SHARED CARE GUIDELINE

Homerton University Hospital NHS
NHS Foundation Trust

NHS
City and Hackney

6-MERCAPTOPURINE
Adults ≥ 18 years

INTRODUCTION

6-mercaptopurine (6-MP) is used as a steroid-sparing agent in both Ulcerative Colitis and Crohn's disease. It is an effective treatment in the management of inflammatory bowel disease to induce and maintain remission in patients intolerant of azathioprine.

6-mercaptopurine is an effective maintenance therapy for Crohn's disease for up to 4 years, following which treatment should be reviewed by the patient's hospital team.

6-mercaptopurine is licensed for a variety of leukaemias. **This Shared Care Guideline, however, will only cover the treatment of adults ≥ 18 years of age with Inflammatory Bowel Disease.** Although unlicensed to treat the above indications, its use is widely established in Inflammatory Bowel Disease.

The main toxic effect is myelosuppression, although hepatotoxicity is also well recognised.

In the UK patients are often given azathioprine first and switched to 6-mercaptopurine if they are intolerant of azathioprine. As 6-mercaptopurine is given at half the dose of azathioprine, it is important to be certain as to which agent is being prescribed to avoid potential serious dosing errors.

DOSE AND ADMINISTRATION

6-mercaptopurine (Puri-Nethol®) is administered orally and is available as 50mg tablets.

- The usual dose of 6-mercaptopurine is 1-1.5mg/kg daily. However, **some patients may respond to lower doses.**
- It is recommended as best practice that the hospital consultant should check the thiopurine methyltransferase (TPMT) activity for any deficiencies.
- **After any dose change, the patient should be transferred back to hospital led care where they will be the responsibility of the consultant/hospital team until shared care is re-requested.**

CAUTIONS

- Hepatic impairment – may need dose reduction.
- Renal impairment – reduce dose.
- **Immunisation using a live organism vaccine has the potential to cause infection in immunocompromised hosts. Therefore, immunisations with live organism vaccines are not recommended. Contact the hospital specialist for advice on any vaccinations if required.**

CONTRA-INDICATIONS

- **Pregnancy**: 6-mercaptopurine is known to be teratogenic, especially during the 1st trimester. Its use should be avoided whenever possible during pregnancy.
- **Breastfeeding**: Patients receiving 6-mercaptopurine should **discontinue breastfeeding**.
- Adequate contraceptive precautions should be advised if either partner is receiving 6-mercaptopurine. Ideally, therapy of 6-mercaptopurine should be withdrawn in advance of the intention to start a family, however this may not be appropriate in the individual and the risk/benefit balance should be considered.

- Moderate/severe renal or hepatic impairment
- TPMT deficiency
- Severe anaemia, leucopenia or thrombocytopenia
- Active infection or immunodeficiency
- Known allergic hypersensitivity to 6-mercaptopurine

SIGNIFICANT INTERACTIONS

- **Allopurinol –** enhanced effects and increased toxicity of 6-mercaptopurine when concomitantly given. **BNF states that the dose of 6-mercaptopurine should be reduced to one quarter of its usual dose.**
- **Anticoagulants** – 6-mercaptopurine possibly reduces the anticoagulant effect of coumarins.
- **Trimethoprim, co-trimoxazole:** avoid concomitant use with 6-mercaptopurine as there is an increased risk of haematological toxicity.
- Avoid concomitant use of 6-mercaptopurine with **clozapine** as there is an increased risk of agranulocytosis.

Please consult the BNF (Appendix 1) for a comprehensive list of other interactions.

SIDE- EFFECTS

The most common side effects are:

- Gastrointestinal disturbances (nausea, vomiting, anorexia).
- Bone marrow suppression (leucopenia, thrombocytopenia) and therefore an increased risk of infection.*
- Oral mucositis (sore mouth).
- Hypersensitivity reactions (fever, rash, myalgia, dizziness).
- Hepatotoxicity (hepatic necrosis, biliary stasis)
- Rarely pancreatitis
- Rarely alopecia.

(*) – Patients must be informed that they should consult either their GP or consultant should they develop symptoms of possible myelosuppression such as sore throat, infection, fever or unexplained bruising. In the case of such presentation an urgent FBC should be carried out.

If a patient is found to be myelosuppressed, 6-mercaptopurine therapy should be stopped immediately and medical advice should be sought.

MONITORING STANDARDS FOR 6-MERCAPTOPURINE

Pre-treatment	**FBC, LFTs, U&Es, CRP, TPMT level and phenotype if low, and Herpes zoster immune status if indicated**	
Subsequent Monitoring	**FBC**	**Every 2 weeks for 3 months then monthly for 3 months, then if stable 3 monthly thereafter.**
	LFTs	**Every 2 weeks for 3 months then monthly for 3 months, then if stable 3 monthly thereafter.**
	U&Es	**Every 6 months (more frequently if there is any reason to suspect deteriorating renal function.**
	CRP	**3 monthly to assess response to treatment.**

Further monitoring will be required following any changes in dose. Blood test results should always be copied between the hospital team and the GP.

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EVENTS AND ACTION

Laboratory Events	Values	Action
• Elevation in liver enzymes (AST, ALT)	> 2 fold rise in AST, ALT (from upper limit of reference range)	Contact IBD nurse or hospital specialist clinician.
	> 4 fold rise in AST, ALT	**Stop 6-mercaptopurine** and contact IBD nurse or hospital specialist clinician **immediately.**
• Mild-to-moderate renal impairment	mild=20 to 50 mL/min.; moderate=10 to 20 mL/min.	
• Lymphocytes	< 0.5 x 10^9/L	Discuss with IBD nurse or consultant
• Neutrophils	< 2.0 x 10^9/L	Discuss with IBD nurse or consultant.
	< 1.5 x 10^9/L	Stop and discuss with IBD nurse or consultant.
• Platelets	< 150 x 10^9/L	Discuss with hospital IBD nurse or consultant.

Symptoms	Management
• Rash (significant new)	**Stop 6-mercaptopurine and check FBC**. If FBC is abnormal, contact IBD nurse or consultant. Wait until rash resolved and consider restarting at reduced dose, providing no blood dyscrasias.
• Severe or persistent infections, fever, chills, sore throat.	**Stop 6-mercaptopurine, check FBC** and contact IBD nurse or consultant. Do not restart until FBC results are known. For sore throats, take the FBC and contact the consultant.
• Abnormal bruising or bleeding	**Stop 6-mercaptopurine until recovery and check FBC**. Do not restart if blood test is abnormal & seek advice from specialist team.
• Varicella	If in contact with the virus, contact the specialist team.
• Nausea	Advise patient to divide dosage and take with food. If no improvement, reduce dose or stop and contact the specialist team if dose reduction is ineffective.

REMEMBER if unsure at any point: Contact the various Specialists and or Specialist Nurse/ Nurse Practitioner via the Homerton Hospital switchboard on 020 8510 5555.

Share care guideline: is a document which provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibility for each party. The intention to shared care should be explained to the patient and accepted by them. Intrinsic in the shared care agreement is that the prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use.

Responsibility of Consultant/ Clinical Nurse Specialist

1. Ensure that the patient/carer is an informed recipient in therapy
2. Ensure that patients understand their treatment regimen and any monitoring or follow up that is required (using advocacy if appropriate).
3. Ensure baseline investigations are normal before commencing treatment
4. 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).
5. Send a letter to the GP requesting shared care for this patient
6. Clinical and laboratory supervision of the patient by blood monitoring and routine clinic follow-up on a regular basis.
7. **Send a letter/results notification to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring (unless otherwise covered by letter from Gastroenterology Clinical Nurse Specialist).**
8. Evaluation of any reported adverse effects by GP or patient
9. Advise GP on review, duration or discontinuation of treatment where necessary
10. Inform GP of patients who do not attend clinic appointments
11. Reporting of adverse events to CSM
12. Ensure that back up advice is available at all time

Responsibility of General Practitioner

1. Check and reinforce patient understanding of the nature, effect and potential side effects of the drug before prescribing it as part of the shared care programme and contact the specialist for clarification where appropriate
2. Check and review blood results prior to issuing a prescription
3. Monitor patient's overall health and well-being
4. Report any adverse events to the consultant where appropriate
5. Report any adverse events to the CSM where appropriate
6. Help in monitoring the progression of disease
7. Reporting to and seeking advice from consultant and/or specialist nurse on any aspect of patient care which is of concern to GPs and may affect disease treatment
8. **Refer the patient back to the hospital team after 4 years of 6-mercaptopurine treatment**

Responsibility of PCT

1. To provide feedback to trusts via Trust Medicines Committee
2. To support GPs to make the decision whether or not to accept clinical responsibility for prescribing
3. To develop and revise shared care guidelines
4. To support trusts in resolving issues that may arise as a result of shared care

Patient responsibility

1. Report any adverse effects to their GP and/or specialist
2. Ensure they have a clear understanding of their treatment
3. Report any changes in disease symptoms to GP and/ or specialist
4. Informing the GP of any other medications they might be taking including OTC products
5. Alert GP and/or specialist of any changes of circumstances which could affect management of disease e.g. plans for pregnancy

References

1. Puri-Nethol Tablets, Mercaptopurine, Aspen Europe GmbH, Summary of Product Characteristics (date of revision October 21st, 2009). Last accessed August 03, 2010. http://www.medicines.org.uk/EMC/medicine/763/SPC/Puri-Nethol+Tablets/
2. BNF 59 (March 2010); Mercaptopurine; 1.5.3 and 8.1.3.
3. NHS Brighton and Hove, NHS Brighton and Sussex University Hospital and NHS West Sussex Shared Care Guidelines for 6-mercaptopurine, July 2008 – review date July 2010.
4. Cambridge University Hospitals NHS Foundation Trust, Shared Care Guidelines, 6-mercaptopurine – In Inflammatory Bowel Disease, version 2; approved May 2008 – review date May 2010
5. NHS Lothian. Shared Care Protocol, 6-mercaptopurine, version 1 (March 2007) – review date March 2009.
6. NHS Lincolnshire. Shared Care Guideline: Unlicensed use of Mercaptopurine for the treatment of Inflammatory Bowel Disease. Date of issue: February 2009 – review date February 2011.