BNSSG Shared Care Guidance
Please complete all sections

Section 1: Heading

Drug	Leflunomide
Amber *one month*	
Indication	Inflammatory arthritis. Vasculitis
Speciality / Department	Rheumatology
Trust(s)	University Hospitals Bristol Foundation Trust, Bristol Royal Infirmary
	North Bristol Trust, Southmead Hospital
	Weston Area Health Trust, Weston General Hospital

Section 2: Treatment Schedule

Usual dose and frequency of administration	Leflunomide is given once daily by mouth at a dose of 10mg or 20mg. When used in combination with other potentially hepatotoxic DMARDs such as methotrexate, a dose of 10mg is recommended. Treatment should be continued as long as clinically indicated unless there is a serious side effect or the drug becomes ineffective.
Route and formulation	Oral tablets
Duration of treatment	Long term. As long as clinically indicated.

Section 3: Monitoring

Please give details of any tests that are required before or during treatment, including frequency, responsibilities (please state whether they will be undertaken in primary or secondary care), cause for adjustment and when it is required to refer back to the specialist.

Baseline tests - where appropriate
Pre-treatment assessment: This will be performed by the rheumatology department. Height, weight, blood pressure, FBC, renal function/GFR, LFT's and screening for viral infection (HIV, Hep B, Hep C) will be done prior to commencing leflunomide. This will be done by the rheumatology department.

If blood pressure >140/90 on 2 consecutive readings at least 2 weeks apart then treat hypertension before commencing leflunomide.

In patients with a clinical suspicion of parenchymal lung disease, formal lung function testing and appropriate imaging (chest radiograph with or without high-resolution CT imaging) should be performed and referral to a respiratory specialist be considered. Some rheumatology departments may arrange baseline chest X-Ray routinely for all patients. Any patient currently smoking should be offered access to smoking cessation services.

Subsequent tests - where appropriate

Monitoring: This will be performed primarily by the patient's GP, with support from the rheumatology team in the event of abnormal results (see below)

Check FBC, creatinine/calculated GFR, ALT and/ or AST and albumin **every 2 weeks** until on stable dose for 6 weeks

Once on stable dose, **monthly** FBC, creatinine/calculated GFR, ALT and/ or AST and albumin for 3 months.
Then FBC, creatinine/calculated GFR, ALT and/or AST and albumin **at least every 12 weeks**.
More frequent monitoring is appropriate in patients at higher risk of toxicity.

BP and weight should also be checked at each monitoring visit.

Dose increases should be monitored by FBC, creatinine/calculated GFR, ALT and/ or AST and albumin every **2 weeks** until on stable dose for **6 weeks**, then revert back to previous schedule. This is the responsibility of primary care.

If methotrexate is used in combination with Leflunomide then monthly monitoring should be extended longer term (Patients who have been stable for 12 months can be considered for reduced frequency of monitoring on an individual patient basis).

Note that a rise in alkaline phosphatase may reflect disease activity rather than drug toxicity. Similarly a low WCC may be a feature of the underlying disease. If in doubt please contact the patient's rheumatologist.

Chicken pox/shingles infection - stop and commence aciclovir.

Dose reduction maybe considered for a mild degree of liver function abnormality (discuss with specialist team). If liver function abnormality persists after dose reduction or the ALT is elevated more than 3x the upper limit of normal, discontinue treatment and consider washout procedure (discuss with specialist team).

Section 4: Side Effects

Please list the most common side effects and management. Please provide guidance on when the GP should refer back to the specialist.

Side effects and management	The most common side effects are rash, diarrhoea, abdominal pain, reversible alopecia, weight loss, headache, increased blood pressure, anorexia, nausea, vomiting, and oral mucosal disorders. Diarrhoea usually settles with continuing therapy but may require loperamide or dose reduction. Elevation of liver enzymes and cases of severe liver injury have been reported. Low white cell count (common) and thrombocytopaenia (uncommon) may occur, but pancytopenia is rare.

	Mild hypertension is reported in up to 10% of patients and should be treated if necessary. In severe uncontrolled cases it is necessary to consider stopping the drug. Weight loss (usually insignificant) is listed as a common side effect on the drug summary of product characteristics Pulmonary infiltration/pneumonitis is a rare, acute allergic reaction that has been described in a small number of patients after starting leflunomide. If the patient becomes short of breath leflunomide should be stopped at once and urgent medical advice should be sought.
Referral back to specialist	**Actions to be taken by patients GP:** Leflunomide should be WITHHELD if any of the following occur. WCC <3.5x10^9/L Neutrophils <1.6 x10^9/L Platelets <100 x10^9/L Unexplained eosinophilia >0.5 x10^9/L Mean cell volume >105 f/l ALT and or AST >twice upper limit of reference range Unexplained reduction in albumin Renal impairment: Creatinine increase >30% over 12 months and/or unexplained reduction in calculated GFR stop drug if acute change. If gradual may need dose reduction. Rash or oral ulceration Severe sore throat, abnormal bruising: immediate FBC and withhold until the result of FBC is available. Hypertension (BP>140/90) if not controlled with standard anti-hypertensives Breathlessness Unexplained weight loss >10% **Please repeat monitoring bloods in 1 week and if still low/high then discuss with the rheumatology team. Falling trends may also prompt discussion.**

Section 5: Drug Interactions

Please list clinically significant drug interactions (eMC link please click here)

Significant Drug Interactions	Phenytoin: Leflunomide may increase plasma concentration of phenytoin Tolbutamide: Hypoglycaemic effect of tolbutamide may be increased although significant interactions are unlikely. Warfarin: enhances the anticoagulant effect of warfarin and the INR should be closely monitored in patients on warfarin who are given leflunomide, including for several weeks after leflunomide is discontinued. NSAIDs: If the patient is already receiving nonsteroidal anti-inflammatory drugs (NSAIDs) and/or corticosteroids, these may be continued after starting leflunomide. There is an increased risk of toxicity with other haematotoxic and hepatotoxic drugs.
Reminder to ask patient about specific problems	Nil

Section 6: Contra-indications, Cautions and Special Recommendations

Please list

Cautions:

- Localised or systemic infection
- History of TB
- Anaemia- avoid if significant (Hb of less than 100 g/L), due to a cause unrelated to RA or if any unexpected unexplained drop in Hb
- Drug potentiation: caution should be used if co-prescribed with methotrexate or other haematotoxic or hepatotoxic drugs
- Washout procedures recommended before switching to other DMARDs
- Excessive alcohol consumption. Patients should be advised to limit their alcohol intake to well within national recommendations
- There is limited data that suggests Leflunomide is compatible with paternal exposure.
- Avoid concomitant use of live vaccines (e.g. yellow fever vaccination) due to risk of generalised infections.
- Patients should avoid contact with people who have active chickenpox or shingles and report any contact to their GP and hospital specialist. If immunosuppressed patients are exposed to chickenpox or shingles, they will need to be assessed for susceptibility and the need for aciclovir post exposure prophylaxis, see: UKHSA guidance: Guidelines on post-exposure prophylaxis (PEP) for varicella/shingles and the Green Book Chapter 34.

Contra-indications:

- Pregnancy: teratogenic
- Conception and contraception: effective contraception must be used whilst taking leflunomide and for two years after stopping the drug in female users (or consider the wash out procedure to reduce this).
- There is no data on compatibility with breastfeeding- manufacturer advises avoid
- Severe immunodeficiency
- Serious infection
- Impaired liver function due to any cause (active metabolite may accumulate)
- Severe hypoproteinaemia
- Moderate to severe renal impairment- manufacturer advises avoid
- Impaired bone marrow function

Section 7: Advice to the patient

Advice for prescribing clinician to inform patient

1. Discuss potential benefits and side-effects of treatment with the Specialist and/or GP.
2. Share any concerns they have in relation to their treatment.
3. To report any side-effects to the Specialist and/or GP (see individual drug fact sheet for specific information).
4. To ensure that the patient held record is presented at every consultation (in primary or secondary care).
5. To agree to and attend for the monitoring of therapy (including having blood tests carried out at agreed intervals) and assessment of outcomes, to assist health professionals to provide safe, appropriate treatment.
6. To avoid excessive alcohol intake and stay well within national recommendations.
7. To use adequate contraception (both male and females), report any suspected pregnancy to the GP and/or Specialist and inform specialist in a timely manner any plans to conceive.
8. To inform GP/Specialist/pharmacist of all medicines (including OTC preparations) that they are currently taking.

Section 8: Responsibilities for Secondary Care

1. Confirm diagnosis and indication for drug treatment.
2. Discuss potential benefits and side-effects of treatment with patient.
3. Carry out baseline monitoring requirements and initiate therapy. The GP will receive copies of the baseline blood test results.
4. The specialist will advise the GP of any dose adjustments required. The GP will then take over immediate prescribing and blood test monitoring responsibilities.
5. An initial prescription will be provided by the specialist for 1 month.
6. Secondary care will advise on the appropriate monitoring blood tests as well as frequency.
7. Monitor the patient's response to therapy.
8. Decide when to stop therapy on safety grounds and inform the GP.
9. Secondary care will direct the GP to a copy of the concise drug information sheet and the shared care guidelines via the BNSSG Joint Formulary website.
10. Secondary care will supply the patient with a 'patient held record' and explain its role.
11. The dosage regimen should be clearly explained to the patient.
12. The patient should be asked to report side-effects (see individual drug fact sheet for specific information) and the GP should be informed if any side effects are reported to secondary care. Serious side-effects should be reported to the MHRA via the yellow card scheme.

Other specific to drug

Nil

Section 9: Responsibilities for Primary Care

1. Take on shared care proposal from the specialist after the first month of treatment (including prescription and blood monitoring)
2. If shared prescribing is declined, an arrangement should be made with the rheumatology department to ensure patients are adequately supported. The GP practice and rheumatology department should also inform the interface pharmacists at the CCG, see contact details section below.
3. To ensure that all relevant staff and patients are aware of the shared care arrangements. Blood test results, dosage adjustments, should be recorded in the patient held record and GP medical record. Any dosage adjustments should also be recorded in computer-based prescribing systems.
4. The dosage regimen should be clearly explained to the patient.
5. Contact the specialist to discuss any significant changes in the blood test results or patient's condition e.g. the medication becomes less effective.
6. Respond to dosage changes advised and prescribe appropriately. Receive copies of any blood test results carried out in secondary care for information and record in patient's record appropriately.
7. Monitor the patient for any side-effects to therapy and refer back to the Specialist should any serious side-effect occur. Side-effects/discontinuation of medication should be documented in the patient held record.

Other specific to drug

Nil

Section 10: Contact Details

Organisation	Contact	Contact details	Availability
University Hospitals Bristol Foundation Trust, Bristol Royal Infirmary	Rheumatology Telephone Advice Line	Tel: 0117 3424881 Registrar bleep:7021	**Mon – Thu 9am to 5pm Fri 9am to 1pm**
North Bristol Trust, Southmead Hospital	Consultant secretary as per clinic letter OR Rheumatology Telephone Advice Line	Tel: 0117 4140600 Fax: 0117 4140570 Tel: 07894800989 On Call Tel: 07894800989 Sat/Sun 9am-noon (GP service for existing NBT rheum patients only)	**Mon – Fri 9am to 5pm**
Weston Area Health Trust, Weston General Hospital	Rheumatology Telephone Advice Line	Tel:01934 881075 Fax: 01934 647025 On Call registrar bleep: 279	**Mon – Fri 9am to 5pm**
BNSSG CCG	Emily Knight and Tash Mogford (Interface Pharmacists)	Emilyknight1@nhs.net Natasha.mogford@nhs.net	**Mon-Fri 9am to 5pm**

Section 11: Document Details

Date prepared	August 2017
Prepared by	Collated and updated from previous guidelines by Dr Randa Alshakh on behalf of Bristol and Weston Rheumatology consultants. Change to information about PEP for varicella/shingles February 2023 added by BNSSG Formulary Team.
Date approved by JFG	January 2018
Date of review	January 2020
Document Identification: Version	V3.1

Section 12: Collaboration

Specialists in any one discipline are encouraged to collaborate across the health community in preparing shared care guidance. Please give details

This document has been sent to rheumatology consultants across Bristol and Weston for comment and approval.

Section 13: References

Please list references

1. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs, February 2017
2. BSR and BHPR guideline on prescribing drugs in pregnancy and breastfeeding—Part I: standard and biologic disease modifying anti-rheumatic drugs and corticosteroids, January 2016
3. BNF 73 (March –September 2017)
4. https://www.medicines.org.uk/emc/medicine/25437