Shared Care Guideline: *Leflunomide*

County Durham and Darlington NHS
NHS Foundation Trust

NHS
County Durham and Darlington
Area Prescribing Committee

Overview	Leflunomide is a disease modifying anti-rheumatic agent which has immunosuppressant characteristics.
Indication	Licensed • Rheumatoid arthritis • Psoriatic arthritis
Dose	• Rheumatoid arthritis - 10 to 20mg ONCE daily • Psoriatic arthritis - 10 to 20mg ONCE daily
Specialist's Responsibilities	**Initial investigations:** • Full Blood Count (FBC), calculated creatinine clearance (CrCl) estimated Glomerular Filtration Rate (eGFR), Liver Function Tests (LFTs) , Erythrocyte Sedimentation Rate (ESR) /C-Reactive Protein(CRP), weight, height and Blood Pressure (BP) • BP to be less than 140/90 on 2 consecutive occasions (2 weeks apart) prior to commencing treatment. Hypertension should be treated and controlled prior to initiation of leflunomide. • Ensure pregnancy can be excluded before treatment • Check Varicella status if there is an uncertain history and recent exposure to the virus. **Initial prescribing until stable:** **Prescribing responsibility and monitoring to stay with the specialist until patient has been on a stable dose for at least 6 weeks at which point shared care is requested.** Specialist to issue a prescription for enough medication to last until shared care is accepted by GP. This will usually be a minimum of 28 days **Communication and Documentation to GP:** • Obtaining agreement of GP to participate in shared-care arrangement for leflunamide therapy (by sending a copy of this document and letter to the GP). • Prompt communication with the GP regarding the patient's progress, any reassessment and changes in treatment. • Provide additional information and advice to the GP on actions he/she may need to take e.g. on dosage adjustment, other changes in therapy and management of adverse effects, as required. • Clinic letters and results to GP.
GP's Responsibilities	**Maintenance prescription:** Prescribe leflunomide in accordance with the specialist's recommendations as outlined in the shared care agreement. **Clinical monitoring:** FBC, calculated CrCl/ eGFR, LFTs, ESR/CRP, weight and BP **Criteria Requiring Specialist contact:** • Failure to attend for review or undertake blood tests • Intolerance of drugs • Communications failure **Documentation to specialist:** • Accepting or rejecting request for shared care within 28 days, if rejecting please state concerns and reasons

	• Blood results to specialist via use of patient-held record.
Clinical monitoring	FBC, calculated CrCl/eGFR, LFTs, albumin, ESR/CRP, weight and BP **Frequency:** Fortnightly until on stable dose for SIX weeks then monthly for THREE months After THREE months reduce frequency of monitoring to 3 monthly NOTE - If leflunomide is co-prescribed with Methotrexate, another immunosuppressant or potentially hepatotoxic agent, **monthly** monitoring should continue for at least a year. At this time patients may be considered for reduced monitoring to 3 monthly on the advice of specialist NOTE – this guideline sets out the standard monitoring requirements, however it is essential that each patient is considered on an individual basis and monitoring frequency should reflect this. The GP should be made aware of any deviations

Safety monitoring	Please refer to Summary of Product Characteristics (SPC) or BNF /eBNF for full details of adverse effects, contraindications, cautions and drug interactions.
	• Monitoring for response and adverse drug reactions (ADRs)
	• Ask about the following at each visit
	  ○ cough
	  ○ rash

Adverse Events	

Adverse event	Action to be taken
White Blood Cells (WBC) less than 3.5 x 10^9/L	Withhold and discuss with specialist team
Neutrophils less than 1.5 x 10^9/L	Withhold and discuss with specialist team
Platelets less than 120 x 10^9/L	Withhold and discuss with specialist team
More than a TWO fold rise in Alanine transaminase (ALT) / Aspartate aminotransferase (AST) from upper limit of normal	Consider dose reduction* Recheck weekly until returns to normal. If still abnormal after ONE week, withhold and discuss with specialist team
More than a THREE fold rise in AST / ALT from upper limit of normal	Recheck within 72 hours, if still MORE than THREE times the upper limit, stop and consider washout**. Discuss with specialist team
Rash or itch	If mild, consider dose reduction +/- antihistamine. If severe, stop and consider washout. Discuss with specialist team
New or increasing dyspnoea or cough	Stop and consider washout**. Discuss with specialist team
Hair loss	If mild, consider dose reduction* Discuss with specialist team
Sustained Hypertension (BP over 140/90)	Treat according to NICE guidance. If BP remains uncontrolled, withhold and discuss with specialist team
Abnormal bruising or sore throat	Withhold, check FBC and discuss with specialist team
Headache	If severe, consider dose reduction*. If headache persists, stop and consider washout**. Discuss with specialist team.
Nausea or diarrhoea	Give symptomatic treatment and consider dose reduction*. If severe, withhold and discuss with specialist team

Weight loss	Monitor carefully. If more than 10% weight loss with no other cause Discuss with specialist team and consider wash out**

*If taking 20mg daily reduce dose to 10mg daily. If taking 10mg daily, withhold and discuss with specialist team
** washout is carried out by consultants

Please note: Any rapid fall or consistent downward trend for blood counts or rapid rise or consistent upward trend for liver enzymes should prompt caution. Action may be required even if values are within normal range. If in doubt please contact specialist team

Some common adverse effects include the following (note list is not exhaustive),

- Gastrointestinal effects including; Nausea, vomiting, abdominal pain and Weight loss
- Stomatitis, mouth ulcers
- Rash
- Pruritis
- Alopecia
- Headache
- Mild increase in blood pressure
- Parasthesia
- Dizziness
- Leucopenia
- Infections
- Hepatitis

All suspected serious reactions should be reported to the specialist and the MHRA.

Contra-indications

- Known hypersensitivity to leflunomide.
- Pregnancy
- Breast feeding.
- Hepatic Impairment
- Women of child bearing age who will not be using reliable contraception both during treatment with leflunomide and after treatment is stopped until the plasma levels of the active metabolites are confirmed to be less than 20micrograms/L
- Severe immunodeficiency states e.g. HIV
- Significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid arthritis or psoriatic arthritis.
- Current serious infection.
- Severe hypoproteinaemia e.g. nephrotic syndrome.

Cautions

- The active metabolite of leflunomide, A771726, has a long half-life, usually 1 to 4 weeks. Serious adverse effects can therefore occur even after treatment with leflunomide has been stopped.
- Anaemia
- History of Tuberculosis or impaired bone marrow function
- Stage 3, 4 or 5 Chronic Kidney Disease (dose should be reduced by 50%)
- Hepatic Impairment or blood dyscrasias
- 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. 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. It is highly recommended that LFTs be monitored at least once a month if leflunomide is co-prescribed with potentially hepatotoxic drugs, such as methotrexate.
- Alcohol must be avoided during treatment.

	• Increased risk of peripheral neuropathy in patients who have diabetes, are taking neurotoxic medications or aged over 60 years.
Drug Interactions	• Leflunomide may cause increased plasma levels of drugs metabolised by CYP2C9 e.g. phenytoin, warfarin, phenprocoumon and tolbutamide. • Care prior to treatment if patient taking other DMARDs. Can lead to increased side effects, such as hepatotoxicity or haematoxicity.
Other Information	**Vaccinations** • "Live" vaccines (including Oral Polio, Oral Typhoid, measles, mumps and rubella (MMR), Bacillus Calmette-Guérin (BCG) and yellow fever) are not recommended whist on treatment • Seasonal influenza vaccination is recommended annually. • Pneumococcal vaccination is recommended in line with current guidance **Contraception, Fertility, Pregnancy and Breast Feeding** Leflunomide is teratogenic and is contraindicated in pregnancy. • Leflunomide should not be given to women of child bearing age unless reliable contraception is used. • Women planning to have children should discontinue treatment with lefunomide TWO years prior to conception or have a washout procedure to remove active metabolite. Blood levels of active metabolites should be checked before conception. • Men should use effective contraception both during treatment and for THREE months after stopping leflunomide. • Breast feeding must be avoided. More information on use of leflunamide in pregnancy and breastfeeding can be found on the British Society for Rheumatology (BSR) websites **https://www.guidelines.co.uk/BSR/RA-in-pregnancy-and-breastfeeding/252703.article** **General** • The patient should be advised to report any signs of bone marrow suppression or hypersensitivity (i.e. infection, fever, chills, cough, unexplained bruising or bleeding, fatigue, hypotension, myalgia, dizziness). • If patient is taking other immunosuppressive therapy, including steroids they are at an increased risk of secondary infections
Contact Details	Thank you for sharing the care of this patient. If you have any concerns or queries, please contact the Consultant or secretary or call the helpline below. UHND Rheumatology Helpline: 0191 3332763 DMH Rheumatology Helpline: 01325 743881

County Durham and Darlington NHS
NHS Foundation Trust
Department of Rheumatology
County Durham and Darlington Foundation Trust

GP name
GP address

Dear Dr ……

Request for Shared Care of LEFLUNAMIDE **Date:**

Re: Patient's name DOB:
Address Hospital Number:

This patient has been prescribed **Leflunamide** for the management of

□ Rheumatoid arthritis
□ Psoriatic arthritis

The patients' current dose is ……per day

The patient was commenced on this drug on ……..and has been stable on the current dose since……..

I would now like to ask you to take over the responsibility for prescribing this medication for this patient, as agreed by your CCGs and the Area Prescribing Committee.

The shared care document lists the monitoring requirements for this medication. Can I ask that any problems are reported back into secondary care.

The next blood monitoring is due on …… and should be continued in line with the shared care guideline.

In addition, the following patient specific monitoring is required for this patient

……..

This is part of the shared care guideline approved by the Area Prescribing Committee, available at http://medicines.necsu.nhs.uk/guidelines/durham-darlington/.

The patient will remain under regular clinical review by his or her usual consultant/ specialist nurse as described in the shared care agreement.

Please send back the second part of this letter, with 28 days, so we know that we have your agreement to this arrangement. If you are not happy to accept this patient or have any concerns, then please contact my secretary as soon as practically possible

Yours sincerely

Consultant name

Contact details

GP Agreement

Patient's Name:
DOB:
Hospital No:

I agree to take over the prescribing and monitoring of Leflunamide in line with the approved shared care document as found at http://medicines.necsu.nhs.uk/guidelines/durham-darlington/

Dose to be prescribed ……..

Dated ……/……/

Signed: ……

GP's Name:

GP contact details

Please return to Consultant's secretary. You may wish to keep a copy for your records.