NHS LINCOLNSHIRE in association with
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SHARED CARE GUIDELINE: Unlicensed use of Azathioprine 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* 61, March 2011, 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 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 NHS Lincolnshire Prescribing Advisers.

Date of Issue: June 2011
Review Date: June 2013

Drug Details
Approved Name: azathioprine
Brand Name: Imuran – generic preparations also available
Form and Strength: 25mg and 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 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. 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 azathioprine therapy. The patient will be informed to stop medication and contact their GP immediately if any of the following occur, rash, mouth ulcers, bruises, itching, bleeding, fever, 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. **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 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 FBC and LFTs two and four weeks following any changes in dose.
4. Undertake the ongoing monitoring as detailed on page 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 azathioprine 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.
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 2-2.5 mg/kg or less if TPMT is low.

Background Pharmacology

Azathioprine is a cytotoxic purine analogue which interferes with nucleic acid synthesis and is extensively metabolised to mercaptopurine.

Preparations Available

Azathioprine 25mg & 50mg tablets

Adverse Effects

Common – nausea which can be relieved by administering tablets after meals.
Uncommon - Bone marrow suppression, leucopenia & 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, arthralgia, dizziness, rigors, hepatitis, pancreatitis, alopecia and increased susceptibility to viral, fungal and bacterial infections

Drug Interactions

Allopurinol- avoid use as enhances effect and causes increased toxicity.
Sulfamethoxazole (as co-trimoxazole) and trimethoprim – increased risk of haematological toxicity.
Anticoagulants – reduced effect of coumarins
Clozapine – increased risk of agranulocytosis
Febuxostat - avoidance of azathioprine advised by manufacturer.
Antivirals – myelosuppressive effects of azathioprine possibly enhanced by ribavirin.
Administration of live attenuated vaccines should be avoided.
For full details of potential drug interactions refer to BNF or the product SPC.

Precautions and Contraindications

Patients who have not previously had chicken pox should be advised to seek medical attention if they come into contact with this or shingles.
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.

Use with caution in patients with renal failure, hepatic disease and cardiac failure.

Use with caution in patients with confirmed or suspected alcoholism.

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 the advice is to continue use of azathioprine during pregnancy as the risks to the fetus 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.

Contraindications

Marked leucopenia (WBC $<2.5 \times 10^9$ /L)
Thrombocytopenia (platelets $<100 \times 10^9$ /L)
Severe anaemia
Previous hypersensitivity to mercaptopurine or azathioprine
Breast feeding

Monitoring

Baseline:

Baseline monitoring FBC, U&Es, LFTs and creatinine.
Pre screening for TPMT may be considered.

Full Blood Count (FBCs) and Liver function tests (LFTs)

Following initiation of treatment monitor at 2 weeks, 4 weeks, and then monthly for three months or until stable.
Thereafter monitor FBC, full LFTs, creatinine every three months or as requested by specialist service.
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**
Fever, arthralgia, myalgia on starting - **stop drug**
Skin rash and stomatitis - may respond to dose reduction, **stop drug if severe**.
Sore throat or abnormal bruising – **withhold drug until FBC results known**
Nausea or anorexia – may be self limiting, **reduce dose, stop drug if persistent**

Indication of Likely Cost of Therapy in Primary Care

Azathioprine 25mg tablets -	£6.02 (28) or £9.96 (100)
Azathioprine 50mg tablets -	£5.04(56) or £8.57 (100)
Imuran 25mg	£10.99 (100)
Imuran 50mg	£7.99 (100)

(Ref June 2011 Drug Tariff, June 2011 MIMS)

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. The 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/pdf_word_docs/aza_ibd_pt.doc
BSG info sheet for prescribers: http://www.bsg.org.uk/pdf_word_docs/aza_ibd_dr.doc

Contact Details

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