Reclassification of allopurinol to improve access and equity

This application seeks to make first-line preventative medication (allopurinol) more accessible to help overcome the low rate of long-term preventative management for gout[1]. Specially trained pharmacists would be able to supply allopurinol to a person previously prescribed allopurinol by a doctor, where that person meets specific criteria for supply. This would be as continuation supply with or without dose modification to allow escalation of dosing according to HealthPathway guidelines[2].

Part A
Administrative details

1. International Non-proprietary Name of the medicines.

   Allopurinol

2. Proprietary name(s).

   Allopurinol
   DP-Allopurinol is the only brand that is currently funded in New Zealand. It comes in 100 mg and 300 mg tablets

   Many other brands have been registered in New Zealand but have had their approval lapse or are not available, e.g. Z300 and Zyloprim 100 mg tablets from GlaxoSmithKline. Without funding, there is no point in marketing the medicines.

3. Name of the company / organisation / individual requesting a reclassification.

   Dr Natalie Gauld

4. Dose form(s) and strength(s) for which a change is sought.

   Tablets: 100 mg and 300 mg.

5. Proposed pack size, storage conditions and any other qualifications.

   Pharmacists would dispense the medicine for a suitable patient in up to three month's supply at a time. The product would be packed and labelled by the pharmacist for the specific patient, thus there would be no specific non-prescription pack size as such.

   Storage conditions: store at or below 25°C.

6. Indications for which change is sought.

   For the management of primary gout or secondary hyperuricaemia associated with chronic gout.

7. Present classification of the medicine.

Prescription medicine

8. Classification sought.

   Prescription medicine except when provided by a pharmacist who has completed gout training with the Pharmaceutical Society of New Zealand and is providing the medication to a person who has previously been prescribed allopurinol tablets to prevent gout, and where the supply meets the approved criteria.

9. Classification status in other countries (especially Australia, UK, USA, Canada).

   Prescription medicine.

   However, patient group directions in Scotland can allow urgent supply of gout medication to National Health Service (NHS) patients by pharmacists where the medication is currently prescribed by the patient's prescriber, and the patient's prescriber is unavailable to support continuity of patient care.

10. Extent of usage in New Zealand and elsewhere (eg, sales volumes) and dates of original consent to distribute.

    Exact sales volumes are not available, but the Health Quality and Safety Commission (HQSC) reports in figures from 2018 that 199,000 people were identified as having gout[1]. Urate lowering therapy (ULT, usually allopurinol) was dispensed to just over half of these patients (56-59% depending on ethnicity), with 35-44% of gout sufferers collecting regular prescriptions for these agents, equating to approximately 80,000 New Zealanders regularly taking these medicines.

    Zyloprim (allopurinol) was first registered in 1969 according to a Medsafe product application search.

11. Local data or special considerations relating to New Zealand (if applicable)

    See data in question 10 above. There is a strong need for gout to be better managed in New Zealand with a focus on equity of access. This requires more patients with gout to be diagnosed early in the condition, and more patients with gout to be regularly prescribed preventative treatment. Pacific peoples and Maaori particularly need to be able to access best practice care easily.

12. Labelling or draft labelling for the proposed new presentation(s).

    The labelling would be as per the usual dispensing process with patient name, date of supply, dose, and prescriber (the pharmacist involved). Patients will be provided with Stop Gout booklets (Appendix 1).

13. Proposed warning statements (if applicable).

    The labelling would be as for a prescription. The patient would receive the Stop Gout booklet (Appendix 1) which includes the following wording: *"Stop*

taking uric acid medicine immediately if you get a bad skin rash and tell your doctor, nurse or pharmacist." However, all patients will have taken these tablets before (with the pharmacist checking if there was any side effect and specifically checking for rash), so anyone with an allergic reaction to allopurinol should be excluded.

14. Other products containing the same active ingredient(s) and which would be affected by the proposed change.

    Nil

Part B
Evidence supporting the classification change proposal including benefit-risk analysis.

Gout is a debilitating condition of increasing incidence particularly affecting males[1]. It affects 13% of people aged 65 years and over, and 6% of people aged 45-64 years. Most importantly, gout has a disproportionate effect for Pacific peoples (incidence of 14%) and Maaori (incidence of 9%), with young Pacific and Maaori people much more likely to be affected than non-Maaori/non-Pacific. The prevalence in Pacific peoples and Maaori is growing at a greater rate than for non-Pacific, non-Maaori.

Table 1 Population identified as having gout, by age, ethnicity and gender, 2018[1]

Ethnicity	Age and gender							
	20–44 years		45–64 years		65+ years		All age groups	
	Female	Male	Female	Male	Female	Male	Female	Male
Māori	0.9	5.8	5.3	20.1	18.9	37.3	4.4	13.8
Pacific peoples	1.8	12.3	9.2	34.0	25.9	48.6	6.7	22.5
Non-Māori, non-Pacific	0.3	1.6	1.4	7.4	6.0	17.2	2.0	6.9
All ethnic groups	0.5	2.9	2.2	10.2	7.4	19.3	2.6	8.6

Gout is under-treated (Table 2), and this is inequitable[3]. Without appropriate preventative therapy in the right dosage to get a serum urate of <0.36 mmol/L, patients risk irreversible joint damage, outpatient visits and, in severe cases, hospitalisation[4]. It is controllable with long-term treatment, usually with allopurinol.

Table 2: Percent of people identified as having gout, who were dispensed a urate-lowering therapy in a year, and regularly in a year, by age and ethnicity, 2018[1]

Dispens-ing type	Age and ethnicity											
	20–44 years			45–64 years			65+ years			All age groups		
	Māori	Pacific	Non-Māori, non-Pacific	Māori	Pacific	Non-Māori, non-Pacific	Māori	Pacific	Non-Māori, non-Pacific	Māori	Pacific	Non-Māori, non-Pacific
Any dispensing	47	51	44	59	60	53	67	64	59	59	59	56
Regular dispensing	15	17	20	38	37	38	56	53	51	40	35	44

Please see the attached papers from BPAC on gout.

1. Indications and dose

   Indications for the reclassification
   The licensed indications for allopurinol are for the management of primary gout or secondary hyperuricaemia associated with chronic gout[5].

   Allopurinol is not a treatment for an acute attack of gout.

The Auckland Health Pathways[2] includes the following indications for ULT which provides more clarity for pharmacist-supply:

- Recurrent gout (≥ 2 attacks per year)
- Gouty tophi
- Chronic gouty arthritis

Other indications which reclassification would not cover

Allopurinol is also indicated for reducing urate/uric acid formation in conditions where urate/uric acid deposition may occur such as: uric acid nephropathy; recurrent uric acid stone formation; certain enzyme disorders or blood disorders which lead to overproduction of urate (e.g. Lesch-Nyhan syndrome; haemolytic anaemia); hyperuricaemia associated with malignancy and cytotoxic therapy which result in a high cell turnover rate[5].
DP-Allopurinol is indicated for the prevention and treatment of calcium oxalate/phosphate renal stones in the presence of high uric acid levels of the blood and/or urine[5].

Appropriateness of the indication for pharmacist-supply.

Diagnosis of gout is common, and repeat attacks require ULT to prevent them. Once a patient has been prescribed allopurinol to prevent gout, that therapy should be on-going, but many people are not taking allopurinol regularly (as seen in Table 2 above). A pharmacist should easily be able to identify from their previous dispensing history if a person has taken allopurinol before, and from discussion with the patient whether that was for prevention of gout. This would be supported by serum urate measurements in the blood test history. This would be similar to pharmacist-supply of topical calcipotriol for psoriasis which requires a previous medical diagnosis of psoriasis. It is also similar to oral contraception in which the patient has previously been prescribed the oral contraceptive agent. In this case, only pharmacists who have successfully completed the Pharmaceutical Society of New Zealand's course would be able to provide the medication without a prescription.

An important concern for gout is misdiagnosing an infected joint, however, allopurinol is not for acute gout, so this is not relevant to this reclassification. Regardless, pharmacists would receive information regarding gout and joint infection in their training.

Consumers will not need to diagnose themselves or work out appropriateness or dosage, the pharmacist would be doing this instead.

Treatment population

The treatment population is adults with history of gout and allopurinol medication. Incidence increases in Maaori, Pasifika, with older age and with male gender[1].

Dose

Allopurinol may be taken once daily after a meal. With daily doses over 300 mg and/or where gastrointestinal intolerance occurs, divided doses may be appropriate[5].

The Auckland Region HealthPathways[2] notes to start low and go slow, increasing by 50 to 100 mg increments every 4 weeks, aiming for a target serum urate <0.36 mmol/L. Full details are available on the HealthPathways site according to eGFR, but for a person with eGFR >130 mL/minute/1.73 m2, the starting dose would be 200 mg once daily, with an eGFR of 91-130 this would be 150 mg once daily, with an eGFR 61-90 the starting dose is 100 mg once daily, and the dose is lower for eGFR below this with a clear table on the HealthPathways site. If there is no response the dose is increased gradually. The allopurinol dose can be increased up to 900 mg per day, even if renal impairment is present. However, there will be clear criteria for patients pharmacists can provide allopurinol for without a prescription.

Usual doses taken
A dose escalation study in New Zealand of patients with gout found that people who reached the target serum urate levels averaged 390 mg/day with a range of 50 to 900 mg/day[6]. Those not reaching the target serum urate levels averaged 290 mg/day.

2. Presentation

Tablets 100 mg and 300 mg

Disposal considerations are no different to if the medicine is prescribed. Ideally the medication will be taken by the patient rather than needing disposal.

The dose form and dosage are practical and manageable with help from the pharmacist for any dosage adjustment.

3. Consumer benefits

Gout is a painful and debilitating joint disease[7]. Gout management is frequently suboptimal, resulting in reduced mobility, lost wages from work absences, reduced social participation and long-term damage to joints and kidneys. It disproportionately affects Maaori and Pacific peoples[3]. Preventative therapy, usually with allopurinol, can help if it is implemented, if the dose is correctly titrated over time and if there is good adherence. Achieving a serum urate level <0.36 mmol/L considerably reduces the risk of repeat acute episodes and long-term damage. Allopurinol is the first-line treatment for preventing gout[2].

Gout is an increasing problem that disproportionately affects Maaori and Pacific in prevalence, hospitalisation, and long-term outcomes[1, 3]. It causes reduced mobility, work absences, reduced social participation and long-term damage to joints and kidneys. Dose titration and education through the pharmacist can help as has been found in NDHB and CMDHB[8, 9].

Pharmacists being able to provide continuation supply and dose escalations for the patient without requiring a medical prescription is expected to improve adherence to therapy as the gout sufferer will be less likely to run out of medication. This will assist pharmacists to provide gout programme services to patients also.

4. Contraindications and precautions

The NZ Formulary[10] (NZF) reports *"allopurinol is not for treatment of acute gout or asymptomatic hyperuricaemia."*

NZF[10] further states: *"Initiation can precipitate gout flare—flare prophylaxis with an NSAID or colchicine should be used and continued for at least one month after hyperuricaemia has been corrected (usually for the first 3-6 months); consider testing for HLA-B*58:01 allele in individuals of Han Chinese or Thai origin (avoid unless no alternative—risk of severe and potentially life threatening cutaneous adverse reactions in presence of HLA-B*58:01 allele); ensure adequate fluid intake (2–3 litres/day)"*

Drug interactions are attached in the appendices. Note that capecitabine and didanosine should particularly be avoided with allopurinol. Pharmacists would receive training in this area.

Please also see the attachment from Safer Healthy Prescribing (Waitematā DHB) for further details (Appendix 4).

Prophylaxis against acute gout attacks is required as allopurinol is started and for 3-6 months after the target serum urate is achieved. This could be the topic of a future application. For now, this application simply seeks to allow continuation supply and dose escalation by pharmacists with additional training, and working under strict criteria. Pharmacists will need to keep the patient's usual GP informed of any pharmacist-supplied allopurinol, dose changes in allopurinol, and serum urate test results.

5. Undesirable effects

The NZF[10] lists the following adverse effects (including the box below):

"Gastro-intestinal disorders, rash (see below); rarely malaise, headache, vertigo, drowsiness, visual and taste disturbances, hypertension, alopecia, hepatotoxicity, paraesthesia, neuropathy, gynaecomastia, blood disorders (including leucopenia, thrombocytopenia, haemolytic anaemia, aplastic anaemia), hypersensitivity reactions."

Hypersensitivity reactions and Rash
Hypersensitivity reactions occur rarely and include exfoliation, fever, lymphadenopathy, arthralgia, eosinophilia, vasculitis, hepatitis, renal impairment, and very rarely seizures. If hypersensitivity occurs, allopurinol should be withdrawn immediately and permanently; consultation with a rheumatologist is suggested.

Rash may occur at any time and in severe cases can lead to Stevens-Johnson syndrome, toxic epidermal necrolysis and DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms—see notes). Patients should inform their doctor if a rash occurs and therapy should be withdrawn; if the rash is mild, re-introduce cautiously but discontinue promptly if the rash recurs.

The risk of experiencing hypersensitivity reactions may be increased by renal impairment, ACE inhibitors, and thiazide diuretics. See Prescriber

Update June 2011 and SafeRx bulletin: Allopurinol—Safe Prescribing for more information.

SMARS data is also attached as an appendix, as is the SafeRx information.

See also the data sheet attached and Best Practice Journal article[11] attached.

These adverse effects are well-known and the medication is first-line for gout because it is the most appropriate therapy for most patients with gout. Patients will not be initiated allopurinol by the pharmacist, but would already have been prescribed it, and therefore already been exposed to potential adverse effects. Pharmacists would receive special training that would include contraindications, precautions, adverse effects, drug interactions, and so on. They would have to work according to best practice guidelines. This is a collegial arrangement in which the person has been started by the doctor, and the pharmacist would be ensuring ongoing supply and appropriate titration of therapy while keeping the doctor informed of supplies.

To our knowledge there have not been any withdrawals of the medicine for safety reasons. Hypersensitivity to allopurinol has been identified and information about it made available.

There are no withdrawal effects when allopurinol is ceased.

6. Overdose

   See the attached datasheet for all details regarding overdose. There is no greater risk of overdose with pharmacist-supply than with the current situation of prescribed use only.

7. Medication errors and abuse/misuse potential

   Medication errors are no more likely with pharmacist-supply than with the current situation of prescribed use only.

   The primary concern is lack of use when it is indicated. Overuse is not at all likely with pharmacist-supply.

8. Communal harm and / or benefit

   Not applicable.

9. Integrated benefit-risk statement

   Aiding patient access to this medicine and the pharmacist to adjust the dose of allopurinol in accordance with best practice guidelines will enable patients to continue on the medication and have their dose correctly titrated in line with their Serum Urate levels[7, 11]. This is expected to lead to patient benefit in terms of fewer gout attacks, and therefore reduced time off work, less presenteeism and improved quality of life. This reclassification is intended to

help ensure pharmacists can provide allopurinol to patients enrolled in a gout programme.

10. Risk mitigating strategies

    Risk mitigating strategies will be agreed with a panel of experts and will include:

    - Pharmacists would have to first successfully complete training through the Pharmaceutical Society of New Zealand.
    - Strict criteria for supply will be in place to ensure patient safety.
    - Patients would be given written and verbal information
    - Only patients already taking allopurinol would be eligible for resupply or dose titration.
    - The patient's general practitioner will be informed of the supply and dosage.
    - eGFR and serum urate will be used to aid in dose adjustments

References

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