NORFOLK AND WAVENEY STP THERAPEUTICS ADVISORY GROUP (TAG)

SHARED CARE AGREEMENT

Shared care guidelines for use of Azathioprine in autoimmune diseases
Monitoring level – Amber 2 – perform more intense level of monitoring, eg 3-monthly review

Generic and Proprietary/Brand Name	
Azathioprine / Imuran®	
Indications for shared care	
Autoimmune diseases including connective tissue diseases e.g. systemic lupus erythematosus and vasculitis - dermatomyositis and polymyositis, myasthenia gravis, autoimmune hepatitis (including overlap syndromes with primary biliary cirrhosis and primary sclerosing cholangitis), autoimmune cytopenias (immune thrombocytopenic purpura and autoimmune haemolytic anaemia), Pemphigus vulgaris (Licensed indication), Autoimmune bullous disorders, Atopic eczema, Pyoderma Gangrenosum, Chronic Actinic dermatitis, atopic dermatitis, and following organ transplantation.	
Specialist Prescribing and Monitoring Responsibilities – summary. Full details in main body of document	**GP / Community Team - Primary Care Prescribing and Monitoring Responsibilities – summary. Full details in main body of document**
• To initiate treatment and supply patient with information. • Check FBC, eGFR, ALT and albumin every 2 weeks, until the patient has been on a stable dose for 6 weeks. • Periodically review the patient. • See more detailed information below	• To prescribe ongoing treatment with azathioprine from 6 weeks, after a stable dose has been reached • Report any side effects, deterioration in renal function and any other issues to the hospital specialist. • There is no indication to stop azathioprine at the time of surgery • Azathioprine should be stopped in the event of a severe infection e.g. requiring hospitalisation. • The decision to restart azathioprine after a severe infection where the patient has had a break from therapy e.g. of more than one month, should be undertaken by the hospital specialist team. • Once the patient has been on a stable dose for 6 weeks, check FBC, eGFR, ALT and albumin every month for 3 months. Then where there is a low risk of toxicity, monitoring may be then reduced to 3-monthly as a minimum. • Risk factors for toxicity include: a history of adverse drug events; medical comorbidities including renal and liver impairment (e.g. NAFLD) and malignancy; patients at the extremes of weight (BMI <18 or >30 kg/m2); and old age (>80 years). • Blood tests are also needed every 2 weeks for 6 weeks after each dose increase, should further dose escalation be required. • See further details below
Patient Information	
Contact GP or the relevant clinical team in the event of side effects. The contact number will be given at the time of patient education.	

GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- GPs are **invited** to participate. If GPs are not confident to undertake these roles, they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist.
- **If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable if they are unwilling to do so.**
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP and when the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring.
- **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

Background to Treatment

Azathioprine is used as an immunosuppressant antimetabolite either alone or, more commonly, in combination with other agents (usually oral corticosteroids), which influence the immune response.

Licensed use and agreed local off-label use

Azathioprine tablets are used as an immunosuppressant anti-metabolite either alone or, more commonly, in combination with other agents (usually corticosteroids) and procedures which influence the immune response.
Azathioprine, in combination with corticosteroids and/or other immunosuppressive agents and procedures, is indicated to enhance the survival of organ transplants, such as renal transplants, cardiac transplants, and hepatic transplants; and to reduce the corticosteroid requirements of renal transplant recipients.

Azathioprine, either alone or more usually in combination with corticosteroids and/or other drugs and procedures, has been used with clinical benefit (which may include reduction of dosage or discontinuation of corticosteroids) in a proportion of patients suffering from the following:

- severe rheumatoid arthritis, systemic lupus erythematosus, dermatomyositis and polymyositis.
- auto-immune chronic active hepatitis; polyarteritis nodosa.
- pemphigus vulgaris; autoimmune bullous disorders, atopic eczema, pyoderma gangrenosum, chronic actinic dermatitis, atopic dermatitis.
- auto-immune haemolytic anaemia; chronic refractory idiopathic thrombocytopenic purpura.
- myasthenia gravis.

Criteria for Patient Selection

The main role for azathioprine is steroid sparing. It is considered for patients in whom steroids cannot be reduced or are contraindicated and for maintaining remission in vasculitis.

Form and strength of preparation

Tablets 25mg & 50mg

Side Effects and Management

Link to BNF

Link to SPC

Drug Interactions

Link to BNF

Link to SPC

The following have potentially serious interaction with azathioprine and caution must be used when prescribing concurrently:

- Rifampicin, sulfamethoxazole (as co-trimoxazole), trimethoprim, warfarin.

- Avoid concomitant with allopurinol (unless supervised by a specialist), and clozapine.
- Phenytoin, sodium valproate, carbamazepine (azathioprine reduces the absorption of these drugs).
- Angiotensin-converting enzyme (ACE) inhibitors.
- Aminosalicylates e.g. mesalazine or sulfasalazine.

Cautions and Contraindications

Link to BNF

Link to SPC

Contra-indications:

- Hypersensitivity to azathioprine/mercaptopurine.
- Thiopurine methyltransferase deficiency (see below).

Cautions:

- Pregnancy: Azathioprine should not be given to patients who are pregnant or likely to become pregnant without careful assessment of risk versus benefit.
- Hepatic impairment: Reduce dose if hepatic or haematological toxicity occurs.
- Renal insufficiency: Reduce dose for those patients with moderate to severe renal impairment:
    - In patients with an eGFR of 15-29 ml/min/1.73m2 , 75-100% adjustment of standard dose is recommended
    - In patients with an eGFR of <15 ml/min/1.73m2, 50-100% adjustment of standard dose is recommended
- Sunscreens and protective clothing should be encouraged.
- Cardiovascular disease and prior malignancy are not considered to be contraindications to DMARD therapy.

Vaccines and Immunisations:

- In general patients should avoid “live” vaccines such as oral polio, MMR, BCG, and yellow fever. See Immunisation Against Infectious Disease (Green Book).
- Influenza and pneumococcal vaccination are recommended.

Shingles Vaccine:

The Green Book states that “Long term stable low dose corticosteroid therapy (defined as<20mg prednisolone per day for more than 14 days) either alone or in combination with low dose non-biological oral immune modulating drugs (e.g. azathioprine less than or equal to 3.0mg/kg/ day) are not considered sufficiently immunosuppressive, and these patients can receive the vaccine”.
Avoid contact with people who have active chickenpox or shingles.

Initiation of therapy and ongoing dose regimen

By the specialist team. Prescribing will be provided at the hospital until 6 weeks after a stable dose has been achieved.

Initial dose
Test dose of 50mg once daily for a week, increasing to 2-3mg per kg each day, orally.

Maintenance dose
2.5-3mg/kg/day orally. Hepatology may use lower doses of 75mg daily.
(When used for autoimmune cytopenias the lowest dose at which cytopenias are controlled)

Administration Information

Due to the relatively slow onset of action, benefits may not be observed for 3 months.

Duration of therapy / How the treatment will be reviewed and if appropriate, stopped

Ongoing

Baseline assessment and ongoing monitoring – by Specialist

Thiopurine methyl transferase (TPMT) level to be assessed by the initiating specialist.
Since the dose to be prescribed according to weight, advice to be given to the patient about the need to report significant fluctuation in their weight.

Check FBC, Liver Function Tests (ALT) and albumin, and creatinine and eGFR.

Lung disease:
Routine CXR are no longer undertaken but clinical assessment of coexisting pulmonary disease may result in pulmonary function tests to assess lung reserve and CT assessment being undertaken. Pre-existing lung disease is not a contraindication to DMARD use but prescription is undertaken with caution.

Liver disease:
In patients with deranged liver biochemistry, hepatotoxic DMARDs should be used with caution, with careful attention to trends in test results. In patients with impaired liver synthetic function (e.g. cirrhosis), DMARD therapy should be used with extreme caution. Patients with chronic viral hepatitis infection should be considered for anti-viral treatment prior to DMARD initiation and a treatment plan should be discussed with a consultant hepatologists.

Occult viral infections:
Screening for occult viral infections such as HIV and hepatitis B and C should be offered, and Varicella status recorded.

Specialist monitoring:

- Check FBC, eGFR, ALT and albumin every 2 weeks, until the patient has been on a stable dose for 6 weeks.
- Periodically review the patient.

GP / Community Team or other Primary Care monitoring responsibilities

Once the patient has been on a stable dose for 6 weeks, check FBC, eGFR, ALT and albumin every month for 3 months. Then where there is a low risk of toxicity, monitoring may be then reduced to 3-monthly as a minimum.

Risk factors for toxicity include: a history of adverse drug events; medical comorbidities including renal and liver impairment (e.g. NAFLD) and malignancy; patients at the extremes of weight (BMI <18 or >30 kg/m2); and old age (>80 years).

Blood tests are also needed every 2 weeks for 6 weeks after each dose increase, should further dose escalation be required.

Some patients who have abnormal indices due to disease e.g. lupus, portal hypertension, may have abnormal baseline tests and thresholds for intervention will be set by the individual clinician for these individual situations.

NB Look for trends in the monitoring e.g. rapidly falling WCC

If there are abnormalities on these tests, or if the patient reports one of the adverse events below, these are recommendations for considering the withdrawal of azathioprine therapy:

Results & Actions to be taken:

Test / Symptom	Result	Action
WBC	<3.5 x 10^9 per litre	Withhold drug & discuss with specialist
Neutrophils	<1.6 x 10^9 per litre	Withhold drug & discuss with specialist
Platelets	<140 x 10^9 per litre (if prescribed for ITP Haematology will give individual advice about monitoring)	Withhold drug & discuss with specialist
AST, ALT or Alk. Phos.	> 2-fold rise or twice upper limit of normal	Withhold drug & discuss with specialist
Rash or oral ulceration		Withhold drug & discuss with specialist
MCV	>105fL	Investigate and if B12 or folate low, start appropriate supplementation
Abnormal bruising, bleeding or sore throat, infection, fever, chills		Urgent FBC Withhold until FBC result available
Upper abdominal or back pain		Urgent amylase Withhold until amylase level available
Unexplained falling albumin	<30g/l	Withhold drug & discuss with specialist
Creatinine increase / eGFR reduction	>30% over 12 months and / or eGFR <60ml/min/1.73m^2	Discuss with specialist
Unexplained eosinophilia	>0.5x10^9/L	Withhold drug & discuss with specialist

Consultant / Specialist prescribing responsibilities

- To initiate treatment and supply patient with information.

GP prescribing responsibilities

- To prescribe ongoing treatment with azathioprine from 6 weeks, after a stable dose has been reached, and monitor as above.
- Report any side effects, deterioration in renal function and any other issues to the hospital specialist.
- There is no indication to stop azathioprine at the time of surgery
- Azathioprine should be stopped in the event of a severe infection e.g. requiring hospitalisation.
- The decision to restart azathioprine after a severe infection where the patient has had a break from therapy e.g. of more than one month, should be undertaken by the hospital specialist team.

Pregnancy, Paternal Exposure and Breastfeeding

All patients should be informed of the risks and benefits of taking this medicine during pregnancy and breastfeeding. The specialist team should be contacted if a patient becomes pregnant or is planning to become pregnant or breastfeed.
the following:

Pregnancy:
The BSR and BHPR guideline on prescribing DMARDs in pregnancy and breastfeeding advises that azathioprine is compatible throughout pregnancy at doses ≤2mg/kg/day.
Current available data do not suggest that mercaptopurine exposure during pregnancy increases the risk of miscarriage, congenital malformation, intrauterine death, fetal growth restriction, or preterm delivery but the data are limited for some outcomes. A careful assessment of risk versus benefit should be made before mercaptopurine is prescribed to patients who are pregnant.

The British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease advises that both maintenance and flares can be treated as normal with thiopurines (azathioprine and mercaptopurine) during pregnancy.

Information for healthcare professionals:
https://www.medicinesinpregnancy.org/bumps/monographs/USE-OF-AZATHIOPRINE-OR-MERCAPTOPURINE-IN-PREGNANCY/
Information for patients and carers: https://www.medicinesinpregnancy.org/Medicine--pregnancy/Azathioprinemercaptopurine/

Breastfeeding:
Azathioprine is compatible with breastfeeding, although the active metabolite mercaptopurine is present in breast milk. A risk versus benefit assessment is advised. If used during breastfeeding, monitor for signs of infection or immunosuppression. If high doses of azathioprine are used, monitor infant blood counts. If mercaptopurine is used, monitor infant's blood count and liver function.

Information for healthcare professionals:
https://www.sps.nhs.uk/medicines/azathioprine/
https://www.sps.nhs.uk/medicines/mercaptopurine/

Paternal exposure:
Azathioprine and mercaptopurine are compatible with paternal exposure. There is currently no evidence of adverse fetal effects relating to paternal use.

Information for healthcare professionals:
https://www.medicinesinpregnancy.org/bumps/monographs/PATERNAL-USE-OF-AZATHIOPRINE-OR-MERCAPTOURINE/

Indications for referral back to Specialist

- See above under GP monitoring

Contact details

JPUH:	**Via 01493 452452**
Gastroenterology:	Dr Anups de Silva Dr Williams Dr Brett Dr Badreldin Dr Banim Dr Saleem **IBD Specialist Nurse:** Rowan Shaw
Rheumatology	Dr Damu Makkuni. Dr Joegi Thomas, Dr Tarnya Marshall (ext 2216)

Neurology	Dr Warren Woodward, Dr David Dick
QEH	**Via 01553 613613**
Gastroenterology:	Dr Andrew Douds (ext 3989), Dr Shailesh Karanth (ext 3708), Dr Alan Wiles (ext 3004) **IBD Specialist Nurse:** Fran Bredin (ext 4642).
Rheumatology	Dr John Pradeep Dr Imran Riaz
NNUH	**Via 01603 286286**
Gastroenterology	Dr Mark Tremelling (sec ext 4612) Dr Simon Rushbrook (ext 4359) Dr Richard Tighe (sec ext 4230) Dr Martin Phillips (ext 4117) Dr Ian Beales (sec ext 4366) Dr Arun Shankar (ext 4345) Dr Alison Prior (sec ext 4358) Dr Syed Alam (ext 4363) **IBD Specialist Nurses:** Nickie Fisher & Natasha Thomson (Bleep 0493).
Rheumatology	Prof Alex MacGregor (ext 4677) Dr Chunlanie Desilva (ext 4623) Dr Tarnya Marshall (ext 4677) Dr Karl Gaffney (ext 5670) Dr Peter Merry (ext 3003) Dr Louise Hamilton (ext 4678) Dr Chetan Mukhtyar (ext 3118) **Rheumatology help line (ext. 3801)**
Neurology	Dr Jeff Cochius (ext 3302) Dr Linda Damian (3724) Dr David Dick (ext 3523) Dr Martin Lee (ext 3914)
Haematology	On call consultant (01603) 286286 ext 6744
Dermatology	Dr Syed Shah (ext 4254)

Further information and supporting documents

- BSR and BHPR guidelines for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs (February 2017) - **Link**

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1.	May 2016	Dr Tarnya Marshall, Mrs Heather Hasthorpe, Dr Jeff Cochius, Dr Simon Rushbrook, Dr Hamish Lyall, Dr Syed Shah – Norfolk & Norwich University Hospital NHS Foundation Trust /Fiona Marshall, TAG Lead Pharmacist, NEL CSU Anglia	Superseded	Supported by the TAG and N&W D&TCG – May 2016
2.	May to August 2017		Current	Reviewed and updated following publication of revised British Society for Rheumatology (BSR) and the British Health Professionals in Rheumatology (BHPR) guidance for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs Feb 2017 - Link Circulated by the authors across all stakeholder specialisms and to the JPUH and the QEH for consultation. Changes made to monitoring requirements and responsibilities, side-effects, available products, advice to GPs regarding thresholds and responsibilities regarding referral back to specialists. Advice regarding shingles vaccination updated in line with the Green Book. Revised version supported by the TAG – July 2017. Approved by the D&TCG August 2017.
3.0	Aug 2021	Jen Carroll, TAG Lead Technician	FINAL	Discussed at August 2021 TAG meeting. Review dates extended for a year from meeting due to covid pressures
4.0	Feb 2024	Jen Carroll, TAG Lead Technician	FINAL	Content not updated. Existing SCA transferred to new template Pregnancy section added as per RMOC national guidance For TAG approval
