BNSSG Paediatric Shared Care Guidance

Please complete all sections

Section 1: Heading

Drug	Mercaptopurine
Amber *one month*	
Indication	Mercaptopurine is an immunosuppressive drug, which is effective in Crohn's disease and Ulcerative Colitis as a second line treatment and also a steroid sparing agent.
Speciality / Department	Paediatric Gastroenterology
Trust(s)	University Hospitals Bristol NHS Foundation Trust

Section 2: Treatment Schedule

Usual dose and frequency of administration *(Please indicate if this is licensed or unlicensed for this age group and any relevant dosing information)*	Under the care of the paediatric gastroenterology team: 1-1.5mg/kg once daily (maximum 50mg), increased up to 75mg once daily if necessary In patients with intermediate enzymatic activity or heterozygous TPMT, dose should be reduced to 0.5mg/kg once daily.
Route and preferred formulation *(Please indicate licensed or unlicensed preparation)*	Oral 50mg tablets. Unlicensed 10mg tablets and 20mg/ml oral suspension
Duration of treatment	Long term

Section 3: Monitoring

Please give details of any tests that are required before or during treatment, including frequency, responsibilities (please state whether they will be undertaken in primary or secondary care), cause for adjustment and when it is required to refer back to the specialist)

Baseline tests to be done by secondary care
Secondary care: FBC, U&Es, LFTs, Thiopurine Methyl Transferase (TPMT) level (not reliable if red blood cells have been transfused within the previous 3 months)
Subsequent tests - where appropriate *(Please indicate who takes responsibility for taking bloods and interpreting results. If the drug is dosed by weight please also indicate intended frequency of weight monitoring/dose adjustment)* Secondary care: Initially FBC, LFT and U&Es on week 2 and 4.

Primary care:

If bloods are stable, FBC, LFT and U&Es on week 8 and 12 and 12 weekly thereafter.

Test		Frequency	Who by	Action/Management
Full Blood Count values:		Week 8, Week 12, 12 weekly thereafter	Primary care	
	WBC >2.5 x 10^9/L (mild)			Discuss with hospital team. Dose should be reduced and FBC repeated.
	WBC 1.5-2.5 x 10^9/L (moderate)			Withhold drug and repeat in 1 week. Discuss with hospital team.
	WBC <1.5 x 10^9/L (severe)			Stop drug and refer to hospital team.
	Neutrophils <1.0x 10^9/L			Repeat and discuss with hospital team if still low.
	Lymphocytes <0.5 x 10^9/L			Repeat and discuss with hospital team if still low.
	Platelets <150 x 10^9/L			Repeat and discuss with hospital team if still low.
LFTs Elevation of liver enzymes (ALT, AST, ALP)				If >2 fold but <4 fold, repeat and if still high discuss with hospital team. If >4 fold, withhold medication, repeat and discuss with hospital team. Azathioprine is hepatotoxic.
U&Es Renal Impairment				If creatinine is outside of specific limit for patient given by secondary care, use generic table given below. If creatinine falls outside of reference range, contact hospital team to discuss. Reference table for children's creatinine levels shown below.

Creatinine reference table for children			
Female		**Male**	
Age range	**Reference interval**	**Age range**	**Reference interval**
0 - 14 days	27 - 77 µmol/L	0 - 14 days	27 - 77 µmol/L
14 days - 1 year	14 - 34 µmol/L	14 days - 1 year	14 - 34 µmol/L
1 year - 3 years	15 - 31 µmol/L	1 year - 3 years	15 - 31 µmol/L
3 years - 5 years	23 - 37 µmol/L	3 years - 5 years	23 - 37 µmol/L
5 years - 7 years	25 - 42 µmol/L	5 years - 7 years	25 - 42 µmol/L
7 years - 9 years	30 - 47 µmol/L	7 years - 9 years	30 - 47 µmol/L
9 years - 11 years	29 - 56 µmol/L	9 years - 11 years	29 - 56 µmol/L
11 years - 12 years	36 - 64 µmol/L	11 years - 12 years	36 - 64 µmol/L
12 years - 13 years	36 - 67 µmol/L	12 years - 13 years	36 - 67 µmol/L
13 years - 14 years	38 - 74 µmol/L	13 years - 14 years	38 - 76 µmol/L
14 years - 15 years	43 - 75 µmol/L	14 years - 15 years	40 - 83 µmol/L
15 years - 16 years	44 - 79 µmol/L	15 years - 16 years	47 - 98 µmol/L

16 years - 17 years	48 - 81 µmol/L	16 years - 17 years	54 - 99 µmol/L
17 years - Adult	45 - 84 µmol/L	17 years - Adult	59 - 104 µmol/L

Frequency of ongoing follow up by secondary care *(Please indicate how often child will continue to be seen by secondary care i.e. at least every 6 months)*	3 monthly

Section 4: Side Effects

Please list only the most pertinent side effects and management. Please provide guidance on when the GP should refer back to the specialist. For everything else, please see BNFc or SPC.

Side effects and management

Referral back to specialist

Problem	Management
Gastrointestinal tolerance (such as diarrhoea, nausea/vomiting and/or loss of appetite)	Tolerance to these side effects should occur within 2 weeks. Nausea can be reduced by taking with food or taking at night. If symptoms persist refer back to the hospital team
Severe rash	Stop drug and refer back to hospital team
Fever, flu-like symptoms, myalgia and arthralgia	Refer back to the hospital team
Alopecia	Usually resolves spontaneously despite continuing treatment – link between mercaptopurine and alopecia uncertain
Signs of bone marrow suppression: severe or persistent infection, sore throat, oral ulceration, fever and/or unexplained bruises or bleeding	Check FBC (see below) and discuss with specialist clinician. Mercaptopurine should be stopped in all but minor infections as the body defences may be reduced and delay recovery. Bone marrow suppression is reversible if mercaptopurine is stopped early enough.
Raised amylase or symptoms suggesting pancreatitis	Stop drug and refer to hospital team. Usually occurs within the first 6 weeks. This is usually reversible on stopping treatment
Chicken pox/shingles	Stop drug, commence oral aciclovir and refer to hospital team

Patients receiving mercaptopurine are at an increased susceptibility to viral, fungal and bacterial infections.

There is a low risk of lymphoma for any given patient.

Section 5: Other Issues

(e.g. Drug Interactions, Contra-indications, Cautions, Special Recommendations)

Please list only the most pertinent and the action for GP to take (For full list please see BNFc or SPC)

Issues

Interactions

Drug	Significance/Action
Allopurinol	The mercaptopurine dose should be reduced by two thirds or three quarters.
Aminosalicylate derivatives (e.g. Olsalazine, Mesalazine or Sulfasalazine)	Aminosalicylate derivatives inhibit the TPMT enzyme. Therefore lower doses of mercaptopurine may need to be considered when administering concomitantly.
Captopril and Enalapril	Haematological abnormalities (especially in renal impairment)
Clozapine	Avoid concomitant use – increased risk of agranulocytosis
Co-trimoxazole	Information limited and interaction not established. There is a possible increased risk of haematological toxicity
Cytostatic/myelosuppressive agents (i.e. Penicillamine)	Should be avoided due to enhanced myelosuppression
Live vaccines (Varicella vaccine, MMR, BCG, oral polio, oral typhoid, yellow fever and Fluenz Tetra nasal spray)	Risk of generalised infections when given with live vaccines. Avoid concomitant use.
Warfarin	Anticoagulant effect may be reduced. Warfarin doses may need to be increased

Contra-indications

Hypersensitivity to mercaptopurine, absent thiopurine methyltransferase (TPMT) activity, significant haematological impairment, excessive sunbathing and exposure to UV light (increased risk of melanoma and non-melanoma skin cancers), patients with hypoxanthine-guanine phosphoribosyltransferase deficiency and pregnant patients or those likely to become pregnant.

Caution

Renal & liver impairment, contact specialist clinician as reduced dose is likely to be needed. Hypersensitivity to azathioprine.

Special recommendations

- Patients treated with mercaptopurine are more sensitive to the sun. Exposure to sunlight and UV light should be limited and patients should be recommended to wear protective clothing and to use a sunscreen with a high protection factor
- Patients should avoid people who have active chickenpox or shingles – report any such contact to GP/hospital specialist
- Care should be taken to avoid mercaptopurine during EBV infection due to the risk of EBV-associated lymphomas
- A diminished response to live attenuated vaccines (polio, oral typhoid, MMR, BCG, Varicella, Fluenz nasal influenza and yellow fever) is likely, and such a response to hepatitis B has been observed among patients treated with combination of mercaptopurine and corticosteroids
- Report immediately any evidence of infection, unexpected

	bruising or bleeding or other manifestation of bone marrow depression - Present in breast milk in low concentrations. Mothers should not breastfeed whilst on mercaptopurine. - A shift to mercaptopurine may be successful in 50% of azathioprine intolerant patients, especially in myalgia or arthralgia but may also be effective in hepatotoxicity, gastrointestinal symptoms, flu-like illness or rash.
Reminder to ask patient about specific problems	N/A

Section 6: Advice to the patient

Advice for prescribing clinician to inform patient

1. Explain the importance and need for regular blood tests
2. Patients should wear protective clothing and a high factor sunscreen during the summer
3. Parents/carers/patients should be aware that they need to report any signs or symptoms of bone marrow suppression, for example any bruising or bleeding, infection or any other side effects
4. Patients not immune to chickenpox/shingles and who have been in contact with individuals with chickenpox/shingles should report this to their GP
5. Therapeutic effect may take up to 10 to 14 weeks after the start of treatment.
6. Mercaptopurine should not be taken with milk or dairy products. Mercaptopurine should be taken at least 1 hour before or 2 hours after milk or dairy products.

Section 7: Generic principles of shared care for SECONDARY CARE

Core responsibilities

1. Initiating treatment and prescribing for the length of time specified in **section 1.**
2. Undertaking the clinical assessment and monitoring for the length of time specified in **section 1** and thereafter undertaking any ongoing monitoring as detailed in **section 3.**
3. Communicate details of the above in 1 and 2 to GP within the first month of treatment. This information should be transferred in a timely manner.
4. Refer patients to GP and provide information of further action where appropriate e.g. if blood test is due.
5. To provide advice to primary care when appropriate.
6. Review in frequency specified in **section 3** and adjust dose for child's age/body weight as appropriate.
7. Review concurrent medications for potential interaction prior to initiation of drug specified in **section 1.**
8. Stopping treatment where appropriate or providing advice on when to stop.
9. Reporting adverse events to the MHRA.
10. Reminder to ask patients about particular problems see **section 5.**

Section 8: Generic principles of shared care for PRIMARY CARE

Core responsibilities

1. Responsible for taking over prescribing after the length of time specified in **section 1.**
2. Responsible for any clinical assessment and monitoring if detailed in **section 3** after the length of time specified in **section 1.**
3. Review of any new concurrent medications for potential interactions.
4. Reporting adverse events to the MHRA.
5. Refer for advice to specialist where appropriate.
6. Reminder to ask patients about particular problems see **section 5.**

Section 9: Contact Details

Name	Organisation	Telephone Number	E mail address
Paediatric GI consultant via switchboard	Bristol Royal Hospital for Children	0117 923 0000	Click here to enter details
Paediatric GI secretary	Bristol Royal Hospital for Children	01173428828	Click here to enter details
Paediatric Medicine Pharmacist	Bristol Royal Hospital for Children	01173427042	Click here to enter details

Section 10: Document Details

Date prepared	January 2018
Prepared by	Rachel Crampton and Eimear Mc Geehan (Paediatric Medicine Pharmacists) and Eleni Volonaki (Consultant Paediatric Gastroenterologist)
Date approved by JFG	November 2018
Date of review	November 2020
Document Identification: Version	V2

Section 11: Collaboration

Specialists in any one discipline are encouraged to collaborate across the health community in preparing shared care guidance. Please give details

N/A

Section 12: References

Please list references

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4. UK IBD Working Group on behalf of the British Society of Paediatric Gastroenterology, Hepatology and Nutrition (BSPGHAN), October 2008. Guidelines for the Management of Inflammatory Bowel Disease (IBD) in Children in the United Kingdom
5. NICE guideline. Crohn's disease: management. Published October 2012 (accessed 09.01.2018) http://www.nice.org.uk/guidance/cg166
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7. Fraser A, Gibbs K, 2010. BNSSG Mercaptopurine Shared Care Guideline
8. Turner D, Levine A, Escher JC, et al. Management of pediatric Ulcerative Colitis: Joint ECCO and ESPGHAN Evidence-based Consensus Guidelines. JPGN 2012; 55: 340-361 Ruemmele F.M Veres G, Kolho KL, et al. consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. Journal of Crohn's and Colitis 2014; 8(10): 1179-1207.doi 10.1016/j.crohns. 2014.04.005
9. Ruemmele, F.M, Veres, G, Kolho, K.L et al. Consensus guidelines of ECCO/ESPGHAN on the medical management of pediatric Crohn's disease. Journal of Crohn's and Colitis. 2014; 8: 1179 - 1207