DMARDs in Adult Rheumatology –Information for GPs

LEFLUNOMIDE

Clinicians should also refer to the overarching DMARD shared care guideline document for details of the individual responsibilities for each group e.g. e.g. GP / Specialist Rheumatology team under this shared care agreement.

Information for GPs

NB : Patients who are prescribed leflunomide in combination with another DMARD e.g. methotrexate require more frequent monitoring (see Blood test monitoring section below).

Indications	• Leflunomide is recommended by NICE and National Societies for the treatment of numerous Rheumatological conditions including Rheumatoid arthritis and Psoriatic arthritis. • Clinicians should refer to the Summary of product characteristics (SPC) for specific licensing information. • Use outside of the licensed indications is regarded as “off label” use.
Drug dose	• Typically, the Specialist Rheumatology team will initiate Leflunomide 10mg once a day for two weeks then increase to 20mg once a day. • Typical maintenance dose is 10- 20mg once a day. • Maximum dose is 20mg once a day • Dose may be reduced if leflunomide is prescribed in combination with another DMARD e.g. methotrexate. **(NB: Local Specialists do <u>not</u> routinely recommend a loading dose).** • **VARIATION TO LEFLUNOMIDE DOSING** SPC states to avoid in moderate and severe renal impairment. SPC states to avoid in hepatic impairment.

Contra-indications / Cautions/ Dose modifications in Special Populations	• Clinicians should refer to the Summary of Product Characteristics (SPC's) and current electronic BNF for full details www.medicines.org.uk/emc www.bnf.org/products/bnf-online
Side effects	• Clinicians should refer to the Summary of Product Characteristics (SPC) and current electronic BNF for full details www.medicines.org.uk/emc www.bnf.org/products/bnf-online • Prescribers should note that as the active metabolite of leflunomide has a long half-life, side effects may continue or occur even after treatment with leflunomide has stopped. • **In the event of any serious side effects, leflunomide should be discontinued and a wash-out procedure should be instituted (due to the long half-life of the drug) – see discontinuation section below for more details.** • **Blood dyscrasias** (e.g. leucopenia and neutropenia) can occur hence the importance of regular blood tests • **Hepatic toxicity:** (Ref; BSR guidelines) Leflunomide is a potentially hepatotoxic drug and caution is advised when using leflunomide concomitantly with another hepatotoxic drug, such as methotrexate, or if there is evidence of current or recent hepatitis with Hepatitis B or C viruses. Rare cases of severe liver injury (some with fatal outcome) have been reported during treatment with leflunomide. Most cases occurred within 6 months and in a setting of multiple risk factors for hepatotoxicity It is highly recommended that LFTs be monitored closely (at least once a month). • The risk of hepatotoxicity and haematotoxicity are increased if leflunomide is prescribed with other drugs known to have similar toxicities. • As leflunomide is an immunosuppressant, clinicians should note to inform patients to contact their doctor immediately if they have any side effects, in particular – breathlessness, dry cough, whites of eyes becoming yellow, severe itching of skin, rash, dark urine, infections (including fever, chills or severe sore throats), new unexplained bleeding or bruising, mouth ulcers, vomiting and diarrhoea (particularly at the start of treatment, or if it is severe, at any stage in treatment). Examples of some common side effects include: ○ diarrhoea ○ nausea ○ mouth ulcers ○ weight loss ○ stomach pain ○ headaches ○ dizziness ○ weakness

	○ pins and needles ○ dry skin ○ rashes ○ hair loss (rare and usually minor) ○ rise in blood pressure. • **Clinicians should also refer to Table 1 for details of when to contact the Specialist Rheumatology team with regards blood test results and development of certain side effects etc.**
Drug Interactions	• Leflunomide can interact with a variety of drugs, some of which can be **significant.** Examples include: ○ other potentially hepatotoxic and haematotoxic drugs e.g. **methotrexate** (NB: This combination is often used by Rheumatology Specialists - NB: more frequent blood test monitoring is required). ○ **warfarin.** ○ **Live vaccines** – avoid, due to risk of generalised infections • **This list is not exhaustive. C**linicians should refer to the Summary of Product Characteristics (SPC) and the electronic BNF for a **full list** of potential drug interactions before starting any new medication or when stopping any existing medication. www.medicines.org.uk/emc www.bnf.org/products/bnf-online
Pre-treatment Blood Test monitoring and Additional Screening *(To be done by Specialist Rheumatology team)*	• FBC, U+Es, LFT • Blood pressure reading • Weight (to allow assessment of any future weight loss)
Blood Test Monitoring requirements *(Typically to be monitored by the GP from week 4 onwards.)* **(Ref: Based on British Society of Rheumatology Guidelines , 2017 and current clinical practise)**	• FBC, U+E, LFT **fortnightly until dose and monitoring stable for 6 weeks**, then **monthly for 3 months** then **every 12 weeks* thereafter.** *More frequent monitoring is appropriate for patients at a higher risk of toxicity. • (**NB: After any dose increase,** blood test monitoring should be carried out every fortnight until on a new stable dose for 6 weeks and then the frequency can revert back to the previous schedule). • CRP / ESR should be monitored every 3-6 months as this can help assess disease activity. **Patients who are prescribed leflunomide in combination with another DMARD e.g. methotrexate require more frequent monitoring :**

	○ FBC, U&Es, LFT **every 2 weeks until on a stable dose for 6 weeks, then monthly* blood tests long- term.** *More frequent monitoring is appropriate for patients at a higher risk of toxicity (Patients who have been stable for 12 months on combination therapy can be reviewed by the Specialist team and considered for reduced frequency of monitoring on an individual basis.) • Ensure a prompt two way communication of blood test results between GP and Specialist team is available. (Paper copies should be sent between parties if electronic access via ICE is not available.)
Additional Monitoring Requirements *(To be monitored by the GP from week 4 onwards.)*	• Monitor BP and weight every 3 months
Washout Procedure (for rapid drug removal)	• Leflunomide has a very long half-life and the active metabolite persists for a long period. • To aid drug elimination in the event of a serious adverse effect, or before staring another DMARD, or before conception, stop treatment and follow the wash-out procedure: **Wash-out Procedure** <u>Colestyramine (Cholestyramine)</u> 8 g 3 times a day for 11 days. **Or, alternatively** <u>Activated charcoal (by mouth using granules)</u> 50g 4 times a day for 11 days • <u>Pregnancy</u> For the use of a washout procedure in patients who become pregnant or who wish to plan a pregnancy – see Pregnancy / Contraception sections below.
Time to response	• Response can usually be seen in 4-6 weeks with further improvement during the next four to six months.
Infections	• Leflunomide is an immunosuppressant and increases the patient's susceptibility to infections, including opportunistic infections. • Initiate prompt anti-infective treatment when indicated on the basis that the patient may be immunosuppressed to some degree. • During a serious infection*, leflunomide should be temporarily discontinued until the patient has recovered from the infection. (* Serious infection: warrants admission to hospital or requires parenteral anti-microbial therapy.) • <u>If exposed to measles and / or chickenpox</u> : Check immunity to measles and varicella-zoster; if non-immune and exposed to measles or chickenpox contact the Specialist Rheumatology team ASAP for consideration of appropriate immunoglobulin therapy.

	• If patient develops shingles or chickenpox, stop the drug and treat with aciclovir.
Vaccinations	• The immune response to vaccination may be impaired. • Pneumovax and annual flu vaccination are recommended. • **Live vaccines should be avoided** and GPs should contact the Specialist Rheumatology team for advice regarding the use of **any** live vaccine in patients who are prescribed leflunomide. • The long half-life of leflunomide should be considered if considering the administration of a live attenuated vaccine after stopping leflunomide.
Alcohol	• As both leflunomide and alcohol can affect the liver , patients are advised to only drink alcohol in small amounts (no more than 4–8 units per week).
Elective surgery	• **Contact the Specialist Rheumatology team for advice**
Contraception Advice (males and females)	• The Specialist Rheumatology team should discuss family planning with both female and male patients before initiating treatment with leflunomide. • GPs should refer any female or male patient who is wishing to start a family to the Specialist Rheumatology team.
Pregnancy and Breast feeding	• Leflunomide is teratogenic and is contra-indicated in pregnancy and breast feeding. • Patients who become pregnant should stop leflunomide and be referred **urgently** to the Specialist team for a wash-out treatment.
Drug Formulations	**Oral** Available as 10mg , 15mg, 20mg (NB: a loading dose with 100mg strength tablets is no longer used) Tablets contain lactose.
Practical Points for GPs to note:	• Advise patients to attend for a blood test a week before their next prescription is due to ensure that the results can be reviewed before the next prescription is requested for issue. • Check the results of recent blood test **before** issuing a prescription. (Refer to table 1 for actions to take in the event of blood test abnormalities and side effects - page 6). • Increase the frequency of blood test monitoring after a dose increase as detailed above. • **Patients who are prescribed leflunomide in combination with another DMARD e.g. methotrexate require more frequent monitoring.** • Prescribers should note that whilst absolute blood test values are useful indicators, trends are equally important, and any rapid fall or consistent downward trend in any parameter warrants extra vigilance. • Monitor BP and weight every 3 months.

	• Advise patients to contact their doctor immediately if they have any side effects, in particular – breathlessness, dry cough, whites of eyes becoming yellow, severe itching of skin, rash, dark urine, infections (including fever, chills or severe sore throats), new unexplained bleeding or bruising, mouth ulcers, vomiting and diarrhoea (particularly at the start of treatment, or if it is severe, at any stage in treatment). • Advise any patients who wish to consider starting a family to contact their GP and Specialist Rheumatology team as soon as possible for advice. • Advise that any patient who becomes pregnant should stop taking leflunomide and contact their GP and Specialist Rheumatology team as soon as possible for a wash out procedure. • Provide a maximum of 4 weeks supply at a time
Patient Information Leaflets	• Patients should be advised to read the Arthritis Research UK patient information leaflet and the package insert. The current Arthritis Research UK leaflet can be downloaded from: www.arthritisresearchuk.org/arthritis-information/drugs/leflunomide.aspx

Table 1

Actions to be taken

Prescribers should note that whilst absolute values are useful indicators, trends are equally important, and any rapid fall or consistent downward trend in any parameter warrants extra vigilance and urgent discussion with Specialist Rheumatology team.

WBC <3.5 x 10^9/L	**Withhold and contact Specialist Rheumatology team urgently if any of the results opposite develop.**
Neutrophils <1.6 x 10^9/L	
Unexplained eosinophilia >0.5 x 10^9/L	
Platelet count <140 x 10^9/L	
MCV > 105 f/L	
Creatinine >30% above baseline and/or calculated GFR <60	
ALT and/or AST >100 units/L	
Unexplained fall in serum albumin	
Any rapid fall or consistent downward trend in any indices	
Uncontrolled Blood Pressure despite antihypertensive therapy	
Signs of peripheral neuropathy	

Pins and Needles in hands and feet to suggest peripheral neuropathy	
Weight loss	
Breathlessness	

Abnormal bruising with or without sore throat	**Immediate FBC and withhold until result available and contact the Specialist Rheumatology team.**
Nausea, vomiting, abdominal pain, diarrhoea, dyspepsia	**Withhold until discussed with Specialist rheumatology team.**

BACK-UP ADVICE AND SUPPORT

- **GP queries should be directed to the Rheumatology consultants.**
- **Patient queries should be directed to the Rheumatology Specialist Nurses**

All urgent requests should be answered within one working day.

Contact Details:

The Luton & Dunstable Hospital

Consultants

Dr Daniel Fishman, Dr Muhammed Nisar, Dr Tanya Baqai

Dr Balaji Ramabhadran, Dr Vanessa Quick, Dr Marian Chan

Tel: 01582 497233 / 01582 497464

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Specialist Nurses

Nicki Wood, Julie Begum, Sue O'Connor : **Nurse Advice Line**: 01582 718305

Bedford Hospital

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References:

- BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with British Association of Dermatologists. Rheumatology.2008 K Chakravarty et al. www.rheumatology.org.uk/includes/documents/cm_docs/2009/d/diseasemodifying_antirheumatic_drug_dmard_therapy.pdf
- SPC (Summary of product characteristics) www.electronicmedicinescompendium.com
- BSR/BHPR Non-biologic DMARD guidelines ((2017) https://academic.oup.com/rheumatology/article/56/6/865/3053478
- BNF (electronic) www.bnf.org/products/bnf-online