City and Hackney Clinical Commissioning Group
Homerton University Hospital Foundation Trust

SHARED CARE GUIDELINE

LEFLUNOMIDE

Treatment of Psoriatic Arthritis and Rheumatoid Arthritis in Adult Rheumatology Patients

DOCUMENT TO BE SCANNED INTO ELECTRONIC RECORDS AND FILED IN NOTES

INTRODUCTION – Indication and Licensing

Leflunomide is a disease modifying anti-rheumatic drug (DMARD). The active metabolite of Leflunomide inhibits the human enzyme dihydroorotate dehydrogenase (DHODH) and exhibits antiproliferative activity. Leflunomide exerts anti-inflammatory effect mainly by inhibiting the production of lymphocytes. Therapeutic effect usually starts after 4 to 6 weeks and may further improve up to 4 to 6 months.

Licensed indications: psoriatic arthritis, rheumatoid arthritis.

PATIENT PATHWAY

Clinical Speciality / Indication	Prescribing Initiated by	Prescribing Continued by	Monitored by	Duration of treatment
Rheumatology	Rheumatologist	Hospital to transfer the prescribing to GP once patient is on a stable dose and blood results are stable.	Hospital or GP as per shared care agreement letter.	Ongoing if efficacious.

Reviews & dose adjustments
The patient will be reviewed periodically by the hospital specialist team in clinic. Dosing adjustments are to be done by the hospital and this information communicated to the GP in writing within 14 days.

Patients outside of City and Hackney area
It may be more appropriate for blood test monitoring to be done locally if this is more convenient for the patient. The patient should be given a copy of their latest blood results to bring to their clinic appointment (if the hospital specialist team is not able to access this information electronically).

ORAL DOSE AND ADMINISTRATION

- **Initial dosing:** 10mg once daily
- **Usual maintenance dose:** 10 – 20mg once daily
- No dose adjustment is required in patients with mild renal insufficiency (eGFR >60ml/min/1.73) and in those above 65 years of age.

Vaccinations
- Annual vaccination against influenza is recommended.
- Pneumococcal vaccination should preferably be given prior to the initiation of Leflunomide, however if this is not possible it should still be administered and repeated every 5 years.
- Concomitant use of a live vaccine should be avoided, these include: oral polio, MMR, BCG and yellow fever vaccines.
- Treatment with Leflunomide at standard doses is not a contraindication for the shingles vaccine (Zostavax) for most patients (see JCVI Green Book). Discuss with the specialist team if the shingles vaccine is required.
- Patients who have not been immunised against chicken pox should report to their GP or specialist if they come in to contact with the virus. Passive immunisation should be carried out using varicella zoster immunoglobulin.

Alcohol intake
Patients should be advised to keep alcohol intake well within the government guidelines (maximum 2 units a day or 14 units per week). Note some specialists may suggest stricter limits which should be followed by the patient.

Washout procedure

Leflunomide has a long half-life and adverse effects may be seen for a long time after the drug is stopped. A washout procedure should be considered in patients having severe side effects and in men or women considering conception. This is only to be performed on advice of the specialist team.

- Colestyramine 8g three times daily for 11 days **or**
- Activated charcoal powder 50g four times daily for 11 days (use of colestyramine is more cost-effective than activated charcoal).

Measure the plasma concentration of Leflunomide metabolite A771726 twice at intervals of at least 14 days (testing kit available from the manufacturer), this should be below 0.02mg/L on both occasions. The washout procedure can be repeated as necessary.

- **Females:** waiting period of one-and-a-half months between the first occurrence of a plasma concentration below 0.02 mg/L and conception is required.
- **Males:** after a waiting period of at least 3 months and if both plasma concentrations are below 0.02 mg/L, the risk of foetal toxicity is very low.

CAUTIONS

- Impaired bone-marrow function including anaemia, leucopenia or thrombocytopenia (avoid if significant and due to causes other than rheumatoid arthritis).
- Recent/concomitant treatment with other hepatotoxic or myelotoxic drugs.
- Localised or systemic infection including hepatitis B or C and history of tuberculosis.

CONTRAINDICATIONS

- Mothers who are breastfeeding.
- Pregnancy (including male and female patients who are trying to conceive).
- Liver impairment.
- Severe immunodeficiency states (e.g. AIDS) and serious infections.
- Moderate to severe renal insufficiency (no information available).
- Severe hypoproteinaemia (e.g. in nephrotic syndrome).

INTERACTIONS

- **Phenytoin** – plasma concentration of phenytoin possibly increased by Leflunomide.
- **Rifampicin** – possibly increases plasma concentration of the active metabolite of Leflunomide.
- **Warfarin** – Leflunomide possibly enhances the anticoagulant effect of warfarin.
- **Colestyramine and activated charcoal:** concomitant use not recommended unless using for washout procedure. Elimination of Leflunomide is enhanced by these drugs.
- **AVOID herbal remedies** if possible due to unknown interaction potential.

MONITORING STANDARDS FOR MEDICATION AT THE ACUTE NHS TRUST

Pre-treatment monitoring to be done by the specialist team
FBC, LFTs, U&Es (including eGFR), CRP, ESR, height*, weight* and BP* (treat hypertension before initiating drug) Respiratory examination and check history of respiratory symptoms *Additional tests to be determined on an individual patient basis:* Chest X-ray, pulmonary function tests, varicella zoster, hepatitis B & C serology
Ongoing monitoring to be done by specialist team until patient is stable then GP to take over monitoring as per shared care agreement
FBC, LFTs, U&Es (including eGFR) every 2 weeks until on a stable dose for 6 weeks, then monthly for 3 months, then every 8 - 12 weeks thereafter. ***Concomitant use of methotrexate:*** extend monthly monitoring until stable for 12 months then consider reducing the frequency on an individual patient basis. **Weight and BP** at each hospital clinic visit

*There are established associations between inflammatory autoimmune disease and cardiovascular risk. Leflunomide use is also associated with hypertension and weight loss.

KEY ADVERSE EFFECTS & ACTIONS

Laboratory events	**Values**	**Actions (*what action should the GP take if identified in primary care)***
↓ WBC	<3.5 x 10^9/L	Reduction in WBC alone is not usually considered clinically significant. If this is accompanied by a reduction in neutrophil count then **stop drug and seek advice** from the specialist team.
↓ Neutrophil count	<1.6 x 10^9/L	**Stop drug and seek advice** from the specialist team.
↓ Platelet count	<100 x 10^9/L	
↑ ALT or AST	>2 times upper limit of normal	**Stop drug and seek advice** from the specialist team.

Please note: a rapidly increasing or decreasing trend in any values should prompt caution and extra vigilance. Some patients may have abnormal baseline values, specialist team will advise.

Adverse effects	**Actions (*what action should the GP take if identified in primary care)***
Gastrointestinal disturbances (nausea, diarrhoea), rash or itch	Give symptomatic treatment and consider dosage reduction. If symptoms are persistent, **stop drug and seek advice** from the specialist team.
Abnormal bruising or severe sore throat	**Stop drug** and check FBC immediately. Seek advice from the specialist team.
Breathlessness (pulmonary infiltration/pneumonitis reactions)	If increasing shortness of breath occurs, **stop drug and seek advice** from the specialist team.
Infection	Treat infection. Cautious vigilance is necessary to detect early evidence of infection. **Leflunomide may be stopped** during this period. **Seek advice** from the specialist team if in doubt.
Hypertension	Treat in line with NICE guidance. **Stop drug** if BP remains uncontrolled (after discussion with the specialist team).
Headache	If severe, consider dosage reduction. **Stop drug** (after discussion with the specialist team) if headache persists.
Weight loss	Monitor carefully and discuss with the specialist team.
Hair Loss	Consider dosage reduction, **stop drug** (after discussion with the specialist team) if severe.

Patients should be advised to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), fever or any other signs of infection, liver toxicity (e.g. nausea, vomiting, abdominal discomfort, yellowing of the skin or eyes or dark urine), and respiratory effects (e.g. shortness of breath).

The SCG lists only the key information. Please refer to the current British National Formulary and Summary of Product Characteristics for comprehensive information on cautions, contraindications, interactions and adverse effects.

PREGNANCY AND BREAST FEEDING

- Leflunomide is teratogenic and must be **AVOIDED** in pregnancy and lactation.
- **Females:** exclude pregnancy before treatment and effective contraception is essential during treatment and for at least 2 years after treatment in women. If a waiting period of up to approximately 2 years under reliable contraception is considered unpractical, prophylactic institution of a washout procedure may be advisable.
- **Males:** effective contraception is essential during treatment, to minimise any possible risk, prophylactic institution of a washout procedure is recommended in men wishing to father a child.
- Leflunomide is not known to reduce fertility in animal models.

Please refer to the current British National Formulary and Summary of Product Characteristics for comprehensive information.

SHARED CARE

Shared care guideline*:* is a document which provides information allowing patients to be managed safely by primary care, secondary care and across the interface. It assumes a partnership and an agreement between a hospital specialist, GP and the patient and also sets out responsibilities for each party. The intention to shared care should be explained to the patient and accepted by them. Patients are under regular follow-up and this provides an opportunity to discuss drug therapy. Intrinsic in the shared care agreement is that the prescribing doctor should be appropriately supported by a system of communication and cooperation in the management of patients. The doctor who prescribes the medicine has the clinical responsibility for the drug and the consequence of its use**.**

Consultant

1. Ensure that the patient/carer is an informed recipient in therapy.
2. Ensure that patients understand their treatment regimen and any monitoring or follow up that is required (using advocacy if appropriate). Issue any local patient information leaflets where appropriate.
3. Ensure baseline investigations are normal before commencing treatment.
4. Initiate treatment and prescribe until the GP formally agrees to share care (as a minimum, supply the first month of treatment or until patient is stabilised).
5. Send a letter to the GP requesting shared care for this patient.
6. Clinical and laboratory supervision of the patient by blood monitoring and routine clinic follow-up on a regular basis.
7. Send a letter/results notification to the GP after each clinic attendance ensuring current dose, most recent blood results and frequency of monitoring are stated (unless otherwise covered by letter e.g. from Rheumatology Clinical Nurse Specialist).
8. Where the GP is out of area and is not performing the phlebotomy, the blood test form/EPR request MUST specify that blood results are also copied to the GP. Specialist team to check with pathology IT if unsure on how to do this.
9. Evaluation of any reported adverse effects by GP or patient.
10. Advise GP on review, duration or discontinuation of treatment where necessary. Where urgent action is required following tests the hospital team will telephone the patient and inform GP.
11. Inform GP of patients who do not attend clinic appointments.
12. Counsel the patient on contraception and what to do if pregnancy occurs. Document in the notes.
13. Ensure that backup advice is available at all times.
14. Advise that the patient receives appropriate vaccination in primary care either prior to commencing treatment and/or during a treatment that is likely to cause immunosuppression.

General Practitioner

1. Ensure that the patient understands the nature, effect and potential side effects of the drug before prescribing it as part of the shared care programme and contact the specialist for clarification where appropriate.
2. Monitor patient's overall health and well-being.
3. Report any adverse events to the consultant, where appropriate.
4. Report any adverse events to the MHRA / CHM, where appropriate.
5. Prescribe the drug treatment as described.
6. Provide contraception advice and prescription as appropriate.
7. Provide appropriate vaccinations to patients receiving treatments likely to cause immunosuppression.

City and Hackney Medicines Management Team

1. To provide feedback to acute trusts via Joint Prescribing and Medicines Management Group.
2. To support GPs to make the decision whether to accept clinical responsibility for prescribing.
3. To support acute trusts in resolving issues that may arise as a result of shared care.

Patient/ Carer

1. Report any adverse effects to their GP and/or specialist.
2. Ensure they have a clear understanding of their treatment.
3. Report any changes in disease symptoms to GP and/or specialist.

4. Alert GP and/or specialist of any changes of circumstance which could affect management of disease e.g. plans for pregnancy.
5. Take/ administer the medication as prescribed.
6. Undertake any monitoring as requested by the GP and/or specialist.

Costs

Drug Product	Cost in primary care
Leflunomide 10mg tablets	30-tab pack = £10.18
Leflunomide 20mg tablets	30-tab pack = £11.13

Based on BNF edition 73 (March – September 2017)

RESOURCES AVAILABLE

- Arthritis Research UK website accessible *via* http://www.arthritisresearchuk.org
- Drinkaware website accessible *via* https://www.drinkaware.co.uk
- The Joint Committee on Vaccination and Immunisation (JCVI) Green Book accessible *via* https://www.gov.uk

Relevant contact details	
Consultant or Registrar on-call *via* switchboard	020 8510 5555
Clinical Nurse Specialist (helpline)	07917 521 117
Generic email for department	huh-tr.rheumliaison@nhs.net (clinical queries) huh-tr.rheumatologyadmin@nhs.net (admin queries)
Trust Homerton University Hospital NHS Foundation Medicines Information	020 8510 7000
City and Hackney Medicines Management Team	0203 816 3224

References

- SCG template adopted from NELMMN and Barts Health NHS Trust
- BNF edition 73, accessible *via* https://ebnf.homerton.nhs.uk (last accessed 20 April 2017).
- Summary of product characteristics, accessible *via* www.medicines.org.uk (last accessed 20 April 2017).
    1. Arava 10mg tablets
    2. Leflunomide 10 mg Film-coated Tablets (Sandoz)
- The British Society for Rheumatology, accessible *via*: http://www.rheumatology.org.uk (last accessed 7 April 2017).
    1. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease modifying anti-rheumatic drugs (2017).
    2. BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists (2008).

Date SCG approved by Joint Prescribing Group (JPG): 05/2017 Review date: 05/2020