Leflunomide for rheumatoid arthritis and other rheumatological diseases (Adults)

It is vital for safe and appropriate patient care that there is a clear understanding of where clinical and prescribing responsibility rests between consultants and general practitioners (GPs).
This guideline reinforces the basic premise that:
When clinical and / or prescribing responsibility for a patient is transferred from hospital to GP, the GP should have full confidence to prescribe the necessary medicines. Therefore, it is essential that a transfer of care involving medicines that a GP would not normally be familiar with, should not take place without the "sharing of information with the individual GP and their mutual agreement to the transfer of care."
These are not rigid guidelines. On occasions, consultants and GPs may agree to work outside of this guidance. As always, the doctor who prescribes the medication has the clinical responsibility for the drug and the consequences of its use.

Indications:	**Dosage and administration:**
Leflunomide is used for the management of moderate to severe active rheumatoid arthritis and active psoriatic arthritis.	Rheumatoid arthritis: 10mg or 20mg orally once daily when monotherapy is used. Psoriatic arthritis: 20mg once daily Leflunomide may be taken with or without food.

Additional Information

- It usually takes 4-6 weeks of treatment for therapeutic response to be seen; this may improve further with 4-6 months of treatment.
- Potentially life-threatening hepatotoxicity has been reported in patients taking leflunomide, usually during the first 6 months of treatment. Recent or concurrent treatment with other hepatotoxic Disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexate may increase the risk of serious adverse reactions.
- To aid drug elimination in case of serious adverse effect, or before starting another DMARD, or before conception, stop treatment and give either colestyramine 8 g 3 times daily for 11 days or activated charcoal 50 g 4 times daily for 11 days; the concentration of the active metabolite after washout should be less than 20 micrograms/litre (measured on 2 occasions 14 days apart) in men or women before conception. Procedure may be repeated as necessary. Consult product literature for further details.
- In women of childbearing potential, effective contraception is essential during treatment and for at least 2 years after completion of treatment. Male patients must also use reliable contraception during treatment and for at least 3 months after completion of treatment. Plasma concentration monitoring should be satisfactory before planning a family; the washout procedure may be used to reduce waiting time.
- If a woman becomes pregnant during treatment with leflunomide she should contact her specialist or GP immediately to discuss the risks to the foetus.
- Leflunomide should be avoided in breast feeding.

Monitoring requirements:

Before treatment:

- Full blood count (FBC)
- LFTs particularly alanine aminotransferase (ALT)

- Blood pressure (BP): If > 140/90mmHg on 2 consecutive readings 2 weeks apart then treat hypertension before commencing the drug.
- U/Es and creatinine

During treatment:

- FBC, LFTs, U/E's and creatinine weekly for the first 4 weeks then monthly for 3 months then every 8 weeks thereafter if stable.
- BP should be checked at each monitoring visit - maintain ≤ 140/90mmHg.
- Annual fasting lipids (HDL, Cholesterol, HDL/Cholesterol ratio)
- ESR (discretionary) monthly for disease monitoring purposes

Responsibility for monitoring rests with the GP

Action to be taken if abnormal results/adverse effects:

- WBC < 3.5 x 10^9/l Check neutrophil count
- Neutrophils < 2.0 x 10^9/l Monitor weekly. If it falls below 1.5 x 10^9/l STOP DRUG and contact helpline.
- Platelets < 150 x 10^9/l Monitor weekly. If it drops below 100 x 10^9/l contact helpline.
- 3 fold rise in ALT/AST Monitor weekly. If ALT persistently raised or continues to rise, contact helpline.
- Raised blood pressure If >140/90mmHg and persistently raised (more than 2 occasions), active management is required and contact helpline
- Rash – mild Reduce to 10mg if necessary and observe
- Rash - severe STOP DRUG and contact helpline for advice
- Diarrhoea / nausea Assess severity, consider symptomatic treatment e.g. anti-diarrhoeal / anti-emetic
  Usually does not require discontinuation of therapy. Dose reduction (where possible) may be considered

Please note that in addition to absolute values for haematological indices, a rapid fall or a consistent downward trend in any value should prompt caution and extra vigilance.

Contraindications:

- Hypersensitivity to the active substance (especially previous Stevens-Johnson Syndrome, toxic epidermal necrolysis, erythema multiforme) or to any of the excipients
- Avoid in hepatic impairment- active metabolite may accumulate
- Severe immunodeficiency status e.g. AIDS
- Serious infections
- Significantly impaired bone marrow function due to causes other than rheumatoid or psoriatic arthritis
- Avoid in moderate to severe renal insufficiency (CKD stages 3, 4 and 5 with a GFR less than 60ml/minute).
- Severe hypoproteinaemia e.g. in nephrotic syndrome
- Women who are pregnant, breast feeding or are of childbearing potential but not using reliable contraception.
- Live vaccines are contra-indicated in patients with impaired immune response

Drug interactions – please refer to appendix 1 of the current BNF or the SPC for full details

- Concurrent use of methotrexate increases the risk of hepatotoxicity and haematotoxicity.

Cautions:

- Renal impairment. Impaired bone marrow function, including anaemia, leucopenia or thrombocytopenia
- Recent treatment with other hepatotoxic or myelotoxic DMARDs.
- History of tuberculosis

Adverse Effects

Common: GI, including nausea, diarrhoea, vomiting and abdominal pain. Oral mucosal disorders. Raised blood pressure.

Headache, paraesthesia, dizziness. Skin disorders such as alopecia, eczema, rash. Increased CPK. Tenosynovitis.

Blood disorders: leucopenia (common), anaemia, thrombocytopenia (less common), agranulocytosis, pancytopenia (rare)

Rare: Severe infections, hepatitis and jaundice.

Specialist responsibilities:

- Confirm the diagnosis of rheumatoid arthritis
- Discuss with the patient the benefits and side effects of treatment with leflunomide
- If the patient is a woman of child bearing potential or male – ensure that they are aware of the importance of effective contraception and the need to discuss with their consultant if they wish to become pregnant
- Ensure that the patient understands and accepts their responsibilities (see section below)
- Seek consent for treatment and document in the patient's notes.
- Ensure baseline monitoring of full blood count and biochemical profile.
- Discuss how the patient / carer can be aware of possible signs of leflunomide toxicity or intolerance
- Provide written instruction to the GP for initiation and escalation of leflunomide.
- Provide the patient with a monitoring booklet and enter the blood results into the booklet.
- Review the patient at the intervals specified below to monitor the patient's disease activity, the efficacy of the treatment and the ability to tolerate it, and consider whether continuation of treatment is appropriate.
- Discontinue if no response or patient has a significant adverse effect.
- Promptly communicate with the GP via a clinic letter any changes in treatment, results of monitoring undertaken, and assessment of adverse events. The clinic letter should clearly state if the dose has remained the same or if a dose adjustment had been made – specifically highlighting the new dose in comparison with the preceding one.
- Advise GPs when to stop treatment.
- Provide clear arrangements for back-up, advice and support.
- Report serious adverse events at https://yellowcard.mhra.gov.uk/

GP's responsibilities:

- Initial referral to Consultant Rheumatologist raising the possibility of rheumatological disease
- Provide the patient with monthly repeat prescriptions of medication following written instructions for initiation and escalation by the specialist. The patient should allow at least 48 hours for the prescription from the GP to be generated.
- Continue monitoring as outlined on the first page and document the results in the shared care booklet.
- Ensure patient's monitoring booklet and practice computer system are updated with any dose changes.
- Refer promptly to the specialist if there is a change in the patient's status or concerns regarding compliance. In most cases, do not stop treatment without discussion with the Rheumatology Helpline.
- If patient fails to attend more than 2 monitoring visits it is not safe to continue treatment – contact the Rheumatology Helpline for advice.
- Report serious adverse events to the specialist and at https://yellowcard.mhra.gov.uk/ .
- Administer Pneumococcal Vaccine/ Pneumovax® II and annual influenza vaccines.
- Consider passive immunisation with Varicella zoster immunoglobulin in non-immune patients exposed to chicken pox or shingles.

Patient responsibilities:

- Read the written patient information provided about the drug and have a clear understanding of the risks / benefits of oral leflunomide treatment.
- Attend for blood tests.
- Limit intake of alcohol to the national safe weekly limits
- Report any adverse effects to their GP and/or specialist whilst treated with leflunomide.
- Take monitoring booklet every time the patient sees the GP, has a hospital appointment or visits the pharmacist.

Secondary care review: During initiation: 4 – 6 weekly until controlled
Once disease controlled: Annual review by consultant

Availability: 10mg tablet: 30 = £7.47 20mg tablet: 30 = £7.82

Prices from Online Drug Tariff February 2016

Back up advice and support: Rheumatology Helpline		**Telephone:** 0151 604 7505
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