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:	
Contact number:	Contact number:	

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

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.

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 patient/carer with relevant (written) information on use, side effects and the need for monitoring for infection.
- **Advise on need for adequate contraception.**
- Arrange pre-treatment baseline investigations either in secondary or primary care.
- Baseline tests:
  - **FBC**
  - **LFTs**
  - **U&Es + creatinine**
  - **ESR or CRP**
  - **Blood pressure (if >140/90 on 2 occasions 2 weeks apart treat before starting leflunomide)**
  - **Weight**
  - **Varicella Zoster IgG in suspected non-immune patients** and notify general practitioner as appropriate
  - **Screen for active or latent tuberculosis/hepatitis B/C**

- Review results of safety monitoring and request additional tests as required.
- Monitor disease response to treatment and need to continue therapy.
- Continue to review the patient at agreed specified intervals, 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.
- Consider active washout if patient stops leflunomide and transfers to another immunosuppressive DMARD.

Authors: C Daly/S Lyttle, Shropshire CCG Dr M Garton, Sr S Bird, RJAH Rheumatology Dept
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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.
- Arrange and record ongoing monitoring as agreed with specialist.
- **FBC, LFT, ESR or CRP** every 2 weeks for 6 months and if stable 2 monthly
- If co-prescribed with another immunosuppressant or potentially hepatotoxic agent check **FBC** and **LFT** monthly as appropriate.
- **Blood pressure and weight** at each monitoring visit.
- If patient develops symptoms/signs of systemic infection, this should be treated promptly and withhold leflunomide until the infection has cleared. Consider accelerated drug washout if infection is severe or likely to be prolonged (e.g. osteomyelitis)

Withhold leflunomide and contact specialist if:

- WBC < 3.5×10^9/L
- Neutrophils < 2×10^9/L
- Platelets < 150×10^9/L
- ALT / AST > 3 x ULN - Recheck LFTs within 72 h, if still more than three times the reference range, stop drug and consider washout.

  2-3 x ULN- 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.
- Oral ulceration, sore throat, unusual bruising, unexplained rash, itch
- Severe infections
- Increasing shortness of breath
- Hair loss
- Hypertension (BP > 140/90 after treatment)
- Severe headache
- Severe GI upset
- Unexplained weight loss (>10%)

Please note: A rapidly increasing or decreasing trend in any values should prompt caution and extra vigilance

Results should be recorded in the patient's shared care monitoring record booklet, if issued

- Identify and report adverse events to the initiating specialist and the MHRA (via yellow card).
- Ensure no drug interactions with other medicines
- Check patient is using adequate contraception.
- Continue prescribing for patients attending regular review.
- Repeat prescriptions should be removed from the surgery repeats pile and retained separately for prescribers to review prior to signing. Maximum 28 days supply.
- Ask about unexplained rash, oral ulceration/sore throat or unusual bruising at every consultation.
- Administer influenza vaccine annually unless otherwise advised by the initiating specialist.
- Check patient has had ONE DOSE of pneumococcal vaccine (revaccination is not recommended, except every 5 years in individuals in whom the antibody concentration is likely to decline rapidly (e.g. asplenia). If there is doubt, the need for revaccination should be discussed with a microbiologist.

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- **Varicella zoster**
  - *Non-immune patients* should avoid contact with people with chicken pox or shingles; consider passive immunisation using varicella immunoglobulin (VZIG) if exposure is suspected (contact Public Health England/Blood Transfusion Service for advice). Consider immunisation of non- immune patients before starting immunosuppression (if recommended by specialist)
  - Varicella infection can be severe in immunosuppressed patients, and early systemic anti-viral and supportive therapy may be required. Suspend leflunomide until recovered, and consider accelerated drug washout if required.
- Ensure a clinician updates the patient's record following specialist review.
- Report any adverse drug reactions to initiating specialist and the usual bodies (e.g. MHRA)
- Consider active washout if patient stops leflunomide and transfers to alternate immunosuppressive therapy for the same or a separate condition.

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.

Adverse effects, Precautions and Contra-indications continued

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 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 reliable contraception should be used by men and women whilst on leflunomide. 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. 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
- 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
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- 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

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

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)

SPC Arava : http://www.medicines.org.uk/emc/medicine/26345

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.