NORFOLK AND WAVENEY STP THERAPEUTICS ADVISORY GROUP (TAG)

SHARED CARE AGREEMENT

Shared care guidelines for Leflunomide in the treatment of rheumatoid or psoriatic arthritis
Monitoring level Amber 2 – Prescribe the drug and perform a more intense level of monitoring e.g. quarterly

Generic and Proprietary/Brand Name	
Leflunomide / Arava®; Generics are also available	
Indications for shared care	
Rheumatoid arthritis, psoriatic arthritis (licensed indications).	
Specialist Prescribing and Monitoring Responsibilities – summary. Full details in main body of document	**GP / Community Team - Primary Care Prescribing and Monitoring Responsibilities – summary. Full details in main body of document**

Prescribing:
• Rheumatology medical team are responsible for the initiation and first 6 weeks of stable prescription of leflunomide.
• Patient education will be undertaken by the Rheumatology multidisciplinary team
Monitoring:
• Undertake pre-treatment monitoring of FBC, liver function tests (ALT and albumin), and creatinine eGFR.
• Check FBC, eGFR, ALT and albumin every 2 weeks until a stable dose has been achieved for 6 weeks.
• Specific monitoring explained in more detail below in main body of document regarding:
  ○ Lung disease
  ○ Liver disease
  ○ Occult viral infections
  ○ Blood pressure
  ○ Weight
	Prescribing:
	• After 6 weeks of stable dosage, to prescribe and monitor leflunomide therapy, communicating adverse events to the appropriate Rheumatology Consultant.
	Monitoring:
	• Once a stable dose has been achieved for 6 weeks, check FBC, eGFR, ALT and albumin every month for 3 months.
	• Where there is a low risk of toxicity, monitoring may then be reduced to a minimum of 3-monthly
	• Blood checks should be continued long-term, at least once a month, if leflunomide is co-prescribed with another immunosuppressant or potentially hepatotoxic agent, including methotrexate.
	• Blood pressure and weight should be checked at each monitoring visit.

Patient Information	
Contact GP, or the NNUH Rheumatology Advice line on (01603) 287801, if fever, cough, sore throat, skin rash, breathlessness or mouth ulcers occur.	
Specialist Contact Details	
NNUH: • Rheumatology Nurse Practitioner (01603) 287801 • Dr. Gaffney's secretary (01603) 289670 • Professor MacGregor's secretary (01603) 289906 • Dr. Marshall's secretary (01603) 287203	

- Dr. Merry's secretary (01603) 287003
- Dr Mukhtyar`s secretary (01603) 287118
- Dr De Silva's secretary (01603) 288623

QEH:

- Dr John Pradeep, Consultant Rheumatologist (01553) 613177
- Dr I Riaz……..(01553) 613177
- Rheumatology Nurse Specialists (01553) 613393

GENERAL PRINCIPLES FOR SHARED CARE PRESCRIBING

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- GPs are **invited** to participate. If GPs are not confident to undertake these roles, 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 practicable if they are unwilling to do so.**
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP and when the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring.
- **The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.**

Background to Treatment

Leflunomide is an immunosuppressant which reduces the signs symptoms and progression of rheumatoid arthritis and psoriatic arthritis.

Decreases the autoimmune response and arrests autoimmune lymphocytes thought to be involved in the pathogenesis of rheumatoid arthritis and psoriatic arthritis.

Licensed use and agreed local off-label use

Moderate to severe active rheumatoid arthritis and active psoriatic arthritis.

Criteria for Patient Selection

Rheumatoid arthritis and psoriatic arthritis. Patient suitability for leflunomide assessed by Rheumatology medical staff.

Form and strength of preparation

Leflunomide is administered orally in 10mg, 20mg or 100mg (loading dose only) tablets.
In rheumatoid arthritis, the typical dose is 10-20mg once a day when monotherapy is used. In combination therapy, when another potentially hepatotoxic DMARD like methotrexate is used, 10mg daily is the recommended starting dose.

In psoriatic arthritis, the recommended dose is 20mg once a day. Clinical judgement may indicate a starting dose of 10mg daily.

A loading dose (100mg daily for 3 days) is occasionally required to speed up the onset of action, but this is often omitted in routine practice as unacceptable gastrointestinal side effects such as diarrhoea may occur. A loading dose is not recommended when used as part of combination therapy.

Side Effects and Management

Link to BNF

Link to SPC

Common: Increase in blood pressure, diarrhoea, nausea, vomiting, anorexia, oral mucosal disorders, headache, abdominal pain, weight loss, increased hair loss, mild allergic reaction including macular papular rash, monitoring abnormalities including elevation of liver parameters (in particular transaminases), and leucopenia (leucocyte <4 x 109/L).

Less common: severe disturbance in liver function, pancytopenia, severe leucopenia (<2 x 109/L), thrombocytopenia, anaemia, breathlessness due to pulmonary infiltration / pneumonitis. Angular stomatitis, Stevens-Johnson syndrome, toxic epidermal necrolysis.

In cases of severe side effects, including severe monitoring abnormalities, leflunomide and any other concomitant myelosuppressive medication must be discontinued and the Rheumatology Department contacted for consideration of washout procedure.

Drug Interactions

Link to BNF

Link to SPC

Leflunomide can interact with many drugs, such as phenytoin, oral hypoglycaemic drugs and warfarin. Significant interaction is unlikely but International Normal Ratio (INR) should be very closely monitored in the first few weeks after initiation.

Avoid cholestyramine for the treatment of hypercholesterolaemia as this significantly reduces the efficacy of leflunomide.

Live vaccines must be avoided in patients on leflunomide. However the annual influenza and one-off pneumococcal vaccinations are recommended to be given.

Passive immunisation should be undertaken in patients taking leflunomide who are exposed to chickenpox or shingles.

The Green Book Chapter 28a v3_0 regarding the shingles vaccine, states “Long term stable low dose corticosteroid therapy (defined as <20mg prednisolone per day for more than 14 days), either alone or in combination with low dose non-biological oral immune modulating drugs (e.g. methotrexate less than or taking 25mg/week), are not considered sufficiently immunosuppressive and these patients can receive the vaccine. Patients on higher doses should be discussed with the consultant”.

Cautions and Contraindications

Link to BNF

Link to SPC

Contraindications:

- Pregnancy and breast-feeding. Leflunomide is teratogenic and remains in the enterohepatic circulation for up to 2 years. Therefore women of child-bearing years should be counselled about the need for effective contraception, and if planning a family or in any doubt about pregnancy status a pregnancy test should be carried out to exclude pregnancy.
- Women who wish to become pregnant should undergo the Washout Procedure* of cholestyramine 8g TDS for 11 days, with subsequent drug level testing under the guidance of the Rheumatology Department within 2 years of stopping Leflunomide. When the first plasma level is < 0.02 mg/l women must wait a further 6 weeks before fertilisation. Breast-feeding should be avoided. Men should use effective contraception and also undergo the washout procedure and drug level testing prior to conception they need to wait for 3 months after the 1st plasma level of < 0.02mg/l
- Severe immunodeficiency
- Severe infections
- Impaired liver function due to any cause
- Severe unexplained hypoproteinaemia

Moderate to severe renal impairment:

- leflunomide does not accumulate in renal failure and therefore may be used with caution in patients with an eGFR >29ml/min/1.73m2

- Impairment of bone marrow function (anaemia and cytopenias due to causes other than rheumatoid arthritis and psoriatic arthritis

Cautions:

- Alcohol intake. This should be limited to 4-8 units per week. Caution is advised in anyone with a heavier alcohol intake.
- Delay treatment commencement in a patient with active infection. Any infection which occurs during therapy should be treated appropriately.
- Drug potentiation: Hepatotoxic and haematoxic drugs such as methotrexate. Leflunomide SPC (http://www.medicines.org.uk/EMC/) states caution with methotrexate although combination therapy using these drugs has been used.
- Cardiovascular disease and prior malignancy are not considered contraindications to DMARD therapy.

Initiation of therapy and ongoing dose regimen

Initiation:
First six weeks to be prescribed by Rheumatology medical team. GPs are requested to take over prescribing once the patient has been on a stable dose for at least 6 weeks.

Initial dose and administration:
10mg or 20mg daily. Rarely 100mg daily for 3 days as part of the loading procedure.

Maintenance dose:
10 to 20mg daily. The dose may be reduced from 20 to 10mg daily if side effects occur.

Leflunomide absorption is not affected by food. The elimination half-life of leflunomide is 2 weeks.

Duration of Therapy

Time to response is 8 to12 weeks and can be longer if the loading dose is not prescribed. Further improvement may occur for up to 6 months. Maintenance therapy is long term.

Baseline assessment and ongoing monitoring – by Specialist

Pre-treatment assessment:
Undertake pre-treatment monitoring of FBC, liver function tests (ALT and albumin), and creatinine eGFR.

Lung disease:
Routine CXR are no longer undertaken but clinical assessment of coexisting pulmonary disease may result in pulmonary function tests to assess lung reserve and CT assessment being undertaken. Pre-existing lung disease is not a contraindication to DMARD use but prescription is undertaken with caution.

Liver disease:
In patients with deranged liver biochemistry, hepatotoxic DMARDs should be used with caution, with careful attention to trends in test results. In patients with impaired liver synthetic function (e.g. cirrhosis), DMARD therapy should be used with extreme caution. Patients with chronic viral hepatitis infection should be considered for anti-viral treatment prior to DMARD initiation.

Occult viral infections:
Screening for occult viral infections such as HIV and hepatitis B and C should be offered and record Varicella status. GP advised of any abnormal results. In-house checklist into patient's notes.

Blood pressure:
If >140/90 on two consecutive readings, 2 weeks apart, treat hypertension before commencing the drug. Consider an ECG in patients who have a history of hypertension prior to starting leflunomide.

Weight:
Assess for risk of weight loss which may be attributable to leflunomide.

The Rheumatology Department is responsible for the pre-assessment, and for at least 6 weeks' initial supply of stable dose, and related monitoring of leflunomide.
Check FBC, eGFR, ALT and albumin every 2 weeks until a stable dose has been achieved for 6 weeks.

GP / Community Team or other Primary Care monitoring responsibilities

- Once a stable dose has been achieved for 6 weeks, check FBC, eGFR, ALT and albumin every month for 3 months.
- Where there is a low risk of toxicity, monitoring may then be reduced to a minimum of 3-monthly, but only after discussion with the relevant consultant, and usually not in children, or in those at high risk of toxicity with renal impairment.
- Risk factors for toxicity include: a history of adverse drug events, medical comorbidities including renal and liver impairment (e.g. NAFLD) and malignancy, patients at the extremes of weight (BMI <18 or >30 kg/m2) and old age (>80 years).
- Blood checks should be continued long-term, at least once a month, if leflunomide is co-prescribed with another immunosuppressant or potentially hepatotoxic agent, including methotrexate.
- Blood pressure and weight should be checked at each monitoring visit.

Consultant / Specialist prescribing responsibilities

Rheumatology medical team are responsible for the initiation and first 6 weeks of stable prescription of leflunomide.

Patient education will be undertaken by the Rheumatology multidisciplinary team.

GP prescribing responsibilities

After 6 weeks of stable dosage, to prescribe and monitor leflunomide therapy as described above, communicating adverse events to the appropriate Rheumatology Consultant.

Indications for referral back to Specialist

- Report any suspected adverse drug reactions to the hospital specialist.
- Look for trends in the monitoring results e.g. rapidly falling WCC
- If the patient has:
    - WBC < 3.5 x 109/L
    - Neutrophils < 1.6 x 109/L
    - Platelets < 140 x 109/L
    - Unexplained eosinophilia > 0.5 x 109/l
    - ALT > twice upper limit of normal or
    - Unexplained falling albumin < 30g/l
    - MCV > 105fl
    - Creatinine increase > 30% over 12 months and/or eGFR < 50ml/min/1.73m2
    - Symptoms of pneumonitis
- **Rash or itch** consider dosage reduction with or without antihistamines - if severe, stop and consider washout*
- **Hair loss** - Consider dosage reduction; if severe, stop and consider washout*
- **Abnormal bruising or severe sore throat** - Check FBC immediately and withhold until results are available.
- **Hypertension** - If BP>140/90, treat in line with NICE guidance. If BP remains uncontrolled, stop leflunomide and consider washout*.

- **Headache** - If severe, consider dosage reduction. If headaches persist, stop and consider washout*
- **GI upset (nausea, diarrhoea**) - If loading dose has been used, give symptomatic treatment. If steady state has been reached, give symptomatic treatment and consider dosage reduction. If symptoms are severe or persistent, stop and consider washout.
- **Weight loss** - Monitor carefully. If >10% weight loss with no other cause identified, reduce dosage or stop and consider washout.
- **Breathlessness** - If increasing shortness of breath occurs, stop leflunomide and consider washout*.
- There is no indication to stop leflunomide at the time of surgery.
- Leflunomide should be stopped in the event of a severe infection e.g. requiring hospitalisation.
- The decision to restart leflunomide after a severe infection where the patient has had a break from therapy e.g. of more than one month, should be undertaken by the hospital specialist team.

Further information and supporting documents

BSR DMARD guidelines 2017

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Date of Approval	April 2024
Reviewed by	Therapeutics Advisory Group for information
Last review date	August 2021
Date of next review	March 2025

Document history:

Version	Date	Author / Editor	Status	Comment
1.	May 2000	Dr Peter Merry (NNUH)	Superseded	Recommended by the TAG as suitable for GPs to prescribe under Shared Care if consultant prescribes for the first 6 months.
2.	September / November 2008	Dr Tarnya Marshall, Consultant Rheumatologist and Mrs Margaret Somerville, Rheumatology	Superseded	Handover period reduced to 1 month. Extended use in psoriatic arthritis supported by the TAG.

		Practitioner, NNUHFT / Fiona Marshall TAG Lead Pharmacist		Revised version of the Shared Care Agreement supported by the TAG.
3.	November 2010	Dr Tarnya Marshall, Consultant Rheumatologist and Mrs Eileen Taylor, Rheumatology Practitioner, NNUHFT / Fiona Marshall TAG Lead Pharmacist	Superseded	No changes from version 2. Approved by the TAG November 2010. Due for review November 2012.
4.	January 2013	Dr Tarnya Marshall, Consultant Rheumatologist and Mrs Corrinne Ellis, Rheumatology Practitioner, NNUHFT / Fiona Marshall TAG Lead Pharmacist	Superseded	No changes from version 3. Approved by the TAG - January 2013 Supported by the N&W D&TCG January 2013
5.0	January 2015	As above	Draft for review	Reformatted into current TAG SCA template. Sent to authors, and to Dr John Pradeep (QEH) for review in preparation of returning to the TAG for approval.
5.1	July 2015	As above	Superseded	No further recommendations for change at present. Continued use supported by the TAG. Dr Pradeep's contact details added. Link to leflunomide PIL added.
6.	May to July 2017	Dr Tarnya Marshall, Consultant Rheumatologist and Heather Hasthorpe, Rheumatology Practitioner, NNUHFT, Dr John Pradeep, Consultant Rheumatologist, QEH / FM, TAG Lead Pharmacist	Current	Reviewed and updated following publication of revised British Society for Rheumatology (BSR) and the British Health Professionals in Rheumatology (BHPR) guidance for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs Feb 2017 - ***Link*** Circulated by the authors across all stakeholder specialisms and to the JPUH and the QEH for consultation. Changes made to monitoring requirements and responsibilities, side-effects, available products, advice to GPs regarding thresholds and

				responsibilities regarding referral back to specialists. Advice regarding shingles vaccination updated in line with the Green Book. Revised version supported by the TAG – July 2017. Final version approved by the D&TCG August 2017.
7.0	Aug 2021	JC, TAG Lead Technician, NWICB	FINAL	Discussed at August 2021 TAG meeting. Review dates extended for a year from meeting due to covid pressures
8.0	March 2024	JC, TAG Lead Technician, NWICB	Final	SCA moved to new template ready for publication on KNoW. Content not yet reviewed but remains current