Leflunomide

Shared Care Guideline

Specialist details	Patient identifier
Name: _____	
Location: _____	
Tel: _____	**Date:** _____

Introduction

Licensed indications include: active rheumatoid arthritis and active psoriatic arthritis in adults.

Unlicensed indications include: seronegative polyarthritis and vasculitis.

Adult dosage and administration

Dose: 10 - 20mg once daily.

Available as: 10mg, 15mg and 20mg tablets.
A 100mg tablet is also available for a three day loading dose referred to in product literature. This can speed up the onset of effect but may increase the incidence of adverse effects and is often omitted in practice.

Hospital specialist responsibilities

- Assess if the patient is suitable for treatment with leflunomide.
- Agree shared care with patient's GP.
- Varicella Zoster immune status: if non-immune, consider immunisation prior to starting treatment.
- Provide the patient/carer with relevant (preferably written) information on use, side effects and need for monitoring of medication.
- Undertake baseline tests as indicated in monitoring table.
- Review results of safety monitoring and request additional tests as required.
- Monitor disease response to treatment and need to continue therapy.
- Continue to review the patient at agreed specified intervals, sending a written summary to the GP whenever the patient is reviewed.
- Provide any other advice or information for the GP if required.

Monitoring table		Hospital specialist	GP				Hospital specialist
			During treatment				
Test	Indication	Pre-treatment baseline	Until on stable dose for 6 weeks	Next 3 months	Thereafter*	Only where indicated by specialist**	At review
FBC	Baseline assessment, dose adjustment	✓	Every 2 weeks	Every month	Every 3 months	Every 6 months	As part of review or as clinically indicated
LFTs							
U&Es, eGFR							
Blood pressure							
Weight	To check for weight loss						
ESR/CRP	Disease Activity Scoring	✓	Every 3 months				
Height & weight	Baseline assessment	✓	Not routinely required				If clinically indicated
Chest x-ray	Baseline respiratory assessment and TB screening	If clinically indicated					
PFTs, TB screening if indicated							
Ask about oral ulceration/sore throat, unexplained rash or unusual bruising/bleeding		✓	At every consultation				✓

If a further DMARD/JAK is added as combination therapy, or the dose is increased, the initial starting schedule should be reinstated.
There may be clinical circumstances where the frequency of monitoring may vary. This should be specified by initiating specialist.
* If used in combination with methotrexate, monthly monitoring should continue.
** Patients who have been stable for 12 months can be considered for reduced frequency monitoring on an individual patient basis as recommended by specialist at review or by specialist communication

GP responsibilities

- Prescribe leflunomide.
- Arrange and record ongoing monitoring as advised by specialist (see monitoring table), ensuring practice systems are in place to recall patients for monitoring blood tests.
- Follow-up any non-compliance with the monitoring schedule. The risks of cessation of therapy versus risks of toxicity should be considered. Contact the specialist if treatment is stopped or further advice required.
- Report any adverse drug reactions to the initiating specialist and the usual bodies (eg. MHRA/CHM).
- Ensure no drug interactions with other medicines.
- Administer **inactivated** influenza vaccine annually unless otherwise advised by the initiating specialist.
- Check patient has had ONE DOSE of pneumococcal vaccine (revaccination is not recommended except every five years in patients whose antibody levels are likely to have declined more rapidly eg. asplenia), see BNF or Green Book.
- Provide COVID 19 and **inactivated** shingles (Shingrix®) vaccination as appropriate as per local arrangements and Green Book
- Post exposure prophylaxis (antivirals or VZIG if antivirals are contraindicated) should be considered in non-immune at risk patients if exposed to chickenpox or shingles. Contact the consultant virologists, Regional Virus Laboratory, Royal Group of Hospitals on 07889 086 946 for advice if exposure is suspected. For other queries eg. those concerning exposure, infection or any recommendations relating to healthy susceptible household contacts, consult the Green Book and/or take additional advice from Regional Virus Laboratory, Royal Group of Hospitals
- Ask about unexplained rash, oral ulceration, sore throat or unusual bruising/bleeding at every consultation.

Withhold leflunomide and contact specialist if:

- WCC < 3.5 x 10^9/L
- Neutrophils < 1.6 x 10^9/L
- **Unexplained** eosinophilia > 0.5 x 10^9/L
- Platelets < 120 x 10^9/L
- MCV > 105fL, (check B12 & folate & TFT)
- AST/ALT > 3 times the upper limit of normal (for results between 2 – 3 x ULN, continue leflunomide, repeat bloods and seek specialist advice). Minor elevations of AST/ALT are common
- If renal impairment develops (not always appropriate to stop but may need dose adjustment)
- Unexplained fall in serum albumin
- Oral ulceration / sore throat
- Unexplained rash / abnormal bruising
- New or increasing dyspnoea or dry cough
- Severe weight loss (see below*)
- Uncontrolled hypertension.

Normal reference range may vary slightly between labs.
Please note an unusual fall or rise or a consistent downward or upward trend in any value should prompt review of the patient and extra vigilance. Some patients may have abnormal baseline values, specialist will advise.

Adverse effects, precautions and contraindications

Please note that leflunomide has a very long half life.
Washout procedure with colestyramine is recommended in cases of significant drug toxicity (check SPC or BNF for further information).
Dizziness / headache may occur. If severe, discuss with specialist.
Nausea can occur at any time during therapy. The symptom may resolve with dose reduction from 20mg to 10mg and/or addition of anti-emetic. Anorexia and up to 10% body weight loss* has been reported. Stop treatment if severe and discuss with specialist.
Diarrhoea occurs in approximately 20% of patients and is sometimes self-limiting. May respond to dose reduction or to loperamide / codeine phosphate. If persistent/severe, refer to specialist.
Hypertension. Mild increases in blood pressure are common. BP increases tend to affect those with pre-existing hypertension and may require additional antihypertensive therapy or cessation of treatment. Treat hypertension as per normal hypertension guidelines. If remains uncontrolled, withhold and refer to specialist.
Decreased resistance to infection especially respiratory / urinary tract or shingles / chickenpox. Temporarily withhold leflunomide if patient is systemically unwell with significant infection requiring anti-infective intervention (a washout procedure may be necessary if severe or persistent infection occurs). If in doubt, discuss with specialist.
Blood disorders: leucopenia, thrombocytopenia and anaemia. GPs should be alert to any unexplained bruising or bleeding.
Interstitial lung disease as well as rare cases of pulmonary hypertension have been reported. Pulmonary symptoms, such as cough and dyspnoea, may be a reason for discontinuation of the therapy and for further investigation, as appropriate. Patients should be made aware of this rare complication.
Alopecia. Diffuse hair loss may occur in up to 10% of patients. It is usually mild and is reversible on stopping medication. May respond to dose reduction.
Rash/skin itch. If mild, continue full dose and monitor. If moderate or severe, stop treatment and discuss with specialist (washout may be necessary).
Alcohol. Patients should be advised that alcohol consumption should be avoided or kept well within recommended safe national guidelines, due to the increased potential for liver toxicity.
Peripheral neuropathy has been reported.
Pregnancy / Contraception. Pregnancy must be excluded before start of treatment with leflunomide and reliable contraception should be used by men and women whilst on leflunomide. Contraception should be continued for at least 2 years in women and 3 months for men after discontinuing leflunomide. A **washout procedure** with colestyramine may reduce this period if required. Women considering pregnancy should stop leflunomide and undergo colestyramine washout before switching to alternative medication compatible with pregnancy. Refer immediately if a patient discovers she is pregnant whilst taking leflunomide.
Breastfeeding. Women must not **breastfeed** while receiving leflunomide.
Cancer risk. Patients receiving long-term immunosuppressive drugs are at increased risk of developing a malignancy. The most frequently occurring types are lymphoma and skin malignancy. The avoidance of excessive exposure to the sun, and the use of high factor sunscreen and protective clothing are advised. Adherence to population screening programmes is particularly important in this population.
Live vaccines. Consult the Green Book and take additional advice from initiating specialist if required.
Contraindications include:

- Serious infections
- Severe immunodeficiency states
- Patients with severe hypoproteinaemia
- Severe renal or hepatic impairment
- Severe anaemia, leucopenia or thrombocytopenia
- Pregnant/ breast feeding women or women of childbearing potential who are not using a reliable contraception.

Common drug interactions

Caution is advised when leflunomide is given together with drugs (other than NSAIDs) metabolised by cytochrome P450 2C9 such as **phenytoin**, **tolbutamide** and **warfarin**.
Rosuvastatin levels may be increased by leflunomide. A maximum rosuvastatin dose of 10mg is recommended. Caution is recommended with other statins and dose reduction may be required.
Rifampicin: plasma concentration of active metabolite of leflunomide possibly increased by rifampicin.
Note increased risk of toxicity with other **hepatotoxic** or **haematotoxic medicines**. If combined with methotrexate there may be an increased risk of hepatotoxicity and more frequent monitoring may be necessary.
Switching from leflunomide to another DMARD without following the washout procedure may also increase the risk of serious adverse reactions (eg. hepatotoxicity or haemotoxicity) even for a long time after the switching.

Communication

For any queries relating to this patient's treatment with leflunomide, please contact the specialist named at the top of this document.

This information is not inclusive of all prescribing information and potential adverse effects.
Please refer to full prescribing data in the SPC at www.medicines.org.uk or the BNF

Date prepared: June 2023 Date of review: June 2028