Ref: APCSCG/015 **South East London Shared Care Prescribing Guideline for Azathioprine for the prevention of organ rejection in ADULT liver transplant recipients in EXISTING patients only (i.e. those already being prescribed the drug in primary care). Date reviewed and approved:** July 2020 **Next review date:** July 2022 (or sooner if evidence or practice changes)

SHARED CARE PRESCRIBING GUIDELINE: Continuation of Azathioprine for the prevention of organ rejection in adult liver transplant recipients in existing patients only (i.e. those already being prescribed the drug in primary care)

NOTES to the GP

The information in the shared care guideline has been developed in consultation with the boroughs under South East London CCG and it has been agreed that it is suitable for shared care.

This document should provide sufficient information to enable you to make an informed decision regarding the clinical and legal responsibility for prescribing azathioprine for the prevention of organ rejection in adult liver transplant recipients.

Due to a planned repatriation of immunosuppressants in the future, shared care is **not** appropriate for new patients. **Shared care will only be requested for existing patients who are already being prescribed this drug in primary care by their GP practice**. Having a shared care agreement in place will help support safer prescribing in primary care and clarify responsibilities of clinicians and patients.

The questions below will help you confirm this:

- Is the patient already being prescribed azathioprine for this clinical indication by your practice?
- Is the patient's condition predictable or stable?
- Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this shared care prescribing guideline?
- Have you been provided with relevant clinical details including monitoring data?

If you can answer YES to all these questions (after reading this shared care guideline), then it is appropriate for you to accept prescribing responsibility.

If the answer is NO to any of these questions you should contact the requesting consultant or your local Borough Medicines Management Team. There may be implications for the patient where the invitation to share care is declined. For example, the patient may need to be changed to an alternative treatment regimen. It would not normally be expected that shared care prescribing would be declined on the basis of cost.

Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient by the doctor initiating treatment. **It is important that patients are consulted about treatment and are in agreement with it**.

Prescribing should follow requirements in the South East London Interface Prescribing Policy.
The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use. The patient's best interests are always paramount.

Once you have read the shared care guideline and considered the information above, please complete the GP decision form on the next page and email (preferred) or fax back to the requesting clinician if you are in agreement to continue participation in shared care.

GP DECISION FORM

This shared care agreement outlines suggested ways in which the responsibilities for ***continuing*** to manage prescribing of azathioprine for the prevention of organ rejection in adult liver transplant recipients can be shared between the specialist and general practitioner (GP). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

AGREEMENT TO PARTICIPATE IN SHARED CARE
Azathioprine for the prevention of organ rejection in adult liver transplant recipients already being prescribed this drug in primary care (i.e. existing patients only)

Consultant/Specialist Name:	**Patient name:**
Consultant/Specialist signature:	**Patient Hospital Number:** **Patient NHS Number:**
Date completed:	**Patient Agreement:**
Hospital requesting shared care:	Patient agrees to shared care £ Patient does not agree to shared care £
GP Name:	
This is to confirm that I agree to continue participation in shared care for azathioprine for the prevention of organ rejection in adult liver transplant recipients for this patient as outlined in this shared care document	
GP Signature:	
Date signed:	

ACTION

1. HOSPITAL CONSULTANT — **Tick to confirm**

- § Explain shared care to patient and obtain agreement — Date agreement obtained:_____ o
- § Indicate requesting hospital — o
- § Complete and sign agreement — o
- § Email full shared care guideline (including signed agreement to GP) — o
- § Place original in patient's notes — o

2. GP PRACTICE

§ If **in agreement** to participate in shared care, sign and email this sheet back **within 2 weeks** of receipt **of request from specialist** to the liver pharmacy team (kch-tr.liverpharmacy@nhs.net)

§ If **do not agree** to participate in shared care, contact consultant and local Borough Medicines Management Team within 2 weeks of receipt to discuss. If after discussion it is agreed not to undertake shared care for this patient, both the consultant and the local Borough Medicines Management team should be informed.

§ Once decision reached file a copy in the Patient's medical notes.

Azathioprine tablets for the prevention of organ rejection in adult liver transplant recipients already being prescribed this drug in primary care (i.e. existing patients only)

Azathioprine is an antimetabolite immunosuppressant, used in combination with other immunosuppressive agents after liver transplant. Azathioprine should not be used as monotherapy following liver transplantation.

CIRCUMSTANCES WHEN SHARED CARE IS APPROPRIATE

- Prescribing responsibility will only be transferred when the consultant and the GP are in agreement that the patient's condition is stable or predictable.
- Shared care will only be requested for **existing** patients who are already being prescribed this drug in primary care by their GP practice. Having a shared care agreement in place will help support safer prescribing in primary care and clarify responsibilities of clinicians and patients.
- The hospital will provide the patient with a supply of therapy for at least the first 3 months post discharge.

2. AREAS OF RESPONSIBILITY

Consultant / Specialist Team responsibilities

- Establish or confirm diagnosis and assess patient suitability for treatment
- Baseline monitoring tests:
  - Liver function tests including aspartate transaminase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin and albumin
  - Creatinine, urea and electrolytes
  - Full Blood Count including differentials, platelets and CRP.
  - Clotting – INR
  - Thiopurine S-methyltransferase (TPMT) level must be taken prior to starting treatment.
- Discuss treatment with patient and ensure they have a clear understanding of it. Where appropriate obtain signed consent.

Information provided to patient

  - Detailed patient education programme including self-medication program on ward prior to discharge
  - Post-transplant patient education booklet which includes diet and lifestyle advice.

- Email a signed shared care guideline with patient details completed to GP for consideration of shared care request.
- Acceptance of shared care should NOT be assumed. Confirmation to participate is required from GP.
- It is the responsibility of the initiating hospital clinic to contact GP.
- Initiate treatment and provide a supply of therapy for at least the first 3 months post discharge.
- Prescribe and monitor treatment according to local guideline or formulary until patient's condition is stable or predictable.

After agreement to shared care

- Inform GP when patient's condition is stable or predictable and > 3 months post-transplant.
- Inform GP of abnormal monitoring results and any changes in therapy.
- Evaluate adverse events reported by GP or patient.
- Carry out ongoing monitoring and follow up in line with page 5 and 6 of this shared care guideline, including continued need for therapy.
- To review patient at the request of GP should any problems arise (side-effects / lack of efficacy) within 2 weeks.
- To communicate promptly with the GP if immunosuppression treatment is changed within 3 working days.
- To report any suspected adverse effects to the MHRA: http://www.yellowcard.gov.uk.

General Practitioner responsibilities

- Consider shared care proposal within 2 weeks of receipt.
- If in agreement to continue shared care prescribing responsibility, confirmation to the requesting consultant is required within 2 weeks of receipt of this shared care request by completing and emailing the agreement on page 2.
- If do not agree to shared care discuss with requesting consultant or local Borough medicines management team within 2 weeks of receipt of shared care request.

After agreement to shared care

- Prescribe dose as recommended once the patient's condition is stable or predictable and > 3months post-transplant. To adjust dose as advised by the specialist.
- Monitor general health of patient and check adverse effects as appropriate.
- Inform Transplant Specialist of suspected adverse effects and also report to the MHRA via yellow card scheme via http://www.yellowcard.gov.uk if necessary.
- Stop treatment on advice of specialist.
- Check compatibility interactions when prescribing new or stopping existing medication. If advice is needed from the specialist team, please see communication information on page 8.
- Carry out monitoring and follow up according to page 6 of this shared care guideline.
- Discuss any abnormal results with specialist consultant and agree any action required.
- Refer to Transplant Specialist urgently if patient non-compliance with immunosuppression is suspected.
- Only ask specialist to take back prescribing if unmanageable problems arise, for example erratic blood levels or nonadherence.
- To refer back to specialist if the patient's condition deteriorates.
- Add SNOMED code for shared care prescribing "415522008"

Patient's / Carer's responsibilities

- To contact the specialist or GP if he or she does not have a clear understanding of any aspect of the treatment.
- To inform prescribing specialist, GP and other healthcare professionals of any other medication being taken, including over the counter products, alternative therapies or recreational drugs.
- To inform community pharmacists that they are using azathioprine before purchasing medication over-the-counter
- To attend all hospital and GP appointments
- To take medicines as agreed and take steps to ensure that no doses are missed and not to share medicines with others
- To read the patient information leaflet included with the medication.
- To report any adverse effects or warning symptoms to GP or hospital specialist
- To inform GP and hospital of any changes in addresses or telephone contact numbers.

3. CLINICAL INFORMATION

NOTE: The information here is not exhaustive. Please also consult the current Summary of Product Characteristics (SPC) for azathioprine prior to prescribing for up to date prescribing information, including detailed information on adverse effects, drug interactions, cautions and contraindications (available via www.medicines.org.uk)

Indication(s)

Prevention of organ rejection following liver transplantation.

Place in Therapy

In combination with other immunosuppressants. Azathioprine should never be used as a single agent post liver transplant. Azathioprine is usually given in combination with tacrolimus (Prograf or Advagraf) and /or steroids. Azathioprine may be added in to augment immunosuppression in those with graft rejection or at increased risk of graft rejection, or for those with nephrotoxicity with tacrolimus (Prograf or Advagraf). Azathioprine should never be prescribed with mycophenolate mofetil.

Dose & route of administration

The dose will be advised by the Transplant Consultant. Doses are adjusted according to individual patient requirements. Azathioprine is available as 25mg and 50mg tablets.

1. Renal-sparing immunosuppressant regimen

Azathioprine as part of a renal-sparing immunosuppressive regimen where calcineurin inhibitor (tacrolimus or ciclosporin) minimisation or withdrawal is being considered should be initiated as follows;

- Azathioprine should be initiated at a dose of 1mg/kg/day rounded to the nearest 25mg dose before the calcineurin inhibitor is withdrawn.
- Therapeutic effect is evident only after several weeks and thus other immunosuppressants should be reduced or withdrawn with caution until a minimum of two weeks after initiating azathioprine.
- Azathioprine should not be used as monotherapy following liver transplantation.
- Patients on azathioprine without a calcineurin inhibitor should be maintained on prednisolone 7.5mg daily.

2. Adjunctive therapy for patients at high-risk of rejection

Azathioprine as adjunctive therapy to calcineurin (tacrolimus or ciclosporin) and/or steroids for patients at increased risk of rejection should be initiated as follows:

- Initiate azathioprine at a dose of 1mg/kg/day.
- Maintain adequate calcineurin (tacrolimus or ciclosporin) levels until a minimum of two weeks after initiating azathioprine as therapeutic effect of azathioprine is only evident only after several weeks.

Duration of treatment

Lifelong or as defined by Transplant Consultant.

Criteria for stopping treatment

Only after discussion with Transplant Consultant.

Monitoring Requirements including frequency

Transplant Consultant:

The following will be monitored and reviewed by the Transplant Consultant at each liver post-transplant outpatient appointment;

- Clinical assessment including examination of suspicious skin lesions.
- Immediately post-transplant, clinic appointments will be weekly. The interval between appointments will be gradually increased based on individual patient needs. All post-transplant patients will be reviewed at least annually in the liver outpatient clinic..
- Bloods are taken for FBC, CRP, INR, urea and creatinine, eGFR and LFT's (aspartate transaminase (AST), alkaline phosphatase (ALP), gamma glutamyl transferase (GGT), bilirubin and albumin, INR). These will be performed every 2 weeks for 2 months then monthly for 3 months and if stable then every 3 months thereafter. Additional tests may be required for individual patients.
- Patients receiving azathioprine should be instructed to report immediately any evidence of infection, unexpected bruising or bleeding or other manifestations of bone marrow depression.

GP:

Provide an annual review of the following to monitor for adverse effects of medication:

- Monitor patients overall health and wellbeing
- Monitor blood results (FBC, U+Es and LFTs, CRP) in line with recommendations from the hospital consultant/SPR.
- Monitor for any signs or symptoms of bone marrow suppression e.g. infection or unexplained bruising or bleeding. Any suspicion of bone marrow suppression should necessitate immediate liaison with the Transplant Centre.
- Skin care – Skin cancers account for the commonest malignancies after liver transplantation. Suggested preventative measures include:
    - Patients should carry out regular self-examination and report any new lesions to ensure early detection and ablation of premalignant lesions. Any suspicious lesions require prompt specialist referral.
    - Patients should avoid direct sun exposure, use appropriate clothing for outdoor activities and apply sunscreens with high sun protection factor. Guidelines for patients can now be found on the web (http://www.scopenetwork.org, http://www.itscc.org).

- Report any adverse events to the hospital specialist, where appropriate.
- Report any suspected adverse effects to the MHRA: http://www.yellowcard.gov.uk.
- Influenza vaccine: annual immunisation with influenza vaccine is strongly recommended for all post-transplant patients who are taking immunosuppressant medications such as azathioprine.
- Pneumococcal vaccine is recommended for all adults who are immuno-compromised. Revaccination is not recommended. Confirm patient's vaccine status.

Follow up arrangements

Transplant Consultant:

- Frequency of outpatient appointments is dependent on individual patient progress. Each patient will be reviewed annually as a minimum. Following each outpatient clinic or inpatient stay, any medication changes will be communicated to the patient and the GP by letter within 3 working days. The patient will be informed by telephone of any changes in drug doses that need to be made on an urgent basis.
- Assess need for further investigation.

GP:

- Monitor patients overall health and wellbeing.
- Carry out monitoring requirements as detailed above annually or at more frequent intervals dependent on individual patient needs.

Practical issues including other relevant advice/information

Reminder: The information here is not exhaustive. Please also consult the current Summary of Product Characteristics (SPC) for azathioprine prior to prescribing for up to date prescribing information, including detailed information on adverse effects, drug interactions, cautions and contraindications (available via www.medicines.org.uk).

Adverse drug reactions

N.B These are common adverse effects but this list is not exhaustive. Refer to British National Formulary for list of all potential adverse effects.

Red cell aplasia

Cases of pure red cell aplasia have been reported with azathioprine; dose reduction or discontinuation should be considered under specialist supervision.

Neutropenia and thrombocytopenia

Usually resolved by reducing the dose – refer to specialist.

Hypersensitivity reactions

Hypersensitivity reactions (including malaise, dizziness, vomiting, diarrhoea, fever, rigors, myalgia, arthralgia, rash, hypotension and interstitial nephritis) call for immediate withdrawal – refer to specialist.

Nausea, vomiting and diarrhoea

Nausea, vomiting and diarrhoea may occur, usually starting early during the course of treatment.

Important Drug Interactions

N.B These are the common drug interactions but this list is not exclusive. Refer to BNF or Summary of Product Characteristics (www.medicines.org.uk) for list of all potential drug interactions with azathioprine. The Liver Team at King's would appreciate the opportunity to discuss the introduction of any new drug which may interfere with the metabolism of azathioprine before it is initiated. The liver pharmacists can be contacted for advice on 0203 299 9000 extension 35714 or 0203 299 9000 and ask to page 699581 via switchboard.

- **Ribavirin**
  Ribavirin inhibits the enzyme, inosine monophosphate dehydrogenase (IMPDH), leading to a lower production of the active 6-thioguanine nucleotides. Severe myelosuppression has been reported following concomitant administration of azathioprine and ribavirin; therefore co-administration is not advised unless initiated under the supervision of the Liver Team.
- **Co-trimoxazole (Sulphamethoxazole and trimethoprim)**
  Where possible, concomitant administration of cytostatic drugs, or drugs which may have a myelosuppressive effect, such as penicillamine, should be avoided. There is an increased risk of haematological toxicity when azathioprine given with co-trimoxazole.
- **Allopurinol**
  Do not prescribe concomitant allopurinol due to risk of severe myelosuppression.
- **Aminosalicylate (mesalazine,sulfasalazine,olsalazine,balsalazide)**
- There is a possible increased risk of leucopenia when azathioprine is prescribed with aminosalicylates. Therefore, lower doses of azathioprine may need to be considered when administered together.

- **Methotrexate**
  When azathioprine is administered concomitantly with high dose methotrexate, the dose should be adjusted to maintain a suitable white blood cell count.
- **Anticoagulants**
  Inhibition of the anticoagulant effect of warfarin and acenocoumarol has been reported when co-administered with azathioprine; therefore higher doses of the anticoagulant may be needed. It is recommended that coagulation tests are closely monitored when anticoagulants are concurrently administered with azathioprine.
- **Febuxostat**
  Avoid co-prescribing azathioprine with febuxostat. Inhibition of xanthine oxidase by febuxostat may cause increased plasma concentrations of azathioprine leading to toxicity.

Vaccines

Live vaccines are contra-indicated and should be avoided.. For further information on vaccines see BNF, chapter 14 for a list of live vaccines.
Please contact the Liver Pharmacy team for further advice on vaccines.

Contraception

Please contact the Liver Team at King's regarding contraception advice.

Pregnancy

In general, immunosuppression should be continued during pregnancy. All patients who wish to become or who are pregnant should be reviewed by a Transplant Consultant for consideration of immunosuppressive regimen choice and/or dose adjustment. It is essential to maintain adequate immunosuppression levels during pregnancy and pregnancy can dramatically affect immunosuppressant drug handling.

Breastfeeding

Azathioprine is present in milk in low concentration. No evidence of harm in small studies so can be used with caution if potential benefit outweighs risk.

Information provided to the patient

- Detailed patient education program including self-medication program on ward prior to discharge
- Post-transplant patient education booklet including information about brand prescribing and how to obtain further supplies.

Evidence Base for treatment and key references

1. British National Formulary 70 September 2019.
2. Summary of Product Characteristics. Azathioprine 50mg tablets. Accord UK Ltd. Accessed via www.medicines.org.uk. Last updated 13/10/17

4. COMMUNICATION AND SUPPORT

NOTE: King's College Hospital NHS Foundation Trust is the only Trust in SEL that manages this patient group.

King's College and Princess Royal Hospitals switchboard: 0203 299 9000	
Consultant/specialist team - Liver Transplantation Prof. Michael Heneghan Dr. Kosh Agarwal Dr. Varuna Aluvihare Dr. Abid Suddle Dr Deepak Joshi Professor Alberto Sanchez-Fueyo Dr Marianne Samyn	Consultant Hepatology Transplant Secretary Tel: 0203 299 4952 Fax: 0203 299 3899
Consultant Surgical Team – Liver Transplantation Prof. Nigel Heaton Mr. Andreas Prachalias Mr. Parthi Srinivasan Mr. Hector Vilca-Melendez Mr Krishna Menon Mr Wayel Jassem Miss Miriam Cortes	Consultant Surgical Transplant Secretary Tel: 0203 299 3762
Immediate medical advice, and out of hours Transplant Registrar	Tel: 0203 299 9000 Bleep 142 or out-of-hours via switchboard (0203 299 9000)
Immediate general advice, and out of hours Transplant Co-Ordinators	Tel: 0203 299 4024 or out of hours via switchboard (0203 299 9000), Aircall 842688 via switchboard (0203 299 9000)
Medication – Prescribing advice, interactions, availability of medicines Transplant Pharmacist: Lindsay Smith	Pharmacy Department Secretary; 0203 299 3347 699392 via switchboard (0203 299 9000) Direct extension: 0203 299 5714 Email: kch-tr.liverpharmacy@nhs.net
Transplant ward Todd ward	Tel: 0203 299 3310
Immunosuppressant Drug Monitoring Phillip Morgan	Tel: 020 3299 3147