Leflunomide in Rheumatoid arthritis

Licensed Indication and key points

- **Leflunomide is an immunomodulatory agent unrelated to other disease modifying anti-rheumatic drugs (DMARDs).**
- **It is indicated for the treatment of moderate to severe active rheumatoid arthritis.**
- **Therapeutic effects usually take 4 to 6 weeks with maximum benefits reached in 4 to 6 months.**
- **Recent or concurrent treatment with hepatotoxic or haematotoxic DMARDs (e.g.methotrexate) may result in an increased risk of serious adverse reactions; therefore, the initiation of leflunomide treatment has to be carefully considered regarding these benefit/risk aspects**

Initiation and Maintenance

Oral:
Leflunomide is administered orally and is available as 10mg, 25mg, and 20mg tablets. 100 mg tablets available as proprietary product Arava®.
Dose:
- **Optional loading dose of Leflunomide 100mg daily for three days, then Leflunomide 20mg daily. May be reduced to 10mg or lower if side effects.**
- **10mg daily if in combination therapy with another potentially hepatotoxic disease-modifying anti-rheumatic drug (DMARD) such as methotrexate.**

There is no dose adjustment recommended in patients with mild renal insufficiency but it is contraindicated in moderate /severe renal failure. No dosage adjustment is required in patients above 65 years of age.

Teratogenesis - Female patients should be advised to stop leflunomide **at least 2 years** before possible conception and males **at least 3 months** before (advise at initiation). A washout procedure (using colestyramine or activated charcoal) may reduce this period to 2 to 3 months – see wash out procedure below for guidance (hospital responsibility). Women who wish to become pregnant after receiving leflunomide should have plasma levels of the leflunomide metabolite checked (after wash out period) and **pregnancy should be avoided until levels have reached below 0.02mg/l**

Monitoring

MONITORING	RESPONSIBILITY	CONDITIONS	TESTS
Pre-treatment	Hospital team	All	• FBC, creatinine and U&Es, LFTs. • Check BP. If > 140/90, treat hypertension before starting leflunomide. • Record body weight **Results to be known before drug is commenced**
Initiation to stabilisation	Hospital team/GP	All	FBC, LFTs, BP and weight **every month** for six months
Ongoing	GP	All	After six months: FBC, LFTs, BP and weight **every three months**. If co-prescribed with another immunosuppressant or potentially hepatotoxic drug, continue monitoring at least **once a month**

Criteria for managing events & symptoms occurring during Leflunomide therapy in primary care

LABORATORY EVENTS	VALUES	ACTION
WBC	Decrease to < 3.5 x 10^9/L	**Withhold** until discussed with specialist team.
Neutrophils	Decrease to < 1.6 x 10^9/L	
Platelets	< 140 x 10^9/L	
AST and ALT	2 - 3x upper limit of reference range	If current dose >10mg daily, reduce to 10mg daily and re-check weekly until normalised. If AST and ALT returning to normal leave on 10mg daily. **If LFTs remain elevated, withdraw and discuss with specialist team**
	> 3x upper limit of reference range	**Re-check LFTs within 72h**, if remain more than three times the reference range, **stop drug** and discuss with specialist team
Unexplained fall in albumin	<30 g/l	Repeat LFTs as early sign of liver toxicity. **Stop and discuss** with specialist team if continue to deteriorate.
MCV	> 105 fL	**Seek advice from specialist team** • check serum B12, folate and TFTs and alcohol intake • May require folinic acid rescue for bone marrow toxicity
Significant deterioration in renal function	Creatinine increase >30% over 12 months or calculated GFR <60ml/min	**Seek specialist advice.** Caution dose reduction advised in renal impairment
BP >140/90		Treat in line with National Institute For Clinical Excellence (NICE) guidance. If patient develops severe hypertension which remains uncontrolled despite optimal antihypertensive treatment, stop leflunomide and consider washout

SYMPTOMS	MANAGEMENT
Rash/Itch, Hair Loss, Headache	Consider dose reduction; if severe, stop, consider washout*.
Gastrointestinal disturbances (diarrhoea, nausea)	Symptomatic treatment and consider dose reduction; if severe or persistent, stop and consider washout*.
Hypertension	If blood pressure >140/90 treat in line with NICE guidance. If remains uncontrolled stop and consider washout*.
Abnormal bruising or severe sore throat	Check FBC immediately and withhold until results available. Follow relevant course of action from table above. Discuss with specialist team if necessary
Weight loss	Monitor carefully. If >10% weight loss with no other cause identified, reduce dosage or stop and consider washout*.
Dry cough, breathlessness	**Stop** if increasing shortness of breath occurs. **Seek urgent** advice from specialist team.

Washout Procedure -Hospital responsibility

Leflunomide has a **long half-life of up to 6 weeks**. Adverse effects may be seen for a long time after the drug is stopped. A washout procedure can be considered in patients having severe side effects or in men or women considering conception. (If a waiting period of up to approximately 2 years under reliable contraception is considered impractical, prophylactic institution of a washout procedure is advisable).

It is usually recommended to give Colestryramine 8g TDS or activated powdered charcoal 50g QDS for 11 days then measure metabolite A771 726 twice at intervals of at least 14 days. This should fall to less than 0.02 mg/I. It is recommended to wait at least 3 months before considering conception.

Drug interactions, contraindications and precautions

See BNF and manufacturer's SPC Home - electronic Medicines Compendium (eMC) for up-to-date advice

Prescribing responsibilities

- Refer to principles of shared care document

Contact details

Consultant, medical staff and nurse practitioners at the Basildon and Thurrock University Hospitals NHS Foundation Trust (BTUH) are available to give advice and can be contacted either through the main hospital switchboard or direct.

Department / Specialist	Contact Telephone Number
Hospital switchboard – ask for specialist or On-Call specialist rheumatologist out-of-hours	01268 524900
Rheumatology	01268 598461
Email contact for shared care queries ONLY: RheumatologyOsteoporosisPOD@btuh.nhs.uk) (48 hours response)	

Local Enhanced Services for Shared Care Monitoring

Level 1: The prescribing of this medication only.
Level 2: The prescribing and monitoring of this medication and disease

Document Control	
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Shared Care Guidelines are also available electronically via: https://basildonandbrentwoodccg.nhs.uk/your-health/medicines-management	
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