Basingstoke, Winchester & Southampton District Prescribing Committee

Shared Care Guideline for Azathioprine or Mercaptopurine (GP Summary)

It is essential that a transfer of care only takes place with agreement of the GP and when sufficient information has been received. If the GP does not agree to share care they will inform the Consultant responsible for the patient's care.

This Guideline is suitable for both Adults and Children

Specialist Contact Details	Patient ID Label
Name: _____	Surname: _____
Location: _____	Forename: _____
Date: _____	NHS Number: _____
Tel: _____	Date of Birth: _____

Indications	**Licensed:** Rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis and polymyositis, autoimmune chronic active hepatitis, pemphigus vulgaris, polyarteritis nodosa **Unlicensed:** Cutaneous vasculitis & vasculitides e.g. polyarteritis & giant cell arteritis, granulomatosis with polyangiitis (GPA), psoriasis & psoriatic arthritis, severe chronic eczema and other autoimmune skin conditions, pulmonary fibrosis & sarcoidosis. Steroid sparing agent in PMR/GCA and vasculitis. Use in inflammatory bowel diseases including ulcerative colitis and Crohn's disease is encouraged by NICE guidance. (Mercaptopurine, the active metabolite of azathioprine, is used for inflammatory bowel diseases when azathioprine cannot be tolerated. , or for younger children a more suitable preparation (suspension) **Off – label use:** Uveitis
Dose & Response	• Dose is variable, depends on the clinical indication and will be decided by the clinical team initiating treatment. Clinical response may not be evident before 6 weeks and may take up to 3 months. Lower doses are required in severe renal or hepatic impairment, or frail older people. **Azathioprine:** Typically 1mg/kg/day (Usual paed starting dose is 1.5 – 2mg/kg/day, Crohn's starting dose 2mg/kg/day) increasing at 4-6 weekly intervals to a maximum of 3mg/kg/day adjusted within these limits depending on clinical response and haematological tolerance. Doses are rounded to the nearest 25mg (may be started at 25mg daily increasing by 25mg daily at weekly intervals until the desired dose is reached to improve tolerance). Doses do not usually exceed 300mg/day **Mercaptopurine:** Typically 50mg daily increasing to 1-1.5mg/kg/day (usual Paed starting dose 1 – 1.5mg/kg/day). Doses do not usually exceed 100mg/day. (Max **BNFc** 75mg/day) • **Duration.** Indefinite - may be withdrawn after a prolonged period of disease remission in selected cases. • **Preparations available:** o Tablets containing 25mg and 50mg azathioprine (50mg mercaptopurine). o Azathioprine 50mg/5ml suspension is available as a cost-effective, drug-tariffed special. o Unlicensed 10mg capsules of azathioprine & mercaptopurine are available as specials, and are non-formulary o Azathioprine injections should not be prescribed or administered within primary care o Mercaptopurine 20mg/ml oral suspension (Xaluprine), off-label use. Non formulary
Secondary care responsibilities	**The specialist is responsible for checking TPMT level & confirming within normal levels before initiating treatment. Very low TPMT levels are an absolute contraindication to azathioprine.** • Prescribing initial doses until dose is stable - usually 2-3 months and adjusting doses where necessary in severe renal and hepatic impairment • Requesting and monitoring of blood results until dose stable – usually 2-3 months • **Ensure the patient understands their treatment and which warning signs to report. Advise patients to report symptoms of bone marrow suppression, such as inexplicable bruising, bleeding or severe sore throat/oral ulceration, immediately.** • Regular review of patient depending on individual need.
GP	• Prescribing maintenance dose of azathioprine according to the dose regimen suggested by

responsibilities	the specialist (dermatologist, gastroenterologist, rheumatologist) • Request blood test results once dose is stable (usually 2-3 months) and requested by hospital to take over shared care. • Review blood test results before prescribing **Recommended monitoring for new DMARDs** • **FBC, Cr (or eGFR), ALT, albumin every 2 weeks until stable dose for 8 weeks (Specialist responsibilities)** • **Then monthly FBC, Cr or eGFR, ALT, albumin for 3 months** • **Then FBC, Cr or eGFR, ALT, albumin at least every 12 weeks** • **For dose increases -FBC, Cr or eGFR, ALT, albumin every 2 weeks until stable dose for 6 weeks then back to previous schedule (Specialist responsibilities)** • Communicate with specialist regarding any problems/compliance issues. • Patients with Arthritis are recommended to have Pneumococcal vaccine every 10 years. Patients with arthritis and on immunosuppression to have Pneumococcal vaccine at start of treatment, a repeat dose 5 years later (due to a weaker response to vaccine), then every 10 years • Although the shingles (Zostavax) vaccine is a live attenuated vaccine, treatment with azathioprine (<3.0mg/kg/day) is not considered sufficiently immunosuppressive and is not a contraindication to administering the vaccine. • During Covid, and only for stable patients, the following applies https://www.sps.nhs.uk/articles/dmard-drug-monitoring-in-primary-care-during-covid-19/
Patient responsibilities	• Report to the specialist or GP if they do not have a clear understanding of their treatment • Communicate with the GP any side-effects or problems encountered which may have an impact on taking the medicines • Ensure blood monitoring is undertaken at the requested time intervals • Read the Patient Information leaflet which accompanies the medicine • Inform specialist team where bloods are taken to facilitate access where necessary • Be aware that safe handling of the tablets is important and that the tablets should not be crushed. Carers should use gloves if possible, although film coated tablets are deemed less hazardous.
Actions to be taken in response to monitoring	**Thresholds at which to discontinue treatment and contact specialist team for urgent review:** • **WCC<3.5 x10^9/L** • **Neutrophils<1.6 x10^9/L** • **Unexplained eosinophilia>0.5 x10^9/L** • **Platelets<140 x10^9/L** • **MCV>105** • **ALT>100 units/L** • **Unexplained fall in albumin** • **Creatinine>30% above baseline +/- eGFR<60**
Contra-indications	• **Hypersensitivity to azathioprine / mercaptopurine** • **Immunisations** - avoid live immunisations if immunosuppressed. Passive immunisation may be given with VZIg in non-immune patients exposed to chicken pox or shingles. Contact specialist for advice.
Cautions	• **Hepatitis B or C infection, or history of tuberculosis**. • **Hepatic impairment** - use doses at the lower end of normal range; monitor haematological response carefully. • **Renal insufficiency** - use doses at the lower end of normal range; monitor haematological response carefully. • **Pregnancy & Breastfeeding** – discuss relative risks with specialist prior to any consideration of stopping treatment. In particular, treatment of patients with lupus should be managed by lupus specialist and high risk pregnancy expert. As with all cytotoxic chemotherapy, adequate contraceptive precautions should be advised if either partner is receiving 6-mercaptopurine tablets, during treatment and for at least three months after receiving the last dose • **Older people** - reduce dose and monitor closely for toxicity throughout treatment.

	• **Skin Care**: There is an increased risk of skin cancer. Patients should be aware of the need to limit exposure to sunlight and use adequate sun protection measures. This risk is greater in patients who have a history of previous treatment with PUVA.
Important adverse effects & management	**A rapid fall or consistent downward trend in any value should prompt caution and extra vigilance** • **Hypersensitivity reactions at initiation** (fever, arthralgia, myalgia) – stop therapy immediately • **Rash or oral/pharyngeal ulceration** - withhold drug until discussed with specialist • **Abnormal bruising, severe sore throat** - request urgent FBC and withhold treatment until results are known and discussed with specialist • **Significant infection or patient is systemically unwell** - withhold treatment and discuss with specialist • **General signs of malaise** such as headaches, dizziness occur infrequently. Discuss with specialist if severe or persistent. • **Nausea.** Can occur initially but may be reduced by taking tablets after food. Abnormal liver function can occur early in treatment • **Acute abdominal symptoms of pancreatitis**. Stop treatment.
Important drug Interactions	• **ACE Inhibitors -** caution. Increased risk of anaemia and leucopenia. Consider alternative to ACEI. • **Allopurinol -** avoid. Enhances effects & risk of myelosuppression. Reduce azathioprine or mercaptopurine to 25% of the original dose if concomitant use cannot be completely avoided. • **Aminosalicylates (mesalazine, olsalazine, balsalazide, sulfasalazine)** – caution. Increased risk of haematological toxicity. • **Anticonvulsants (Phenytoin, carbamazepine, sodium valproate)** - caution. Possible reduced absorption of these anticonvulsants. • **Co-trimoxazole -** avoid. Increased risk of serious haematological toxicity • **Febuxostat** - avoid. Increased risk of toxicity**.** • **Trimethoprim -** avoid. Increased risk of serious haematological toxicity**.** • **Warfarin -** caution. Possible reduced anticoagulant effect. May need to reduce azathioprine/mercaptopurine dose or increase warfarin dose. • **Cytostatic/myelosuppressive agents: Concomitant use of azathioprine and cytostatic drugs, or other drugs which may have myelosuppressive effects (such as penicillamine), should be avoided.**

This guidance should be read in conjunction with the BNF and SmPC (www.medicines.org.uk)

Contact numbers for urgent GP advice

Southampton - Nurse specialist advice line 023 8120 5352 or bleep SpR 1801 (Mon-Fri 9-5). Out of hours – on-call consultant via hospital switchboard

Basingstoke - Administration team 01256 312768, advice line (answerphone) 01256 313117 or on-call consultant via switchboard

Winchester – Administration team 01964 824150, Advice line 01962 824256, on-call SpR bleep 3425 via switchboard.

Southampton Medicines Advice Service (Mon-Fri 9am – 6.30pm) 023 8120 6908/9 or medicinesadvice@uhs.nhs.uk and also for advice on pregnancy/breastfeeding.

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Uveitis added as an indication – January 2022