



# Managing gout in primary care

## Part 2 – Controlling gout with long-term urate-lowering treatment

Urate-lowering medicines should be considered and discussed with patients with gout from the first presentation. Doses of urate-lowering medicines need to be titrated to effect so that patients consistently have serum urate levels that are below target. There are a number of urate-lowering medicines available and patients who are unable to achieve treatment targets with allopurinol alone should be offered an alternative regimen.

### KEY PRACTICE POINTS:

- Allopurinol is the recommended first-line urate lowering medicine; renal function is used to determine the starting dose
- Doses of urate-lowering medicines need to be titrated so that the patient achieves a serum urate level that is below 0.36 mmol/L; a target below 0.30 mmol/L is recommended for those with features of severe disease, e.g. tophi
- Probenecid, benzbromarone and febuxostat are available for patients who find allopurinol ineffective or intolerable
- Patients with gout require ongoing management of cardiovascular risk and monitoring for associated co-morbidities, e.g. chronic kidney disease and diabetes

✔ For further information about managing patients with gout, including treating flares, see: **Part 1 – Talking about gout: time for a rethink.**

### Allopurinol is the first-line urate-lowering medicine

Allopurinol is a xanthine oxidase inhibitor that decreases the production of urate by inhibiting the metabolism of purines; it is the first-line urate-lowering medicine for patients with gout.<sup>1,2</sup>

### The starting dose of allopurinol is determined by the patient's renal function

Allopurinol is started at a low dose and slowly titrated upwards, to minimise the occurrence of adverse effects, until the patient reaches the target serum urate level.<sup>4</sup> Allopurinol can be safely used in patients who have reduced renal function, with a lower starting dose and slower titration (Table 1). Dose reductions are not routinely required in patients with declining renal function who are already established on allopurinol.

**Table 1:** Suggested starting doses and dose titrations for allopurinol determined by renal function.<sup>5</sup>


Estimated glomerular filtration (eGFR) mL/min/1.73m <sup>2</sup>	Initial dose of allopurinol	Dose increase
>60	100 mg, daily	Increase by 100 mg, every four weeks*, if tolerated, until the serum urate target is reached, or to a maximum of 900 mg, daily
30–60	50 mg, daily	Increase by 50 mg, every four weeks, if tolerated, until the serum urate target is reached, or to a maximum of 900 mg, daily <sup>†</sup>
<30	50 mg, every second day	Increase to 50 mg every day, after four weeks, then increase by 50 mg, every four weeks thereafter, if tolerated, until the serum urate target is reached, or to a maximum of 900 mg, daily <sup>†</sup>

\* Some prescribers prefer a more rapid titration, e.g. every two weeks, although this needs to be balanced against the increased risk of adverse effects


† Many people with renal dysfunction will be unable to tolerate the maximum dose of allopurinol; consider referral to or discussion with a rheumatologist if serum urate targets are unable to be achieved and an increase in dose is not tolerated, e.g. over 300 mg allopurinol.

### Dose titration is essential to achieve serum urate targets

Once allopurinol has been initiated, regular follow-up with serum urate testing is required while the dose of allopurinol is titrated upwards, until the serum urate target is reached. In patients without renal dysfunction, 30–50% will require a dose of allopurinol in excess of 300 mg per day to achieve a serum urate target.<sup>1</sup> Treatment with up to 600–800 mg per day of allopurinol can be expected to achieve a serum urate target in 75–80% of patients with gout.<sup>1</sup>


Community pharmacists are likely to have an increasing role in the titration of allopurinol dosing with the use of standing orders provided by general practitioners, e.g. the “Owning my gout”  initiative.

Other urate-lowering medicines (see below) are available for patients who are unable to tolerate allopurinol or achieve the serum urate target with allopurinol alone. However, some patients who continue to have serum urate levels slightly above target despite their maximum tolerated dose of allopurinol may choose to persist with allopurinol alone, rather than taking an additional medicine, if flares are controlled.

 Owning My Gout is a project involving community pharmacists, practice nurses and general practitioners in South Auckland, further information is available from: <http://koawatea.co.nz/wp-content/uploads/2015/06/LS4-Manaaki-Hauora-Project-Review-Owning-My-Gout-March-2016.pdf>

### Adverse effects of allopurinol are relatively uncommon

Allopurinol is generally well-tolerated, although some patients will experience gastrointestinal symptoms.<sup>3,6</sup> Drug rash with eosinophilia and systemic symptoms (DRESS) caused by allopurinol, also referred to as allopurinol hypersensitivity syndrome, is a rare, but potentially fatal, condition characterised by an erythematous, desquamating rash, fever, eosinophilia, leukocytosis, hepatitis and renal failure.<sup>4,7</sup> DRESS is estimated

to occur in 0.1% of patients taking allopurinol, most often in the first four to six weeks of treatment.<sup>7</sup> The risk of DRESS can be substantially reduced by initiating allopurinol at a low dose and slowly titrating upwards after tolerance has been established.<sup>4</sup> Patients should stop taking allopurinol and seek medical advice if they develop a rash or itch; an alternative urate-lowering medicine can be trialled. Risk factors for DRESS in patients taking allopurinol include renal impairment, an elevated starting dose of allopurinol relative to renal function, the use of diuretics, and having the HLA-B\*5801 allele which is often present in people of Korean, Thai or Chinese descent.<sup>5,7</sup> Genetic testing for this allele is available; it is recommended to discuss testing with Genetic Health Service NZ .

 [www.genetichealthservice.org.nz](http://www.genetichealthservice.org.nz)

### Serum urate levels are treated to target

The goal of urate-lowering treatment is to reduce serum urate levels below saturation point in order to dissolve urate crystals, thereby preventing future gout flares.<sup>8</sup> The lower the urate level the quicker the crystals dissolve.<sup>3</sup>

The recommended serum urate levels are:<sup>1</sup>

- < 0.36 mmol/L for most patients
- < 0.30 mmol/L for patients with severe gout, e.g. those with tophi, chronic gouty arthritis or frequent flares

After several years of symptom-free treatment and resolution of tophi, patients treated to < 0.30 mmol/L can be switched to the less stringent target of < 0.36 mmol/L.<sup>3</sup>

**Testing of serum urate levels is recommended prior to dose adjustment**, e.g. initially every four weeks, while urate-lowering treatment is being titrated and then every six to 12 months for monitoring.<sup>9</sup> During a flare, serum urate levels should not be


tested for the purposes of monitoring the patient's response to treatment as their serum urate levels may be lower than normal.<sup>9</sup>

### Flare prophylaxis is recommended when initiating urate-lowering treatment

During the first months of urate-lowering treatment the rapid decline in serum urate is thought to disrupt pre-formed monosodium urate crystals making them more likely to provoke a local inflammatory response which can result in an acute flare of gout. Flare prophylaxis is therefore recommended for the first six months of urate-lowering treatment.<sup>1</sup> Gradual dose titration also reduces the risk of flares, compared to starting full doses of urate-lowering treatment.

The increased risk of flares during initiation of urate-lowering treatment should be discussed with patients and advice given to persist with urate-lowering treatment if a flare does occur. Treatment options for flare prophylaxis include:<sup>3,6</sup>

- Naproxen 250 mg, twice daily for up to six months; consider concurrent use of a proton pump inhibitor if clinically indicated
- Colchicine (unapproved indication), 500 micrograms, twice daily for up to six months; reduce dose to 500 micrograms, once daily, or on alternate days, if not tolerated, e.g. diarrhoea develops, chronic kidney disease or concurrent use of CYP3A4/p-glycoprotein inhibitors (e.g. erythromycin, verapamil)
- If contraindications to NSAIDs or colchicine: Prednisone 5 mg, once daily, for up to six months, tapered slowly on withdrawal

 **Best practice tip:** If the patient is receiving treatment for a gout flare with a NSAID or colchicine, continue the same medicine at a lower dose for prophylaxis once the flare has resolved.

### Add probenecid if serum urate targets are not achieved with allopurinol alone

Probenecid can be added to allopurinol if despite taking a relatively high dose of allopurinol, e.g. 600 mg daily, the patient is unable to achieve the serum urate target; assess adherence to allopurinol first.<sup>1</sup> Probenecid can also be prescribed as monotherapy to patients who are intolerant or resistant to allopurinol.<sup>3</sup>

Probenecid dosing is titrated according to the patient's serum urate concentration:<sup>6</sup>

- Initially, 250 mg, twice daily, for one week, then 500 mg, twice daily, with the dose increased by 500 mg every four weeks, to a total of 1 g, twice daily, if required


Probenecid should be avoided in patients with an eGFR < 30 mL/minute/1.73m<sup>2</sup>.<sup>6</sup> Probenecid is contraindicated in patients with kidney stones.<sup>10</sup> Patients should be advised to drink plenty of fluids, at least two litres per day, to prevent the formation of uric acid stones and to take the medicine with, or just after, a meal.<sup>6</sup> The most common adverse effects associated with probenecid are nausea and vomiting.<sup>6</sup>

### Benzbromarone is an alternative option for urate-lowering

Benzbromarone is a uricosuric medicine that was withdrawn from the European market in 2003 due to concerns regarding serious hepatotoxicity;<sup>14</sup> it is not approved by Medsafe for use in New Zealand. Benzbromarone is, however, subsidised with Special Authority approval for patients with gout and serum urate levels > 0.36 mmol/L who have been treated with allopurinol in combination with probenecid, or for patients where allopurinol is contraindicated or likely to be ineffective. Benzbromarone is more effective at lowering serum urate levels than probenecid (1–2 g, daily).<sup>1</sup>

The maximum recommended dose of benzbromarone is 100 mg, daily, to reduce the risk of hepatic adverse effects. Benzbromarone is not recommended in patients with an eGFR < 30 mL/min/1.73m<sup>2</sup>.<sup>1</sup>

Liver function tests are required each month for at least the first six months of benzbromarone treatment and three-monthly thereafter.<sup>6</sup> Patients taking benzbromarone should ensure they are consuming at least two litres of fluid a day to reduce the risk of uric acid stone formation.<sup>6</sup>

 Further information on benzbromarone is available from: [www.bpac.org.nz/BPJ/2013/March/managing-gout.aspx](http://www.bpac.org.nz/BPJ/2013/March/managing-gout.aspx)

### Blister packs simplify treatment for patients and encourage adherence

Multiple medicines are often required for the initial treatment of gout, including acute flare management and prophylaxis, and increasing doses of allopurinol. This requires careful instruction to ensure that the patient takes the right dose of the right medicine at the right time. A potential solution for some patients is to have medicines dispensed in a blister pack. In many cases, pharmacies will charge patients for this service, but some PHOs may fund this, e.g. Alliance in Auckland – check with your local PHO.

## Febuxostat is a further option for urate-lowering

If treatment with allopurinol is ineffective or cannot be tolerated, febuxostat is a second-line xanthine oxidase inhibitor.<sup>3</sup> Febuxostat is subsidised with Special Authority approval in New Zealand for patients with gout who:

- Have a serum urate level > 0.36 mmol/L after having been treated with allopurinol at doses of at least 600 mg per day in addition to probenecid at doses up to 2 g per day or to a maximum tolerated dose; or
- Have intolerable adverse effects associated with allopurinol treatment requiring treatment withdrawal and have trialled probenecid at doses up to 2 g per day or to a maximum tolerated dose; or
- Have had treatment with allopurinol optimised, however, renal impairment means that probenecid cannot be added or is that it is likely to be ineffective

The recommended dose of febuxostat for patients with gout is:<sup>6</sup>


- 80 mg, once daily, increased to 120 mg, once daily, after two to four weeks if the serum urate is > 0.36 mmol/L\*

\* The maximum daily dose of febuxostat for patients with mild hepatic impairment is 80 mg

Febuxostat can be used in patients with renal dysfunction as this is not a significant route of elimination,<sup>3</sup> however, caution is advised in patients with an eGFR < 30 mL/min/1.73m<sup>2</sup> due to a lack of safety data.<sup>6</sup> A liver function test is recommended prior to initiating febuxostat to provide a baseline as abnormal liver function tests have been observed in approximately 5% of patients taking febuxostat; liver function tests are recommended periodically thereafter on the basis of clinical

judgement.<sup>11</sup> Febuxostat should be avoided in patients with moderate or severe hepatic impairment as dosing information is not available. Caution is advised when considering prescribing febuxostat to patients with ischaemic heart disease or congestive heart failure (see: "Febuxostat is associated with an increased risk of cardiovascular and all-cause mortality in patients with cardiovascular disease").<sup>6</sup>

Probenecid can be added to the treatment regimen if the patient is unable to achieve the target serum urate level with febuxostat alone.<sup>3</sup>

 Further information on febuxostat is available from: [www.bpac.org.nz/bpj/2014/july/febuxostat.aspx](http://www.bpac.org.nz/bpj/2014/july/febuxostat.aspx)

### The adverse effects of febuxostat

Adverse effects most often associated with febuxostat are diarrhoea, nausea, elevated liver enzymes, oedema, headache and rash.<sup>6</sup> Rarely, hepatotoxicity or severe hypersensitivity reactions can occur in patients taking febuxostat.<sup>6</sup> Hypersensitivity reactions most often occur in the first weeks of treatment, including Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria and anaphylaxis.<sup>6</sup>

There is an increased risk of flares in patients taking febuxostat, compared to allopurinol, therefore flare prophylaxis is particularly important in the first months of treatment.<sup>3</sup>

## Monitoring patients taking urate-lowering medicines

Patients with gout need to be monitored to:

- Ensure serum urate levels are reached and remain below saturation point
- Encourage ongoing treatment adherence

**Febuxostat is associated with an increased risk of cardiovascular and all-cause mortality in patients with cardiovascular disease**, compared to patients taking allopurinol. The Cardiovascular Safety of Febuxostat and Allopurinol in Patients with Gout and Cardiovascular Morbidities (CARES) trial was conducted in response to a U.S. Food and Drug Administration (FDA) requirement.<sup>12</sup> The CARES trial enrolled 6,190 patients with gout and a history of cardiovascular disease.<sup>13</sup> The primary composite end point was cardiovascular mortality or first occurrence of non-fatal myocardial infarction, non-fatal stroke, or revascularisation due to unstable angina.<sup>13</sup>

The authors reported that febuxostat was not associated with an increased rate of cardiovascular events, compared with allopurinol, however, a significant increase in all-cause mortality and cardiovascular mortality was reported.<sup>13</sup> The FDA are due to release a full report now that the final results from the manufacturer have been received.<sup>12</sup>

- Manage cardiovascular risk factors
- Treat any co-morbidities that may emerge


Regular exercise and weight loss, where appropriate, should underlie all strategies to prevent the development of diabetes and cardiovascular disease.

Patients with gout that is well-controlled with urate-lowering medicines should have at least annual assessments of:<sup>3</sup>

- Serum urate
- Renal function
- HbA<sub>1c</sub>
- Blood pressure

For patients with gout and hypertension, losartan or calcium channel blockers are the antihypertensive medicines of choice as they reportedly have mild uricosuric (urate-excreting) properties.<sup>1</sup> Patients who are taking diuretics for hypertension, for reasons other than heart failure, should be switched to an alternative antihypertensive, if possible.<sup>3</sup> Aspirin is known to decrease excretion of uric acid, however, patients who are taking low-dose aspirin for the secondary prevention of cardiovascular disease should continue to do so.<sup>15</sup>


Kidney stones are likely to have caused problems for one in seven patients with gout and patients taking uricosuric medicines, e.g. probenecid, are at increased risk.<sup>3</sup> Increasing water consumption will decrease the risk of uric acid stone formation for all patients with gout. Treatment with a xanthine oxidase inhibitor, e.g. allopurinol, and a reduction in dietary purines (see Part 1– Talking about gout) will also decrease the likelihood of uric acid stones forming.

 Further information on managing kidney stones and renal colic is available from: [www.bpac.org.nz/bpj/2014/april/colic.aspx](http://www.bpac.org.nz/bpj/2014/april/colic.aspx)

### When to consider referral to a rheumatologist

Patients should be referred to a rheumatologist if they have:

- A serum urate level  $\geq$  0.36 mmol/L, despite adherence to optimal urate-lowering treatment
- Persistent arthritis, despite a serum urate level that is consistently below 0.36 mmol/L
- Significant renal dysfunction and there are concerns about increasing the dose of urate-lowering treatment

 A podcast on the management of gout is available from: [www.goodfellowunit.org/podcast/gout-nicola-dalbeth](http://www.goodfellowunit.org/podcast/gout-nicola-dalbeth)

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