DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE
SHARED CARE AGREEMENT

Azathioprine/6-mercaptopurine for patients 16+ years

1. REFERRAL CRITERIA

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient’s GP.
- Safe prescribing must be accompanied by effective monitoring.
- Patients will only be referred to the GP once the GP has agreed in each individual case.
- Patients will only be transferred over to GP’s when monitoring reaches monthly intervals.
- When transfer agreed the patient will be given a supply of Azathioprine/6-mercaptopurine sufficient for 4 weeks maintenance therapy.

2. AREAS OF RESPONSIBILITY

<table>
<thead>
<tr>
<th>GP responsibilities</th>
<th>Consultant responsibilities</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If NOT participating in shared care reply to the request from the consultant/specialist as soon as practicable (see appendix 1)</td>
<td>1. Discuss the possible benefits and side effects of treatment with the patient.</td>
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<tr>
<td>2. Ensure compatibility with other concomitant medication.</td>
<td>2. Perform baseline tests (as recommended in section vii)</td>
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<tr>
<td>3. Prescribe the dose and formulation recommended.</td>
<td>3. Provide results of baseline tests</td>
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<tr>
<td>4. Perform monitoring tests as specified in section vii.</td>
<td>4. Prescribe Azathioprine/6-mercaptopurine for the first three months or until medication monitoring is stable.</td>
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<tr>
<td>5. Adjust the dose as advised by the specialist.</td>
<td>5. Recommend dose of the drug and frequency of monitoring.</td>
</tr>
<tr>
<td>6. Stop treatment on the advice of the specialist or immediately if any urgent need to stop treatment arises.</td>
<td>6. To contact patient’s GP to request prescribing under shared care and send a link to or copy of the shared care protocol.</td>
</tr>
<tr>
<td>7. Ensure the patient is offered an annual flu vaccination and a one off pneumococcal vaccination. Live vaccinations are not recommended – See section vi</td>
<td>7. Annually review the patient and advise the GP promptly on when to adjust the dose, stop treatment or consult with the specialist.</td>
</tr>
<tr>
<td>8. Report any adverse effects to the referring specialist and the MHRA yellow card scheme</td>
<td>8. Ensure that clear backup arrangements exist for GPs to obtain advice and support.</td>
</tr>
</tbody>
</table>

**Patient responsibilities**

- Report to the specialist or GP if there is not a clear understanding of the treatment and share any concerns in relation to treatment.
- Inform specialist or GP of any other medication being taken including over-the-counter products.
- Report any adverse effects or warning symptoms to the specialist or GP whilst taking the drug.
### 3. COMMUNICATION AND SUPPORT

#### i. Hospital contacts:

**Chesterfield Royal Hospital NHS Foundation Trust**
- Contact the referring consultant/nurse via switchboard: 01246 277271

**Derby Teaching Hospitals NHS Foundation Trust**
- **Rheumatology**
  - Rheumatology helpline: 01332 787710
- **Gastroenterology**
  - IBD helpline: 01332 785504
  - Consultant/specialist nurse via switchboard: 01332 340131
- **Renal**
  - Specialist Pharmacist: 07500 976569
  - If unable to contact the specialist renal pharmacist consultants secretaries can be contacted: 01332 789344
- **Dermatology**
  - Consultant/specialist nurse via switchboard: 01332 265500
- **Respiratory**
  - Consultant via switchboard: 01332 340131

#### ii. Out of hours contacts and procedures:

- Contact the on-call Medic for the relevant speciality via switchboard: 01246 277271
- Pharmacy, DTHFT, ask for on-call pharmacist via switchboard: 01332 340131

#### iii. Specialist support/resources available to GP including patient information:

- **Rheumatology**
- **Renal**
  - Kidney Transplant Guideline, Transplant Unit, Nottingham University Hospital
  - Vasculitis and Immunosuppressive Protocol, Renal Unit, Royal Derby Hospital

### 4. CLINICAL INFORMATION

#### i. Prescribed indications

<table>
<thead>
<tr>
<th>Licensed</th>
<th>Unlicensed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rheumatoid Arthritis</td>
<td>Vasculitis</td>
</tr>
<tr>
<td>Dermatology &amp; Polymyositis</td>
<td>Psoriatic arthritis</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Autoimmune bullous disorder</td>
</tr>
<tr>
<td>Pemphigus vulgaris</td>
<td>Systemic lupus erythematosus</td>
</tr>
</tbody>
</table>

#### ii. Therapeutic summary

Azathioprine is a pro-drug and is rapidly broken down to 6-mercaptopurine (6-MP) *in vivo*.

It is an immunosuppressive drug which is effective in controlling several inflammatory and autoimmune diseases.

For rheumatoid diseases improvement may take 2 to 3 months to occur.

#### iii. Dose & Route of administration

**Azathioprine**
- Initially up to 2.5 mg/kg daily in divided doses, adjusted according to response, rarely more than 3 mg/kg daily; maintenance 1–3 mg/kg daily, consider withdrawal if no improvement within 3 months.

**Mercaptopurine**
- 6-Mercaptopurine for azathioprine intolerance:
  - **Ulcerative colitis - By mouth**
    - **Adult**
      - 1–1.5 mg/kg daily, some patients may respond to lower doses.
  - For other indication see BNF or as per specialist advice
  - Doses outside the recommended range may be considered with prior agreement with the specialist team and GP involved.
  - Lower doses should be considered for frail elderly and patients with renal impairment.

#### iv. Duration of treatment

Indefinite but may be withdrawn after a prolonged period of disease remission in selected cases.

It is also used as a rotational treatment in eczema.
| v. Adverse effects | Blood and lymphatic system disorders  
Bone marrow suppression  
Hypersensitivity reactions (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, rash, hypotension)  
Increased risk of skin cancer  
Nausea  
Neoplasms benign and malignant (including cysts and polyps)  
Increased risk of developing non-Hodgkin's lymphomas and other malignancies  
Viral, fungal and bacterial infections |
| vi. Immunisation | **Live vaccinations** are not recommended in patients on immunosuppression. JCVI Green book addresses this, recommending that low dose corticosteroids (prednisolone <20mg daily) and oral DMARD therapy at standard doses are not a contraindication in most patients, although clinician discretion is advised.  
• Annual flu vaccination is recommended  
• One off Pneumococcal vaccination recommended |
| vii. Monitoring Requirements | Best practice recommends the following precautions for specialists before commencing immunosuppressant therapy:  
Record patients blood pressure, height and weight if clinically indicated  
Screening for lung disease should be undertaken at clinician discretion on a case-by-case basis. The extent of screening should be influenced more by a patient's clinical features and risk factors for lung disease (e.g. underlying autoimmune disease or smoking history) rather than subsequent immunomodulating choice. Pre-existing lung disease should not be considered and absolute contraindication to any immunomodulating medication.  
Consultant to consider ECG where appropriate *especially when commencing medications associated with hypertension*  
Screen for viral hepatitis B&C and HIV in all new patients  
Investigate patient medical history including co-morbidities and previous immunomodulating medication use.  
For rheumatic patients CRP/ESR may be done every 3 months (this is not done for dermatology patients). These tests are part of the assessment of the underlying rheumatic disease rather than a requirement for monitoring of immunomodulation therapy. The monitoring CRP/ESR may be coordinated between secondary and primary care on an individual basis.  
Individuals with severely reduced TPMT activity (*homozygous*) should not be prescribed **AZATHIOPRINE** as serious and fatal toxicity may occur within 6 weeks of starting the drug. For mild/moderate (heterozygous) deficiency serious adverse events may occur anytime and as late as 6 months after treatment commences. Serious Adverse Events can be exacerbated by minor infections or drug interactions (See Drug Interactions & contra-indications). **Heterozygous** individuals should be prescribed Azathioprine/6-Mercaptopurine with Caution and reduced drug dosage. |

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**Consultant/specialist monitoring schedule**  
Baseline and 2 weekly until on a stable dose for at least 6 weeks  
• FBC  
• ALT and albumin  
• Creatinine/calculated GFR  
• U&E  
Annually review the patient and advise the GP promptly on when to adjust the dose, stop treatment or consult with the specialist.  
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**GP responsibility monitoring schedule**  
In patients following the 6 weeks of dose stability conduct monthly monitoring as above for three months followed by three monthly monitoring thereafter of:  
• FBC  
• ALT and albumin  
• Creatinine/calculated GFR  
• U&E
### Actions to be taken

1. Immunosuppressants prescribed to prevent transplant rejection should not be stopped without discussion with a member of the specialist team.
2. In addition to responding to absolute values in laboratory tests, it is also relevant to observe trends in results (e.g., gradual decreases in white blood cells (WBC) or albumin, or increasing liver enzymes).
3. Parameters below are to be used as a guide for clinicians rather than absolute values, where monitoring should be based on individualized basis. It is important to consider alternative explanations other than the immunomodulation agents, especially in patients who have been stable for prolonged periods.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Action</th>
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<tbody>
<tr>
<td>WBC &lt;3.5 x 10^9/l</td>
<td>Contact Specialist urgently and consider interruption</td>
</tr>
<tr>
<td>Neutrophils &lt;1.6 x 10^9/l</td>
<td>Contact Specialist urgently and consider interruption</td>
</tr>
<tr>
<td>Platelets &lt;140 x 10^9/l</td>
<td>Contact Specialist urgently and consider interruption</td>
</tr>
<tr>
<td>ALT and/or AST &gt;100 U/l</td>
<td>Contact Specialist urgently and consider interruption</td>
</tr>
<tr>
<td>Unexplained fall in albumin &lt;30g/l</td>
<td>Contact Specialist urgently and consider interruption</td>
</tr>
<tr>
<td>Mean cell volume &gt;105 f/l</td>
<td>Withhold and check serum B12, folate &amp; TFT and discuss with specialist team.</td>
</tr>
<tr>
<td>Creatinine increase for example &gt;30% over 12 months and/or calculated GFR &lt;60ml/min/1.73m²</td>
<td>Contact Specialist urgently and consider interruption</td>
</tr>
</tbody>
</table>

### Drug specific

- Abnormal bruising or severe sore throat: Withhold until FBC results available and discuss with the specialist team.
- Rash or oral ulceration: Contact Specialist urgently and consider interruption.
- IgG: Contact Specialist urgently and consider interruption.
- CRP/ESR: Contact Specialist urgently and consider interruption.

Note: Specific monitoring of eosinophil counts has been removed, as historically eosinophilia was an important marker for identifying toxicity from only gold therapy. This has been agreed with local specialists.

### Dosage increase

For dose increase, monitor 2 weekly until stable for 6 weeks. Dose and monitoring to be agreed with consultant:
- FBC
- ALT and albumin
- Creatinine/calculated GFR
- U&E

Monitoring to then continue at 3 monthly intervals.

When restarting treatment after an abnormality has been detected repeat bloods in 2 weeks and then monthly for 3 months. Following this resume monitoring frequency to what it was prior to the abnormality.

### Clinically relevant drug interactions

<table>
<thead>
<tr>
<th>Drug Interactions</th>
</tr>
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<tbody>
<tr>
<td>ACE inhibitors</td>
</tr>
<tr>
<td>Allopurinol</td>
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<tr>
<td>Aminosalicylates</td>
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<tr>
<td>Antiepileptic medications</td>
</tr>
<tr>
<td>Trimethoprim and Co-trimoxazole</td>
</tr>
<tr>
<td>Warfarin and other anticoagulants</td>
</tr>
</tbody>
</table>

### For a full list of interactions please refer to the BNF

### Contraindications and cautions

**Contraindications**
- Pregnancy & breastfeeding:
- Suspected serious infection (requiring IV antibiotics or hospitalization) treatment should be discontinued.
- TPMT: see advice above.

**Cautions:**
- 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.
- TPMT deficiency: may be associated with delayed haematoxicity including bone marrow toxicity (see above).
- Patients with clinically significant renal impairment from any cause.
- Localised or systemic infection including hepatitis B or C and a history of TB.
• Appropriate to continue with therapy in patients with minor infections (e.g., uncomplicated urinary tract infections treated with a short course of antibiotics) seek advice from specialist
• Unexplained anaemia and/or cytopenia associated with marrow failure.
• Patients with deranged liver biochemistry or synthetic function
• Patients with Chronic Kidney disease

| x. Supply of ancillary equipment | N/A |
| xi. Supply, storage and reconstitution instructions | N/A |

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The Derbyshire Medicines Management Shared Care and Guidelines Group

This does not replace the SPC, which should be read in conjunction with it

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### References
1. EMC Summary of Product Characteristics for Azathioprine and Mercaptopurine accessed online 08/03/2017
2. British National Formulary 70, September 2015
3. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs, The British Society for Rheumatology, February 2017
4. The Green book, Immunisation against infection disease, September 2014, accessed online 08/03/2017
PRIVATE & CONFIDENTIAL
«GP_TITLE» «GP_INITIALS» «GP_SURNAME»
«GP_ADDRESS_1»
«GP_ADDRESS_2»
«GP_ADDRESS_3»
«GP_ADDRESS_4»
«GP_POSTCODE»

DEERSHIRE JAPC SHARED CARE AGREEMENT LETTER

Dear «GP_TITLE» «GP_SURNAME»

Your patient was seen on {Insert date} with a diagnosis of {Insert diagnosis}. I have initiated the following medication {Insert drug name} and am writing to ask you to participate in the shared care for this patient.

This medication has been accepted as suitable for shared care by the Derbyshire Joint Area Prescribing Committee (JAPC). I agree to the secondary care responsibilities set out in the shared care agreement for this medication (available from www.derbyshiremedicinesmanagement.nhs.uk/clinical_guidelines/shared_care_guidelines). I am therefore requesting your agreement to share the care of this patient. Where preliminary tests are set out in the agreement I have carried these out and results are below.

<table>
<thead>
<tr>
<th>Dose Regimen</th>
<th>Date {Insert medicine name} started</th>
<th>Date for GP to start prescribing {Insert medicine name} from</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tbody>
</table>

The baseline test results are (if applicable):
See overleaf for initiation criteria.

I confirm I have explained to the patient: the risks and benefits of treatment, the baseline tests conducted the need for monitoring, how monitoring will be arranged, and the roles of the consultant / nurse specialist, GP and the patient in shared care. I confirm the patient has understood and is satisfied with this shared care arrangement at this time.

If you do NOT wish to participate in shared care for this patient, usually under clinical grounds, please complete the attached form.

Yours sincerely

{Consultant name}
**GP RESPONSE TO SHARED CARE** (only complete & send if **NOT** participating in shared care)

Shared care is produced by GPs and specialists knowledgeable in the field of that drug usage. The shared care has been approved by the JAPC. This allows a more convenient service to the patient and cost effective use of NHS resources.

<table>
<thead>
<tr>
<th>Patient:</th>
<th>NHS No:</th>
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<table>
<thead>
<tr>
<th>Consultant:</th>
<th>Medicine requested for shared care:</th>
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</table>

I will **NOT** be undertaking the GP responsibilities as described in the agreed shared care guideline. My clinical reasons for declining shared care for this patient are listed in the box below:

Yours sincerely

{GP name}
{Surgery}

Please send a copy of this response to:

1. The specialist/consultant requesting shared care
2. **AN ANONYMISED COPY OF THIS FORM ONLY** to the Medicines Management and Clinical Policies and Decisions Team, 1st Floor East Point, Cardinal Square, 10 Nottingham Road, Derby, DE1 3QT or E-MAIL: ddccg.medicinesmanagement@nhs.net

*(Sending a copy of this form to the Medicines Management and Clinical Policies and Decisions Team will help to identify any inappropriate requests for shared care e.g. indication not covered, hospital monitoring requirements not fulfilled. It will also help to inform the CCG prescribing group of the reasons shared care is not being undertaken allowing for changes to be made in future updates to improve patient care).*