Sussex MSK Partnership

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Brighton and Hove Clinical Commissioning Group
Crawley Clinical Commissioning Group
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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**

INDICATIONS COVERED: Rheumatoid Arthritis, Psoriatic Arthritis and other chronic inflammatory conditions in adults.

NHS Brighton and Hove CCG, Crawley CCG and Horsham and Mid-Sussex CCG

Traffic Light System Classification: Amber

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

For medicines 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 shared care guideline?
- 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 within 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.

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Approved by (Specialist or Consultant): Dr Kelsey Jordan on behalf of SMSKP		
Approved by (Chief Trust Pharmacist): Iben Altman Chief Pharmacist SCFT		
Approved by (CCG Medicines Management Pharmacist): Via APC		
Approved by Brighton and Hove and HWLH CCG on: 27/2/2018		
Approved by Crawley CCG, Horsham and Mid-Sussex CCG on: 27/3/2018		

Information

This information sheet does not replace the Summary of Product Characteristics (SMPC), 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 SMPC website**: http://www.medicines.org.uk/emc/ .

2. **Background to use for the indication(s), 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 not crushed or chewed. 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:**

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

- Switching from leflunomide to another DMARD may require a washout procedure to reduce the risk of serious adverse reactions, which can occur even for a long time after the switching (this would be under specialist prescribing).
- Concomitant administration of hepatotoxic or haematotoxic DMARDs (e.g. methotrexate) should only be initiated under specialist recommendation.
- Alcohol consumption may potentially have additive hepatotoxic effects with leflunomide.
- Varicella Zoster Virus Infection – in patients with exposure to chickenpox or shingles contact the specialist. Passive immunisation should be carried out using Varicella Zoster immunoglobulin.

Pregnancy and Lactation:

- 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.
- Leflunomide is excreted into breast milk in low concentrations and advice suggests avoidance of leflunomide during breast feeding.

- 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 rheumatologist if drug washout has not been performed. Notify pharmaceutical company in the event of pregnancy while on leflunomide.

Washout procedure:

Cholestyramine 8g is administered 3 times daily. Alternatively, 50g 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.

5. Contraindications:

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

- 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.
- Moderate to severe renal impairment, due to insufficient clinical experience in this patient group.
- The presence of severe/ or significant hepatic impairment including liver diseases such as fibrosis, cirrhosis, and recent or active hepatitis.
- Significantly impaired bone marrow function or significant anaemia, leucopenia, neutropenia or thrombocytopenia due to causes other than rheumatoid or psoriatic arthritis.
- Active Infectious disease. During a serious infection leflunomide should be temporarily discontinued until the patient has recovered from the infection.
- Overt or laboratory evidence of immunodeficiency syndrome(s).
- Serious cases of anaemia, leucopenia or thrombocytopenia.
- Patients with severe hypoproteinaemia, e.g. in nephrotic syndrome.
- Patients who are pregnant or breastfeeding. Pregnancy must be excluded before start of treatment with leflunomide.
- Hypersensitivity to peanut or soya, some products may contain soya lecithin (see individual SmPC).
- Hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption, as product may contain lactose (see individual product SmPC).
- Live vaccines (see drug interaction section).

6. Side effects:

- Common – nausea, anorexia, oral ulceration, minor hair thinning, abdominal discomfort, diarrhoea, headaches, hypertension.
- Uncommon – rash, bone marrow suppression, causing thrombocytopenia, neutropenia, and rarely anaemia. Patients should be warned to report a sore throat and abnormal

bleeding/bruising.

- Hepatotoxicity. Rarely leflunomide may cause liver fibrosis/cirrhosis. There is a potential for increasing toxicity in combination with other hepatotoxic medicines 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.

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

7. Notable Drug Interactions

Leflunomide can interact with many drugs and has a very long half-life (active metabolite usually 1-4 weeks) and therefore potential interactions may take time to become clinically apparent on discontinuation and require close monitoring:

- Interacts with warfarin and increases the international Normal Ratio (INR).
- Enhances the effects of phenytoin and tolbutamide.

Vaccines

- Severe or fatal infections may occur if a live vaccine is given concurrently. **AVOID LIVE VACCINES**
- Inactivated vaccines such as influenza vaccine are safe to use although they may elicit a lower response
- Also consider appropriate washout period after stopping therapy before administering live vaccines if required.

NB 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**.**

Prescribers are advised to check the BNF or ask a pharmacist for advice where required. This is not a comprehensive list

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 improvement 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 in case of serious side-effect.

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 SmPC for further details.

10. References:

1. Guidelines for the management of inflammatory bowel disease in adults. Mowat C, et al. Gut (2011).

2. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs. 2017 Jo Ledingham et al. http://www.rheumatology.org.uk/includes/documents/cm_docs/2017/f/full_guideline_dmards.pdf (accessed 9/10/17)

3. Immunisation of individuals with underlying medical conditions https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/566853/Green_Book_Chapter7.pdf (accessed 09/10/2017)

4. Handbook of systemic drug treatment in dermatology 2nd edition (2015) S Wakelin et al 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 (accessed 13/11/17).

5. Summary of Product Characteristics. Available at: http://www.medicines.org.uk/emc/ (accessed 13/11/17).

6. 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 13/11/17)

RESPONSIBILITIES and ROLES

Consultant or specialist responsibilities
• Confirm diagnosis and indication for treatment with Leflunomide. • To discuss fully the aims, benefits, risks and side effects of treatment and a treatment plan with the patient and/or carer and written information to be supplied to the patient and/or carer. • Prior to treatment ask GP whether patient has had pneumococcal vaccination and flu vaccination and, if not, immunise (unless contra-indicated). • Inform GP when initiating treatment so the GP is aware what is being prescribed and can add to GP clinical record. • Undertake baseline monitoring as required (specific to the medication). • Record other medications and address potential medicine interactions before starting therapy. • Discuss the potential implications of pregnancy and breastfeeding in women of child bearing potential and agree a strategy. • To initiate treatment by prescribing and monitoring usually for a minimum of 3 months. • Undertake monitoring if dose changed. • Monitor and prescribe according to guidelines until handover is appropriate (including when dose changes are made). • Discuss the possibility of shared care with the patient and/or carer and ensure that they understand the plan for their subsequent treatment. • 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. • Advise GP if treatment dose changes or treatment is discontinued. • Inform GP if patient does not attend planned follow-up.

GP or primary care prescriber responsibilities
• Continue prescribing at the dose recommended and undertake monitoring requirements. • Undertake all relevant monitoring as outlined in the monitoring requirements section below, and take appropriate action as set out in this shared care guideline. • Monitor for adverse effects throughout treatment and check for medicine interactions on initiating new treatments. • Add information about the medicine to the 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. • Report any adverse events to the MHRA and specialist team. • Refer patient back to the Consultant/Specialist if any concerns. • Provide patient with pneumococcal polysaccharide vaccine and flu vaccination unless contra-indicated. • 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).

Patient and/or carer role
• Make sure that you understand the treatment and ask for more information, if needed. • Share any concerns in relation to treatment with whoever is prescribing this medicine for you. • Tell the prescriber of this medication about any other medication being taken, including over-the-counter products. • 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. • Report immediately any signs or symptoms of bone marrow suppression e.g. infection or inexplicable bruising or bleeding. • Attend any follow up appointments with the consultant or specialist.

Monitoring Requirements

Monitoring schedule[2]

Test	Frequency	Duration
FBC	Every 2 weeks	For first six weeks and until on stable dose for 6 weeks
Creatinine/ calculated GFR	Monthly	For three months
ALT and / or AST Albumin	3 Monthly	To continue

- Additionally BP and weight to be monitored at each visit.
- Patients taking other immunosuppressant drugs or potentially hepatotoxic drugs (including methotrexate) should remain on monthly monitoring for at least 12 months.
- More frequent monitoring (monthly) is appropriate in patients at higher risk of toxicity.

Contact specialist team urgently and consider interruption in treatment if any of the following develop:

White Cell Count $<3.5x10^9/l$	Mean cell volume >105 f/l
Neutrophils $<1.6\ x10^9/l$	Creatinine increase >30% over 12 months and/or calculated GFR <60ml/min/1.73m^2
Unexplained eosinophilia $>0.5\ x\ 10^9/l$	ALT and/or AST >100 U/l
Platelet count $<140\ x10^9/l$	Unexplained reduction in albumin <30 g/l

Whilst absolute values are useful indicators, trends are equally important, and any rapid fall or consistent downward trend in any parameter warrants extra vigilance.

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

Other Warning Signs

Withhold treatment and discuss with specialist service if any of the following occur:

- Steady decline in any of the above parameters:
- Rash or persistent itch
- Hair loss.
- Breathlessness
- Oral ulceration
- Nausea & vomiting or diarrhoea
- Headache (severe or persistent)
- Abnormal bruising or severe sore throat: Check FBC and withhold treatment until results available.
- Unexplained weight loss > 10%: Withhold treatment and discuss with specialist service.

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

SHARED CARE GUIDELINE

MEDICATION NAME: Leflunomide

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:

The following tests and investigations have been carried out:

Date treatment initiated:

At the last patient review the medication 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 CG, Horsham and Mid Sussex CCG:

http://www.horshamandmidsussexccg.nhs.uk/EasySiteWeb/GatewayLink.aspx?alId=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://