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**DMARD MONITORING GUIDELINES – Reviewed 23.01.15**

**RNHRD GP TELEPHONE ADVICE LINE (from 11.00am to 1.00 pm daily): 07747 630875**

**The current BSR DMARD and Denosumab Monitoring Guidelines are now available via the following link:** http://www.rnhrd.nhs.uk/our-services/for-clinicians

## Leflunomide

**A. Indications: (Licensed)** RA and psoriatic arthritis (PsA). Not used in Psoriasis.
BAD: Dermatologists generally do not use this drug.

**B. Dose: Grade of evidence: C**

Typical dose is:

**RA: 10–20 mg once a day** [1–3] when monotherapy is used. In cases of combination therapy with another potentially hepatotoxic DMARD like methotrexate, 10 mg once a day is recommended (therapeutic efficacy may be reduced with the reduced dosage [4]).

**PsA: 20mg once a day** [2, 3].

**Loading dose:** ***Not used in clinical practice at the RNHRD***

**C. Route of administration**: Oral

**D. Time to response:** 8–12 weeks (longer if loading dose is not employed)

**E. Caution: Grade of evidence: A & C [2, 3, 6–9]**

(1) Localized or systemic infection including hepatitis B or C and history of tuberculosis.
(2) Drug potentiation: Haematotoxic or hepatotoxic drugs such as methotrexate. Leflunomide SPC states caution if used together with methotrexate although combination therapy using these drugs is used in routine clinical practice if felt to be clinically appropriate [10].

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## F. Contraindications: Grade of evidence: C [1, 2, 5]

(1) Severe immunodeficiency.
(2) Serious infections.
(3) Impaired liver function due to any cause.
(4) Severe unexplained hypoproteinaemia.
(5) Renal impairment (moderate to severe).
(6) Impairment of bone marrow function as indicated by anaemia and cytopenias due to causes other than RA and PsA.

## G. Monitoring schedule: Grade of evidence C [1,2]

| | BSR |
|---|---|
| **(a) Pre-treatment assessment** | **FBC, U&E, creatinine and LFTs [2]**<br>**Blood pressure: If > 140/90 on two consecutive readings 2 weeks apart, treat hypertension before commencing the drug [9,11].**<br>**Weight: to allow assessment of weight loss; this may be attributable to leflunomide.** |
| **(b) Monitoring** | **FBC, LFTs every month for 6 months and, if stable, 2-monthly thereafter [2].**<br>**Blood checks should be continued long-term, at least once a month, if co-prescribed with another immunosuppressant or potentially hepatotoxic agent [8].**<br>**Blood pressure and weight should be checked at each monitoring visit.** |

## H. Action to be taken: Grade of evidence C [5]

| | |
|---|---|
| **WBC < 3.5 x $10^{9}$/l** | **Withhold until discussed with specialist team.** |
| **Neutrophils < 2.0 x $10^{9}$/l** | **Withhold until discussed with specialist team.** |
| **Platelets < 150 x $10^{9}$/l** | **Withhold until discussed with specialist team.** |
| **AST, ALT between two and three times the upper limit of reference range** | **If the current dose is more than 10mg daily, reduce the dose to 10mg daily and recheck weekly until normalized. If the AST & ALT is returning to normal, leave on 10mg a day. If LFTs remain elevated, withdraw the drug and discuss with the specialist team.** |
| **AST, ALT more than three times the upper limit of reference range.** | **Recheck LFTs within 72 hours. If still more than three times the reference range, stop drug and consider washout (see section J).** |
| **Rash or itch** | **Consider dosage reduction with or without antihistamines; if severe stop and consider washout (see section J).** |
| **Hair loss** | **Consider dosage reduction; if severe stop and consider washout (see section J).** |
| **Abnormal bruising or severe sore throat** | **Check FBC immediately and withhold until results are available.** |

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| | |
|---|---|
| **Hypertension** | **If BP > 140/90 treat in line with NICE guidance. If BP remains uncontrolled, stop leflunomide and consider washout (see section J).** |
| **Headache** | **If severe, consider dosage reduction. If headaches persist, stop and consider washout (see section J).** |
| **GI upset (nausea, diarrhoea)** | **If loading dose has been used, give symptomatic treatment. If steady state has been reached, give symptomatic treatment and consider dosage reduction. If symptoms are severe or persistent, stop and consider washout (see section J).** |
| **Weight loss** | **Monitor carefully. If >10% weight loss with no other cause identified, reduce dosage or stop and consider washout (see section J).** |
| **Breathlessness** | **If increasing shortness of breath occurs, stop leflunomide and consider washout (see section J).** |

**NICE: National Institute for Health and Clinical Excellence**

NB. Simple dose reduction is unlikely to produce a rapid diminution of adverse effects as the half-life of the drug is 2 weeks (1–4 weeks). If a rapid response is required, consider washout—see section J.

## I. Caveats

### (1) Immunization

(a) Patients receiving leflunomide must not receive immunization with live vaccines. However, the RNHRD have produced specific local guidance with regards to the varicella-zoster vaccine which can be found at http://www.rnhrd.nhs.uk/our-services/for-clinicians, under the heading “Zostavax GP guidelines”.

(b) Inactivated polio is available although suboptimal response may be seen.
(c) Annual flu vaccination is recommended.
(d) In patients receiving leflunomide exposed to chickenpox or shingles, passive immunisation should be carried out using VZIG.

**(2) Pregnancy and lactation:** Leflunomide is teratogenic and must not be given to pregnant women or women of child bearing potential unless reliable contraception is used.
Women planning to have children should either discontinue the drug 2 yrs prior to conception [2, 3] or have a rapid removal of its active metabolite by following the washout procedure. Men should use effective contraception for 3 months after stopping leflunomide [3].

(a) Blood concentrations should be checked prior to planned pregnancy especially if within 2 years of stopping leflunomide or following wash out [2, 3]. Any pregnancy within 2 yrs of discontinuation of leflunomide should be discussed with rheumatologist if drug washout has not been performed [2, 3]. Notify pharmaceutical company in the event of pregnancy while on leflunomide [3].

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**(b) Breast feeding** should be avoided as animal studies indicate that metabolites of leflunomide are secreted in the breast milk [2].

**(3) Hepatic toxicity:** 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 [3, 4, 6–9]. 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 [9, 10]. It is highly recommended that LFTs be monitored closely (at least once a month) if leflunomide is co-prescribed with potentially hepatotoxic drugs, such as methotrexate [5, 9, 10]. Patient should be asked to limit alcohol intake well within national limits 4–8 units a week (National Survey data 2005).

**(4) Drug interactions:** Leflunomide can interact with many drugs, particularly with phenytoin, tolbutamide and may enhance the effects of these drugs [1–3] although significant interaction is unlikely [5]. Leflunomide also interacts with warfarin and the International normal ratio (INR) should be very closely monitored for several weeks even after stopping the leflunomide. As leflunomide has an extremely long half-life (2 weeks) the interactions can potentially be serious and more actions may be required beside just discontinuation of the drug such as washout. This may be of practical importance when changing from leflunomide to another DMARD.

**(5) GI effects:** Diarrhoea often occurs early in therapy when full loading doses of 100 mg/day for 3 days are given. Such effects lead to patient dissatisfaction and issues related to compliance and subsequent withdrawal of the drug in some circumstances. Omission of loading dose is acceptable with the knowledge that there may be a slight delay in response time.

**(6) Hypertension:** Regular monitoring of blood pressure is necessary during treatment and if there is a significant rise in blood pressure, then this should be treated. However, it is important to undertake a risk – benefit assessment at all times. In severe uncontrolled cases it is necessary to consider stopping the drug and washout if necessary.

**(7) Infections:** Any infection should be treated on its own merit.
All types of infection can occur and a cautious vigilance is necessary to detect early evidence of infection.

**(8) Pulmonary infiltration/pneumonitis/reactions:** Pulmonary infiltration/pneumonitis as an acute allergic reaction has been described in a small number of patients after starting leflunomide [12–16]. Patients should be made aware of this rare complication (see drug SPC) and if they become short of breath they should stop the tablets at once and seek urgent medical advice. If combination therapy is used with methotrexate, the patient should be made aware of the possible added risk even though this may not be clinically significant (Dr Clive Kelly, Gateshead Hospital, personal communication).

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**J. Washout procedure: Grade of evidence: C**

To aid drug elimination in cases of serious adverse effect or before conception, stop treatment and give either colestyramine 8 g three times daily for 11 days or activated charcoal 50 g four times daily for 11 days; the concentration of active metabolite after washout should be less than 20 µg/l (measured on two occasions 14 days apart) in men and women before conception (consult product literature).

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