NORTH AND EAST DEVON HEALTHCARE COMMUNITY SHARED CARE PRESCRIBING GUIDELINE

Leflunomide

Treatment of rheumatoid arthritis and psoriatic arthritis

Specialist: Please complete letter on page 8 before sending guideline to GP

GP: Please indicate whether you wish to share patient's care by completing letter on page 8 and return to specialist

Aim of treatment

Leflunomide is a disease-modifying anti-rheumatic drug.
Indication: Treatment of adults with active rheumatoid arthritis or active psoriatic arthritis.

Specialist responsibilities

- Female patients of child-bearing age – exclude pregnancy before initiating treatment.
- Initiate leflunomide, supply 28 days' medication.
- Discuss benefits and side effects of treatment with patient or patient's carers including, where appropriate, for female and male patients the risks associated with pregnancy and need for reliable method of contraception.
- Refer patient to specialist nurse service where appropriate (eg. new patient) for advice on taking the drug, its cautions, side effects associated with treatment, monitoring requirements and the timing of re-assessment and by whom.
- Ascertain immune status by enquiring about history of chickenpox. Measurement of antibodies to varicella-zoster is not recommended.
- Issue a booklet for recording test results to patient.
- Conduct baseline tests – see monitoring section, below. Copy results to GP.
- Specify review dates.
- Prompt verbal communication followed up in writing to GP of changes in treatment or monitoring requirements, results of monitoring, assessment of adverse events or when to stop treatment. Urgent changes to treatment should be communicated by telephone to GP.
- Reporting adverse events to MHRA.

General practitioner responsibilities

If GP has agreed to share care:

- Continue to prescribe leflunomide in accordance with these guidelines.
- Conduct monitoring during treatment as specified below. Review results and undertake any necessary action.
- Take appropriate action if patient reports any sign(s) or symptom(s) specified under Monitoring.
- Be aware of criteria for referral to Rheumatology team.
- Respond to advice from secondary care on dose changes and frequency of monitoring.
- Report to and seek advice from specialist on any aspect of patient care of concern to GP which may affect treatment. Prompt referral to specialist if there is a change in patient's health status.
- Report adverse events to specialist.
- Stop treatment in case of a severe adverse event or as per shared care guideline.
- Offer influenza vaccine annually unless otherwise advised by the initiating specialist.
- Check that the patient has had one dose of pneumococcal vaccine (revaccination is not recommended, except every five years in patients whose antibody levels are likely to have declined more rapidly e.g. asplenia) – see BNF or Green Book

- Ensure that women and men understand the need for effective contraception, the risk of harm to the baby, and the need to immediately consult the GP and rheumatology team if there is a possibility of pregnancy

Monitoring

Prior to starting therapy: rheumatology team
Full blood count including differential white blood cell count and a platelet count, liver (ALT and/or AST, and albumin) and renal function, blood pressure, height & weight, and chest x-ray.
Consider patient risk factors for viral infections and screen for occult viral infections (hepatitis B and C and HIV) where appropriate
Pregnancy test in women of childbearing age (unless pregnancy has been unequivocally excluded). Consider contraception as appropriate

Monitoring during treatment: General practice
GP to conduct monitoring including reviewing and acting on results as detailed overleaf:

<table>
<tr><th>Test</th><th>Frequency</th><th>Results</th><th>Action</th></tr>
<tr><td>FBC</td><td rowspan="3">Every two weeks until on stable dose for 6 weeks, then every month for 3 months, then at least every 12 weeks*.
Following dose increases, monitor every 2 weeks until on a stable dose for 6 weeks, then as above.
Patient factors where continued monthly monitoring is recommended (unless otherwise specified):
• Previous toxicity or deranged FBC or LFTs while on DMARDs
• Chronic kidney disease (CKD 3 or worse)
• Pre-existing liver disease</td><td>WCC < 3.5 x 10^9/L
Neutrophils < 1.6 x 10^9/L
Eosinophils >0.5 x 10^9/L
Platelets < 140 x 10^9/L
MCV > 108fl</td><td rowspan="3">If results meet specified criteria, stop treatment and refer to specialist.
If isolated MCV rise, check for other causes (B12, folate, thyroid function and alcohol consumption). If results are normal, refer to specialist.
If concerned about sequential drops in FBC indices (possibly still within normal range), consider an early re-test/seek specialist advice.
If deterioration in renal function, dose adjustment may be necessary; if toxicity suspected or dosing advice required refer to specialist team.</td></tr>
<tr><td>Creatinine/eGFR</td><td>Creatinine increase >30% over 12 months and/or
eGFR <60ml/min/1.73m^2</td></tr>
<tr><td>ALT and/or AST and albumin</td><td>Additional urgent monitoring tests should be carried out within 24 hours for any patient with acute kidney injury (AKI).</td><td>ALT and/or AST >100 U/L
Albumin unexplained reduction to <30g/L</td></tr>
<tr><td>Blood pressure</td><td>At each monitoring visit (as above)</td><td>Raised BP</td><td>Treat hypertension as per local formulary guidance
A rise in BP does not indicate withdrawal of leflunomide unless resistant to treatment – refer to specialist team.</td></tr>
<tr><td colspan="4">* For patients on a combination of leflunomide and methotrexate, extend monthly monitoring for at least 12 months before considering reduced frequency on an individual patient basis (specialist to advise). Refer also to N&E Devon methotrexate shared care guideline: https://onedevon.org.uk/download/oral-and-subcutaneous-methotrexate-mtx-rheumatology-shared-care-guideline-north-and-east-devon
Other factors that may increase risk of toxicity include moderate renal impairment, extremes of body weight, polypharmacy (especially other haematotoxic/ hepatotoxic/ nephrotoxic drugs), comorbidities, age > 80 years. Where more frequent ongoing monitoring is required due to a combination of patient factors this will be advised by the specialist prescriber.</td></tr>
</table>

2. Signs and symptoms

Patients MUST report mouth ulcers, sore throat, fever, epistaxis, unexpected bruising or bleeding, shortness of breath and/or dry cough, and any unexplained illness/infection.

Action to be taken by GP:

- **Review patient with any of the signs or symptoms listed above within 24 hours** for clinical assessment, full blood count, liver function tests, U&Es. Signpost patient to alternative provider if this is not possible e.g. weekend/bank holiday
- **Stop treatment and refer urgently (for possible washout procedure)**
    - Abnormal bruising
    - Severe sore throat
    - New or increasing dyspnoea or cough
    - Severe, uncontrolled infection
    - Severe nausea or diarrhoea
    - Severe mouth or genital ulceration
    - Severe skin reactions

During a **serious** infection **STOP** treatment. During minor infections (e.g. uncomplicated UTI treated with a short antibiotic course) treatment can be continued.

Do not stop treatment prior to surgery unless significant risk of infection.

Contact Microbiology if a patient, not known to be immune to chickenpox, comes into contact with shingles or chickenpox, for advice on whether zoster immune globulin or other treatment is indicated.

Patients can have treatment discontinued abruptly. However, it is important to note that leflunomide has a long half-life. If necessary, a 'washout' procedure can be carried out.

Patient/carer responsibilities

Patients (and/or their carers):

- MUST report mouth ulcers, sore throat, fever, epistaxis, rash, unexpected bruising or bleeding, new or increasing breathlessness and dry cough, and any unexplained illness/infection to their GP and/or specialist (or out of hours service e.g. NHS 111 if their practice is closed for weekend/bank holiday).
- MUST notify their doctor immediately for pregnancy testing, if there is a delay in onset of menses or any other reason to suspect pregnancy.
- Report any other adverse effect to their GP and/or specialist whilst being treated with leflunomide.
- Ensure that they have a clear understanding of their treatment.
- Ensure they attend for monitoring requirements.
- Be aware that treatment will be stopped if patient does not attend for monitoring.

Back-up advice and support

Contact details	Telephone No	E-mail address
Dr R Haigh Dr S Earl Dr M Brown Dr R Mascarenhas Dr M Abusalameh Dr M Cates Dr S Kyle Dr R Manhas Dr V Arya	(01392) 403705 (01392) 406351 (01392) 403567 (01392) 406355 (01392) 403772 (01392) 403707 (01271) 311571 (01271) 311571 (01271) 311571	richardhaigh@nhs.net Susannah.earl@nhs.net mary.brown11@rnhs.net r.mascarenhas@nhs.net m.abusalameh@nhs.net matthewcates1@nhs.net stuartkyle@nhs.net roopemanhas@nhs.net vivek.arya2@nhs.net
Contact details	**Fax no.**	
RD&E rheumatology dept NDDH rheumatology dept	01392 404772 (preferred) 01392 403505 0844 802 3038	rde-tr.rheumatology@nhs.net ndht.rheumatology@nhs.net

Please do not use rheumatology department emails for enquiries relating to patients receiving DMARDs under the care of other specialties e.g. dermatology, gastroenterology etc.

Supporting Information

This guideline highlights significant prescribing issues, not all prescribing information and potential adverse effects is listed Please refer to SPC/data sheet for full prescribing data.

Dose

The dose is 10mg to 20mg once daily. Loading doses are not used by the Rheumatology team.
The tablet should be swallowed whole with a sufficient amount of fluid.

Contraindications

- Hypersensitivity to leflunomide (especially previous Steven-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme).
- Hepatic impairment.
- Moderate to severe renal impairment.
- Serious infection.
- Severe immunodeficiency states.
- Significantly impaired bone marrow function or blood disorders due to causes other than rheumatoid arthritis or psoriatic arthritis.
- Severe hypoproteinaemia
- Under the age of 18 years.
- Breastfeeding.
- Pregnancy – Male and female patients of child bearing age must use a reliable form of contraception during treatment with leflunomide and after stopping treatment. Leflunomide should not be given if there is a risk of pregnancy or if the patient (male or female) wishes to consider starting a family in the near future. Patients should be advised that a washout and blood tests to measure the levels of active metabolite might be required for up to 2 years before drug elimination is confirmed (see Precautions and Pregnancy and Lactation)

Precautions

- It is recommended that alcohol should be avoided during leflunomide therapy. However, pragmatic advice from the rheumatology team would be to suggest a maximum of 10 units per week.
- Increase vigilance when co-prescribing other hepatotoxic drugs (increased risk of liver problems).
- Combination with other DMARD drugs should not be considered without specialist advice.
- Procreation (recommendations for men): Male patients should be aware of the possible male-mediated foetal toxicity. Reliable contraception during treatment with leflunomide should be guaranteed. To minimise any possible risk, men wishing to father a child should consider discontinuing use of leflunomide and the wash-out procedure should be used (see SPC for details). A waiting period of at least 3 months is required following washout. Men should use effective contraception for 3 months after stopping leflunomide.
- Washout procedure: colestyramine 8g is administered 3 times daily. Alternatively, 50g of activated powdered charcoal is administered 4 times daily. Duration of a complete washout is usually 11 days. The duration may be modified depending on clinical or laboratory variables.

Side effects

Common/uncommon:

- GI disturbances especially diarrhoea (usually settles), taste disturbances, anorexia, weight loss (usually significant)
- Headache, dizziness, paraesthesia, asthenia, anxiety
- Hypertension
- Elevation of liver enzymes rarely hepatitis (transaminases, less often gamma-GT, alkaline phosphatase, bilirubin)

- Increased hair loss, eczema, dry skin, pruritis, rash, urticaria, mild allergic reactions.
- Tenosynovitis, tendon rupture
- Anaemia, leucopenia, mild thrombocytopenia, CPK increased, hypokalaemia, mild hypophosphataemia, hyperlipidaemia

Interactions

The long half-life of 1-4 weeks for leflunomide means that serious adverse effects/interactions may occur after treatment with leflunomide has been stopped.
Increased risk of toxicity with other haematotoxic and hepatotoxic drugs

- Antibacterials: plasma concentration of active metabolite of leflunomide possibly increased by rifampicin
- Anticoagulants: leflunomide possibly enhances anticoagulant effect of warfarin. The INR for warfarin should be very closely monitored for several weeks even after stopping leflunomide.
- Antidiabetics: leflunomide possibly enhances hypoglycaemic effect of tolbutamide
- Antiepileptics: leflunomide possibly increases plasma concentration of phenytoin
- DMARDs: concomitant administration with other DMARDs is not advised. Use in combination may be recommended by a specialist only.
- Lipid-regulating drugs: the effect of leflunomide is significantly decreased by colestyramine (enhanced elimination) – avoid unless drug elimination desired.
- Vaccines – see below

Vaccines

- Vaccinations – no data available on efficacy and safety of vaccines under leflunomide treatment.
- Live vaccines are contraindicated for patients on leflunomide. These vaccines include measles, mumps and rubella; BCG; poliomyelitis – oral Sabin vaccine; yellow fever; typhoid – oral.
- Shingles vaccination should **not** be given to patients on leflunomide
- Passive immunisation should be carried out using Varicella Zoster Immunoglobulin (VZIG) in non-immune patients if exposed to chickenpox or shingles (see local guidance page 3)
- Flu and pneumococcal vaccines may be given if required.
- NB Long half-life of leflunomide should be considered when giving live attenuated vaccines after stopping treatment. For additional information refer to the British Society of Rheumatology guidance on vaccinations for immunosuppressed patients, steroids and biologic therapies: http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/v/vaccinations_in_the_immunocompromised_person.pdf

Pregnancy and lactation

See Contraindications - The active metabolite of leflunomide is suspected to cause serious birth defects when administered during pregnancy. See SPC for further information on duration of contraceptive use after stopping treatment, washout procedures and waiting periods for female patients for intended and unintended pregnancies and for male patients.

Date ratified by Effective Practice Committee: April 2011
Partially updated: October 2019, March 2021

Shared Care Agreement Letter - Consultant Request

To: Dr……

Practice Address: ……

……

……

Patient Name:	
Hospital number:	
Date of birth:	
Address:	

DIAGNOSED CONDITION: **……..**

I recommend treatment with the following drug: **……**

I request your agreement to sharing the care of this patient according to the North and East Devon Health Community Shared Care Prescribing Guidelines for this drug.

Principles of shared care:

GPs are invited to participate. If GP is not confident to undertake these roles, then they are under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug the GP should reply to this request as soon as practical. Sharing of care assumes communication between the specialist, GP and patient. The intention to share care should be explained to the patient and accepted by them.

The doctor who prescribes the medication has the clinical and legal responsibility for the drug and the consequences of its use.

Signed:		**Date:**	
Consultant name:			
Consultant email:			
Department email:			
Contact telephone:			

GP RESPONSE

I agree/ do not agree* to share the care of this patient in accordance with the Shared Care Guideline.

Signed: …….. **Date: ……**

GP name: …….. ***Delete as appropriate**