Royal Berkshire NHS
NHS Foundation Trust

PRESCRIBING GUIDANCE
AZATHIOPRINE/6 MERCAPTOPURINE for the treatment of INFLAMATORY BOWEL DISEASE (IBD)

For the latest information on interactions and adverse effects, always consult the latest version of the Summary of Product Characteristics (SPC), which can be found at: http://www.medicines.org.uk/

Approval and Authorisation

Approved by	Job Title	Name	Date
BW APC	CHAIR	A. PENN	04/05/16
RBFT DTC	CHAIR	S. HUSSEIN	01/06/16

Change History

Version	Date	Author	Reason
V1.1	April 2013	Surrey PCT	Shared care
V1.2	April 2016	A Scott	Adaptation of existing guidance

Introduction

Azathioprine is an immuno-modulator that is used to induce and maintain remission in Ulcerative Colitis and Crohn's Disease. Azathioprine is a pro-drug, which is cleaved rapidly in the liver to 6-mercaptopurine. Although unlicensed to treat these indications, its use is widely established in Inflammatory Bowel Disease (see BNF Section 1.5). The main toxic effect is myelosuppression, although hepatotoxicity is also well recognised.

This information sheet does not replace the SPC, which should be read in conjunction with this guidance. Prescribers should also refer to the appropriate paragraph in the current edition of the BNF.
Link to the relevant SPC website: www.medicines.org.uk

Dose

Azathioprine
In some individual's nausea may be a problem upon initiating therapy and one may consider starting at a lower dose e.g. 50mg, and escalating the dose as tolerated. The target dose for IBD is 2-2.5mg/kg daily, and for autoimmune liver disease 1mg/kg.

6-Mercaptopurine
The initial oral dose is 50mg once daily for 1 week, and then gradually increased in 25mg increments every week to 1-1.5mg/kg daily, if tolerated (unlicensed indications)

Clinical response for both drugs can usually be expected in 6-12 weeks

Cautions
- Patients should try to avoid contact with people who have active chickenpox or shingles and should report any such contact to their GP or hospital specialist.
- Careful assessment of risk versus benefit should be carried out before use during pregnancy and breast-feeding.

Contraindications
- Moderate/severe renal or liver impairment
- Significant haematological impairment
- Thiopurine methyltransferase (TPMT) deficiency
- Hypersensitivity to Azathioprine/6-MP

Side effects
- Gastro-intestinal disturbances - Nausea, vomiting, diarrhoea, anorexia and abdominal discomfort
- Hepatotoxicity (hepatic necrosis, biliary stasis)
- Bone marrow suppression (leucopoenia, thrombocytopenia) and therefore increased risk of infection
- Oral ulceration, rarely gastrointestinal ulceration
- Hypersensitivity reactions (fever, rigors, rash, myalgia, arthralgia, hypotension, dizziness)
- Rarely pancreatitis, interstitial nephritis
- Alopecia

At the beginning of treatment the patient should be advised to report any signs of bone marrow suppression (i.e. infection, fever, unexplained bruising or bleeding) to the IBD nurse. This should then be reported to the Consultant and GP.

Interactions
- Avoid prescribing **allopurinol** in patients on azathioprine/6-MP due to a clinically significant interaction that can lead to increased azathioprine/6-MP toxicity.
- Increased risk of haematological toxicity with **co-trimoxazole/trimethoprim**.
- Patients should avoid 'live' vaccines such as **oral polio, oral typhoid, MMR, BCG** and **yellow fever**, whilst on immunosuppressive therapy. Contact hospital specialist for advice on any vaccinations if required.
- Anticoagulant effect of **warfarin** possibly reduced by Azathioprine/6-MP.

- Possible increased risk of leucopenia when azathioprine/6-MP given with **aminosalicylates.**

Criteria for Use

RESPONSIBILITIES and ROLES

Specialist responsibilities	
1	Initiate treatment and prescribe until the GP formally agrees to share care (as a minimum supply the first month of treatment or until patient is stabilised).
2	Carry out baseline and subsequent monitoring until the GP agrees to share care
3	Send a letter to the GP requesting shared care for the patient.
4	Routine clinic follow-up on a regular basis.
5	Send a letter to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated.
6	Evaluation of any reported adverse effects by GP or patient.
7	Advise GP on review, duration or discontinuation of treatment where necessary.
8	Inform GP of patients who do not attend clinic appointments.
9	Ensure that backup advice is available at all times

General Practitioner responsibilities	
1	Monitor patient's overall health and well being.
2	Prescribe the drug treatment as described
3	Report any adverse events to the hospital specialist, where appropriate
4	Monitor blood results (FBC, U&E's, LFT's & CRP) in line with recommendations below
5	Help in monitoring the progression of disease.

Monitoring requirements and actions

- Pre-treatment FBC, U&Es, LFT's, CRP, TPMT and Varicella status
- If patients heterozygote for TPMT, monitoring should continue at monthly intervals
- Subsequent Monitoring
  - **LFT's & FBC** - Every week for 4 weeks, then if stable 2-3 monthly thereafter.
  - **U&E's** - Every 6 months (more frequently if there is any reason to suspect deteriorating renal function).

FBC	WBC	<4.0 but > 3.0x 10^9/L	½ dose and monitor WBC weekly. When above 4 ↑ dose by 25mg.
		<3.0 x 10^9/L	Stop drug and monitor WBC weekly, when above 4 reintroduce at ½ initial dose. If WBC stable after 1 month, ↑ by 25mgs up to 25mg less than dose that caused ↓ in WBC.
	Lymphocytes	< 0.5 x 10^9/L	Discuss with IBD nurse or Consultant/Registrar
	Neutrophils	< 2.0 x 10^9/L	Discuss with IBD nurse or Consultant/Registrar

		< 1.5 x 10^9/L	Stop treatment and contact IBD nurse or Consultant/Registrar
	Platelets	< 150 x 10^9/L	Discuss with IBD nurse or Consultant/Registrar
LFT's	> 2 fold rise in AST, ALT (from upper limit of reference range)		Discuss with IBD nurse or Consultant/Registrar
	> 4 fold rise in AST, ALT		Stop treatment and contact IBD nurse or Consultant/Registrar immediately.

Symptoms and actions	
Rash (significant new)	• Stop azathioprine/6-MP and check FBC • If FBC abnormal contact IBD nurse or Consultant/Registrar • Wait until rash resolved and consider restarting at reduced dose, providing no blood dyscrasias
Severe or persistent infections, fever, chill	• Stop azathioprine/6-MP • Check FBC and contact IBD nurse or Consultant/Registrar • Do not restart until results of FBC known
Abnormal bruising or bleeding	• Stop azathioprine/6-MP until recovery and check FBC • Do not restart if blood test abnormal • Contact IBD nurse or Consultant/Registrar
Varicella	• If in contact with the virus, contact Consultant/Registrar or IBD nurse
Nausea	• Advise patient to divide dosage and take with food • If no improvement, reduce dosage or stop • Contact IBD nurse or Consultant/Registrar if reducing dose ineffective

Patient's / Carer's role
1 Ask the specialist or GP for information, if he or she does not have a clear understanding of the treatment.
2 Tell the specialist or GP of any other medication being taken, including over-the-counter products.
3 Read the patient information leaflet included with your medication and report any side effects or concerns you have to the specialist or GP

BACK-UP ADVICE AND SUPPORT

Contact details	Specialist	Telephone No.	Email address:
IBD Nurses:	Rebecca Merrick/Charlotte King/Jessica Aparo/Tiago Almeida	(0118) 322 8914	Ibd.nurses@royalberkshire.nhs.uk