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.[3] 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 thrombocytopaenia 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.[1]

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® is available in film-coated tablets of 10 and 20 mg and is marketed by Adcock Ingram.
Rheumalef® 10 mg – R661.20/30
Rheumalef® 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.
2. Scott DL, Smolen JS, Kalden JR, et al. Treatment of active rheumatoid arthritis with leflunomide: two year follow up of a double blind placebo controlled trial versus sulphasalazine Ann Rheum Dis 2001;60:913–923.
3. Kalden JR, Schattenkirchner M, Sörenson H, et al. The efficacy and safety of leflunomide in patients with active rheumatoid arthritis. Arthr & Rheum 2003;48(6):1513–1520.
4. Mehta V, Kisalay S, Balachandran C. Leflunomide. Indian J Dermatol Venereol Leprol 2009;75(4):422–424.
5. Strand V, Cohen S, Schiff M, et al. Treatment of active rheumatoid arthritis with leflunomide compared with placebo and methotrexate. Arch Intern Med 1999;159:2542–2550.