Northern Lincolnshire and Goole NHS
NHS Foundation Trust

NHS
Northern Lincolnshire
Area Prescribing Committee

Prescribing Framework for Azathioprine for Immunosuppression

Patients Name: …… NHS Number: ……

Patients Address: ……(Use addressograph sticker)

GP's Name: ……..

We agree to treat this patient within this Prescribing Framework.

Consultant's / Specialist's
Signature:……..Date:……..

GP's Signature:…… Date:…….

If the General Practitioner is unable to accept prescribing responsibility for the above patient the consultant should be informed within two weeks of receipt of this framework and consultant's / nurse specialist's letter. In such cases the General Practitioner are requested to update the consultant, by letter, of any relevant changes in the patient's medication / medical condition.

Contact Details:

NLaG Contact: Via the Pharmacy Office: 01724 290095

VirginCare Contact: 01482 638571

Rheumatology Specialist Nurses: 03033 304849

APPROVAL PROCESS

Approved by:	Northern Lincolnshire APC
Review Date:	May 2024

Azathioprine for patients within Rheumatology (NLaG) and Dermatology (VirginCare)

1. Background	DMARDs are fundamental to arresting the disease process in Rheumatoid Arthritis and other inflammatory arthritides. While early initiation of therapy is essential to arrest the disease process, sustained use is vital if disease suppression is to be maintained. Prolonged therapy requires long-term monitoring for toxicity and safety profile. Azathioprine is a DMARD that may be used for rheumatoid arthritis (NICE Clinical Guideline 100, https://www.nice.org.uk/guidance/ng100) and other rheumatic diseases e.g. S.L.E. and vasculitis. These guidelines aim to provide a framework for the prescribing of azathioprine by GPs and to set out the associated responsibilities of GPs and hospital specialists who enter into the shared care arrangements.
2. Indications **(Please state whether licensed or unlicensed)**	Immune mediated disorders including moderate to severe rheumatoid arthritis, systemic lupus erythematosus; severe refractory eczema; dermatomyositis and polymyositis; auto-immune hepatitis; polyarteritis nodosa; refractory warm auto-immune haemolytic anaemia; chronic refractory idiopathic thrombocytopenic purpura. Specific information will be provided by the specialist on the indication for Immunosuppression with azathioprine.
3. Locally agreed off-label use	None
4. Initiation and ongoing dose regime Note - •Transfer of monitoring and prescribing to Primary care is normally after the patient is on regular dose and with satisfactory investigation results for at least 4 weeks •The duration of treatment will be determined by the specialist based on clinical response and tolerability. •All dose or formulation adjustments will be the responsibility of the initiating specialist unless directions have been discussed and agreed with the primary care clinician •Termination of treatment will be the responsibility of the specialist.	Blood sample to screen for thiopurine methyl transferase (TPMT) deficiency will be taken by the specialist, prior to commencing treatment. Usual starting dose is 50mg daily for 1 month, then 100mg daily for second month. Usual maintenance dose is 1.5 to 2.5mg/kg daily, doses may vary according to condition being treated, and specific information will be provided where appropriate. NB: In patients with renal and/or hepatic insufficiency, dosages should be given at the lower end of the normal range. Doses may vary for individual patients and this will be documented in specialist letter. Advice will be given to the GP on duration of treatment and dose changes for each individual patient. Prednisolone may be used in combination with azathioprine as part of the immunosuppression regimen. If this is required specific information will be provided by the specialist.
5. Baseline investigations, initial monitoring and dose titration to be undertaken by specialist.	**Baseline:** • FBC • U&E (for renal function & LFTs) • TPMT assay • Consider Hepatitis B and C • Consider Pregnancy test

<table>
<tr><td></td><td colspan="3">

- Consider checking Varicella Zoster Virus status

On-going

- FBC once weekly for at least 4 weeks, reduce to fortnightly if stable
- U&E once weekly for at least 4 weeks, reduce to fortnightly if stable
- LFT once weekly for at least 4 weeks, reduce to fortnightly if stable

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<tr><td rowspan="2">6. Ongoing monitoring requirements to be undertaken by primary care.</td><td colspan="2">Monitoring</td><td>Frequency</td></tr>
<tr><td colspan="2">

- FBC
- LFT
- U&E

</td><td>Once stable reduced to 3 monthly on advice of specialist.</td></tr>
<tr><td>7. Responsibilities of clinicians involved</td><td colspan="3">
<table>
<tr><th>Stage of treatment</th><th>Specialist</th><th>GP</th></tr>
<tr><td>Initiation</td><td>

- Assess the patient following referral by GP.
- Recommend appropriate treatment to GP.
- Carry out full baseline full blood count, differential WCC, platelets, U&E, LFT, TPMT assay
- Check FBC & LFT weekly for at least 4 weeks.
- Prescribe until patient is on a stable dose and monitoring results satisfactory (at least 4 weeks)
- Give patient a DMARD alert card which records the name of the medicines started and dose

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<tr><td>Maintenance</td><td>

- Assess clinical response to treatment.
- Provide adequate advice and support for the GP.
- Provide information to the GP on frequency of monitoring if doses are changed.
- Update DMARD alert card where relevant

</td><td>Prescribe on FP10
Monitor for adverse effects, refer to consultant where necessary

Blood tests for monitoring as listed in section 6

Patients should be asked about the presence of rash or oral ulceration at each visit</td></tr>
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</td></tr>
<tr><td rowspan="4">8. Pharmaceutical aspects</td><td colspan="2">Route of administration :</td><td>Oral</td></tr>
<tr><td colspan="2">Formulation :</td><td>25mg or 50mg Tablet</td></tr>
<tr><td colspan="2">Administration details :</td><td>Tablets to be taken with or after food (not milk or dairy products)</td></tr>
<tr><td colspan="2">Other important information:</td><td></td></tr>
<tr><td>9. Contraindications
Please note this does not replace the Summary of Product Characteristics (SPC) and should be read in conjunction with it.</td><td colspan="3">

- Azathioprine is contraindicated in patients with severe hepatic impairment; severely impaired bone marrow function; severe infections; pancreatitis Hypersensitivity to azathioprine
- Hypersensitivity to 6 – mercaptopurine
- Use with caution in mild to moderate hepatic and / or renal impairment and in the elderly.
- Avoid in porphyria

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<tr><td>10. Significant medicine interactions
For a comprehensive list consult the BNF or Summary of Product Characteristics (SPC)</td><td colspan="3">

- Allopurinol - dose reduction required - discuss with specialist
- Febuxostat - avoid concomitant use
- Trimethoprim, co-trimoxazole - increased risk of toxicity – avoid
- Warfarin - may reduce anticoagulant effect
- Increased risk of side effects with ACE inhibitors, aminosalicylate derivatives, cimetidine, indometacin and other drugs with myelosuppressant properties – use with caution and monitor closely
- Patients receiving azathioprine should be advised against

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</table>

	immunization with live vaccines during treatment and for 6 months after stopping treatment. (Influenza vaccines may be given in this group of patients). Zoster vaccine may be considered when the dosage is low.
11. Adverse Effects **Patients with TPMT deficiency may be more susceptible to delayed haematotoxicity including bone marrow toxicity.**	Hypersensitivity reactions: general malaise, dizziness, nausea, vomiting, diarrhoea, fever, rigors, exanthema, rash, myalgia, arthralgia, renal dysfunction and hypotension
	Haematological reactions: Dose dependent, general reversible bone marrow suppression, usually seen as leucopenia, anaemia, thrombocytopenia, increases in MCV and haemoglobin content of red blood cells, megaloblastic anaemia, euthyroid hypoplasia
	Gastrointestinal: Nausea (often relieved by administering after food), diarrhoea, pancreatitis
	Hepatic: Cholestasis and deterioration in liver function
	Infections: increased susceptibility to viral, fungal and bacterial infections
	Neoplasms: Rare - include non-Hodgkin's lymphomas, skin cancers (melanoma and non-melanoma), sarcomas (Kaposi's and non-Kaposi's) and uterine cervical cancer in situ, acute myloid leukaemia and myelodysplasia
	Other: Reversible pneumonitis, alopecia

Monitoring parameter	Recommended response
WBC < 4.0 x 10 9/1	withhold **until discussed** with specialist team
Neutrophils <2.0 x 10 9/l	withhold **until discussed** with specialist team
Platelets <150 x 10 9/l	withhold **until discussed** with specialist team
>2 fold rise in AST, ALT (from upper limit reference range)	withhold **until discussed** with specialist team
MCV> 105 fl	Check **serum folate** and B12 & TSH. Withhold until results are available and **discuss** with specialist team
Rash or oral ulceration	withhold **until discussed** with specialist team
Abnormal bruising or severe sore throat or rash	withhold **until FBC results** available & discuss with the specialist team

12. Advice to patients and carers The specialist will counsel the patient with regard to the benefits and risks of treatment and will provide the patient with any relevant information and advice, including patient information leaflets on individual medicines.	Patients should be informed about benefits and risks of treatment and need for monitoring. Patients should be told to go to their GP immediately if they experience any fever, rash, bruising, bleeding, sore throat, oral ulceration, jaundice or infection. Azathioprine should be taken with or after food (not dairy or milk products – dose should be taken either 1 hour before or 2 hours after milk or dairy products), and the dose can be divided if preferred. Provide advice on sunscreen and protective clothing Patients receiving azathioprine should be advised against immunization with live vaccines. (Influenza vaccines may be given in this group of patients)
13. Preconception care (men and women), Pregnancy and breast feeding It is the responsibility of the specialist to provide advice on the need for contraception to male and female patients on initiation and at each review but the ongoing responsibility for providing this	Treatment with azathioprine should not generally be initiated during pregnancy, but it may be reasonable to continue during pregnancy. All patients wanting to become pregnant who are taking either azathioprine or mercaptopurine should discuss this with their specialist. Azathioprine has been reported to interfere with the effectiveness of intrauterine contraceptive devices. Therefore it is recommended to use

advice rests with both the GP and the specialist.	other or additional contraceptive measures. Breast feeding – present in milk in low concentration; no evidence of harm in small studies. BNF recommends use if potential benefit outweighs risk – this should be discussed with the patient. Further information on use in pregnancy and breastfeeding can be found at https://bnf.nice.org.uk/ or www.medicines.org.uk
14. Specialist contact information	Contact Dermatology consultant (VirginCare) via 01482 638571 Rheumatology Specialist Nurses: 03033 304849
15. Additional information	Surveillance for skin cancer - monitoring of skin for any new lesions and/or changes Details of contraindications, cautions, drug interactions and adverse effects listed above are not exhaustive. For further information always check with BNF www.bnf.nice.org.uk or SPC (www.medicines.org.uk)
16. References	https://bnf.nice.org.uk/drug/azathioprine.html#interactions
17. To be read in conjunction with the following documents	https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf