LINCOLNSHIRE CLINICAL COMMISSIONING GROUPS in association with UNITED LINCOLNSHIRE HOSPITALS TRUST

SHARED CARE GUIDELINE: Azathioprine covering use in Dermatology and Gastroenterology

All prescribing of Azathioprine for Rheumatology indications remains with the Rheumatology service.

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* 68, September 2014 – March 2015, pg.5)
Aims:
(1) 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.
(2) 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.
(3) 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.
(4) 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 the 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

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.

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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: azathioprine
Brand Name: generic tablets or Imuran®
Form and Strength: 25mg and 50mg film coated tablets

Specialist Responsibilities

The specialist secondary/tertiary care service will:

1. Send a letter to the GP requesting that the GP participates in shared care. As part of the communication the GP should be signposted to where they can find a copy of the shared care protocol e.g. the PACEF website http://lincolnshire-pacef.nhs.uk/lincolnshire-prescribing-and-clinical-effectiveness-forum-pacef.
2. Ensure that the patient receives supplies of azathioprine 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 azathioprine according to dosage regimen and undertake monitoring of clinical response and side effects, until monitoring responsibility is transferred to the patient's GP.
6. Provide patient with pre-treatment information leaflet indicating the risks and benefits associated with azathioprine therapy. The patient will be informed to stop medication and contact their GP immediately if any of the following occur, vomiting, diarrhoea, rash, mouth ulcers, bruises, itching, bleeding, fever, rigors, sore throat, jaundice or other infections.
7. Communicate promptly any changes in biochemistry monitoring and modification of azathioprine dose to the GP if applicable.
8. Periodically review the patient's clinical condition.
9. Have a mechanism in place to receive rapid referral of a patient from the GP in the event of deteriorating clinical condition.

10. Follow up any adverse drug reactions reported by the GP and report back to the GP.
11. Advise the GP on continuing or stopping azathioprine 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 azathioprine for the patient once the dose has been stabilised.
3. Monitor the FBCs and LFTs two and four weeks following any dose changes.
4. Undertake the ongoing monitoring as detailed on page 7 of this protocol.
5. Promote and and monitor compliance and ask patient about adverse effects – particularly unexplained bleeding, bruising, purpura (or other skin changes), sore throat, fever or malaise. Treatment should be stopped and urgent advice should be sought from the specialist if any signs/symptoms that are potentially associated with bone marrow suppression or hypersensitivity are reported.
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. Patients will have been stabilized on azathioprine, normally having received at least 12 weeks treatment.
2. The specialist will have carried out an assessment of efficacy and tolerability.

Licensed Indications

Dermatology

Licensed use –dermatomyositis, pemphigus vulgaris
Unlicensed use – psoriasis, severe chronic eczema, immunobullous disease, chronic actinic dermatitis, other autoimmune skin conditions and as a steroid sparing agent.

Gastroenterology

Licensed use autoimmune chronic active hepatitis
Unlicensed use as 2nd line therapy for patients with ulcerative colitis or Crohn's disease.

Recommended Dosage and Administration

Dermatology

Start at 1.5mg/kg and then increase to maximum dose of 3mg/kg if needed. Adjust if TPMT level abnormal.

Gastroenterology

Adult daily dose 2-2.5 mg/kg or less if TPMT is low.
Rheumatoid arthritis
Initially 1-3mg/kg daily reduced to maintenance.
If no improvement within 3 months consider withdrawal.

Background Pharmacology

Azathioprine is a cytotoxic purine analogue which interferes with nucleic acid synthesis and is extensively metabolised to mercaptopurine.
It is used as an immunosuppressant either alone or in combination with corticosteroids when it produces a steroid sparing effect.
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.

Adverse Effects

Common – nausea, vomiting or diarrhoea. Nausea & vomiting can be relieved by dividing the daily dose and administering tablets after meals.
Uncommon - Bone marrow suppression, leucopoenia & thrombocytopenia. Patients should be warned to report any signs or symptoms of bone marrow suppression such as infections, unexplained bruising or bleeding.
Hypersensitivity reactions including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and interstitial nephritis if any of these occur stop treatment and contact specialist for urgent advice.
Other adverse events frequency not known: cholestatic jaundice, colitis in patients also receiving corticosteroids, hair loss, herpes zoster infection, increased sensitivity to infections in patients also receiving corticosteroids, liver impairment.
Rare adverse effects: Hepatic veno-occlusive disease, lymphoma, pancreatitis, pneumonitis and red cell aplasia.

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.
Allopurinol - avoid use as enhances effect and causes increased toxicity of azathioprine, if concomitant therapy is required advised to reduce dose of azathioprine to one quarter of the usual dose.
Antibacterials - Sulfamethoxazole (as co-trimoxazole) and trimethoprim – Avoid use as increased risk of serious haematological toxicity.
Anticoagulants – reduced effect of warfarin
Antivirals – myelosuppressive effects of azathioprine possibly enhanced by ribavirin.
ACE inhibitors – increased risk of anaemia and leucopoenia when given by captopril especially in renal impairment and increased risk of anaemia when azathioprine given with enalapril, also especially in renal impairment.
Aminosalicylates – increased risk of haematological toxicity (leucopoenia).
Febuxostat - avoidance of azathioprine advised by manufacturer.
Avoid live vaccines such as oral polio, oral typhoid, measles, mumps and rubella (MMR), Bacillus Calmette-Guerin (BCG) and yellow fever whilst on immunosuppressive therapy.
Patients taking azathioprine along with other immunosuppressive therapy, including steroids are at risk of secondary infections.
For full details of potential drug interactions refer to BNF or the product SPC.

Precautions and Contraindications

Contraindications

Hypersensitivity to azathioprine/mercaptopurine.
Moderate/severe renal or liver impairment
Significant haematological impairment.
Thiopurine Methyl Transferase (TPMT) deficiency – homozygous state: **serious and fatal toxicity may occur.**
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.

Cautions

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.
Patients with a deficiency in the enzyme thiopurine methyltransferase (TPMT) as these patients may have a higher risk of bone marrow toxicity. This can be exacerbated by co-administration with drugs that inhibit TPMT such as sulfasalazine, mesalazine, balsalazide or olsalazine.
Use with caution in patients with renal failure, hepatic disease and frail elderly: dosages used should be at the lower end of the range.
Hepatitis B&C infection or a history of tuberculosis.
Use with caution in patients with confirmed or suspected alcoholism.
Patients prescribed azathioprine should be advised to limit exposure to sunlight by wearing protective clothing and using high factor sunscreens.
Patients should be advised to report any signs of bone marrow suppression or hypersensitivity i.e. infection, fever, cough, unexplained bruising or bleeding, fatigue, hypotension, myalgia, dizziness to their GP and this should be reported to the hospital clinician or specialist nurse.

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 foetal 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 the advice is to continue use of azathioprine during pregnancy as the risks to the foetus from disease activity appears to be greater than continued therapy.
The current edition of the BNF states:
There is no evidence that azathioprine is teratogenic, however there have been reports of low birth weight babies and premature births.

Monitoring

Baseline:

Baseline monitoring FBC, U&E's, LFTs and creatinine. Check Varicella status - check varicella zoster serology in patients where there is an unclear history of chicken pox or shingles.

Pre-screening for TPMT is routine for all dermatology patients but is at the consultant's discretion for gastroenterology patients.

Ongoing monitoring

Full Blood Count (FBC's) and Liver function tests (LFTs) weekly for 6 weeks then every 2 weeks until dose stable for 6 weeks then monthly.

U&E's and creatinine should continue to be monitored every 6 months.

After dose increase repeat FBC and LFTs after two weeks and then monthly.

If dose and test results stable for 6 months consider monitoring of FBC and LFTs can be reduced to every 3 months or as requested by specialist service.

In patients with heterozygote for TMPT, monitoring should continue at monthly intervals.

CRP – every three months to assess response to treatment.

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

Laboratory results WBC < 3.5 x 10^9 /L

Neutrophils <1.5 x 10^9 /L

Platelets <150 x 10^9 /L

Lymphocytes <0.5 x 10^9 /L

LFTs > Twice upper limit of normal ALT and Alk Phos

In additional to absolute 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

Rash or oral ulceration: withhold treatment and seek specialist advice.

Abnormal bruising or severe sore throat withhold azathioprine until FBD results available and then discuss with specialist team.

Acute abdominal symptoms of pancreatitis – stop drug and seek specialist advice.

Fever, arthralgia, myalgia on starting - stop drug and seek specialist advice.

Decreased resistance to infection stop azathioprine if patient systemically unwell with significant infection and seek specialist advice.

Drug related acute shortness of breath - Stop drug contact specialist for urgent advice and if severe refer for urgent assessment.

Sudden cough – if persistent organise a chest X ray and if abnormal seek specialist advice.

Indication of Likely Cost of Therapy in Primary Care

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Azathioprine 25mg tablets - £2.63 (28's)
Azathioprine 50mg tablets - £2.79(56's)
Imuran 25mg £10.99 (100's)
Imuran 50mg £7.99 (100's)

Information Given to the Patient

Dermatology

British Association of Dermatologists have produced an information sheet for patients on the use of azathioprine which is available at www.bad.org.uk/shared/get-file.ashx?id=71&itemtype=document

Gastroenterology

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

ULHT Dermatology Team:
Dermatology nurses
Lincoln (01522) 573712
Pilgrim (01205) 446111
Dermatology secretaries Lincoln (01522) 573412 and 573680
Dermatology secretaries Pilgrim (01205) 446436 and 446165
Dermatology secretaries Grantham (01476) 565232

ULHT gastroenterology team
Nurse specialists
For Lincoln & Louth
Consultant Nurse Specialist - Inflammatory Bowel Disease Tel no 01522 512512 ext. 2006 Bleep 2128
For Boston & Grantham
Consultant Nurse Specialist - Inflammatory Bowel Disease Tel 01205 446549 Bleep 621

References

1. BNF 70 September 2015 - March 2016.
2. Drug Tariff January 2016
3. Cambridgeshire and Peterborough clinical commissioning group shared care guidelines Azathioprine for inflammatory conditions.

4. BSR and BPHR quick reference guideline for monitoring of disease modifying antirheumatic drug (DMARD) therapy. Prepared May 2007 and updated November 2009.

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Plus add lead details for gastroenterologist.