In the first study, 47% and 20% of patients in the 8 mg every two and four weeks respectively achieved PUA<6 mg/dL for ≥80% of the time. There was a significant difference in both groups when compared to placebo (0%, P<0.001 and P=0.044, respectively). In the second study, 38% and 49% of patients in the 8 mg every 2 and 4 weeks respectively achieved PUA<6 mg/dL for ≥80% of the time. There was a significant difference in both groups when compared to placebo (0%, P<0.001 for both pegloticase groups).^{10,31}
- Regarding febuxostat, the three major trials that were the basis for approval were the FACT, APEX, and CONFIRMS trials. These studies were all randomized, double-blind, controlled trials that compared the treatment of febuxostat, in doses ranging from 40 to 240 mg/day, to allopurinol or placebo in patients with gout. The FACT and APEX studies demonstrated that a significantly greater number of patients treated with febuxostat 80, 120 and 240 mg were able to reach a serum urate goal of less than six mg/dL. In the CONFIRMS trial patients in the 80 mg group had similar outcomes to the FACT and APEX studies; however the CONFIRMS trial also evaluated a 40 mg dose where the proportion of patients with serum urate level <6 mg/dL was not found to be significantly different between the febuxostat 40 mg and the allopurinol groups. These studies also reported that febuxostat was more efficacious than allopurinol in patients with mild to moderate renal impairment. However, in all three studies there were no differences between any of the groups for the number of patients who required treatment for acute gout flares. Regarding adverse events, there were generally no significant differences in the incidence of adverse events between the febuxostat and allopurinol groups and they were generally mild to moderate in severity. There was also no statistically significant difference between groups in the incidence of cardiovascular events.³⁶⁻³⁸
- FDA-approval of lesinurad was based on three randomized, placebo-controlled studies of lesinurad in combination with xanthine oxidase inhibitor. Combination with allopurinol was assessed in studies CLEAR 1 and CLEAR 2, and combination therapy with febuxostat was assessed in the CRYSTAL

study. For up to 12 months, a total of 511, 510 and 516 patients were treated with lesinurad 200 mg, 400 mg and placebo, respectively. Results from these trials demonstrated combination therapy significantly increased the proportion of patients achieving target serum uric acid levels in patients with inadequate response to xanthine oxidase inhibitor monotherapy ($P < 0.001$).⁴⁶⁻⁴⁹

Key Points within the Medication Class

- According to Current Clinical Guidelines:
 - Recommend a nonsteroidal anti-inflammatory drug (NSAID), colchicine, or a corticosteroid for the treatment of an acute gout attack.¹⁸⁻²¹
 - According to the more recent guidelines for the management of gout, initiation of urate lowering therapy is recommended in patients with an established diagnosis of gout and tophus or tophi, frequent attacks of acute gouty arthritis (≥ 2 attacks/year), chronic kidney disease stage 2 or worse, and past urolithiasis.¹⁸
 - Agents used to lower serum urate levels include allopurinol, probenecid, and febuxostat. The main difference between these agents is that allopurinol and febuxostat inhibit urate production and probenecid promotes urate excretion.¹⁸⁻²²
 - The 2012 ACR guideline recommends either allopurinol or febuxostat as the first-line urate lowering therapy approach for the management of gout, with no preference stated between the two. While the updated EULAR guidelines recommend allopurinol as first line followed by febuxostat if allopurinol is not tolerated.¹⁸
 - In comparison, older guidelines, published prior to approval of febuxostat, recommend allopurinol first-line and note febuxostat as a second-line option when allopurinol is not effective or not appropriate.¹⁹⁻²¹
 - The ACR recommends probenecid as an alternative first-line urate lowering therapy option in patients with a contraindication or intolerance to either allopurinol or febuxostat.¹⁶
 - During initiation of urate lowering therapy the guidelines recommend concurrent prophylaxis with either colchicine or an NSAID, although generally colchicine is the preferred, to prevent acute attacks while starting therapy.¹⁹⁻²¹
 - Concomitant therapy is generally recommended for up to six months at which point only the urate lowering agent is continued. Treatment with the urate lowering agent has the potential to be lifelong.^{19,20}
- Other Key Facts:
 - Colchicine tablets and colchicine capsules have different FDA-approved indications and ages approved.^{1,2}
 - Colchicine tablets are approved for use in children ≥ 4 years of age for the treatment of Familial Mediterranean Fever (tablets).¹

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