

Leflunomide

Traffic light classification- Amber 1

Information sheet for Primary Care Prescribers

Part of the Shared Care Protocol: Management of Rheumatological Conditions with Disease-Modifying Anti Rheumatic Drugs in Adults

Indications¹

Rheumatoid Arthritis (RA) and psoriatic arthritis – licensed.

Therapeutic Summary

Leflunomide can be used to reduce disease activity in patients with rheumatological disease. Clinical benefit may take up to 6 months¹. NSAIDs and simple analgesics may need to be continued. Patient reported adverse effects usually occur early in therapy, but please see explicit criteria for review below. A wash out procedure may be performed on advice of a specialist, when switching from leflunomide to another DMARD or in the case of a desired pregnancy (see contraindications), due to its long half-life.

Products available

Leflunomide film coated tablets - 10mg, 20mg and 100mg.

Dosages and route of administration^{1,2}

Leflunomide is given orally.

Typical regime – 10-20mg once a day when monotherapy is used. In cases of combination therapy with another potentially hepatotoxic DMARD, like methotrexate, 10mg once a day is usually recommended (therapeutic efficacy may be reduced with the reduced dosage).

Loading dose – 100mg once a day for 3 days may be used to speed up the onset of effect. Unacceptable gastrointestinal side effects such as diarrhoea may occur when a loading dose is given and this is often omitted in routine practice. A loading dose is not recommended when used as part of combination therapy.

Duration of treatment

All DMARDs are long term treatments. Clinical benefit may take up to 6 months.¹

Monitoring Requirements and Responsibilities²

Pre-treatment assessment to be performed by specialist and will include:

- FBC, U&E, LFT, blood pressure, weight (to allow assessment of weight loss as this may be attributable to leflunomide)

Ongoing monitoring:

Time period in treatment	Frequency of monitoring	Tests to be done			
		FBC	LFTs	U&Es	BP
0-6 weeks	Fortnightly	✓	✓	✓	✓
6 weeks – 3 months	Monthly	✓	✓	✓	✓
>3 months and stable dose for 6 weeks	3 monthly*	✓	✓	✓	✓
Patient is taking another immunosuppressant or methotrexate	Monthly	✓	✓	✓	✓
Any dose increase	2 weeks post dose increase then revert to above protocol	✓	✓	✓	✓

GP to weigh patient at each visit due to possibility of weight loss (see section on explicit criteria for review and discontinuation of the medicine).

- GP to assess and manage cardiovascular risk factors – patient at higher risk of cardiovascular events due to rheumatological disease activity.
- No additional monitoring requirements are required in primary care for patients receiving additional biological therapy including anti-TNF therapy.
- Routine influenza and pneumococcal vaccinations are highly recommended.

Explicit criteria for review and discontinuation of the medicine² – Other benchmark values may be set by secondary care in specific clinical circumstances.

This will be communicated by secondary care.

Adverse Event	Action
WBC<3.5x10 ⁹ /l	Withhold until discussed with rheumatology specialist team
Neutrophils<2.0x10 ⁹ /l	Withhold until discussed with rheumatology specialist team
Platelets<150x10 ⁹ /l	Withhold until discussed with rheumatology specialist team
AST / ALT between two and three times upper limit of reference range	If the current dose is more than 10mg daily reduce the dose to 10mg daily and recheck weekly until normalised. If the ALT is returning to normal, leave on 10mg a day. If LFTs remain elevated withhold until discussed with rheumatology specialist team.
AST / ALT > three times upper limit of reference range	Recheck LFTs within 72hrs, if still more than three times the reference range, withhold and discuss with rheumatology specialist team.
Moderate or severe renal impairment GFR <20ml/min	Discuss with rheumatology specialist team
Rash or itch	Discuss with rheumatology specialist team
Hair loss	Discuss with rheumatology specialist team
Abnormal bruising or severe sore throat	Check FBC immediately and withhold until results available and until discussed with rheumatology specialist team.
Hypertension	If BP>140/90 treat in line with NICE hypertension guidance. If BP remains uncontrolled, discuss with rheumatology specialist team
Headache	Check BP and treat if necessary. If headache severe or persistent, discuss with rheumatology specialist team.
GI upset (nausea, diarrhoea)	If loading dose has been used, give symptomatic treatment. If steady state has been reached, give symptomatic treatment. If symptoms are severe or persistent, withhold until discussed with rheumatology specialist team.
>10% weight loss with no other cause identified	Discuss with rheumatology specialist team.
Breathlessness or dry cough	If increasing shortness of breath or dry cough occurs, discuss with rheumatology specialist team.
Ulcerative stomatitis	Discuss with rheumatology specialist team.
Skin lesions suggestive of Stevens Johnson Syndrome or toxic epidermal necrolysis	Discontinue, consider admission to secondary care, discuss with rheumatology specialist team and initiate a leflunomide washout procedure immediately (see below).

In addition to absolute values for haematological or biochemical indices a rapid fall or rise or consistent downward or upward trend in any value should prompt caution and extra vigilance.²

For a full list of Side Effects refer to the BNF or Summary of Product Characteristics.

IF YOU ARE IN ANY DOUBT ABOUT ANY POTENTIAL ADVERSE REACTION, PLEASE CONTACT THE RHEUMATOLOGY SPECIALIST TEAM.

Relevant Contraindications²

- Severe immunodeficiency
- Serious infections
- Impaired liver function due to any cause – active metabolite may accumulate
- Severe unexplained hyperproteinaemia.
- Renal impairment (moderate or severe)⁴ – because insufficient clinical experience is available in this patient group – see monitoring requirements above.
- Impairment of bone marrow function as indicated by anaemia and cytopenias due to causes other than RA.
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at www.dh.gov.uk): Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently. N.B. Routine influenza and pneumococcal vaccinations are highly recommended.
- **Pregnancy:** Leflunomide is teratogenic and **must not** be given to pregnant women or women of childbearing potential unless reliable contraception is used. Women planning to have children should either discontinue leflunomide 2 years prior to conception or have rapid removal of its active metabolite by following the washout procedure (see section). Men should use effective contraception for 3 months after stopping leflunomide or consider washout procedure. Any pregnancy within 2 years of discontinuation of leflunomide should be discussed with the rheumatology specialist team if drug washout has not been performed.
- **Breast-feeding:** Should be avoided as animal studies indicate that metabolites of leflunomide are secreted in breast milk.

Relevant Precautions^{1,2}

- Localised or systemic infection including hepatitis B or C and history of tuberculosis.
- Drug potentiation: Concomitant administration of hepatotoxic or haematotoxic medicines (e.g. methotrexate) is not advisable although combination therapy with methotrexate has been used.
- Long half-life: The active metabolite of leflunomide, A771726, has a long half-life, usually 1 to 4 weeks. Therefore, serious adverse effects might occur even if the treatment with leflunomide has been stopped. Refer to rheumatology specialist team prior to washout procedure if serious adverse effects occur.
- Alcohol - Intake must be kept well within national limits of 4-8 units a week.
- Liver reactions - Rare cases of severe liver injury, including cases with fatal outcome, have been reported during treatment with leflunomide.
- Pre-existing anaemia, leucopenia, and/or thrombocytopenia as well as patients with impaired bone marrow function or those at risk of bone marrow suppression – increased risk of haematological disorders.
- Infections – may be more severe, consider early and vigorous treatment
- Interstitial lung disease – advise patient to report new cough and dyspnoea
- Patients who have no history of exposure to varicella zoster virus (VZV) i.e. chickenpox or herpes zoster (shingles), should avoid contact with individuals with chickenpox or herpes zoster. Varicella-zoster immunoglobulin (VZIG) is recommended for individuals who are at increased risk of severe varicella (including patients taking immunosuppressant medicines e.g. azathioprine, ciclosporin, methotrexate, leflunomide) and who have no antibodies to varicella-zoster virus and who have significant exposure to chickenpox or herpes zoster. See www.dh.gov.uk/en/PublicHealth/Immunisation/Greenbook for detailed guidance. If the patient is infected with VZV, appropriate measures should be taken, which may include antiviral therapy and supportive care.

Washout procedure (if advised by appropriate specialist)²

After stopping treatment with leflunomide:

- colestyramine 8g is administered 3 times daily for a period of 11 days,
- alternatively, 50g of activated powdered charcoal is administered 4 times daily for a period of 11 days.

N.B. Both colestyramine and activated powdered charcoal may influence the absorption of oestrogens and progestogens such that **reliable contraception with oral contraceptives may not be**

guaranteed during the washout procedure with colestyramine or activated powdered charcoal. The use of alternative contraceptive methods is recommended.

Clinically relevant medicine interactions and their management^{1,3,5}

- Methotrexate: Increased risk of toxicity – increased frequency of monitoring required (see monitoring)
- Warfarin: may increase INR, monitor closely
- Phenytoin: no clinical reports, potentially increased phenytoin levels
- Live vaccines (see BNF or Immunisation against infectious disease - 'The Green Book' available at www.dh.gov.uk): Avoid as severe antigenic reactions may occur if a live vaccine is given concurrently.

For a full list of contraindications, precautions and drug interactions refer to the Summary of Product Characteristics.

Information given to patient

- The patient must not become pregnant whilst taking leflunomide or for 2 years after stopping therapy. If there is any delay in onset of menses or any other reason to suspect pregnancy, the patient must notify the physician immediately for pregnancy testing.
- The patient must be warned to report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine), and respiratory effects (e.g. shortness of breath or dry cough) to the GP.
- Patients should be advised to avoid contact between themselves and individuals with chickenpox or shingles if they have no prior history of exposure. Any exposure of patients with no varicella–zoster virus antibodies to chickenpox and shingles sufferers should be reported to the GP for assessment and possible treatment.
- The patient will also be given an approved drug information leaflet from Arthritis Research UK. Further copies available at www.arthritisresearchuk.org.

Patient's roles and responsibilities

The patient will:

- Take their medication as agreed, unless otherwise instructed by an appropriate healthcare professional.
- Attend for all regular blood tests and all follow-up appointments with GP and specialist. If they are unable to attend any appointments they should inform the relevant practitioner as soon as possible and arrange an alternative appointment.
- Inform all healthcare professionals of their current medication prior to receiving any new prescribed or over-the-counter medication.
- Report all suspected adverse reactions (as above) to medicines to their GP.
- If there is any delay in onset of menses or any other reason to suspect pregnancy, the patient must notify the physician immediately for pregnancy testing.
- Store their medication securely away from children.
- Read the information supplied by their GP, specialist and pharmacist and contact the relevant practitioner if they do not understand any of the information given.

References

1. Arava 10, 20 and 100mg tablets – Sanofi-Aventis. Summary of Product Characteristics [09/08/2017] on Electronic Medicines Compendium: (accessed on 22/06/2020) via www.medicines.org.uk/emc
2. Ledingham J, Gillick N, Irving K. et al. (2017) BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. Rheumatology doi:10.1093/rheumatology/kew149..
3. BNF [online] via www.medicinescomplete.com [accessed 22/06/2020]
4. Ashley C, and Currie A [Eds]. The Renal Drug Handbook [3rd edition] Oxford: Radcliffe Publishing Ltd [2009].
5. Baxter K (ed), Stockley's Drug Interactions. [online] London: Pharmaceutical Press accessed via www.medicinescomplete.com (accessed on 22/06/2020)