Tertiary and Quaternary Level Essential Medicine List
Medication Review

Date of review update: January 2018 *(follow up response to appeal motivation)*

Medication name: Leflunomide (LEF)

Indication: Patients with RA who have intolerance or contraindications to both Methotrexate (MTX) and Sulphasalazine (SSZ).

Introduction and contextualisation:
RA is a potentially destructive disease with profound impact on patients' function and quality of life. Strategies of treating to the target of sustained remission or low disease activity, leads to favourable outcomes in terms of symptoms, joint damage and disability and therefore quality of life. As such achieving a state of sustained remission or low disease activity is the goal of treating all patients with RA.

This target has been shown to be achievable in less than half of patients receiving MTX, chloroquine (CQ), sulphasalazine (SSZ) and low dose corticosteroids. Biologic DMARDs which have been shown to be effective in patients with refractory RA, are however currently unaffordable within the public healthcare sector. Hence LEF could be considered in patients with intolerance or refractory disease to standard DMARDs.

Efficacy
The efficacy and safety of LEF monotherapy has been demonstrated to be equivalent to MTX or SSZ.

A meta-analysis[1] of randomised trials involving 2861 patients, evaluated the use of leflunomide monotherapy compared to placebo, MTX and SSZ, in the management of RA. With regards to the end point of percentage of patients achieving ACR50 response (a measure based on the American College of Rheumatology criteria, with at least a 50% improvement in the number of tender and swollen joints and a 50% improvement in at least 3 of the patients global assessment of disease status) after 4 months of treatment, and after 2 years of treatment, there was no significant difference between LEF and MTX, Relative risk (RR)=1.71 (95% CI 0.39-7.48) and RR = 1.23 (95% CI 0.91-1.66) respectively.

In a retrospective chart review of 194 patients treated with MTX plus LEF for RA for more than 4 months, 58.6% of patients achieved a good EULAR (European League Against Rheumatism) response at 4 months, improving to 62.3% at 12 months.[2]

Summary:
LEF is a DMARD with comparable potency to MTX and SSZ for the treatment of RA. MTX and/or SSZ are the recommended first-line therapies for RA. As LEF and MTX show comparable efficacy, LEF is a potential alternative to replace MTX and/or SSZ in the treatment of RA in cases of intolerance. There is no convincing evidence to support the addition of LEF to MTX and SSZ in the case of refractory RA.

MTX intolerance:	hepatitis; pneumonitis; renal impairment; hypersensitivity including skin rash and unmanageable neutropenia
SSZ intolerance:	hypersensitivity to SSZ and sulphonamides as well as salicylates. Severe renal failure, CrCL less than 30ml/min; fibrosing alveolitis; and unmanageable bone marrow suppression

Recommendation:
The Committee recommended that LEF should be included on the Essential Medicines List, for patients who are intolerant to standard DMARD therapy. *(See RA treatment algorithm)*

References

[1] Golicki D, Newada M, Lis J, Pol K, Hermanowski T, Tłustochowicz M. Leflunomide in monotherapy of rheumatoid arthritis: meta-analysis of randomized trials. Pol Arch Med Wewn. 2012;122 (1-2):22-32.