

**Cardiff & Vale (C&V) UHB Corporate Medicines Management Group (c MMG)**  
**SHARED CARE and NEAR PATIENT TESTING**

Azathioprine is a Near Patient Testing (NPT) drug in Cardiff and Vale UHB for all indications except solid organ transplants (see separate SCP CV 04) and patients who are heterozygote for TPMT where it is then Shared Care only (Secondary Care is responsible for the monitoring of these patients)

**Drug: AZATHIOPRINE**

**Protocol number CV 51**

**Indications:** For adults and children with various auto-immune conditions, usually when corticosteroid therapy alone provides inadequate control.

### **General Guidance**

This protocol sets out details for the shared care of patients taking **azathioprine** and should be read in conjunction with the General Guidelines for Shared Care. Sharing of care requires communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. **The doctor who prescribes the medication legally assumes responsibility for the drug and the consequences of its use.** The prescriber has a duty to keep themselves informed about the medicines they prescribe, their appropriateness, effectiveness and cost. They should also keep up to date with the relevant guidance on the use of the medicines and on the management of the patient's condition.

### **A. Consultant responsibilities**

1. When treatment is **initiated** send Shared Care/ Near Patient Testing request form with Shared Care Protocol to GP.
2. Baseline and continued monitoring of biochemical and hematological parameters until patient is stabilized including pre-treatment check of thiopurine methyl transferase (TPMT)
3. Initiate azathioprine following full discussion with the patient of benefits and risks and undertake monitoring of clinical response and side effects.
4. Check patient's immune status to *Herpes Zoster*
5. A monitoring booklet will be provided. The patient will be informed to contact their GP immediately if any of the following occur: diarrhoea, rash, mouth ulcers, bruises, itching, bleeding, fever, sore throat, jaundice or other infection.
6. When a GP positive response to SC/NPT has been received and patient has been stabilised send a letter to GP "handing over" the SC/NPT of the patient to the GP.
7. Respond to any request from GP to review the patient due to adverse effects of therapy.
8. Advise the GP on continuing or stopping azathioprine therapy following medical review of the patient and associated drug therapy

- If Near Patient Testing not agreed notify GP if patient is failing to attend for appropriate monitoring and advise GP on appropriate action.

## **B. General practitioner responsibilities**

- Within one week of receipt return the completed Shared Care/Near Patient Testing request form to indicate whether or not willing to undertake Shared Care/Near Patient Testing.
- Prescribe **azathioprine** as part of the shared care agreement
- Where Near Patient Testing is agreed monitor the parameters indicated (see page 2), document results in the patient's monitoring booklet and report to and seek advice from the consultant on any aspect of patient care which is of concern. If not appropriate/possible for taking blood at the practice, the nearest hospital phlebotomy service may be used.
- Monitor the general health of the patient.
- Report to and seek advice from the consultant on any aspect of patient care which is of concern.
- Report adverse effects of therapy to the consultant and the Medicines and Health Care products Regulatory Agency (MHRA).
- Recommend that patient receives pneumococcal vaccination and annual influenza vaccine.
- If Near Patient Testing not agreed to act on advice provided if patient does not attend for appropriate monitoring.

## **C. Patient responsibilities**

- Consent to treatment with azathioprine.
- Attend regular appointments with specialist centre and GP.
- Report any side effects to the specialist or GP whilst taking azathioprine
- Provide monitoring booklet to be updated.

## **Dosage Regimen**

Dose depends on indication but usual maintenance dose is in the range of 1-3mg/kg/day. The target azathioprine dose will depend upon the patient's weight, baseline thiopurine methyltransferase (TPMT) level and patient factors such as renal and hepatic impairment.

<b>TPMT activity: (U/ml)</b>	Deficient (homozygous deficient) <10	Carrier/Intermediate (heterozygous) 10-24	Normal (homozygous normal) 25-50
Target Azathioprine dose *	Do not use	Reduced dose or use alternative treatment.	Normal dose

\* specific doses not detailed as these may vary with indication.

If TPMT level is low, alternative immunosuppressive therapy should be considered. If TPMT level is intermediate then a more gradual dose titration schedule should be used with close FBC and LFT monitoring or an alternative treatment regimen considered depending upon coexistence of other risk factors such as renal or hepatic insufficiency.

## **Monitoring**

### Before treatment

FBC, Creatinine & electrolytes, LFTs & TPMT assay. The TPMT assay provides additional information of risks related to treatment but does not replace routine monitoring. Patients with higher levels of serum TPMT may require higher doses of azathioprine. Homozygous deficiency is associated with serious and fatal toxicity that may occur within 6 weeks of starting azathioprine.

### During treatment

***In patients, heterozygote for TPMT, monitoring of FBC and LFTs should continue at monthly intervals at a minimum.***

***These patient groups should be monitored in Secondary Care and not by the GP***

**Monitoring for all other indications in patients homozygous normal for TPMT activity.**

FBC weekly or fortnightly for first four to eight weeks (or until two weeks after the final dose increase- whichever is sooner) and then every three months.

Repeat FBC two weeks after any dose increase.

LFTs at one month, two months, and then every three months.

Repeat LFTs two weeks after any dose increase

**Withhold azathioprine and discuss with specialist if any of the following occurs: -**

WBC <  $4.0 \times 10^9 /L$  \*

Neutrophils <  $1.5 \times 10^9 /L$

Platelets <  $150 \times 10^9 /L$

AST/ALT > twice upper limit of normal

Rash or oral ulceration

Abnormal bruising or severe sore throat (check FBC immediately)

\* **patients may continue treatment if WBC is  $3.0 - 4.0 \times 10^9 /L$  if the neutrophil count is above  $1.5 \times 10^9 /L$**

If **MCV >105fl** – check serum folate and B12 and TSH. Treat any underlying abnormality. If results normal discuss with specialist team

Please note that in addition to absolute values for haematological indices a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance

### **Adverse effects**

Adverse reactions occur in 15-28% of patients taking azathioprine.

**Haematological:** Bone marrow suppression (neutropenia, thrombocytopenia, rarely anaemia)-commonest dose-limiting adverse effect. Haemolytic anaemia and macrocytosis is rare.

**Hepatic:** Dose-related reversible cholestatic hepatotoxicity (hepatitic reactions are far commoner than cholestasis which is rare but more serious), occasionally pancreatitis.

**Gastrointestinal:** Nausea, anorexia and occasionally vomiting. This is usually dose-related and will resolve after a brief interruption and restarting at a lower dose. Short term use of concomitant anti- emetics may also be useful. Other adverse effects can include mucositis, abdominal pain, diarrhoea and pancreatitis.

**Mucocutaneous:** Skin rash (uncommon), photosensitivity reactions, rarely alopecia.

**Renal:** Acute renal insufficiency (very rare).

**Pulmonary:** Acute pneumonitis (very rare, reversible).

**Other** Severe hypersensitivity reactions, with rash, fever, eosinophilia, headache, arthralgia, myalgia, rhabdomyolysis, neurotoxicity and cardiac, renal, pulmonary and hepatic involvement have been reported. The risk of non-melanoma skin cancer and lymphoproliferative malignancy may be increased. The manufacturers of azathioprine state that the risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. The risk is increased, for example, in transplant recipients receiving aggressive treatment and such therapy should be maintained at the lowest effective consultants.

### **Interactions**

- Allopurinol should be stopped and an alternative agent used.
- The anticoagulant effect of warfarin may be reduced by azathioprine. Regular INR monitoring should be undertaken if both agents are used.
- Thiazide diuretics and furosemide have been observed to increase metabolism of azathioprine resulting in treatment failure.

- Angiotensin-converting enzyme inhibitors have been reported to induce severe leucopenia in patients taking azathioprine.
- Phenytoin, Sodium Valproate, Carbamazepine – concomitant use of azathioprine reduces absorption of these drugs
- Co-trimoxazole and trimethoprim can cause life-threatening haematotoxicity.

### **Special recommendations**

- Patients who have not previously had chickenpox should be identified and advised to seek medical attention if they subsequently come into contact with somebody who has chickenpox or shingles. Passive immunization should be carried out using varicella zoster immunoglobulin (VZIG).
- Live vaccines should be avoided in patients taking azathioprine. A diminished response to killed vaccines, such as Hepatitis B has been observed in patients receiving a combination of azathioprine and corticosteroid therapy.
- Exposure to sunlight and UV light should be limited and patients should wear protective clothing and use a sunscreen with a high protection factor.
- Patients should also be warned to seek advice if severe abdominal pain develops as azathioprine can cause pancreatitis. Serum amylase should be checked urgently in this situation.
- Manufacturer's advice is that azathioprine should not be given to patients who are pregnant or likely to become pregnant without careful assessment of risk versus benefit. In clinical practice azathioprine is used routinely in pregnancy.
- Azathioprine is present in breast milk in low concentrations and it not thought to be harmful to the baby.

### **Contact Details**

The Shared Care Request form and handover letter (when patient is stabilised) will include necessary contact details.

**Review date** December 2017