NEW DRUGS

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Rufinamide

Approved indication: seizures

Inovelon (Eisai)
100 mg film-coated tablets
Australian Medicines Handbook section 16.1.3, Other antiepileptics

Rufinamide is indicated as adjunctive therapy for seizures associated with Lennox-Gastaut syndrome in patients aged four years and older. This is a severe and rare form of epilepsy which typically develops between 3 and 5 years of age and can continue into adulthood. Patients with this syndrome have multiple different types of seizures, developmental delays, intellectual disability and behavioural problems. They also have characteristic electroencephalogram patterns.

Rufinamide is a triazole derivative which is structurally unrelated to other antiepileptics. It modulates the activity of sodium channels and prevents them from switching to the active state.

Its approval in Australia is mainly based on a randomised, placebo-controlled trial in 138 patients aged 4–30 years old. To be eligible, they had to be having a minimum of 90 seizures a month and a recent history of a slow spike-and-wave pattern on electroencephalogram. After a four-week run-in baseline period in which patients continued taking their usual antiepileptic drugs, rufinamide (n=74) or matched placebo (n=64) was added and treatment was continued for 12 weeks.[1]

Rufinamide was more effective at reducing total seizure frequency than placebo (by 33 vs 12%, p=0.0015) after four weeks of treatment. In particular, it reduced tonic and atonic seizures or 'drop attacks' by a median of 43% while placebo increased them by 1.4% (see Table).[1]

In the trial, somnolence (24 vs 13%) and vomiting (22 vs 6%) were significantly more common with rufinamide than with placebo. Some patients discontinued treatment because of these adverse events. Status epilepticus was reported in three patients taking rufinamide but in no patients taking placebo.

Rufinamide shortens the QTc interval and should not be given to those with hereditary short QT syndrome. Care should also be taken in people taking concomitant medicines with the same effect.

The recommended dose of rufinamide is 45 mg/kg/day. It should be given with food in two equal doses – in the morning and the evening – and tablets can be crushed and given in water. Maximum plasma concentrations are reached within six hours of administration and the elimination half-life is 6–10 hours. After being metabolised, most of the dose is excreted in the urine. Careful dose titration is recommended in mild–moderate hepatic impairment and the drug should not be used in people with severe impairment. Dose adjustment is not needed in renal impairment, but haemodialysis can reduce rufinamide concentrations by 30%.

Exposure to rufinamide can be affected by concomitant antiepileptic drugs. Valproate increases plasma concentrations of rufinamide, so a lower initial rufinamide dose is needed in patients already taking valproate. Concurrent phenytoin, primidone, phenobarbital (phenobarbitone) or carbamazepine can decrease rufinamide concentrations, but it is not known if these decreases are clinically significant. Rufinamide is a mild inducer of cytochrome P450 (CYP) 3A4 so it may reduce concentrations of CYP3A4 substrates.

Rufinamide is not recommended in pregnancy. The drug may reduce ethinylestradiol and norethindrone, so women taking the combined pill should be advised to use additional contraception.

Rufinamide appears to be an effective adjunctive treatment of refractory seizures, particularly drop attacks, in patients with Lennox-Gastaut

Table **Efficacy of rufinamide in patients with seizures associated with Lennox-Gastaut syndrome**[1]

	Rufinamide*			Placebo		
	Before treatment	**After treatment**	**Median reduction in seizures**	**Before treatment**	**After treatment**	**Median reduction in seizures**
Total seizures over 4 weeks (median)	290 (n=74)	204	33%	205 (n=64)	205	12%
Tonic and atonic seizures over 4 weeks (median)	92 (n=64)	61	43%	93 (n=60)	76	-1.4%

n number of patients
* The maximum target dose of rufinamide was 45 mg/kg/day in two divided doses or matched placebo.

syndrome. However, dose titration is required at the beginning of treatment because of the risk of drug interactions with other antiepileptic drugs.

TT manufacturer provided additional useful information

REFERENCES

1. Glauser T, Kluger G, Sachdeo R, Krauss G, Perdomo C and Arroyo S. Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. Neurology 2008;70:1950-8. https://doi.org/10.1212/01.wnl.0000303813.95800.0d

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, the European Medicines Agency and the Therapeutic Goods Administration.