

OPT-OUT SHARED CARE GUIDELINE

It is assumed that shared care **will** be accepted unless the specialist is informed otherwise within 28 days of receipt of the request at the end of this document.

MEDICATION NAME: LEFLUNOMIDE 10mg and 20mg tablets
INDICATIONS COVERED: Rheumatoid Arthritis, Psoriatic Arthritis and other chronic inflammatory conditions in Adults

NHS Brighton and Hove CCG, Crawley CCG, Horsham and Mid-Sussex CCG
Traffic Light System Classification: Amber

NOTES to the general practitioner (GP) or primary care prescriber

For drugs which require specialist initiation and/or dose titration and specific ongoing monitoring. For initiation, dose stabilisation and prescribing (including monitoring) by a specialist until the patient is stabilised (usually for 3 months) after which the GP may be asked to work under shared care through the use of approved shared care guidelines.

The expectation is that these guidelines should provide sufficient information to enable GPs or primary care prescribers to be confident to take clinical and legal responsibility for prescribing these medicines.

The questions below will help you confirm this:

- Is the patient currently under your care (e.g. shared care should not be agreed if the patient is currently in intermediate care following hospital discharge)?
- Do you have the relevant knowledge, skills and access to equipment to allow you to monitor treatment as indicated in this effective shared care guidance?
- Have you been provided with relevant clinical details including monitoring data?

If you can answer YES to all these questions (after reading this shared care guideline), then it is appropriate for you to accept prescribing responsibility. It is assumed that shared care will be accepted unless the specialist is informed otherwise with 28 days of receipt of this request.

If the answer is NO to any of these questions, you should not accept prescribing responsibility. You should inform the consultant or specialist within 28 days, outlining your reasons for NOT prescribing. If you do not have the confidence to prescribe, we suggest you discuss this with your local Trust or specialist service, who will be willing to provide training and support. If you still lack the confidence to accept clinical responsibility, you still have the right to decline. Your CCG medicines management pharmacist will assist you in making decisions about shared care if you are unsure.

Prescribing unlicensed medicines or medicines outside the recommendations of their marketing authorisation alters (and probably increases) the prescriber's professional responsibility and potential liability. The prescriber should be able to justify and feel competent in using such medicines.

The GP or primary care prescriber has the right to refuse to agree to shared care, in such an event the total clinical responsibility will remain with the consultant or specialist.

Reason for update: New	Prepared by: Dr.U.Davies, D.Finney, Dr.S.Griffith, Dr.K.Jordan, Dr.R.Makadsi, Dr.G.Papasavvas, Dr.W.Shattles, SCT Medicines Management Team	Updated by: N/a
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Approved by (Chief Trust Pharmacist): Iben Altman, Sussex Community NHS Trust/Sussex MSK Partnership		
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Approved by NHS Brighton and Hove CCG on: 22.09.2015/01.12.2015		
Approved by Crawley CCG, Horsham and Mid-Sussex CCG on: 26.01.16		

Information

This information sheet does not replace the Summary of Product Characteristics (SPC), which should be read in conjunction with this guidance. Prescribers should also refer to the appropriate paragraph in the current edition of the BNF.

1. **Link to the relevant SPC website:** <http://www.medicines.org.uk/emc/>

2. Background to use for the indications, including licence status:

Leflunomide tablets are used as an immunosuppressant either alone or in combination with other agents which influence the immune response. It has a marketing authorisation for the treatment of active rheumatoid arthritis and psoriatic arthritis.

Its therapeutic effect starts after 4 to 6 weeks (longer if loading dose is not employed) and improvement may continue for a further 4 to 6 months.

3. Dose & administration:

Leflunomide is given in tablet form once a day. The tablets should be swallowed whole with sufficient amounts of liquid. The extent of leflunomide absorption is not affected if it is taken with food.

The recommended maintenance dose is leflunomide 10 mg to 20 mg once daily. The dose can be increased to 30mg once a day (not licensed).

4. Cautions:

- Switching from leflunomide to another DMARD should follow the recommended washout procedure to reduce the risk of serious adverse reactions, which can occur even for a long time after the switching.
- Avoid alcohol, due to a potential for additive hepatotoxic effects.
- Varicella Zoster Virus Infection – in patients with exposure to chickenpox or shingles contact the specialist. Passive immunization should be carried out using Varicella Zoster immunoglobulin.

This list is not exhaustive; refer to the Summary of Product Characteristics (SPC) or BNF for further guidance.

5. Contraindications:

- Hypersensitivity (especially previous Stevens-Johnson syndrome, toxic epidermal necrolysis, erythema multiforme) to the active substance, to the principal active metabolite teriflunomide or to any of the excipients.
- Hepatic impairment.
- Moderate to severe renal insufficiency, because insufficient clinical experience is available in this patient group.
- Active infectious disease.
- Overt or laboratory evidence of immunodeficiency syndrome(s).
- Significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis.
- Severe hypoproteinaemia, e.g. in nephrotic syndrome.
- Pregnancy must be excluded before start of treatment with leflunomide. Patients of either gender should use adequate contraception during treatment and women should wait for 2 years after discontinuation of leflunomide (3 months for men) before trying to conceive or 11 days if washout is provided. Leflunomide is teratogenic and there is a theoretical risk of sperm mutation in males, therefore leflunomide should not be used in male patients planning to conceive. Blood concentrations should be checked prior to planned pregnancy especially if within 2 years of stopping leflunomide or following wash out. Any pregnancy within 2 years of discontinuation of leflunomide should be discussed with specialist if drug washout has not been performed. Notify pharmaceutical company in the event of pregnancy while on leflunomide.
- Breastfeeding mothers.
- Hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, as product may contain lactose (see individual SPC).
- Hypersensitivity to peanut or soya, as some products may contain soya lecithin (see individual SPC).
- Live vaccines (see drug interaction section).

This list is not exhaustive; refer to the Summary of Product Characteristics (SPC) or BNF for further guidance.

6. Side effects:

The most frequently reported adverse effects: mild increase in blood pressure, leucopenia, paraesthesia, peripheral neuropathy, headache, dizziness, diarrhoea, nausea, vomiting, oral mucosal disorders (e.g. aphthous stomatitis, mouth ulceration), abdominal pain, increased hair loss, eczema, rash (including maculo-papular rash), pruritus, dry skin, tenosynovitis, CPK increased, anorexia, weight loss (usually insignificant), asthenia, mild allergic reactions and elevation of liver parameters (transaminases (especially ALT), less often gamma-GT, alkaline phosphatase, bilirubin)).

Uncommon – rash, bone marrow suppression, causing thrombocytopenia, neutropenia, and rarely anaemia. Patients should be warned to report a sore throat and abnormal bleeding/bruising.

Increased susceptibility to infections, including opportunistic infections, due to the immunosuppressive properties.

When the patient has had close contact with chicken pox or shingles seek specialist advice.

Hepatotoxicity. Rarely leflunomide may cause liver fibrosis/cirrhosis. There is a potential for increased toxicity in combination with methotrexate or there is co-infection with hepatitis B or C.

Pulmonary toxicity. Acute pneumonitis or chronic pulmonary fibrosis may occur. This is not dose related. It presents with dry cough, dyspnoea and often fever

Ulcerative stomatitis has been reported.

Very rare cases of Stevens Johnson syndrome or toxic epidermal necrolysis necrolysis and Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS).

Rare cases of Progressive Multifocal Leukoencephalopathy (PML).

In the case of side effects such as dizziness the patient's ability to concentrate and to react properly may be impaired. In such cases patients should refrain from driving cars and using machines.

This list is not exhaustive; refer to the Summary of Product Characteristics (SPC) or BNF for further guidance.

Table 1. Side effects and actions to take for abnormal results

SIDE EFFECT	ACTIONS
AST, ALT between two and three times the upper limit of reference range.	If the current dose is more than 10mg daily reduce the dose to 10mg daily and recheck weekly until normalized. If the AST & ALT is returning to normal, leave on 10mg a day. If LFTs remain elevated withdraw the drug and discuss with the specialist team.
AST, ALT more than three times the upper limit of reference range.	Recheck LFTs within 72 hours, if still more than three times the reference range, stop drug, contact specialist and consider washout.
WBC < 3.5x10 ⁹ /l, or Neutrophils < 1.5 x10 ⁹ /l, or Platelets < 150x10 ⁹ /l	Withhold leflunomide and discuss with specialist.
Hypertension. If BP remains >140/90 two occasions two weeks apart	If BP>140/90 treat in line with NICE guidance. If BP remains >140/90 in spite of optimal treatment stop leflunomide, discuss with specialist and consider washout.
Significant deterioration in renal function.	Withhold and discuss with specialist.
Severe sore throat, significant oral ulceration, abnormal / significant bruising.	Withhold and check FBC immediately. Discuss with specialist.
New or increasing dyspnoea or cough.	Assess chest and withhold treatment until discuss with specialist, consider washout.
Rash or itch.	Consider dosage reduction with or without antihistamines; if severe, stop, contact specialist and consider washout.
Hair loss.	Consider dosage reduction; if severe, stop, contact specialist and consider washout.
Headache.	If severe, consider dosage reduction. If headaches persist, contact specialist, stop leflunomide 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, contact specialist, stop leflunomide and consider washout.
Weight loss.	Monitor carefully. If >10% weight loss with no other cause identified, contact specialist, consider reduce dose or stopping leflunomide and consider washout.

Please note that in addition to absolute values, a rapid fall/rise or consistent downward/upward trend in haematological or biochemical index should prompt caution and extra vigilance.

7. Notable drug interactions:

Leflunomide can interact with many drugs and has a very long half-life and therefore potential interactions may take time to become clinically apparent on discontinuation and require close monitoring:

- Interacts with warfarin or other coumarin anticoagulants and increases the International Normal Ratio (INR). Monitor INR for several weeks even after stopping leflunomide.

- Enhances the effects of phenytoin and tolbutamide.
- Vaccines: Severe or fatal infections may occur if a live vaccine is given concurrently. **AVOID LIVE VACCINES.** Herpes zoster vaccine is not contraindicated in these patients, please see <http://tinyurl.com/nvdeqp2> . Inactivated vaccines such as influenza vaccine are safe to use although they may elicit a lower response. The long half-life of leflunomide should be considered when contemplating administration of a live attenuated vaccine after stopping drug therapy.
- Combination with another DMARD (e.g. methotrexate) is at the discretion of the specialist and is not contraindicated providing monitoring requirements are undertaken.
- Colestyramine or activated powdered charcoal not recommended, because this leads to a rapid and significant decrease in the concentration of the active metabolite of leflunomide.
- Medicinal products metabolised by CYP2C8 (such as repaglinide, paclitaxel, pioglitazone or rosiglitazone) - monitoring recommended.
- Medicinal products metabolised by CYP1A2 (such as duloxetine, alosetron, theophylline and tizanidine) should be used with caution during treatment, as it could lead to the reduction of the efficacy of these products.
- Co-administered with substrates of organic anion transporter 3 (OAT3) (such as cefaclor, benzylpenicillin, ciprofloxacin, indomethacin, ketoprofen, furosemide, cimetidine, methotrexate, zidovudine) caution is recommended.
- The dose of rosuvastatin should not exceed 10 mg once daily. For other substrates of Breast Cancer Resistance Protein (BCRP) (e.g., methotrexate, topotecan, sulfasalazine, daunorubicin, doxorubicin) and the organic anion transporting polypeptide (OATP) family especially HMG-CoA reductase inhibitors (e.g., simvastatin, atorvastatin, pravastatin, methotrexate, nateglinide, repaglinide, rifampicin) concomitant administration should also be undertaken with caution. Patients should be closely monitored for signs and symptoms of excessive exposure to the medicinal products and reduction of the dose of these medicinal products should be considered.
- There are no contra-indications to using standard doses of NSAIDs with standard doses of leflunomide as long as the required leflunomide monitoring is undertaken. National guidance relating to cardiovascular, gastro-intestinal and renal risk should be followed.

This list is not exhaustive; refer to the Summary of Product Characteristics (SPC) or BNF for further guidance.

8. Criteria for use:

Chronic inflammatory conditions as determined by the appropriate specialist.

Specialist has initiated and dose stabilised (usually for a minimum 3 months).

GP or Primary Care Prescriber confident to take clinical and legal responsibility for prescribing this drug.

9. Any further information (e.g. supporting therapies):

Simple dose reduction is unlikely to produce a rapid diminution of adverse effects due to the long half-life of the drug. If a rapid response is required, consider washout.

Important: discontinue treatment and institute washout procedure (see caution section) in case of serious side-effect.

Washout procedure: Colestyramine 8g is administered 3 times daily. Alternatively, 50 g 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.

The concentration of the active metabolite after washout should be less than 20 micrograms/litre (measured on 2 occasions 14 days apart) in men or women before conception. Procedure may be repeated as necessary. See SPC for further details.

10. References:

- Brighton and Hove CCG, *Effective Shared Care Agreement (ESCA): Leflunomide 10mg and 20mg Tablets*. January 2013. Available at: http://www.brightonandhoveccg.nhs.uk/sites/default/files/resources/ch_10_musculoskeletal_cp.pdf (accessed 14.04.15).
- British Society for Rheumatology, Immunisation against shingles in people with inflammatory rheumatic disease. Available at http://www.rheumatology.org.uk/includes/documents/cm_docs/2013/i/immunisation_with_zostavax_for_people_with_inflammatory_rheumatic_disease.pdf (access 11.08.15).
- Chakravarty, K. et al, *BSR/BHPR guideline for disease-modifying anti-rheumatic drug (DMARD) therapy in consultation with the British Association of Dermatologists, British Society for Rheumatology*, Oxford University Press, 2008. Available at: http://www.rheumatology.org.uk/includes/documents/cm_docs/2009/d/diseasemodifying_antirheumatic_drug_dmar_d_therapy.pdf (accessed 20/04/15).
- Crawley CCG, Horsham and Mid-Sussex CCG, *Effective Shared Care Agreement (ESCA): Leflunomide 10mg and*

20mg Tablets. August 2011. Available at:

<http://www.horshamandmidsussexccg.nhs.uk/intranet/clinical/programmes/medicines-management/>
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- Joint Formulary Committee. *British National Formulary; Leflunomide*, British Medical Association and Royal Pharmaceutical Society. London. Available at: <https://www.medicinescomplete.com/mc/bnf/current/index.htm> (accessed 20.04.15).
- Summary of Product Characteristics, *Arava® Tablets*. Sanofi. Last update 10.10.14. Available at: <http://www.medicines.org.uk/emc/medicine/26345> (accessed 14.04.15).
- Summary of Product Characteristics, *Leflunomide Tablets*. Sandoz Ltd. Last update 21.10.14. Available at: <http://www.medicines.org.uk/emc/medicine/25438> (accessed 14.04.15).
- Summary of Product Characteristics, *Leflunomide Tablets*. Aspire Pharma Ltd. Last update 01.04.15. Available at: <http://www.medicines.org.uk/emc/medicine/28900> (accessed 14.04.15).
- UKMI. *Suggestions for Drug Monitoring in Adults in Primary Care*. February 2014. Available at <http://www.medicinesresources.nhs.uk/upload/documents/Evidence/Drug%20monitoring%20document%20Feb%202014.pdf> (accessed 20.04.15).

RESPONSIBILITIES and ROLES

Consultant or Specialist responsibilities

- 1 Confirm diagnosis and indication for treatment with leflunomide.
- 2 To discuss fully the aims, benefits, risks and side effects of treatment and a treatment plan with the patient and/or carer and for written information to be supplied to the patient and/or carer. Inform patients to report immediately any exposure to Varicella Zoster Virus.
- 3 Prior to treatment ask GP whether patient has had pneumococcal vaccination and flu vaccination and, if not, immunise (unless contra-indicated). Inform patient not to start medication until after immunisation.
- 4 Inform GP when initiating treatment so the GP is aware what is being prescribed and can add to GP clinical record.
- 5 Undertake baseline monitoring as required.
- 6 Record other medications and address potential drug interactions before starting therapy.
- 7 Exclude existing pregnancy in women with child bearing potential.
- 8 To discuss the potential implications of pregnancy and breastfeeding in women of child bearing potential and agree a risk minimisation strategy where appropriate, ensuring adequate contraception during treatment. Provide both verbal and written information.
- 9 To initiate treatment by prescribing and monitoring usually for a minimum of 3 months
- 10 Undertake monitoring if dose changed.
- 11 Monitor and prescribe according to guidelines until handover is appropriate (including when dose changes are made).
- 12 Discuss the possibility of shared care with the patient and/or carer and ensure that they understand the plan for their subsequent treatment.
- 13 Supply GP with a summary of the patient's review (including anticipated length of treatment) and a link to, or a copy of, the shared care guideline when requesting transfer of prescribing to GP or primary care prescribers.
- 14 Advise GP if treatment dose changes or treatment is discontinued.
- 15 Inform GP if patient does not attend planned follow-up

GP or Primary Care Prescriber responsibilities

- 1 Continue prescribing of leflunomide at the dose recommended and undertake monitoring requirements.
- 2 Undertake all relevant monitoring as outlined in the monitoring requirements section below, and take appropriate action as set out in this shared care guideline.
- 3 Monitor for adverse effects throughout treatment and check for drug interactions on initiating new treatments.
- 4 Add information about the medicine to patient record, initially as "hospital prescribed", and highlight the importance that this medicine is only to be prescribed under a shared care guideline in primary care.
- 5 Prescribe any change in leflunomide dose as advised by the specialist team.
- 6 In diagnosed hypertension, treat as per normal practice. If BP cannot be controlled: withhold and discuss with specialist team.
- 7 Provide with pneumococcal vaccination and flu vaccination unless contra-indicated.
- 8 Inform the consultant or specialist of any issues that may arise.
- 9 Inform patient to report immediately any exposure to Varicella Zoster Virus.
- 10 Refer patient back to the Consultant/Specialist if any concerns.
- 11 Ensure that if care of the patient is transferred to another prescriber, that the new prescriber is made aware of the shared care guideline (e.g. ensuring the patient record is correct in the event of a patient moving surgery).

Monitoring requirements and appropriate dose adjustments

- 1 **Pre-treatment:** FBC, U&Es, creatinine, LFTs, ESR and / or CRP. Blood pressure on two occasions, two weeks apart. If >140/90 on two consecutive readings 2 weeks apart treat hypertension before commencing leflunomide. Body weight: to allow assessment of weight loss: this may be attributable to leflunomide.
- 2 **Initiation:** FBC, LFTs, ESR and / or CRP every 2 weeks for the 1st three to six months. BP and weight at each monitoring visit.
- 3 **Maintenance:** Every eight weeks thereafter: LFTs, FBC, U&Es, creatinine, ESR and / or CRP.
- 4 Monitor blood pressure and weight every 6 months.
- 5 Adverse drug reactions throughout treatment.
- 6 Check for drug interactions on initiating new treatments.

Patient's or Carer's role

- 1 Make sure that you understand the treatment and ask for more information, if needed.
- 2 Share any concerns in relation to treatment with whoever is prescribing this medicine for you.
- 3 Tell the prescriber of this medication about any other medication being taken, including over-the-counter products.
- 4 Read the patient information leaflet included with your medication and report any side effects or concerns you have to whoever is prescribing this medicine for you.
- 5 Attend the follow up appointments with the consultant or specialist.
- 6 Attend any monitoring appointments (e.g. blood tests).
- 7 Bring hand-held monitoring booklet to appointments with GP / consultant / specialist.
- 8 Report immediately the onset of any feature of blood disorders (e.g. sore throat, bruising, and mouth ulcers), liver toxicity (e.g. nausea, vomiting, abdominal discomfort, and dark urine), respiratory effects (e.g. shortness of breath) or fever and if exposed to Varicella / chicken pox.

SHARED CARE GUIDELINE

DRUG NAME: Leflunomide 10mg and 20mg tablets

INDICATION: Rheumatoid Arthritis, Psoriatic Arthritis and other chronic inflammatory conditions in Adults

DATE OF REQUEST:

Agreement to transfer prescribing to general practice or primary care prescriber:

Patient details:

Name:

Address:

DoB:

NHS No:

Hospital No:

Medication name, form and strength: Leflunomide tablets

The following tests and investigations have been carried out:

Date treatment initiated:

At the last patient review the drug appeared to be effectively controlling symptoms or providing benefit:

Yes/No

The patients has now been stabilised on a dose of:

The patient has been given written information about their medication:

Yes/No

The patient understands that this medication is being prescribed under a shared care agreement between their GP and specialist and that they have responsibilities under the agreement to ensure they attend their GP to be regularly monitored.

Yes/No

The patient has been informed that the GP can opt-out of taking on prescribing responsibility if they do not feel clinically able to prescribe or if the patient persistently does not attend for monitoring:

Yes/No

Date of next clinic appointment:

If the practice declines shared care, then the named consultant or specialist should be informed within 28 days of receipt of this request. Forms used to decline prescribing can be found here:

Brighton and Hove CCG: <http://www.gp.brightonandhoveccg.nhs.uk/prescribing/joint-formulary-supporting-information>

Crawley CCG, Horsham and Mid Sussex CCG:

<http://www.horshamandmidsussexccg.nhs.uk/EasySiteWeb/GatewayLink.aspx?allid=415216>

BACK-UP ADVICE AND SUPPORT

	Name and position	Telephone	Email
Specialist or Consultant			
Alternative specialist (e.g. departmental contact)			
Specialist pharmacist			
Out of hours (e.g. medical team on call)			

Link to full SCG: [http:// www.sussexmskpartnershipcentral.co.uk/](http://www.sussexmskpartnershipcentral.co.uk/)