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 two or three months 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 and 20mg
Dose & Administration	• 10 – 20mg once daily • 10mg once daily when used in combination with another potentially hepatotoxic DMARD NB: The loading dose described in the SPC is not given due to a high incidence of GI side-effects

Secondary Care Responsibilities	• Confirm the diagnosis
	• Exclude active 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:
	  ○ FBC, LFTs, U&Es, creatinine/ eGFR, and body weight.
	  ○ Blood pressure measured on two occasions 2 weeks apart. Advise GP to treat any hypertension >140/90mmHg.
	• Ensure that the patient understands not to expect improvement from the treatment straight away.
	• 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 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. • Ensure that the patient understands their treatment and which warning symptoms to report (see adverse reactions below) • 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 • 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 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 • Patients must be advised to limit their alcohol intake to well within the national recommended limits; BSR guidance suggests 4-8 units per week. • 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 8 grams three times daily or activated charcoal 50 grams 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	• Recent treatment with other hepatotoxic or myelotoxic disease-modifying anti-rheumatic drugs
Contra-indications	• Severe immunodeficiency • Serious infections • 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 contra-indicated
- 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

This guidance does not replace the SPC's, which should be read in conjunction with this guidance.

Monitoring and Adverse Effects

Treatment status	FBC	LFTs	Weight	ESR or CRP	BP
Initial monitoring for first 6 months	Every month	Every month	Every month	Every 3 months (for RA only)	Every month
After 6 months	Every 2 months	Every 2 months	Every 2 months	Every 3 months (for RA only)	Every 2 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.

AST/ALT: If between 2 and 3 times the upper limit of reference range discuss with the specialist team.
AST/ALT: If more than 3 times the upper limit of reference range, re-check LFTs within 72 hours; if still more than three times the reference range, **stop** drug and consider washout (see under washout below)

In the event of the following adverse laboratory results or patient reported symptoms, withhold leflunomide until discussed with specialist team:

- WCC $< 3.5 \times 10^9$/L or less than the lower limit of reference range as per lab
- Neutrophils $< 2.0 \times 10^9$/L or less than the lower limit of reference range as per lab
- Platelets $< 150 \times 10^9$/L or less than the lower limit of reference range as per lab
- Severe or persistent nausea or diarrhoea
- Abnormal bruising or severe sore throat. Do an FBC.
- Persistent severe headache
- Severe hair loss
- Uncontrolled hypertension, BP >140/90mmHg
- Severe rash or itch
- Cough or dyspnoea. Interstitial lung disease has been reported during treatment with leflunomide. 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 or dyspnoea must be referred immediately to the consultant.
- Systemically unwell with significant infection
- Stevens-Johnson Syndrome and DRESS
- Peripheral neuropathy

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

Other adverse reactions:

- Nausea/diarrhoea: if mild 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.
- Rash or itch: If mild consider dose reduction and/or an antihistamine.
- Hair loss: If mild consider dose reduction.
- Hypertension: If BP >140/90mmHg, treat in line with NICE guidance for hypertension.
- Headache. If severe consider dose reduction.

	• For further possible side effects please refer to the SPC and BNF This list is not exhaustive; please refer to SPCs and BNF. This list is not exhaustive, please refer to SPCs and BNF.

References

1. http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/d/diseasemodifying_antirheumatic_drug_dmard_therapy.pdf
2. http://www.medicines.org.uk/emc/medicine/26728/SPC/Leflunomide+10mg+Tablets/
3. BNF 66 September 2013-March2014
4. http://cks.nice.org.uk/dmards#!scenariorecommendation:7