Rheumalef® (leflunomide)

Approved indication

Rheumalef® is indicated for the treatment of adult patients with active rheumatoid arthritis (RA) as a ‘disease-modifying antirheumatic drug’ (DMARD) and to improve physical function.¹

Mode of action

Leflunomide inhibits de novo pyrimidine synthesis.¹ It is converted on first-pass metabolism through the liver into its active metabolite (terrflunomide), which has immunomodulatory and anti-inflammatory properties.¹

The primary mode of action is specific inhibition of dihydro-orotate dehydrogenase, a key enzyme in the de novo synthesis of pyrimidine, and subsequent inhibition of RNA and DNA synthesis.²

Dosage

The initial dose of leflunomide is 100 mg once daily for three days.¹ The recommended maintenance dose is 10 mg to 20 mg once daily.¹ No dosage adjustment is needed in patients with mild renal insufficiency or in patients over 65 years of age.¹

Evidence of efficacy

Several clinical trials have demonstrated the efficacy of leflunomide in patients with RA.¹ Leflunomide was more effective than placebo and at least as effective as methotrexate and sulphasalazine in improving signs and symptoms of RA.³

Improvements in American College of Rheumatology ACR20, ACR50 and ACR70 response rates observed at year one (72.9%, 48.3% and 14.5%, respectively), were maintained until year four or the end point (69.2%, 43.0% and 19.6%, respectively).³

Leflunomide was also shown to be more effective than both methotrexate and sulphasalazine in improving functional activity over a two-year period.³ Furthermore, following two years of treatment, leflunomide was found to be statistically equivalent to methotrexate and numerically superior to sulphasalazine in slowing disease progression.³ Use of combination therapy with leflunomide and methotrexate has been shown to result in even greater responses to treatment, without an increased frequency of adverse events.³

Precautions

General

The active metabolite of leflunomide has a long half-life, usually one to four weeks.¹ Serious undesirable effects e.g. hepatotoxicity may occur even if treatment has been discontinued. Therefore, when such toxicities occur or when switching to another DMARD or in case of a desired pregnancy or if for any other reason the primary metabolite needs to be cleared rapidly from the body, a wash-out procedure should be performed (see manufacturer’s package insert).¹

Pregnancy and lactation

Leflunomide is contraindicated in women who are pregnant or who are of childbearing potential and are not using reliable contraception.¹ Pregnancy should be excluded before starting treatment with leflunomide.¹ Women should not breast-feed while taking leflunomide.¹ Male patients should be made aware of the possible male-mediated foetal toxicity.¹ Reliable contraception during treatment with leflunomide should be ensured.¹

Major adverse effects

The most common side-effect of leflunomide is diarrhoea.⁴ Other gastrointestinal side-effects include nausea, vomiting, oral mucosal disorders, anorexia, weight loss and abdominal pain.¹ Elevation of liver enzymes and bilirubin may occur more frequently, but hepatitis, jaundice/cholestasis and severe liver injury occur less frequently.¹ Leucopenia has been reported more frequently but other myelosuppressive adverse events such as anaemia and thrombocytopenia occur less frequently.¹

Other more frequently reported adverse events include mild increase in blood pressure, paraesthesia, headache, dizziness, hair loss, asthenia, skin rashes, dry skin and mild allergic reactions.¹

Drug interactions

Increased adverse effects may occur in case of recent or concomitant use of hepatotoxic (including alcohol), haemotoxic or immunosuppressive substances.¹
As the primary metabolite of leflunomide inhibits CYP2C9, caution is advised when leflunomide is given with other medicines metabolised by CYP2C9, such as phenytoin and warfarin.\(^1\)

Vaccination with live vaccines is not recommended.\(^3\)

Administration of cholestyramine or activated charcoal leads to a rapid and significant decrease in plasma primary metabolite concentration.\(^1\)

Administration of rifampicin may increase the peak levels of the primary metabolite by 40%.\(^1\)

**Cost: SEP (Incl VAT)**

Rheumalef\(^\circ\) is available in film-coated tablets of 10 and 20 mg and is marketed by Adcock Ingram.  
Rheumalef\(^\circ\) 10 mg – R661.20/30  
Rheumalef\(^\circ\) 20 mg – R674.90/20

**Patient information**

Swallow tablets whole with sufficient liquid.\(^1\) Tablets may be taken with or without food.\(^1\)

A therapeutic effect usually starts after four to six weeks and may further improve up to four to six months.\(^1\)

**Conclusion**

Leflunomide is as effective as methotrexate and represents an important addition to the treatment options for patients with active RA.\(^5\)

**References**

1. Rheumalef Tablets approved package insert. 2015.