DERBYSHIRE JOINT AREA PRESCRIBING COMMITTEE
SHARED CARE AGREEMENT

Leflunomide for patients 16+ years

(Note: May be used in combination with methotrexate with a different monitoring schedule outlined in section vii)

1. REFERRAL CRITERIA

- Shared Care is only appropriate if it provides the optimum solution for the patient.
- Prescribing responsibility will only be transferred when it is agreed by the consultant and the patient's GP that the patient's condition is stable or predictable.
- Safe prescribing must be accompanied by effective monitoring
- When transfer agreed the patient will be given a supply of Leflunomide sufficient for 4 weeks maintenance therapy.

2. AREAS OF RESPONSIBILITY

GP responsibilities	Consultant responsibilities
1. If NOT participating in shared care reply to the request from the consultant/specialist as soon as practicable (see appendix 1) **2.** Ensure compatibility with other concomitant medication. **3.** Prescribe the dose and formulation recommended. **4.** Perform monitoring tests as specified in section vii. **5.** Be aware of the pregnancy contraindications affecting both men and women, as per the C/I and cautions section below. **6.** Adjust the dose as advised by the specialist. **7.** Stop treatment on the advice of the specialist or immediately if any urgent need to stop treatment arises. **8.** Ensure the patient is offered an annual flu vaccination and a one off pneumococcal vaccination. Live vaccinations may be recommended on case by case basis following consultant/ specialist advice. – See section vi **9.** Report any adverse effects to the referring specialist and the MHRA yellow card scheme	**1.** Discuss the possible benefits and side effects of treatment with the patient. (Including pregnancy contraindications affecting both men and women) **2.** Perform baseline tests (as recommended in section vii) **3.** Provide results of baseline tests **4.** Prescribe Leflunomide for the first three months or until monitoring is stable **5.** To contact patient's GP to request prescribing under shared care and send a link to or copy of the shared care protocol. **6.** Recommend dose of the drug and frequency of monitoring as per section 4vii. **7.** Annually review the patient and advise the GP promptly on when to adjust the dose, stop treatment or consult with the specialist. **8.** Ensure that clear backup arrangements exist for GPs to obtain advice and support. **9.** Report any adverse effects to the MHRA yellow card scheme and GP **10.** Advise on the suitability for e.g. herpes zoster vaccination in accordance with national screening programme **11.** Communicate any dose increase to the GP and transfer monitoring to GP when the patient's condition is stable or predictable following 6 weeks period of titration

Patient responsibilities

- Report to the specialist or GP if there is not a clear understanding of the treatment and share any concerns in relation to treatment.
- Inform specialist or GP of any other medication being taken including over-the-counter products.
- Report any adverse effects or warning symptoms to the specialist or GP whilst taking the drug for example breathlessness, dry persistent cough, vomiting and diarrhoea.
- Report any weight (>10%) loss to specialist or GP
- Women of childbearing potential should be told that a waiting period of 2 years after treatment discontinuation is required before they may become pregnant. If a waiting period of up to approximately 2 years under reliable contraception is considered unpractical, a washout procedure would be advised.
- Male patients should be aware of the possible male-mediated foetal toxicity. Reliable contraception during treatment with leflunomide should be guaranteed. Men should use effective contraception for 3 months after stopping leflunomide.

3. COMMUNICATION AND SUPPORT

i. Hospital contacts:	ii. Out of hours contacts and procedures:
Chesterfield Royal Hospital NHS Foundation Trust Contact the referring consultant/nurse via switchboard: 01246 277271Nurse advice line: 01246 513097 Available Monday-Thursday 9am-4:30pm, Friday 9am-12:30pm **University Hospitals of Derby and Burton NHS Foundation Trust** **Derby Hospitals** Rheumatology helpline: 01332 787710	**Chesterfield** Contact the CRH on-call Medic for the relevant speciality via switchboard: 01246 277271 **Derby** Pharmacy, UHDB, ask for on-call pharmacist via switchboard: 01332 340131 Messages can be left on the Derby Rheumatology nurse advice line: 01332 787710 The aim is to address these next working day

Queens Burton Hospital NHS Foundation Trust **Rheumatology** 01283 511511/566333 Consultants; Dr R Laximinarayan ext 3167 Dr S Das/ Dr D Ray ext 3211/3247 Clinical Rheumatology Nurse Specialist ext 4112 Bleep 274 available during office hours	**Burton** Burton Hospitals 01283 511511 / 566333 ask for on-call pharmacist via switchboard Messages can be left on the nurse advice line out of hours. 01283 511511 ext 4112. If the advice line is not staffed, messages may be left 24 hours a day. The team aim to respond at latest within two working days. The specialist nurses may also be bleeped via switchboard for urgent enquiries

iii. Specialist support/resources available to GP including patient information:

Rheumatology

British Society of Rheumatology Specialist website: http://www.rheumatology.org.uk/
Arthritis Research Campaign Patient Information website: http://www.arthritisresearchuk.org/arthritis-information.aspx
Versus Arthritis Patient Information website: https://www.versusarthritis.org/media/12767/leflunomide-information-booklet-2019.pdf

4. CLINICAL INFORMATION

i. Prescribed Indications	**Licensed** Rheumatoid Arthritis (RA) Psoriatic Arthritis (PsA)	
ii. Therapeutic summary	Leflunomide is an isoxazole derivative with immunomodulatory action on T and B proliferation and immunoglobulin synthesis. Suppression of chemotaxis of neutrophils and adhesion molecules with a reduction of synovial macrophages have also been demonstrated. Time to respond 2-3 months. It has an extremely long half-life and without a 'washout' will remain for at least 6 months. Therapeutic effect usually starts after 4 – 6 weeks and continued improvement is possible.	
iii. Dose & Route of administration	**Rheumatoid arthritis**: 10-20mg once a day with monotherapy is used. Combination therapy with other DMARDs such as methotrexate, is used with caution and extra monitoring, the dose of the second DMARD (e.g. methotrexate) or the leflunomide can be reduced. **Psoriatic Arthritis**: 10mg - 20mg OD Oral form only. Absorption of Leflunomide is unaffected by food but tablets should be swallowed whole. For other indication see BNF or as per specialist advice Doses outside the recommended range may be considered with prior agreement with the specialist team and GP involved. Lower doses should be considered for frail elderly and patients with renal impairment.	
iv. Duration of treatment	Depends on disease activity, benefit of treatment and side effects reported	
v. Adverse effects See BNF / SPC for full list	The active metabolite of leflunomide has a long half-life, usually 1 to 4 weeks. Serious undesirable effects might occur (e.g. hepatotoxicity, haematotoxicity or allergic reactions, see below), even if the treatment with leflunomide has been stopped.	
	Abdominal pain Anorexia and weight loss Asthenia CPK increased Dizziness Dry skin, eczema, pruritus, rash (including maculo-papular rash) GI upset (nausea, vomiting, diarrhoea) Hair loss	Headache Leucopenia Liver Toxicity (transaminases (especially ALT) Mild allergic reactions Mild increase in blood pressure Oral mucosal disorders (e.g. aphthous stomatitis, mouth ulceration) Paraesthesia Tenosynovitis
vi. Immunisation	• **Live vaccinations** JCVI Green book recommends that low dose corticosteroids (prednisolone <20mg daily) and oral traditional DMARD therapy at standard doses are not a contraindication in most patients, although clinician discretion is advised. Live vaccinations may be recommended on case by case basis following consultant/ specialist advice. • Annual flu vaccination is recommended • One off Pneumococcal vaccination recommended unless severely immunocompromised where a different schedule is needed. See JCVI for more information	

vii. Monitoring Requirements	**<u>Consultant/specialist responsibilities</u>** Best practice recommends the following precautions for specialists before commencing immunosuppressant therapy: • Record patient's blood pressure, weight and height if clinically indicated. • Screening for lung disease should be undertaken at clinician discretion on a case-by-case basis. The extent of screening should be influenced more by a patient's clinical features and risk factors for lung disease (e.g. underlying autoimmune disease or smoking history) rather than subsequent immunomodulating choice. Pre-existing lung disease should not be considered an absolute contraindication to any immunomodulating medication. • Consultant to consider ECG where appropriate *especially when commencing medications associated with hypertension* • Screen for viral hepatitis B&C and HIV in all patients • Investigate patient medical history including co-morbidities and previous immunomodulating medication use. For rheumatic patients CRP/ESR may be done every 3 months. These tests are part of the assessment of the underlying rheumatic disease rather than a requirement for monitoring of immunomodulating therapy. The monitoring CRP/ESR may be coordinated between secondary and primary care on an individual basis. **Pregnancy must be excluded before starting treatment** **<u>Consultant/specialist monitoring schedule</u>** Baseline and 2 weekly until on a stable dose for at least 6 weeks • FBC • ALT and/or AST and albumin • U&E including creatinine/calculated GFR • Blood pressure • Patient is asked to report any unexplained weight loss (>10%) Annually review the patient and advise the GP promptly on when to adjust the dose, stop treatment or consult with the specialist. **<u>GP responsibility monitoring schedule</u>** In patients following the 6 weeks of dose stability conduct monthly monitoring as above for three months followed by three monthly monitoring thereafter of: • FBC • ALT and/or AST and albumin • U&E including creatinine/eGFR • Blood pressure • Patient asked to report any unexplained weight loss (>10%) See advice below on pregnancy and breastfeeding in section (Caution and contraindication) Leflunomide in combination with MTX requires extended monthly monitoring for at least 12 months. Patients who have been stable for 12 months can be considered for reduced frequency of monitoring on an individual patient basis. **<u>Dosage increase</u>** For dose **<u>increase</u>**, monitor 2 weekly until stable for 6 weeks. Dose and monitoring to be agreed with consultant. • FBC • ALT and/or AST and albumin • U&E including creatinine/eGFR • Blood pressure • Patient is asked to report and unexplained weight loss (>10%) Monitoring to then continue at 3 monthly intervals. When restarting treatment after an abnormality has been detected, repeat bloods in 2 weeks and then monthly for 3 months. Following this resume monitoring frequency to what it was prior to the abnormality.

Actions to be taken

1. Immunosuppressants prescribed to prevent transplant rejection **should not be** stopped without discussion with a member of the specialist team.
2. In addition to responding to absolute values in laboratory tests, it is also relevant to **observe trends in results** (e.g. gradual decreases in white blood cells (WBC) or albumin, or increasing liver enzymes)
3. Parameters below are to be used as a guide for clinicians rather than absolute values, where monitoring should be based on individualized basis. It is important to consider alternative explanations other than the immunomodulation agents, especially in patients who have been stable for prolonged periods

WBC <3.5 x10^9 /1	Contact Specialist **urgently** and consider interruption
Neutrophils <1.6 x 10^9/l	Contact Specialist **urgently** and consider interruption
Platelets <140 x 10^9/l	Contact Specialist **urgently** and consider interruption
ALT and/or AST >100 U/l	Contact Specialist **urgently** and consider interruption
Unexplained fall in albumin <30g/l	Contact Specialist **urgently** and consider interruption
Mean cell volume >105 f/l	Withhold and check **serum B12, folate & TFT** and discuss with specialist team.
Creatinine increase for example >30% over 12 months and/or calculated GFR <60ml/min/1.73m²	Contact Specialist **urgently** and consider interruption

NB – a rapidly increasing or decreasing trend in any value should prompt caution irrespective of actual value.

Drug specific	
Weight decrease (>10%)	Contact Specialist **urgently** and consider interruption
Rash or itch	*Consider dose reduction, if severe STOP and consider washout***
Hair loss (mild/moderate)	*Consider dose reduction, if severe STOP and consider wash out***
Abnormal bruising or severe sore throat	*Check FBC immediately and without treatment until results are available*
Hypertension	*Adhere to NICE guidelines. Assess the other cardiovascular risks and co prescribe conventional antihypertensive therapy. If BP remains uncontrolled, consider reducing dose or STOPPING treatment and/or consider wash out** after discussion with specialist team*
GI upset	*Give symptomatic treatment. Diarrhoea may be self-limiting in some cases. Occasional respond to codeine phosphate in mild cases but if severe STOP the treatment and wash out* after discussion with specialist team*
Headache	*If severe and in absence of any secondary cause, consider dose reduction. If still persists the STOP the treatment and wash out** after discussion with the specialist team*
Pulmonary Symptoms	*Interstitial pneumonitis has been reported and if patients develop acute dyspnoea on treatment consider stopping the drug and discuss with the specialist team after doing a chest x-ray. See BSR/SPC for further reference*
Liver Toxicity	*It is highly recommended that LFT continue to be checked MONTHLY if used in combination with other hepatotoxic drugs*
CRP/ESR	*Measured to allow disease activity evaluation*

Note: specific monitoring of eosinophil counts has been removed, as historically eosinophilia was an important marker for identifying toxicity from only gold therapy. This has been agreed with local specialists.

****Wash out procedure with cholestyramine**

Wash out should only be carried out after discussion with the consultant/ specialist
8 grams TDS for 11 days or activated Charcoal 50grams QDS for 11 days.
Concentration of active metabolite should be < 20 micrograms /l (measured on 2 occasions 14 days apart) in men & women before conception after a further, but shorter period. It is worth nothing that both agents will reduce absorption and therefore effectiveness of oral contraception.

viii. Clinically relevant drug interactions ***For a full list of interactions please refer to the BNF***	• Colestyramine • Fosphenytoin phenytoin • Methotrexate - increased risk hepatotoxicity (caution needed if used in combination)	• Rifampacin • Tolbutamiune • Warfarin

ix. Contraindications and cautions	**<u>Pregnancy & Lactation</u>** **Pregnancy should be excluded before commencement of Leflunomide. Leflunomide is not recommended in women planning pregnancy** Leflunomide must not be given to pregnant women or women of child bearing potential **unless** a highly reliable contraception is used. Women planning to have children should either discontinue the drug 2 years prior to conception or have the washout procedure undertaken. **Blood concentrations** should be checked **prior to planned pregnancy especially if within 2 years of stopping leflunomide or following washout.** Any pregnancy **within 2 years of discontinuation of** Leflunomide should be discussed with Rheumatologist/Obstetrician **if drug wash out** has not been performed. **NOTIFY pharmaceutical company in the event of pregnancy while on Leflunomide.** **Breast Feeding should be avoided** as animal studies indicate that metabolites of Leflunomide are secreted in the breast milk. **Male patients should be aware of the possible male-mediated foetal toxicity. Reliable contraception during treatment with leflunomide should be guaranteed. Men should use effective contraception for 3 months after stopping leflunomide**. **Contraindications** • Suspected serious infection (requiring IV antibiotics or hospitalization) treatment should be discontinued. • Patients with impairment of liver function • Patients with severe immunodeficiency states or significantly impaired bone marrow function • Patients with moderate to severe renal insufficiency or severe hypoproteinaemia, **Cautions:** • Patients with clinically significant renal impairment from any cause • Localised or systemic infection including hepatitis B or C and a history of TB. • Appropriate to continue with therapy in patients with minor infections (e.g. Uncomplicated urinary tract infections treated with a short course of antibiotics) seek advice from specialist • Unexplained anaemia and/or cytopenia associated with marrow failure. • Patients with deranged liver biochemistry or synthetic function
x. Supply of ancillary equipment	N/A
xi. Supply, storage and reconstitution instructions	N/A
Prepared by **In consultation with** **Reviewed by (2019)**	The Shared Care Guidelines Group, University Hospitals of Derby and Burton, Chesterfield Royal Hospital Dr Austin, Consultant Hepatologist Dr Bleiker, Consultant Dermatologist Dr Ferguson, Consultant Dermatologist Dr Goddard, Consultant Gastroenterologist and Hepatologist Dr O'Reilly, Consulant Rheumatologist Dr Raj, Consultant Rheumatologist Dr Badcock, Consultant Rheumatologist Dr Shum, Consultant Dermatologist The Derbyshire Medicines Management Shared Care and Guidelines Group Dr L Badcock, ACD Consultant Rheumatology Dr R Laxminaryan, Deputy ACD Rheumatology In conjunction with fellow consultant rheumatologist Dr. K Fairburn, Consultant rheumatologist CRH Angela Lawrence, Rheumatology Lead Clinical Nurse Specialist CRH

This does not replace the SPC, which should be read in conjunction with it

Date Prepared: October 2011 **Reviewed:** November 2019 **Review Date**: October 2022

References

1. EMC Summary of Product Characteristics for Leflunomide accessed online 10/04/2017 , 1/8/2019
2. British National Formulary 70, September 2015 accessed online 1/8/2019
3. BSR and BHPR guideline for the prescription and monitoring of non-biologic disease-modifying anti-rheumatic drugs, The British Society for Rheumatology, February 2017
4. The Green book, Immunisation against infection disease, September 2014, accessed online 08/03/2017, 1/8/2019

Sample Transfer Letter

Hospital No: «HOSPITAL_NUMBER»
NHS No: «NHS_NUMBER»

{Insert date}

PRIVATE & CONFIDENTIAL
«GP_TITLE» «GP_INITIALS» «GP_SURNAME»
«GP_ADDRESS_1»
«GP_ADDRESS_2»
«GP_ADDRESS_3»
«GP_ADDRESS_4»
«GP_POSTCODE»

DERBYSHIRE JAPC SHARED CARE AGREEMENT LETTER

Dear «GP_TITLE» «GP_SURNAME»

«FORENAME_1» «SURNAME» «DATE_OF_BIRTH»
«CURRENT_ADDRESS_1» «CURRENT_ADDRESS_2» «CURRENT_ADDRESS_3»
«CURRENT_ADDRESS_4» «CURRENT_POSTCODE»

Your patient was seen on ***{Insert date}*** with a diagnosis of ***{Insert diagnosis}***. I have initiated the following medication ***{Insert drug name}*** and am writing to ask you to participate in the shared care for this patient.

This medication has been accepted as suitable for shared care by the Derbyshire Joint Area Prescribing Committee (JAPC). I agree to the secondary care responsibilities set out in the shared care agreement for this medication (available from www.derbyshiremedicinesmanagement.nhs.uk/clinical_guidelines/shared_care_guidelines). I am therefore requesting your agreement to share the care of this patient. Where preliminary tests are set out in the agreement I have carried these out and results are below.

Dose Regimen	Date ***{Insert medicine name}*** started	Date for GP to start prescribing ***{Insert medicine name}*** from
The baseline test results are (if applicable): **See overleaf for initiation criteria.**		

I can confirm that the following has happened with regard to this treatment:

	Specialist to complete
The patient has been initiated on this therapy and has been on an optimised dose for the following period of time:	
Baseline investigation and monitoring as set out in the shared care documents have been completed and were satisfactory	*Yes / No*
The condition being treated has a predictable course of progression and the patient can be suitably maintained by primary care	*Yes / No*
The risks and benefits of treatment have been explained to the patient	*Yes / No*
The roles of the specialist/specialist team/ Primary Care Prescriber / Patient and pharmacist have been explained and agreed	*Yes / No*
The patient has agreed to this shared care arrangement, understands the need for ongoing monitoring, and has agreed to attend all necessary appointments	*Yes / No*
I have enclosed a copy of the shared care protocol which covers this treatment/the SCP can be found here (insert electronic/ web link)	*Yes / No*
I have included with the letter copies of the information the patient has received	*Yes / No*

I have provided the patient with sufficient medication to last until	
I have arranged a follow up with this patient in the following timescale	

If you do **NOT** wish to participate in shared care for this patient, usually under clinical grounds, please complete the attached form.

Yours sincerely

{Consultant name}

GP RESPONSE TO SHARED CARE (only complete & send if **NOT** participating in shared care)

Shared care is produced by GPs and specialists knowledgeable in the field of that drug usage. The shared care has been approved by the JAPC. This allows a more convenient service to the patient and cost effective use of NHS resources.

Patient:	NHS No:
Consultant:	Medicine requested for shared care:

I will **NOT** be undertaking the GP responsibilities as described in the agreed shared care guideline. My clinical reasons for declining shared care for this patient are listed in the box below:

		Tick which apply
1.	**The prescriber does not feel clinically confident in managing this individual patient's condition, and there is a sound clinical basis for refusing to accept shared care** As the patients primary care prescriber I do not feel clinically confident to manage this patient's condition because *[insert reason]*. I have consulted with other primary care prescribers in my practice who support my decision. This is not an issue which would be resolved through adequate and appropriate training of prescribers within my practice. **I have discussed my decision with the patient and request that prescribing for this individual remain with you as the specialist, due to the sound clinical basis given above.**	
2.	**The medicine or condition does not fall within the criteria defining suitability for inclusion in a shared care arrangement** As the medicine requested to be prescribed is not included on the national list of shared care drugs as identified by RMOC or is not a locally agreed shared care medicine I am unable to accept clinical responsibility for prescribing this medication at this time. **Until this medicine is identified either nationally or locally as requiring shared care the responsibility for providing this patient with their medication remains with you**	
3.	**A minimum duration of supply by the initiating clinician** As the patient has not had the minimum supply of medication to be provided by the initiating specialist I am unable to take clinical responsibility for prescribing this medication at this time. Therefore can you please contact the patient as soon as possible in order to provide them with the medication that you have recommended. ***Until the patient has had the appropriate length of supply the responsibility for providing the patient with their medication remains with you.***	
4.	**Initiation and optimisation by the initiating specialist** As the patient has not been optimised on this medication I am unable to take clinical responsibility for prescribing this medication at this time. Therefore can you please contact the patient as soon as possible in order to provide them with the medication that you have recommended. ***Until the patient is optimised on this medication the responsibility for providing the patient with their medication remains with you.***	
5.	**Shared Care Protocol not received** As legal responsibility for clinical care lies with the clinician who signs the prescription, I need to ensure that I am in possession of sufficient clinical information for me to be confident to prescribe this treatment for my patient and it is clear where each of our responsibilities lie to ensure the patient is safely managed. For this reason I am unable to take clinical responsibility for prescribing this medication at this time, therefore would you please contact the patient as soon as possible in order to provide them with the medication that you have recommended. ***Until I receive the appropriate SCP, responsibility for providing the patient with their medication remains with you.***	
6.	**Other (Primary Care Prescriber to complete if there are other reasons why shared care cannot be accepted)**	

Please do not hesitate to contact me if you wish to discuss any aspect of my letter in more detail and I hope to receive more information regarding this shared care agreement as soon as possible.

Yours sincerely

{GP name}
{Surgery}

Please send a copy of this response to:

1. The specialist/consultant requesting shared care
2. **AN ANONYMISED COPY OF THIS FORM ONLY** to the Medicines Management and Clinical Policies and Decisions Team, 1st Floor East Point, Cardinal Square, 10 Nottingham Road, Derby, DE1 3QT or E-MAIL: ddccg.medicinesmanagement@nhs.net

(Sending a copy of this form to the Medicines Management and Clinical Policies and Decisions Team will help to identify any inappropriate requests for shared care e.g. indication not covered, hospital monitoring requirements not fulfilled. It will also help to inform the CCG prescribing group of the reasons shared care is not being undertaken allowing for changes to be made in future updates to improve patient care).