LINCOLNSHIRE CLINICAL COMMISSIONING GROUPS in association with UNITED LINCOLNSHIRE HOSPITALS TRUST

SHARED CARE GUIDELINE: Unlicensed use of Mercaptopurine for the treatment of Inflammatory Bowel Disease.

General Principles

Shared Care Responsibilities:

In its guidelines on responsibility for prescribing (circular EL (91) 127) between hospitals and general practitioners, the Department of Health has advised that legal responsibility for prescribing lies with the doctor who signs the prescription. (*BNF* 70, September 2015 -March 2016, pg.4)

Aims:

The aim of shared care guidelines is to provide information and/or guidance to GPs and hospital staff relating to the potentially complex implications of sharing patient care for a specific drug between primary and secondary/tertiary care.

Specific shared care guidance should be available for any high cost drug, high-risk drug therapy or device that may be prescribed for a patient following specialist referral. Such guidance will only be produced where shared care is considered an appropriate option.

Each guideline will include a clear statement of the responsibilities of both the GP and the specialist unit within the overall provision of the treatment to the patient.

Shared care guidelines will ensure that the GP has sufficient information available to undertake to prescribe a specialist treatment if s/he so wishes. It is not the intention of these guidelines to insist that GPs prescribe such treatment and any doctor who does not wish to accept clinical or legal responsibility to prescribe such a drug is under no obligation to do so. Nonetheless the development of a shared care guideline will only be undertaken within the context of a broad acceptance between Lincolnshire Prescribing and Clinical Effectiveness Forum (PACEF) and secondary/tertiary care that GP prescribing of such a treatment is appropriate within the constraints of formal shared care. Any drug approved for the development of a shared care guideline will automatically be classified as amber on the Lincolnshire Traffic Lights List and, if high-cost, will be supported financially through the High Cost Drugs Reserve. Thus there should be no financial reason why a GP should be deterred from prescribing a high cost drug under a shared care guideline.

Further copies of any guidelines in this series are available from members of the Arden and GEM commissioning Support Unit – Lincolnshire Prescribing & Medicines Optimisation Team.

Date of Issue: February 2016
Review Date: February 2018

Principles of shared care

The General Medical Council published their Good Practice In Prescribing And Managing Medicines and which came into effect 25th February 2013. A section of the guidance provides recommendations for the sharing of care which applies to any instance when care is shared between different services.

Good practice recommendation 35.

- Decisions about who should take responsibility for continuing care or treatment after initial diagnosis or assessment should be based on patients best interest rather than on convenience or the cost of the medicine and associated monitoring or follow-up

Good practice recommendation 36.

- Shared care requires the agreement of all parties including the patient. Effective communication and continuing liaison between all parties to a shared care agreement is essential.

Good practice recommendation 37.

- If you prescribe at the recommendation of another doctor, nurse or other healthcare professional, you must satisfy yourself that the prescription is needed, appropriate for the patient and within the limits of your competence.

Good practice recommendation 38.

- If you delegate assessment of a patients' suitability for a medicine, you must be satisfied that the person to whom you delegate has the qualifications, experience, knowledge and skills to make the assessment. You must give them enough information about the patient to carry out the assessment required

Good practice recommendation 39.

- In both cases, you will be responsible for any prescription you sign.

Good practice recommendation 40.

- If you recommend that a colleague, for example a junior doctor or general practitioner, prescribes a particular medicine for a patient, you must consider their competence to do so. You must satisfy yourself that they have sufficient knowledge of the patient and the medicine, experience (especially in the case of junior doctors) and information to prescribe. You should be willing to answer their questions and otherwise assist them in caring for the patient, as required

Good practice recommendation 41

- If you share responsibility for a patient's care with a colleague , you must be competent to exercise your share of clinical responsibility.

You should:

a) Keep yourself informed about the medicines that are to be prescribed for the patient
b) Be able to recognise serious and frequently occurring adverse side effects
c) Make sure appropriate clinical monitoring arrangements are in place and that the patient and the healthcare professionals involved understand them
d) Keep up to date with relevance guidance on the use of the medicines and on the management of the patient's condition

Good practice recommendation 42

- In proposing a shared care arrangement, specialists may advise the patient's general practitioner which medicine to prescribe. If you are recommending a new or rarely prescribed medicine you should specify the dosage and means of administration and agree a protocol for treatment. You should explain the use of unlicensed medicines and departures from authoritative guidance or recommended treatments and provide both

the general practitioner and the patient with sufficient information to permit the safe management of the patient's condition.

Good practice recommendation 43

- If you are uncertain about your competence to take responsibility for the patients continuing care you should seek further information or advice from the clinician with whom the patient's care is shared or from another experienced colleague. If you are still not satisfied you should explain this to the other clinician and to the patient and make appropriate arrangements for their continuing care.

Drug Details
Approved Name: Mercaptopurine
Brand Name: generic tablets,
Form and Strength: 50mg tablets

Specialist Responsibilities

The specialist secondary/tertiary care service will:

1. Send a letter to the GP suggesting that shared care is agreed for this patient.
2. Ensure that the patient receives supplies of mercaptopurine from the hospital or prescribed on FP10 HP until the GP formally agrees to share care.
3. Undertake baseline monitoring Full Blood Count (FBC) U&Es, Liver Function Tests (LFTs) & creatinine.
4. Pre-screen for thiopurine methyltransferase (TPMT) deficiency if required and an alternative dosing and monitoring strategy may be recommended, if necessary.
5. Initiate mercaptopurine according to dosage regimen and undertake monitoring of clinical response and side effects. When treatment is stabilised, send share care agreement request to GP.
6. Provide patient with pre-treatment information leaflet indicating the risks and benefits associated with mercaptopurine therapy, including the slight increased risk of skin cancer and the need to avoid exposure to sunlight
7. Communicate promptly any changes in biochemistry monitoring and modification of mercaptopurine dose to the GP if applicable.
8. Undertake fortnightly monitoring of FBCs and LFTs at two weeks, 4 weeks, and then monthly for 3 months or until stable. Thereafter the monitoring is once every three months or as agreed with secondary care
9. Periodically review the patient's clinical condition.
10. Have a mechanism in place to receive rapid referral of a patient from the GP in the event of deteriorating clinical condition.
11. Follow up any adverse drug reactions reported by the GP and report back to the GP.
12. Advise the GP on continuing or stopping mercaptopurine therapy following medical review of the patient and associated drug therapy.

GP Responsibilities

The GP will:

1. Notify the consultant in writing, within two weeks, if they agree to share care.
2. Prescribe mercaptopurine for the patient once the dose has been stabilised.
3. Monitor the FBC two and four weeks following any dose increase.
4. Undertake the ongoing monitoring as detailed on pages 4 & 5 of this protocol.
5. Promote and monitor compliance and ask patient about adverse effects – particularly unexplained bleeding, bruising, purpura (or other skin changes), sore throat, fever or malaise.
6. Monitor the patient for adverse drug reactions and remain vigilant to the risk of potential drug interaction, e.g. concurrent use of allopurinol.
7. Carry out any investigations that are communicated and deemed appropriate
8. Provide repeat prescriptions according to recommendations on dosage by specialist service.

Referral Criteria

1. The specialist service will continue to supply treatment until the GP is prepared to accept responsibility for shared care
2. Patients will have been stabilized on mercaptopurine and will have received at least six weeks treatment prior to transfer of care.

Indications

Unlicensed use as 2nd line therapy for patients with ulcerative colitis or Crohn's disease, intolerant of azathioprine.

Azathioprine and mercaptopurine are both widely used in the treatment of Ulcerative Colitis and Crohn's disease as adjunctive therapy and as corticosteroid sparing therapies although they are unlicensed for IBD.

Thiopurines are effective maintenance therapy for patients with ulcerative colitis who have failed or can't tolerate mesalazine and for patients who require repeated courses of steroids. In Crohn's disease they are effective both as induction and maintenance of remission.

Decision as to whether patient is initiated on either azathioprine or mercaptopurine rests with the consultant.

Recommended Dosage and Administration

Normal daily dose 1 - 1.5mg/kg, or less if TPMT is low.

Background Pharmacology

Mercaptopurine is a cytotoxic purine analogue which interferes with nucleic acid synthesis.

Preparations Available

Mercaptopurine 50mg scored tablets

Adverse Effects

Common (≥1 in 100 and <1 in 10)
Nausea, diarrhea, vomiting, anorexia and abdominal discomfort and headaches.

Uncommon (≥1 in 1000 and <1 in 100)
Rash,
Skin sensitivity
Signs of Bone marrow suppression (leukopenia, thrombocytopenia) and therefore risk of infections i.e. fever, sore throat, oral ulceration, abnormal bruising or bleeding.
Hypersensitivity reactions(fever, rigors, rash, myalgia, arthralgia, hypotension, dizziness)
Hepatotoxicity (hepatic necrosis, biliary stasis, cholestatic jaundice)
Alopecia
Severe diarrhoea in inflammatory bowel disease population.
Rare (≥1 in 10000 and <1 in 1000)
Skin cancers
Pneumonitis (reversible)
Pancreatitis

For further information refer to Summary of Product Characteristics.

Drug Interactions

The drug interactions listed below are those listed in the BNF as being clinically significant. For full list of drug interactions please refer to BNF and summary of product characteristics for the drug prescribed.
Allopuriniol- avoid use as enhances effect and causes increased toxicity of mercaptopurine . if concomitant therapy is required advised to reduce dose of mercaptopurine to one quarter of the usual dose.
Antibacterials -Sulfamethoxazole (as co-trimoxazole) and trimethoprim – increased risk of haematological toxicity.
Anticoagulants – mercaptopurine possibly reduces the effect of coumarins e.g. warfarin.
Clozapine- avoid concomitant use, increased risk of angranulocytosis
Febuxostat manufacturer advises avoidance of mercaptopurine
Administration of live attenuated vaccines should be avoided
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For full details of potential drug interactions refer to BNF or the product SPC

Precautions and Contraindications

Contraindications

- Moderate/ severe renal or liver impairement
- Significant haematological impairment
- Thiopurine methyltransferase (TPMT) deficiency homozygous state: serious and fatal toxicity may occur.
- Hypersensitivity to mercaptopurine or any of the excipients
- Pregnancy- treatment should not generally be initiated during pregnancy but see caution section.
- Breast feeding – present in milk in low concentration, no evidence of harm in small studies – use if potential benefit outweighs risk.

Use in pregnancy

As both ulcerative colitis and Crohn's disease occur in young adults, managing IBD in pregnancy is not uncommon. Maintaining adequate disease control during pregnancy is essential for both maternal and fetal health.

If planning to conceive patients should be advised to contact their gastroenterologist.

If an unplanned pregnancy occurs, drug treatment should not be discontinued but advice should be sought from the specialist service on the future management of the patient.

It is important that the risk benefit ratio of continuing treatment is discussed with the patient and this is the responsibility of the specialist service.

Within the current guidelines on the management of inflammatory bowel disease in adults from the British Society of Gastroenterology there is reference to ongoing treatment with azathioprine during pregnancy but not with mercaptopurine.

The BNF does state that mercaptopurine should not be used in pregnancy although within gastroenterology clinical practice does suggest that it may be appropriate in some patients. **It is important that immediate advice is sought from the consultant gastroenterologist if a patient currently prescribed mercaptopurine becomes pregnant or is planning a pregnancy**.

Cautions

- Renal or hepatic insufficiency
- Patients should be advised to limit their exposure to ultraviolet light and sunlight and to wear high factor suncreams and or protective clothing to limit risk of photosensitivity and skin cancer.
- Patients who have not previously had chicken pox should be advised to seek medical attention if they come into contact with this or shingles. Patients receiving azathioprine exposed to chickenpox or shingles, passive immunisation should be carried out using varicella-zoster immunoglobulin.
- The administration of live vaccines is contra-indicated on theoretical grounds.

Monitoring

Baseline:

Baseline monitoring FBC, U&E's, LFTs and creatinine.
Pre screening for TPMT may be considered.
Check Varicella status - check varicella zoster serology in patients where there is an unclear history of chicken pox or shingles.
Check hepatitis B&C status and Epstein Barr status.

Full Blood Count (FBC's) and Liver function tests (LFTs)

Following initiation of treatment monitor at 2 weeks, 4 weeks and three months and then three monthly thereafter.
Further monitoring at intervals of two and four weeks is required following any changes in dose.

Treatment should be stopped and advice from the supervising specialist Sought if:

Laboratory results

WBC < 3 x 10^9 /L
Neutrophils <1.5 x 10^9 /L
Platelets <150 x 10^9 /L
LFTs > Twice upper limit of normal ALT and Alk Phos
In additional to haematological values a rapid fall or consistent downward trend in any value should prompt caution and extra vigilance.

Expected results

MCV increase above normal range
Lymphocytes reduce below normal range

Clinical condition

Acute abdominal symptoms of pancreatitis – **stop drug and seek specialist advice**
Fever, arthralgia, mylagia on starting - **stop drug and seek specialist advice**
Skin significant and new – **stop mercaptopurine and check FBC**. If FBC abnormal contact specialist for advice. Wait until rash resolves and consider restarting at reduced dose, providing no blood dyscrasias.

Sore throat or abnormal bruising – **withhold drug until FBC results known. Contact hospital specialist**

Nausea or anorexia – may be self limiting, **reduce dose, stop drug if persistent**

Varicella –if in contact with the virus, contact hospital specialist clinician.

Indication of Likely Cost of Therapy in Primary Care

Mercaptopurine 50mg tablets - £54.27 for 25 tablets

(January 2016 Drug Tariff)

Information Given to the Patient

Patient information leaflet supplied to patient during initial clinic visit when treatment first discussed.

All patients are encouraged by the gastroenterology service to contact the National Association for Colitis and Crohn's disease which provides a wide range of advice for patients and carers on the implications of living with these long term conditions which includes patient information leaflets on treatment with azathioprine. These can be downloaded from their website.
http://www.nacc.org.uk

British Society for Gastroenterology has produced an information sheet for patients on the use of azathioprine and mercaptopurine which also may be a useful reference for prescribers. A copy of this sheet can be downloaded from their website.
http://www.bsg.org.uk/pdfworddocs/azaibdpt.doc

Contact Details

Nurse specialists

For Lincoln & Louth
Clinical Nurse Specialist – Inflammatory Bowel Disease
Tel no 01522 512512 ext 2006 Bleep 2128

For Boston & Grantham
Clinical Nurse Specialist – Inflammatory Bowel Disease
Tel 01205 446549 Bleep 621

References

1. British National Formulary (BNF) edition 70 September 2015 - March 2016.
2. Cambridgeshire and Peterborough Clinical Commissioning Group Shared care guideline mercaptopurine – Inflammatory bowel disease. 21st April 2015.
3. eMC Summary of product Charcateistics, mercaptopurine 50mg tablets . Last Updated on eMC 31-Mar-2015 Aspen . Accessed 29th January 2016.
4. Guidelines for the management of inflammatory bowel disease in adults. C. Mowat, A Cole, A Windsor et al. On behalf of the IBD section of the British Society of Gastroenterology. GUT 2010.

Original Authors:

David Allen
Clinical Nurse Specialist – Inflammatory Bowel Disease ULHT

C.M.Johnson
Interface Lead Pharmacist
NHS Lincolnshire

Dr Glenn Spencer
Consultant Gastroenterologist
ULHT

Updated February 2016.
C.M.Johnson
Interface lead pharmacist
Arden & GEM CSU