LEFLUNOMIDE

RHEUMATOLOGY LOCAL SAFETY MONITORING SCHEDULE

This local safety-monitoring schedule supports clinicians under the Local Enhanced Service for High Risk Drug Monitoring (formerly Near Patient Testing). Aligning clinical and prescribing responsibility enhances patient safety because the individual signing the prescription will also be responsible for ensuring that any necessary monitoring has been undertaken and will have access to the results of this.

The prescriber and specialist assume joint clinical responsibility for the drug and the consequences of its use.

Specialist details	**GP details**	**Patient details**
Name:	Name:	Name:
Address:	Address:	Contact number:
Email:	Email:	NHS
Contact number:	Contact number:	DOB
Signature		Signature

INTRODUCTION

Leflunomide is a pyrimidine synthesis inhibitor that acts as an immunosuppressant by affecting the proliferation of lymphocytes.

Licensed indication: active rheumatoid arthritis(RA) and active psoriatic arthritis(PsA) in adults.

ADULT DOSAGE AND ADMINISTRATION

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A typical dose regimen may be:-

- **Rheumatoid Arthritis:** 10 - 20mg **once daily** (lower doses may be advisable in the elderly and when used in combination with other DMARDs).
- **Psoriatic Arthritis:** 10 **-** 20mg **once daily**

Available as: 10mg, 20mg tablets

It may take up to 3 months for significant response to be achieved.

MONITORING

Arrange and record on-going monitoring as agreed with the specialist

- Check FBC, U&E's, LFT's every 2 weeks until on stable dose for 6 weeks, Once on stable dose repeat monthly for 3 months and thereafter at least every 12 weeks. More frequent monitoring is appropriate in patients at higher risk of toxicity.
- Monthly monitoring longer term at least 12 months should continue for methotrexate/leflunomide combinations
- Dose increases should be monitored by FBC, U&E's, and LFT's every 2 weeks until on a stable dose for 6 weeks then revert back to previous schedule.
- CRP & ESR may be done every 3 months
- BP and weight at each monitoring visit.

SPECIALIST RESPONSIBILITIES

- Provide GP with clear written advice on required dosage and frequency of leflunomide, written monitoring guidelines and drug information.
- Check for interactions with other medicines.
- Provide the patient/carer with relevant (written) information on use side effects and need for monitoring of infection.
- **Advise on need for adequate contraception for both male and female patients.**
- Provide shared care monitoring record booklet if required.

In patients with a clinical suspicion of parenchymal lung disease, formal lung function testing and appropriate imaging (chest radiograph with or without high resolution CT imaging) should be performed and referral to a respiratory specialist be considered. Background lung disease should not be considered an absolute contraindication to leflunomide use, although in patients with poor respiratory reserve (in whom an acute pneumonitis would be more hazardous), caution is advised.

- For any patient currently smoking access to smoking cessation services should be offered.
- Arrange pre-treatment baseline investigations
  - Height, weight and blood pressure.
  - FBC
  - U&E's
  - LFT's
  - ESR &CRP
  - Varicella Zoster IgG in suspected non-immune patients and notify general practitioner as appropriate.
  - Hepatitis B & C and HIV serology
- Review results of safety monitoring and request additional tests as required
- Review in clinic as appropriate to assess response to treatment and the need to continue therapy sending a written summary to the GP whenever the patient is reviewed.
- Identify and report adverse events to the GP and the MHRA (via yellow card).
- Provide any other advice or information for the GP if required.

PRIMARY CARE RESPONSIBILITIES

- Prescribe leflunomide at the dose recommended if patient is having appropriate regular monitoring and monitoring results are within acceptable range.
- Repeat prescriptions should be removed from the surgery repeats pile and retained separately for prescribers to review prior to signing. Maximum 28 days supply.
- Monitoring of the drug as outlined on page 1 as per the BSR (British Society of Rheumatologists) guidelines and in conjunction with the Specialist Rheumatologist.
- Arrange and record on-going monitoring as agreed with specialist.
- Ensure no drug interactions with other medicines.
- Check patient (both Male and female) is using adequate contraception.

- These guidelines set out to provide a standard monitoring template. It is essential that each patient is considered on an individual basis and monitoring frequency is appropriately reviewed, for example in elderly patients, those with a history of drug-related toxicity, co-morbidity and polypharmacy more frequent monitoring may be appropriate.
- Patients on combination DMARD therapy may need more frequent monitoring. Please check the local Safety Monitoring Schedule for each drug.
- Report any adverse drug reactions to the initiating specialist and the usual bodies (e.g. MHRA) yellow form.
  - Administer Influenza vaccine annually unless otherwise advised by the initiating specialist
  - Check the patient has had one dose of Pneumococcal vaccine administered as a single dose of the polysaccharide PPV-23 (Pneumovax) ideally this should be administered prior to the initiation of DMARD's however, if this is not possible it should be administered irrespective.
  - **Varicella Zoster**
    - Non immune patients should avoid contact with people with chicken pox or shingles; consider passive immunisation using varicella immunoglobulin (VSIG) if exposure is suspected (contact Public Health England /Blood Transfusion Service for advice) consider active immunisation of non-immune subjects before starting immunosuppression (after discussion with specialist)
    - Varicella infection can be severe in immunosuppressed patients and early systemic anti- viral and supportive therapy may be required. Suspend methotrexate if possible until recovered
  - **Shingles**
    - Consider active immunisation before starting immunosuppression in patients over the age of 69 years.
- Ask about oral ulceration / sore throat, unexplained rash or unusual bruising at every consultation.
- If a patient develops symptoms/signs of systemic infection, tis should be treated promptly and leflunomide withheld until the infection has cleared.
- Ensure a clinician updates the patients record following specialist review

Withhold Leflunomide and contact specialist if:

- White cell Count <3.5 x10^9/l
- Neutrophils <1.6 x 10^9/l
- Unexplained eosinophilia >0.5 x 10^9/l
  Platelet count < 140 x 10^9/l
- Mean cell volume >105 f/l
- Creatinine Increase by > 30% over 12 months and /or calculated GFR<60ml/min/1.73m^2
- ALT and / or AST >100 U/l
  Unexplained reduction in albumin <30 g/l

Please note: A rapidly increasing or decreasing trend in any values should prompt caution and extra vigilance. Some patients may have abnormal baseline values, specialist will advise. Results should be recorded in the patient's shared care-monitoring booklet if issued.

ADVERSE EFFECTS, PRECAUTIONS AND CONTRA-INDICATIONS

Nausea: can occur at any time during therapy. The symptom may resolve with dose reduction from 20mg to 10mg and/or addition of anti-emetic.
Diarrhoea: occurs in approximately 20% of patients and is sometimes self-limiting. May respond to dose reduction or to loperamide / codeine phosphate.

Hypertension: mild increases in blood pressure are common. BP increases tend to affect those with pre-existing hypertension and may require additional antihypertensive therapy or cessation of treatment.
Decreased resistance to infection: especially respiratory/urinary tract or shingles/ chickenpox. Temporarily withhold leflunomide if patient is systemically unwell with significant infection requiring anti-infective intervention (a washout procedure may be necessary if severe or persistent infection occurs). If in doubt, discuss with specialist. Risk of tuberculosis reactivation.
Pulmonary Infiltration / Reactions: Pulmonary infiltration as an acute allergic reaction has been described in a small number of patients, after starting leflunomide. Patients should be made aware of this rare complication (see SPC).
Severe liver injury: reported rarely and more common if concomitant hepatotoxic drugs administered, or patient has chronic hepatitis B/C infection.
Alopecia: diffuse hair loss may occur in up to 10% of patients. It is usually mild and is reversible on stopping medication. May respond to dose reduction.
Rash/skin itch: if mild, continue full dose and monitor. If moderate or severe, stop treatment and discuss with specialist (washout may be necessary).
Washout procedure with colestyramine or activated charcoal is recommended in cases of significant drug toxicity (check SPC for further information).
Alcohol: patients are advised that alcohol consumption should be avoided or kept to a minimum, due to the increased potential for liver toxicity.

Pregnancy and Breastfeeding: pregnancy must be excluded before start of treatment with leflunomide and men and women whilst on leflunomide should use reliable contraception. Contraception should be continued for at least 2 years in women and 3 months for men after discontinuing leflunomide (see also 'Washout procedure' below) Refer immediately if a patient discovers she is pregnant whilst taking leflunomide. There is limited data which suggests leflunomide is compatible with paternal exposure.

Women **must not breastfeed** while receiving leflunomide

Washout procedure: Colestyramine 8g administered 3 times daily usually for 11 days, or activated charcoal can be used to accelerate excretion leflunomide from the body. This may be helpful in patients wishing to conceive, or those with severe infections.

Vaccines: Live vaccines should be avoided in patients taking leflunomide (see Green Book re zoster vaccine).

CONTRAINDICATIONS INCLUDE

- Hypersensitivity to leflunomide
- Uncontrolled hypertension
- Serious infections
- Severe immunodeficiency states (e.g. AIDS)
- Pregnant women or women of childbearing potential who are not using reliable contraception
- Male patients should be aware of the possible male-mediated foetal toxicity. Reliable contraception during treatment with leflunomide should also be guaranteed.
- Breastfeeding
- Impaired liver function due to any cause.
- Severe unexplained hypoproteinaemia.
- Renal impairment (moderate to severe).
- Impairment of bone marrow function as indicated by anaemia and cytopenias due to causes other than RA and PsA

COMMON DRUG INTERACTIONS

Leflunomide has a very long half-life (1-4 weeks) and therefore potential interactions may take time to become clinically apparent

- Caution is advised when leflunomide is given together with drugs (other than NSAIDs) metabolised by cytochrome P450 2C9 such as **phenytoin** and **warfarin**
- Note increased risk of toxicity with other hepatotoxic, nephrotoxic or haematotoxic medicines
- The SPC for leflunomide states that combination treatment with **methotrexate** is not advisable. In selected patients the specialist may recommend the use of this combination, and as the risk of hepato-toxicity may be increased, more frequent monitoring may be required

COMMUNICATION

For any queries relating to this patient's treatment with leflunomide please contact the consultant named at the top of this document.

This information is not inclusive of all prescribing information, potential adverse effects and drug interactions
Please refer to full prescribing data in the SPC or the BNF

REFERENCES

1. GMC: Prescribing guidance: Shared care www.gmc-uk.org/guidance/ethical_guidance/14321.asp(accessed 20/10/2014)

2. NMC: Standards of proficiency for nurse and midwife prescribers http://www.nmc-uk.org/Documents/NMC-Publications/NMC-Standards-proficiency-nurse-and-midwife-prescribers.pdf (accessed 3/11/2014)

3. Chakravarty, K., McDonald, H., Pullar, T. et al. (2008) BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists. *Rheumatology* **47**(6), 924-925.

4. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. *Ledingham J, Gullick N, Irving K, Gorodkin R, Aris M, Burke J, Gordon P, Christidis D, Galloway S, Hayes E, et al. Rheumatology (Oxford). 2017 Jun 1; 56(6):865-868.*

5. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. *Ledingham J, Gullick N, Irving K, Gorodkin R, Aris M, Burke J, Gordon P, Christidis D, Galloway S, Hayes E, et al. Rheumatology (Oxford). 2017 Jun 1; 56(6):865-868.*

6. BSR AND BHPR guideline on prescribing drugs in pregnancy and breastfeeding – Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids. . *Flint J, Panchal S, et al. Rheumatology (Oxford).*

7. EMC DRUGS – Leflunomide - https://www.medicines.org.uk/emc/product/4944/smpc