HERPC

Hull & East Riding Prescribing Committee

Prescribing Framework for Azathioprine and Mercaptopurine in Inflammatory Bowel Disease and Autoimmune Hepatitis

Patients Name:…… Unit Number: ……

Patients Address:……(Use addressograph sticker)

G.P's Name:……..

Communication

We agree to treat this patient within this Prescribing Framework

Specialist Prescriber's Name…… Prof Reg. No. ……

Specialist Prescriber's Signature…… Date:……..

Where prescriber is <u>not</u> a consultant:

Consultant's Name: …… GMC No ……..

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

GP's Signature:…… Date:……..

GP's Name (if different from listed above)……..

The front page of this form should be completed by the specialist and the form sent to the patient's general practitioner.

The patient's GP should sign and **<u>send back to specialist</u>**, to confirm agreement to enter into shared care arrangement. If the General Practitioner is **<u>unwilling</u>** to accept prescribing responsibility for the above patient the specialist should be informed within two weeks of receipt of this framework and specialist's letter.

Full copy of framework can also be found at: http://www.hey.nhs.uk/amber.htm

1. Background

These guidelines aim to provide a framework for the prescribing of azathioprine and mercaptopurine by GPs for patients with inflammatory bowel disease or autoimmune hepatitis and to set out the associated responsibilities of GPs and hospital specialists who enter into the shared care arrangements.

For Azathioprine use in other indications please see

http://www.hey.nhs.uk/herpc/azathioprineImmunosupression.pdf

This document should be read in conjunction with the guidance "Responsibility for prescribing between Primary & Secondary/Tertiary Care" https://www.england.nhs.uk/wp-content/uploads/2018/03/responsibility-prescribing-between-primary-secondary-care-v2.pdf

2. Indication

Steroid dependant / resistant inflammatory bowel disease and autoimmune hepatitis

3. Dose

Blood sample to screen for TPMT deficiency will be taken by the specialist, prior to commencing treatment.

Inflammatory Bowel Disease

Azathioprine: 1.5 to 2.5 mg/kg daily. Initial prescription is half target dose (usually 50-100mg), if TPMT level unknown. Consider lower dose in renal or hepatic impairment.

6-Mercaptopurine: A conversion factor of approximately 0.5 can be used when equating azathioprine doses to 6-mercaptopurine. (i.e. 0.75mg/kg to 1.5mg/kg daily or tolerated dose). Initial prescription ½ target dose, if TPMT level unknown.

Autoimmune Hepatitis

Azathioprine: 0.5 to 1 mg/kg daily. Initial prescription is usually no greater than 50mg, but consider lower dose in renal impairment or with evidence of a loss of synthetic hepatic function.

6-Mercaptopurine: A conversion factor of approximately 0.5 can be used when equating azathioprine doses to 6-mercaptopurine. (i.e. 0.25mg/kg to 0.5mg/kg daily or tolerated dose).

4. Duration of treatment

Advice will be given to the GP on duration of treatment and dose changes for each individual patient.

5. Contraindications and cautions

Azathioprine is contraindicated in patients with severe hepatic impairment; severely impaired bone marrow function; severe infections; pancreatitis
Use with caution in mild to moderate hepatic and / or renal impairment and in the elderly (see also Section 7).Avoid in porphyria

Pregnancy and breast-feeding

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 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 www.bnf.org.uk or www.medicines.org.uk.

6. Adverse effects

Patients with thiopurine methyl transferase (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 dependant, 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

6. Interactions

Patients receiving azathioprine should be advised against immunization with live vaccines. (Influenza vaccines may be given in this group of patients)

Interactions include
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, indomethacin and other drugs with myelosuppressant properties – use with caution and monitor closely

7. Monitoring

Disease monitoring:
Clinical response to therapy

Drug monitoring:

Baseline – FBC, BCP (for renal function & LFTs) and TPMT assay

On-going
FBC & LFT should be checked once weekly for at least 4 weeks then fortnightly for 2 months, if stable the monitoring may be reduced to monthly. Once the dose, disease and blood monitoring is stable the frequency of monitoring may be reduced to 3 monthly on advice of specialist.
If doses are changed then monitoring should done as if the drug has been started.

Monitoring parameter	Recommended response
WBC 3.0-3.5 x 10^9/l < 3.0 x 10^9/1	Recheck FBC. Inform consultant Stop Drug and refer back to consultant
Neutrophils 1.5-2.0 x 10^9/l <1.5 x 10^9/l	Recheck FBC. Inform consultant Stop Drug and refer back to consultant
Platelets <100 x 10^9/l	Stop Drug and refer back to consultant
ALT> twice normal limit (or if baseline ALT is abnormal, twice baseline level increase)	Recheck if not settling within two weeks or if worsening refer back to consultant (initial temporary increase is normal)
Alk Phos >200 i.u./L	Stop drug and refer back to consultant **In Autoimmune Hepatitis, to only stop if 25% increase in ALP**
MCV > 100 fl > 105 fl	Check **serum folate** and **B12 & TSH**. and alcohol consumption Notify consultant
Creatinine Increase above normal range, or above baseline in patients with renal impairment	Stop drug and refer back to consultant
Rash or oral ulceration	withhold **until discussed** with specialist team
Abnormal bruising or **severe** sore throat or throat ulceration	withhold **until FBC results** available & discuss with the specialist team
Pregnancy	Continue but refer to gastroenterologist

Details of contraindications, cautions, drug interactions and adverse effects listed above are not exhaustive. For further information always check with BNF www.bnf.org.uk or SPC (www.medicines.org.uk).

8. Information to patient
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, infection or new abdominal pain.

9. Responsibilities of clinicians involved

Stage of Treatment	Hospital Specialist	General Practitioner
Pre-Initiation	TPMT, Hep B & C, HIV, EBV and HVZ serology may be done in advance if time permits, If not at initiation of treatment	
Initiation	If supply urgent then arrange initial supply via hospital for patient. Assess patient following referral from GP Carry out baseline U&Es, LFTs and FBCs Recommend appropriate treatment to the GP by approved DMARDs clinic letter	Prescribe on FP10
Maintenance	Assess clinical response to treatment Provide adequate advice and support to GPs Inform GP of dose amendments as appropriate	Prescribe suggested medication. Monitor patient for adverse effects: FBC&LFT weekly for 4 weeks, fortnightly for 2 months then monthly; reduce frequency to 3 monthly on specialist advice. Refer to consultant where necessary.

Contact Details:

During office hours

Contact consultant's secretary or inflammatory bowel disease nurse specialist, available via HUTH switchboard (01482 875875) or directly on **01482 608982**

Out of hours – Contact on-call Registrar for specialty via HUTH switchboard.

APPROVAL PROCESS for Shared Care Framework

Written by:	**Marie Miller, Interface Pharmacist, updated by Jane Morgan, Interface Pharmacist March 21**
Consultation process:	**Specialists teams in Gastro-enterology**
Approved by:	**Medicines Management Interface Group**
Ratified by:	**HERPC March 2014 Updated June 2018 Updated March 21**
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