Somerset Healthcare Community Shared Care Protocol: ***Mercaptopurine for the treatment of inflammatory bowel disease (IBD)***

NHS Somerset Clinical Commissioning Group

This shared care protocol (SCP) sets out details for the sharing of care for patients requiring Mercaptopurine. It should be read in conjunction with the Summary of Products Characteristics (SPC, available at http://www.medicines.org.uk/emc/medicine/24688)

As outlined in NHS Circular 1992 (Gen 11), when a consultant considers a patients' condition is stable he/she may seek the agreement of the patients' GP to "share" the patients' care. This document provides information on drug treatment for the shared commitment between the consultant and GP concerned. GPs are invited to participate. If the GP is not confident to undertake these roles, then 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. The doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Introduction

Mercaptopurine is a cytotoxic purine analogue which interferes with nucleic acid synthesis. The drugs Mercaptopurine and Azathioprine (a prodrug of Mercaptopurine) are commonly used unlicensed at low doses to treat inflammatory bowel disease (IBD). Mercaptopurine is an option where Azathioprine has been beneficial but side effects are affecting tolerability. The decision as to whether the patient is initiated on either Azathioprine or Mercaptopurine lies with the consultant.
Mercaptopurine is also known as 6-Mercaptopurine (6-MP). This should not be used on prescriptions because historically it has been associated with an increased risk of prescribing and pharmacy dispensing errors.

For further information please click on the links below or visit;
British National Formulary
Summary of product characteristics
Mercaptopurine Patient Information Leaflet

Licensed indications

- Mercaptopurine is indicated for the treatment of certain leukaemias.

Unlicensed indication

- Severe acute Crohn's disease or ulcerative colitis, maintenance of remission of Crohn's disease or ulcerative colitis

Dose (posology & method of administration)

- Tablets are scored to facilitate division of tablets into two halves, if required. A tablet cutter may be useful.

- Mercaptopurine is usually commenced at 25mg per day (half a 50mg tablet). The dose is gradually increased to achieve the target dose, if tolerated. Responsible consultants will give instructions to individual patients and inform GPs regarding the target dose and rate of increase.

- Typically, the target dose for adults over 18 years is 1–1.5 mg/kg daily; some patients may respond to lower doses.

- As a clinical response is not usually expected for up to 12 weeks, Mercaptopurine is often commenced with oral steroids for more immediate relief of symptoms, with the steroid dose being tapered as the Mercaptopurine begins to take effect.

- Mercaptopurine should be administered at least 1 hour before or 3 hours after food or milk.

Contraindications
- Click for details in SPC

Special warnings and precautions for use
- Click for details in SPC

- Immunisation using a live vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live vaccines are contraindicated.

Interactions
- Click for details in SPC

Pregnancy and Lactation
- Click for details in SPC

- Despite the concerns raised in the SPC, the European Crohn's and Colitis Organisation (ECCO) Consensus on Reproduction and Pregnancy in Inflammatory Bowel Disease review does not conclude that Mercaptopurine needs to be discontinued (van der Woude et al, JCC 2015; 9(2) 107-124, see section 5.2.3 p113). In summary, recent controlled studies and a meta-analysis in 2013 (Hutson et al, J Obst Gynaecol. 2013 Jan 33(1):1-8) conclude that thiopurines do not pose an increased risk for adverse pregnancy outcome, compared with pregnancy outcomes of IBD patients without this treatment. Other studies have reported an increased rate of spontaneous miscarriage, preterm delivery, low birth weight which could have been caused by the underlying disease rather than the use of thiopurines.

- Very small amounts of Azathioprine and Mercaptopurine metabolites have been identified in breast milk in several case reports. The available data show no increased infection risks for the observed breastfed babies of 11 mothers taking Azathioprine compared with those of 12 mothers who were not taking any sort of immunosuppressive therapy. The ECCO consensus statement 6B (6B, see p115) states 5ASA derivatives, thiopurines, anti TNFs and corticosteroids are of low risk for breast-fed infants.

Adverse effects
- Click for details in SPC

Shared Care Responsibilities

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to, and accepted by, the patient. This provides an opportunity to discuss drug therapy.

The clinician who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Specialist responsibilities:-

1. Assess the need for Mercaptopurine.
2. When initiating treatment give counseling in verbal and written form.
3. Complete relevant baseline investigations if the patient is commencing Mercaptopurine treatment.
4. Initiate treatment and prescribe until the patient is stabilised (minimum of twelve weeks).
5. Clinical and laboratory supervision of the patient by routine and regular follow-up.
6. Communicate advice to the patient and the patient's GP regarding dose, monitoring requirements etc.
7. Request GP to monitor as recommended in the monitoring section of this protocol.
8. Evaluation of any reported adverse effects by GP or patient and report any adverse effects to the CSM where appropriate.
9. Advise GP on review, duration or discontinuation of treatment, where necessary.
10. Inform GP, by letter of clinic visits and action taken for management of patient.
11. Inform GP of patients who do not attend clinic appointments.
12. Advise GP regarding any concerns about monitoring or adverse effects at any stage.

Monitoring prior to treatment (Consultant responsibility): FBC, LFTs, U&Es, Creatinine, TPMT. Consider Varicella serology, Epstein Barr virus serology, Hepatitis B and C serology as well as HIV testing.

General Practitioner responsibilities:

1. Monitor the general health of the patient and specific side effects as detailed in the 'monitoring' section.
2. Prescribe the drug, as described by the consultant and be vigilant of possible drug interactions.
3. Undertake the ongoing monitoring as detailed in this protocol.
4. Carry out any investigations that are communicated and deemed appropriate.
5. Discuss any important test abnormality with the consultant before continuing treatment.
6. Report any suspected adverse reactions to the hospital.
7. Report any significant events relating to Mercaptopurine therapy to the CCG.
8. Liaise with the hospital consultant regarding any complications of treatment.

Patient/carer responsibilities

1. Report any adverse effects to their GP and/or specialist whilst taking Mercaptopurine.
2. Ensure that they have a clear understanding of their treatment.
3. Report any changes in their disease symptoms and/or specialist whilst taking Mercaptopurine.
4. Alert GP and/or specialist to any changes which could affect disease management e.g. pregnancy.
5. If in contact with patients with chicken pox/shingles report this to their GP.

Monitoring requirements for Mercaptopurine at Taunton and Somerset NHS Foundation Trust		
Pre-treatment Monitoring	FBC, U&Es, LFTs, TPMT, Varicella serology, Hepatitis B and C serology and consider Epstein Barr serology as well as HIV testing.	
Subsequent Monitoring	FBC	Every 2 weeks for first 8 weeks, then repeat at 12 weeks (hospital responsibility after dose initiation), then if stable 3 monthly thereafter
	LFTs	Every 2 weeks for first 8 weeks, then repeat at 12 weeks (hospital responsibility after dose initiation), then if stable 3 monthly thereafter
	CRP	3 monthly to assess treatment response

After a dose increase, monitor after 2 weeks and then again at 4 weeks

Action and Advice for GPs in response to blood monitoring/side effects	
Blood Test Results	**Action**
Neutrophils	
$<2.0 \times 10^9$/L	Discuss with specialist hospital clinician/IBD CNS
$<1.5 \times 10^9$/L	Reduce dose by 50% and discuss with specialist hospital clinician/IBD CNS. Repeat FBC in 1 week.
$<1.0 \times 10^9$/L	STOP Mercaptopurine and discuss with specialist hospital clinician/IBD CNS. Repeat FBC in 1 week.
MCV	
>105 fL	Check B12 and folate and start appropriate supplementation if below normal level
Platelets	
$<150 \times 10^9$/L	Discuss with specialist hospital clinician/IBD CNS
Liver Function Tests	
>2 fold increase in AST/ALT (from upper limit of reference range)	Contact specialist hospital clinician/IBD CNS, repeat LFTs in 1 week.
>3 fold increase in AST/ALT (from upper limit of reference range)	Reduce dose by 50%, contact specialist hospital clinician/IBD CNS, repeat LFTs in 1 week.
>4 fold increase in AST/ALT (from upper limit of reference range)	STOP Mercaptopurine and contact specialist hospital clinician/IBD CNS, repeat LFTs in 1 week

Symptoms	Actions
Rash (significant new)	Stop Mercaptopurine and take FBC. If FBC abnormal contact specialist hospital clinician. Wait until rash resolves and consider restarting at lower dose providing no blood dycrasias
Severe or persistent infection, fevers, chills	Stop Mercaptopurine and take FBC. Do not restart until results of FBC known
Persistent sore throats	Take FBC and consider contacting specialist hospital clinician
Abnormal Bruising or bleeding	Stop Mercaptopurine until recovery and check FBC. Do not restart if blood test abnormal and discuss with specialist hospital clinician
Varicella	If in contact with varicella contact specialist hospital clinician/IBD CNS
Nausea	Advise patient to divide dosage and take with food or take dose at night. If no improvement reduce dose or stop and contact specialist hospital clinician/IBD CNS

Service Users should be advised to report any signs of bone marrow suppression (thrombocytopenia, neutropenia, leucopenia) i.e. infection, fever, unexplained bruising or bleeding. Treatment should be stopped and FBC checked.

Drug cost
Drug tariff Apr 2016

Formulation	Dose	Cost (25 tabs)
Mercaptopurine tablets	50mg	£49.15

Further support
- Medicines Information department, Musgrove Park Hospital: 01823 342253
- Medicines Information department, Yeovil District Hospital: 01935 384327
- Prescribing & Medicines Management Team, NHS Somerset CCG: 01935 384123

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	Drug & Therapeutics Committee, Taunton & Somerset NHS FT	
	Drug & Therapeutics Committee, Yeovil District Hospital NHS FT	
	Drug & Therapeutics Committee, Somerset Partnership NHS FT	
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Review required by:		*April 2018*

References

- Summary of Product Characteristics, Mercaptopurine 50mg tablets (Accessed 24/07/2016)
  British National Formulary online (accessed June 2016)
- Somerset Clinical Commissioning Group; Specification for a National Enhanced Service; Enhanced Drug Monitoring; Protocol Number 11X-04