NEW DRUGS

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Diroximel fumarate

Approved indication: multiple sclerosis

Vumerity (Biogen)
231 mg capsules

Dimethyl fumarate is an oral drug that was approved for the treatment of relapsing multiple sclerosis almost a decade ago. Follow-up data since then show that annual relapse rates remain low with about 70% of patients having no new or enlarging lesions on MRI during seven years of treatment.[1]

The effect of dimethyl fumarate is thought to be due to its active metabolite monomethyl fumarate. This may stimulate antioxidant production and reduce inflammatory responses.

Diroximel fumarate is another molecule that is rapidly hydrolysed to monomethyl fumarate after oral administration. Although food reduces the maximum concentration, capsules of diroximel fumarate can be taken with or without food. Most of the twice-daily dose is expired as carbon dioxide. No dose adjustments are recommended for patients with renal or hepatic impairment. Pharmacokinetic drug interactions are unlikely.

Regulatory authorities have accepted the premise that, as the drugs have the same active metabolite, the efficacy and safety of diroximel fumarate should be similar to that of dimethyl fumarate. Pivotal trials of dimethyl fumarate, such as the DEFINE study,[2] have therefore supported the approval of diroximel fumarate for the treatment of relapsing multiple sclerosis.

Diroximel fumarate is being studied in an open-label, single-arm phase III trial. An interim analysis, involving 696 patients, was carried out after a median of 60 weeks. MRI at 48 weeks showed that the mean number of lesions had reduced. Almost 89% of the patients had not had a relapse.[3]

Approximately 15% of the patients discontinued treatment with 6.3% stopping because of adverse events. The most frequent adverse effects were flushing and gastrointestinal symptoms such as diarrhoea.[3]

As gastrointestinal adverse effects are common with dimethyl fumarate, another study has compared its tolerability with that of diroximel fumarate. This was a double-blind phase III trial. It randomised 253 patients with relapsing-remitting multiple sclerosis to take diroximel fumarate and 251 to take dimethyl fumarate. The patients rated any gastrointestinal symptoms on a scale of 0–10. Over five weeks there were symptoms (with a score of 2 or more) for an average of 1.4 days with diroximel fumarate and 2.6 days with dimethyl fumarate. The proportions of patients affected by gastrointestinal symptoms were 34.8% versus 49%. Four patients (1.6%) stopped treatment with diroximel fumarate because of adverse events compared with 15 (6%) of those taking dimethyl fumarate.[4]

In the open-label trial 7.3% of the patients had lymphopenia for six months.[3] This could increase the risk of infection, so regular blood counts are recommended. Live vaccines are not recommended.

It is possible that some of the rare adverse events seen with dimethyl fumarate will occur with diroximel fumarate. These include progressive multifocal leukoencephalopathy and Fanconi syndrome. Annual urinalysis is recommended to check for proteinuria. The effect of long-term treatment on the disability of multiple sclerosis will need to be studied. It is also unclear what the clinical importance is in regard to the small difference in gastrointestinal symptoms. While diroximel fumarate appears to have greater gastrointestinal tolerability than dimethyl fumarate over five weeks,[4] more patients will have altered liver function (25.9% vs 16.4% for alanine aminotransferase).

T manufacturer provided the product information

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The Transparency Score is explained in New drugs: transparency, Vol 37 No 1, Aust Prescr 2014;37:27.

At the time the comment was prepared, information about this drug was available on the websites of the Food and Drug Administration in the USA, and the European Medicines Agency.

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