Shared Care Guideline for Leflunomide (GP Summary)

It is essential that a transfer of care only takes place with agreement of the GP and when sufficient information has been received. If the GP does not agree to share care they will inform the Consultant responsible for the patient's care.

Basingstoke, Southampton & Winchester District Prescribing Committee

Indications	Adults (over 18yrs) with active rheumatoid arthritis as a DMARD
Dose & response	**Maintenance dose: Leflunomide 10-20mg once daily** Therapeutic effect usually starts after 4-6 weeks and improvement may continue for 4-6 months. Co-prescribed NSAIDs and/or corticosteroids may be continued https://www.nice.org.uk/guidance/ng100
Specialist responsibilities	• **Prescribe initial treatment until dose stable (usually 2-3 months).** • **Request blood tests and monitor results for the first 2-3 months and when dose is increased.** • **Counsel patients about possible side effects. Ensure the patient understands their treatment and which warning signs to report. Advise patients to report symptoms of bone marrow suppression, such as inexplicable bruising, bleeding or severe sore throat/oral ulceration, immediately.** • **Carry out washout procedure as detailed in product SmPC in cases of toxicity.** • **Advice and support to GPs when there may be abnormal blood tests or issues with patients** • **Review patients at regular intervals depending on individual need**
GP Responsibilities	• Prescribe maintenance dose of leflunomide according to the dose regimen suggested by the specialist (Note: 1x20mg tablet is more cost effective than 2x10mg). • Request blood tests once dose is stable and requested by hospital to take over shared care (usually 2-3 months). • Review blood test results before prescribing. • Communicate with Rheumatologist regarding any problems/compliance issues. **Recommended monitoring for new DMARDs** • **FBC, Cr (or eGFR), ALT, albumin every 2 weeks until stable dose for 6 weeks (Specialist responsibilities)** • **Then monthly FBC, Cr or eGFR, ALT, albumin for 3 months** • **Then FBC, Cr or eGFR, ALT, albumin at least every 12 weeks** • **For dose increases -FBC, Cr or eGFR, ALT, albumin every 2 weeks until stable dose for 6 weeks then back to previous schedule (Specialist Responsibilities)** • **During Covid, and only for stable patients, the following applies** **https://www.sps.nhs.uk/articles/dmard-drug-monitoring-in-primary-care-during-covid-19/** **For patients on methotrexate and leflunomide in combination, long-term monthly monitoring is needed (also during Covid)** **Monitoring specific to leflunomide** • **Check blood pressure at each monitoring visit (see BP Guidelines https://www.nice.org.uk/guidance/ng136)** • **Check weight (advisable, but not essential)** • Patients with Arthritis are recommended to have Pneumococcal vaccine every 10 years. Patients with arthritis and on immunosuppression to have Pneumococcal vaccine at start of treatment, a repeat dose 5 years later (due to a weaker response to vaccine), then every 10 years

Date approved: November 2020
Review date: November 2022

	• Zostavax is a live attenuated vaccine, and treatment with Leflunomide is considered a moderate risk (BSR Update 2018). It is not a contraindication, but, vaccination in patient with multiple DMARD, should be discussed with the specialist. • Communicate with specialist regarding any problems/compliance issues.
Patients Responsibilities	• Report to the specialist or GP if they do not have a clear understanding of their treatment • Communicate with the GP any side-effects or problems encountered which may have an impact on taking the medicines • Ensure blood monitoring and blood pressure is undertaken at the requested time intervals • Report any excessive weight loss that may not be intentional • Read the Patient Information leaflet which accompanies the medicine • Inform specialist team where bloods are taken to facilitate access where necessary
Actions to be taken in response to monitoring	**Thresholds at which to review treatment and contact Rheumatology for urgent review:** • **WCC<3.5 x10^9/L** • **Neutrophils<1.6 x10^9/L** • **Unexplained eosinophilia>0.5 x10^9/L** • **Platelets<140 x10^9/L** • **MCV>105** • **ALT>100 units/L** • **Unexplained fall in albumin** • **Creatinine>30% above baseline +/- eGFR<60**
Contra-indications	• Hypersensitivity reactions (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme • Hypertension which is uncontrolled or difficult to control with routine medication. • Moderate to severe renal insufficiency or impaired hepatic function. • Serious infections or severe immunodeficiency states. • Severe hypoproteinaemia e.g. nephrotic syndrome. • Significant impairment of bone marrow function or significant anaemia, leucopoenia, neutropenia or thrombocytopenia due to cause other than rheumatoid arthritis. • **Pregnancy must be excluded before start of treatment with leflunomide because it is suspected to cause serious birth defects.** Women with childbearing potential must use reliable contraception. Men must also use reliable contraception during treatment to avoid potential for male-mediated foetal toxicity. Contraception should be continued for at least 2 years in women and 3 months for men after discontinuing leflunomide. Advise patients to discuss plans for pregnancy with specialist and consult specialist immediately if pregnancy is suspected. • Breast feeding
Cautions	• Blood and liver abnormalities, see monitoring above, contact rheumatology • **Alcohol:** Avoid - increased potential for liver toxicity.
Important adverse effects & management	**Active metabolite of leflunomide has a long half-life (1-4weeks). Adverse effects may occur/continue after treatment is stopped. In cases of toxicity a washout procedure (as detailed in the product SPC) may be required. This is the responsibility of the specialist.** • **Nausea:** can occur at any time during therapy, may resolve with dose reduction from 20mg to 10mg and/or addition of anti-emetic. Anorexia and up to 10% body weight loss has been reported. Stop treatment if severe and discuss with specialist. • **Diarrhoea:** occurs in approximately 20% of patients and is sometimes self-limiting. May respond to dose reduction or to loperamide / codeine phosphate. • **Headache:** May respond to dose reduction. If persistent and absence of a secondary cause, stop treatment and discuss with specialist • **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 if uncontrolled. Stop leflunomide or seek specialist advice if hypertension is worsening and not responding to treatment. • **Reduced resistance to infection: especially respiratory/urinary tract or shingles/ chickenpox.** Temporarily withhold leflunomide and check FBC if patient is systemically unwell with significant infection or requires anti-infective intervention. If in doubt, discuss with specialist. Consider risk of tuberculosis reactivation. Chicken pox/shingles can be fatal. Stop treatment and contact secondary

	care. Passive immunization may be given with Varicella zoster immunoglobulin (VZIG) in non-immune patients if exposed to chickenpox or shingles. Systemic antivirals may be needed if infection suspected. • **Pulmonary infiltration / reactions:** Discuss increasing shortness of breath with specialist. Pulmonary infiltration as an acute allergic reaction has been described in a small number of patients. Discontinue treatment & seek urgent medical treatment. • **Alopecia:** diffuse hair loss may occur in up to 10% of patients -usually mild and reversible on stopping medication. May respond to dose reduction. • **Rash/skin itch:** if mild, continue full dose and monitor closely with or without anti-histamines. If moderate or severe, stop treatment and discuss with specialist. • **Elevated LFTs:** ALT common, GGT, ALP, bilirubin less common. Hepatotoxicity usually occurs within 6 months of starting therapy & is more likely in patients with existing liver damage or on concomitant hepatotoxic drugs or with history of alcohol abuse. • **Haematological:** Anaemia & mild thrombocytopenia are uncommon. Leucopenia & pancytopenia are rare. Stop treatment and discuss with specialist.
Important Drug Interactions	**Due to long half-life of active metabolite, drug interactions may occur after leflunomide has been stopped** • **Charcoal (Activated): Avoid.** Significantly reduces effect of leflunomide. • **Colestyramine: Avoid.** Significantly reduces effect of leflunomide. • **Phenytoin: Caution.** Possible enhanced effect of phenytoin. • **Rifampicin: Caution.** Possible increase of leflunomide active metabolite. • **Tolbutamide: Caution.** Possible enhanced effect of tolbutamide. • **Vaccines:** Seek specialist advice with live attenuated vaccines. Zostavax may be used with caution. • **Warfarin: Caution.** Possible enhanced effect of warfarin, monitor INR closely during concurrent treatment and for several weeks following discontinuation of leflunomide.

This guidance should be read in conjunction with the BNF and SmPC (www.medicines.org.uk)

Contact numbers for urgent GP advice

Southampton - Nurse specialist advice line 023 8120 5352 or bleep SpR 1801 (Mon-Fri 9-5). Out of hours – on-call consultant via hospital switchboard

Basingstoke - Administration team 01256 312768, advice line (answerphone) 01256 313117 or on-call consultant via switchboard

Winchester – Administration team 01964 824150, Advice line 01962 824256, on-call SpR bleep 3425 via switchboard

Southampton Medicines Advice Service (Mon-Fri 9am – 6.30pm) 023 8120 6908/9 or medicinesadvice@uhs.nhs.uk