DMARDs in Adult Rheumatology –Information for GPs

AZATHIOPRINE

Clinicians should also refer to the overarching DMARD shared care guideline document for details of the individual responsibilities for each group e.g. e.g. GP / Specialist Rheumatology team under this shared care agreement.

Information for GPs

Indication	• Azathioprine is recommended by NICE and National Societies for the treatment of numerous rheumatological conditions including Rheumatoid arthritis, connective tissue disorders and vasculitis. • Clinicians should refer to the Summary of product characteristics (SPC) for specific licensing information. • Use outside of the licensed indications is regarded as "off label" use.
Drug dose	• Azathioprine dosing is based on body weight with usual maintenance doses based between 1- 3mg/kg / day. • Typically, the Specialist Rheumatology team will initiate azathioprine therapy at 25mg once a day and escalate by 25mg every week until a maintenance dose is achieved, usually up to 100mg – 200mg daily. This dose escalation phase will be done by the Specialist Rheumatology Team. • Typical maintenance dose is 100-200mg daily (in divided doses). • Maximum daily dose is 250mg **Variation to Azathioprine dosing:** • In patients with renal and/or hepatic insufficiency, consideration should be given to reducing the dosage**.** Some patients may need a total daily dose of less than 100mg.
Contra-indications / Cautions/ Dose modifications in Special Populations	• **Clinicians should refer to the Summary of Product Characteristics (SPC's) and current electronic BNF for full details** www.medicines.org.uk/emc www.bnf.org/products/bnf-online

Side effects	• Clinicians should refer to the Summary of Product Characteristics (SPC's) and current electronic BNF for full details www.medicines.org.uk/emc www.bnf.org/products/bnf-online • **Blood dyscrasias** (e.g. leucopenia and neutropenia) can occur hence the importance of regular blood tests • As azathioprine is an immunosuppressant, clinicians should note to inform patients to contact their doctor immediately if they have any side effects, in particular – breathlessness, dry cough, whites of eyes becoming yellow, severe itching of skin, rash, dark urine, infections (including fever, chills or severe sore throats), new unexplained bleeding or bruising, mouth ulcers, vomiting and diarrhoea (particularly at the start of treatment, or if it is severe, at any stage in treatment). Examples of Some common side effects include: ○ nausea ○ vomiting ○ diarrhoea ○ loss of appetite (which may be alleviated by taking with food or last thing at night) ○ hair loss ○ skin rashes. • Minor side-effects can sometimes be helped by reducing the dose • **Clinicians should also refer to table 1 for details of when to contact the Specialist rheumatology team with regards blood test results and development of certain side effects etc.**
Drug Interactions	• Azathioprine can interact with a variety of drugs, some of which can be **significant.** Examples include: • **allopurinol*,** • **co-trimoxazole and trimethoprim**** • warfarin • ACE inhibitors • ribavarin • febuxostat • **This list is not exhaustive. C**linicians should refer to the Summary of Product Characteristics (SPC) and the electronic BNF for a **full list** of potential drug interactions before starting any new medication or when stopping any existing medication. www.medicines.org.uk/emc www.bnf.org/products/bnf-online

	***Allopurinol**: Due to severity of interaction, GPs should contact the Specialist for advice before starting a patient on allopurinol, (oxipurinol or thiopurinol) (NB: oxipurinol and thiopurinol are not licensed in the UK but could possibly be obtained on a named patient basis) ****Co-trimoxazole / trimethoprim:** Due to the increase risk of haemotoxicity, GPs should contact the Specialist for advice before starting a patient on either co-trimoxazole or trimethoprim.
Pre-treatment Blood Test Monitoring and Screening requirements *(To be done by Specialist Rheumatology team)*	• Assess baseline Thiopurine methyltransferase (TPMT) status before considering starting therapy. • FBC, U+Es, LFT
Blood Test Monitoring requirements *(Typically to be monitored by the GP from week 4 onwards)* **(Ref: Based on British Society of Rheumatology Guidelines , 2017 and current clinical practise)**	• FBC, U+E, LFT **fortnightly until dose and monitoring stable for 6 weeks**, then **monthly for 3 months** then **every 12 weeks* thereafter.** *More frequent monitoring is appropriate for patients at a higher risk of toxicity. • (**NB: After any dose increase,** blood test monitoring frequency should be carried out every fortnight until on a new stable dose for 6 weeks and then the frequency can revert back to the previous schedule). • CRP / ESR should be monitored every 3-6 months as this can help assess disease activity. • Ensure a prompt two way communication of blood test results between GP and Specialist team is available. (Paper copies should be sent between parties if electronic access via ICE is not available.)
Time to response	• Approx. 6-8 weeks • Specialist Rheumatology team should consider withdrawal if no improvement occurs within 3 months.
Infections	• Azathioprine is an immunosuppressant and increases the patient's susceptibility to infections, including opportunistic infections. • Initiate prompt anti-infective treatment when indicated on the basis that the patient may be immunosuppressed to some degree. • During a serious infection*, azathioprine should be temporarily discontinued until the patient has recovered from the infection. (* Serious infection: warrants admission to hospital or requires parenteral anti-microbial therapy.) • <u>If exposed to measles and / or chickenpox</u> : Check immunity to measles and varicella-zoster; if non-immune and exposed to measles or chickenpox contact the Specialist Rheumatology

	team ASAP for consideration of appropriate immunoglobulin therapy. • If patient develops shingles or chickenpox, stop the drug and treat with aciclovir.
Vaccinations	• The immune response to vaccination may be impaired. • Pneumovax and annual flu vaccination are recommended. • In general **live vaccines should be avoided**. A live vaccine may be advisable in certain circumstances e.g. rubella (in women of child bearing age) and varicella vaccine. GPs should contact the Specialist Rheumatology team for advice in such patients. • Caution is required to ensure that patients are not receiving additional immunosuppressants or biologic drugs, as these may not be documented on patient medication lists. If in any doubt please contact the Rheumatology team for further advice.
Alcohol	• As both alcohol and azathioprine can affect the liver, patients should be advised to only drink alcohol in small amounts and stay within government guidelines, which state that adults should not drink more than 14 units per week and should have alcohol free days without 'saving units up' to drink in one go.
Elective surgery	• **Contact the Specialist Rheumatology team for advice:-** Generally, azathioprine should not routinely be stopped in the peri- operative period, although individualised decisions should be made for high-risk procedures (e.g. 'contaminated', or duration over 60 minutes), in which case it can be stopped 2 weeks prior to surgery and then restarted once wound healing is satisfactory. • Caution for early detection of infections.
Contraceptive advice	• The Specialist Rheumatology team should discuss family planning before initiation of treatment. • GPs should refer any female or male patient who is wishing to start a family to the Specialist Rheumatology team.
Pregnancy and breast feeding	• GP should refer patients who become pregnant to the Specialist Rheumatology team. • Current British Society of Rheumatology Guidelines (Ref: Rheumatology (2016) 55 (9): 1693-1697.) states :- ○ Azathioprine is compatible throughout pregnancy at ⩽2 mg/kg/day ○ Azathioprine is compatible with breastfeeding. ○ Azathioprine is compatible with paternal exposure • It's important that the mother's health is maintained during pregnancy and disease flares are avoided by not stopping azathioprine.
Photosensitivity	• Encourage use of sunscreens / protective covering to reduce sunlight exposure.
Malignancies	• No good data to suggest any strong association with malignancies.

Drug Formulations	**Oral** • Available as 25mg and 50mg film-coated tablets. • Tablets contain lactose
Practical Points for GPs to note:	• Advise patients to attend for a blood test approx. one week before their next prescription is due to ensure that the results can be reviewed before the next prescription is requested for issue. • Check the results of recent blood test **before** issuing a prescription. (Refer to table 1 for actions to take in the event of blood test abnormalities and side effects). • Increase blood test monitoring frequency after a dose increase as detailed above. • Prescribers should note that whilst absolute blood test values are useful indicators, trends are equally important, and any rapid fall or consistent downward trend in any parameter warrants extra vigilance. • Advise patients to contact their doctor immediately if they experience any side effects, in particular – breathlessness, dry cough, whites of eyes becoming yellow, severe itching of skin, rash, dark urine, infections (including fever, chills or severe sore throats), new unexplained bleeding or bruising, mouth ulcers, vomiting and diarrhoea (particularly at the start of treatment, or if it is severe, at any stage in treatment). • Advise patients who wish to conceive or who become pregnant to contact their GP and Specialist Rheumatology team as soon as possible. • Provide a maximum of 4 weeks supply at a time.
Patient Information Leaflets	• Patients should be advised to read the Arthritis Research UK patient information leaflet and the package insert. • The current Arthritis Research UK leaflet can be downloaded from: http://www.arthritisresearchuk.org/arthritis-information/drugs/azathioprine.aspx

Table 1:

Actions to be taken

Prescribers should note that whilst absolute values are useful indicators, trends are equally important, and any rapid fall or consistent downward trend in any parameter warrants extra vigilance and urgent discussion with Specialist Rheumatology team.

WBC <3.5 x 10^9/L	**Withhold and contact Specialist Rheumatology team urgently if any of the results opposite develop**
Neutrophils <1.6 x 10^9/L	
Unexplained eosinophilia >0.5 x 10^9/L	
Platelet count <140 x 10^9/L	
MCV > 105 f/L	
Creatinine >30% above baseline and/or calculated GFR <60	
ALT and/or AST >100 units/L	
Unexplained fall in serum albumin	
Any rapid fall or consistent downward trend in any indices	

Abnormal bruising with or without sore throat	**Immediate FBC and withhold until result available and contact the Specialist Rheumatology team.**
Nausea, vomiting, abdominal pain, diarrhoea, dyspepsia	**Withhold until discussed with Specialist Rheumatology team.**

BACK-UP ADVICE AND SUPPORT

- **GP queries should be directed to the Rheumatology consultants.**
- **Patient queries should be directed to the Rheumatology Specialist Nurses**

All urgent requests should be answered within one working day.

Contact Details:

The Luton & Dunstable Hospital

Consultants

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Dr Balaji Ramabhadran, Dr Vanessa Quick, Dr Marian Chan

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Specialist Nurses

Nicki Wood, Julie Begum, Sue O'Connor : **Nurse Advice Line**: 01582 718305

Bedford Hospital

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References:

- BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with British Association of Dermatologists. Rheumatology.2008 K Chakravarty et al. www.rheumatology.org.uk/includes/documents/cm_docs/2009/d/diseasemodifying_antirheumatic_drug_dmard_therapy.pdf
- SPC (Summary of product characteristics) www.electronicmedicinescompendium.com
- BSR/BHPR Non-biologic DMARD guidelines ((2017) https://academic.oup.com/rheumatology/article/56/6/865/3053478
- BNF (electronic) www.bnf.org/products/bnf-online