SHARED CARE GUIDELINE

Drug: Leflunomide

Introduction	**Indications**: Treatment of active rheumatoid arthritis and active psoriatic arthritis. **Background:** Leflunomide inhibits the enzyme dihydroorotate dehydrogenase and thus inhibits pyrimidine biosynthesis. It has immunomodulating/immunosuppressive characteristics, acts as an antiproliferative agent and displays anti-inflammatory properties. Response to treatment cannot be expected before four to six weeks and may further improve up to four to six months. **Definitions:** Stable dose – the dose will be titrated to achieve efficacy at the lowest dose. Once efficacy achieved and provided the patient can tolerate the dose, this will be termed "stable dose" Stable bloods – results of blood tests remain below the "alert" thresholds as set by national guidelines and have stayed at similar levels for at least two consecutive tests. N.B. The patient can continue to have active disease despite being on a stable dose or having stable bloods, so the "patient" is not referred to as "stable"
Form	Tablets 10mg, 20mg
Dose & Administration	In rheumatoid arthritis the recommended maintenance dose is leflunomide 10 mg to 20 mg once daily depending on the severity (activity) of the disease. In psoriatic arthritis the recommended maintenance dose is leflunomide 20 mg once daily.
Secondary Care Responsibilities	• Confirm the diagnosis • Exclude TB, severe immunodeficiency states e.g. AIDS, and severe infections. Check for absence of pregnancy in women of child-bearing age and ensure the patient understands the importance of contraception. Reliable contraception should be used by both men and women whilst on leflunomide and for at least 2 years after stopping leflunomide unless the washout procedure is used (see "CAUTIONS" below and the SPC for further details). • Discuss the benefits and side effects of treatment with the patient. Ensure that the patient understands which warning signs and symptoms to report. • Perform pre-treatment screening[4]: height, weight, blood pressure, FBC, LFT, albumin and, creatinine/ calculated GFR, • Patients should be assessed for co-morbidities, including evaluation for respiratory disease and screening for occult viral infection • Ensure that the patient understands not to expect improvement from the treatment straight away. • Provide the patient with prescriptions for leflunomide until on stable dose and undergoing 3 monthly monitoring. Provide the patient with a monitoring and dosage record booklet and ensure that the patient knows when and where to attend for monitoring. Encourage the patient to take responsibility for ensuring that results of tests are entered in the monitoring booklet. • Make arrangements for shared care with the patient's GP • Review the patient regularly to monitor the patient's response to therapy. • Advise the GP on frequency of monitoring, management of any dose adjustments and when to stop treatment. • Ensure that clear backup arrangements exist for GPs to obtain advice.
Primary Care Responsibilities	• Provide the patient with prescriptions for leflunomide once on stable dose and undergoing 3 monthly monitoring. • Reinforce advice about using reliable contraception for both men and women whilst on leflunomide and for at least 2 years after stopping leflunomide unless the washout procedure is used. Women to report any missed menses immediately with follow up pregnancy test. • Monitor at the recommended frequencies (see MONITORING below) and ensure that test results are recorded in the monitoring booklet.

	• Report any adverse events to the consultant or specialist nurse and stop treatment on their advice or immediately if an urgent need arises (see MONITORING below). • Report any worsening of control of the condition to the consultant or the specialist nurse. • Refer immediately if a patient discovers she is pregnant whilst taking leflunomide or within 2 years of discontinuation if drug washout has not been performed. • Follow immunisation programme
Immunisations	• Annual flu vaccination is recommended. • Pneumococcal vaccination is recommended • Covid-19 vaccination is recommended. • In patients exposed to chicken pox or shingles, if required, passive immunisation should be considered for varicella. Refer to Green book: Varicella: the green book, chapter 34 - Publications - GOV.UK • Live vaccines should be avoided including shingles unless specialist advice has been sought. The long half-life of leflunomide should be considered when contemplating administration of a live attenuated vaccine after stopping Leflunomide. See Green Book for details of vaccines in patients who may be immunosuppressed.
Common Drug Interactions	• Increased risk of toxicity with other hepatotoxic or haematotoxic drugs • Avoid alcohol or limit to well within the recommended limit • The active metabolite of leflunomide inhibits cytochrome P4502C9 (CYP2C9). Caution is advised when leflunomide is given together with drugs metabolised by CYP2C9 such as phenytoin, tolbutamide and warfarin. This list is not exhaustive; refer to SPC & BNF for further drug interactions.
Washout Procedure	The active metabolite of leflunomide has a long half-life. To aid drug elimination in cases of serious adverse events, before conception or before switching to another potentially hepatotoxic or haematotoxic DMARD, give cholestyramine 8g three times daily or activated charcoal 50g four times daily for 11 days. This is to aid elimination of the drug; total elimination will be longer than 11 days. Please note washout will inhibit action of oral contraceptives and therefore alternative contraception is required.
Cautions	• Impaired bone-marrow function including anaemia, leucopenia or thrombocytopenia • recent treatment with other hepatotoxic or myelotoxic disease-modifying antirheumatic drugs
Contraindications	• Severe immunodeficiency e.g. AIDs • Serious infections (leflunomide treatment should be temporarily discontinued until the patient has recovered from the infection) • Impaired liver function due to any cause • Severe unexplained hypoproteinaemia e.g. nephrotic syndrome • Moderate to severe renal impairment • Impairment of bone marrow function as indicated by significant anaemia and cytopenias • Pregnancy and breastfeeding: Strictly contraindicated • LIVE vaccines should be avoided; please see green book for further information. • Concomitant administration of hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) is not advisable except on specialist advise • Galactose intolerance, congenital lactose deficiency, glucose-galactose malabsorption as contains lactose
Pregnancy & Breastfeeding information	• Leflunomide is not a human teratogen but it is still not recommended in women planning pregnancy. Women considering pregnancy should stop and

	undergo cholestyramine washout before switching to alternative medication compatible with pregnancy. • If accidental conception occurs whilst a woman is taking leflunomide, the drug should be stopped immediately and cholestyramine washout given until plasma levels are undetectable. • Breastfeeding is not recommended as no data exist on excretion into breast milk. • Very limited evidence suggests leflunomide may be compatible with paternal exposure.
This guidance does not replace the SPC's, which should be read in conjunction with this guidance.	

MONITORING AND ADVERSE EFFECTS

Treatment Status	FBC	Creatinine/ calculated GFR	LFT	Albumin	Weight	ESR or CRP	BP
Initial monitoring until on stable dose for 6 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 3 months (for RA only)	Every 2 weeks
For next three months	Every month	Every month	Every month	Every month	Every month		Every month
Thereafter	Every 3 months	Every 3 months	Every 3 months	Every 3 months	Every 3 months		Every 3 months

N.B. If Leflunomide is co-prescribed with another immunosuppressant or potentially hepatotoxic drug all monitoring should be continued long-term at least once a month.

Following dose increases FBC, creatinine/ calculated GFR, albumin should be monitored every 2 weeks until on a stable dose for 6 weeks. Thereafter monitoring should then revert to the previous schedule used for initiation of leflunomide.

As per secondary care responsibilities, for clarity the frequency of monitoring should be specified in the initial shared care request.

The team responsible for prescribing the medication should also hold responsibility or monitoring
ie prescribing to be carried out in Primary care only once patient on stable dose and undergoing 3 monthly monitoring

In the event of the following adverse laboratory results or patient reported symptoms, withhold leflunomide until urgently discussed with specialist team and consider interruption in treatment:

- WCC < 3.5 x 10^9/L or less than the lower limit of reference range as per lab
- Neutrophils < 1.6 x 10^9/L or less than the lower limit of reference range as per lab
- Platelets < 140 x 10^9/L or less than the lower limit of reference range as per lab
- Mean cell volume > 105 fL
- Creatinine increase > 30% over 12 months and/or calculated GFR < 60 mL/min
- Unexplained eosinophilia > 0.5 x 10^9/L
- ALT and/or AST > 100 U/L
- Unexplained reduction in albumin < 30 g/L
- Severe or persistent diarrhoea
- Abnormal bruising or severe sore throat. Do a FBC.
- Persistent severe headache
- Severe hair loss
- Uncontrolled hypertension >140/90
- Severe rash or itch
- Cough or Increasing shortness of breath
- Systemically unwell with significant infection
- Stevens-Johnson Syndrome and DRESS

The specialist team may advise “washout” in addition to stopping (see above and SPC)

As well as responding to absolute values in laboratory tests, it is also relevant to observe trends in results (e.g. gradual decreases in white blood cells or albumin, or increasing liver enzymes). If urgent clinical abnormalities arise emergency access to specialist rheumatology advice should be sought.

Other adverse reactions:

- Nausea/diarrhoea: Give symptomatic treatment and consider dose reduction.

	• Weight loss: If >10% weight loss with no other cause identified, reduce dose or stop leflunomide and consider washout. • Decreased resistance to infection • **Severe** sore throat or abnormal bruising. • Cough or dyspnoea or breathlessness. Interstitial lung disease has been reported during treatment. It is potentially fatal and may occur acutely during therapy. Patients should be made aware of this rare complication and any patient presenting with an unexplained dry cough, dyspnoea or breathlessness must be referred immediately to the consultant. • Rash or itch: If mild consider dose reduction and/or an antihistamine. • Hair loss: If mild consider dose reduction. • Hypertension: If >140/90, treat in line with NICE guidance for hypertension • Headache. If severe consider dose reduction. • Peripheral neuropathy • For further possible side effects please refer to the SPC and BNF This list is not exhaustive; please refer to SPCs and BNF.

References

1. Summary of product characteristics. Arava 10mg tablets. Sanofi. Last updated on the EMC 9th June 2022. Accessed via: https://www.medicines.org.uk/emc/medicine/4056 [accessed online: 21st June 2022].
2. Summary of product characteristics. Arava 20mg tablets. Sanofi. Last updated on the EMC 7th June 2022. Accessed via: https://www.medicines.org.uk/emc/medicine/4055 [accessed online: 21st June 2022].
3. Ledingham et al. BSR/BHPR Non-Biologic DMARD Guidelines, June 2017. Accessed via: https://academic.oup.com/rheumatology/article/56/6/865/3053478
4. Flint et al. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding, January 2016. Accessed via: https://academic.oup.com/rheumatology/article/55/9/1693/1744535
5. UK Health Security Agency. Immunisation Against Infectious Disease 'The Green Book', 2021. Department of Health and Social Care. London, UK.

RELEVANT CONTACT LIST

Speciality	
Name and Title	Tel. No.

Appendix 1

Shared Care Agreement form

Request by Specialist Clinician for the patient's GP to enter into a shared care agreement

PLEASE NOTE: The use of this form is not compulsory, but the same information must be communicated between the specialist service and primary care in advance of entering into a shared-care agreement.

Part 1 - To be signed by Consultant / Associate Specialist / Speciality Trainee or Specialist Nurse (who must be a prescriber)

Dear Doctor:	Click or tap here to enter text.
Name of Patient:	Click or tap here to enter text.
Address:	Click or tap here to enter text.
	Click or tap here to enter text.
	Click or tap here to enter text.
Date:	Click or tap to enter a date.
Patient NHS Number:	Click or tap here to enter text.
Patient Hospital Number:	Click or tap here to enter text.
Diagnosed Condition:	Click or tap here to enter text.

I request that you prescribe:

(1) Click or tap here to enter text.
(2) Click or tap here to enter text.
(3) Click or tap here to enter text.
(4) Click or tap here to enter text.

for the above patient in accordance with the LMMG shared care guideline(s) (Available on the LMMG website).

Last Prescription Issued:	Click or tap to enter a date.
Next Supply Due:	Click or tap to enter a date.
Date of last blood test (if applicable):	Click or tap to enter a date.
Date of next blood test (if applicable:	Click or tap to enter a date.
Frequency of blood test (if applicable:	Click or tap here to enter text.

I confirm that the patient has been stabilised and reviewed on the above regime in accordance with the Shared Care guideline.

If this is a Shared Care Agreement for a drug indication which is unlicensed or off label, I confirm that informed consent has been received from the patient.

I will accept referral for reassessment at your request. The medical staff of the department are available if required to give you advice.

Details of Specialist Clinicians

Name:	Click or tap here to enter text.
Date:	Click or tap to enter a date.
Position:	Choose an item.
Signature:	Click or tap here to enter text.

(An email from the specialist clinician will be taken as the authorised signature)
In all cases, please also provide the name and contact details of the Consultant.

When the request for shared care is made by a Specialist Nurse, it is the supervising consultant who takes medicolegal responsibility for the agreement.

Consultant	Click or tap here to enter text.

Contact Details	
Telephone Number	Click or tap here to enter text.
Extension	Click or tap here to enter text.
Email Address	Click or tap here to enter text.

Part 2 - To be completed by Primary Care Clinician (GP)

I agree to prescribe and monitor Click or tap here to enter text. for the above patient in accordance with the LMMG shared care guideline(s) commencing from the date of next supply / monitoring (as stated in Part 1 of the agreement form).

Name:	Click or tap here to enter text.
Date:	Click or tap to enter a date.
Signature:	Click or tap here to enter text.

*Please sign and return a copy **within 14 calendar days** to the address above* **OR**

If you **do not** agree to prescribe, please sign below and provide any supporting information as appropriate:

I **DO NOT** agree to enter in to a shared care agreement on this occasion.

Name:	Click or tap here to enter text.
Date:	Click or tap to enter a date.
Signature:	Click or tap here to enter text.
Further information:	Click or tap here to enter text.