without secondary generalisation and for primary generalised tonic-clonic seizures. However, because of problems of sedation, it is usually reserved for use in cases unresponsive to other antiepileptics. It has been suggested that it may be suitable for use in patients with QT-interval prolongation.[1]

1. Christidis D, *et al.* Is primidone the drug of choice for epileptic patients with QT-prolongation? A comprehensive analysis of literature. *Seizure* 2006; **15:** 64–6.

Neonatal apnoea. Results from a preliminary study suggested that adjunctive treatment with primidone[1] might be of value in neonatal apnoea resistant to first-line therapy with xanthines alone, but subsequent confirmatory studies seem to be lacking.

1. Miller CA, *et al.* The use of primidone in neonates with theophylline-resistant apnea. *Am J Dis Child* 1993; **147:** 183–6.

Neonatal seizures. Primidone has been tried in the management of neonatal seizures (p.471).

Tremor. A beta blocker is often the first drug used in patients with essential tremor who require regular treatment (p.1231) but primidone[1] may also be tried. A high incidence of acute adverse reactions has been reported after initial doses (see Tremor, under Adverse Effects, above). There has been concern that long-term use may produce tolerance to primidone's effects, although a small study has found a reduced response in only a few patients.[2] A later study[3] found a dose of 250 mg daily to be as or more effective than 750 mg daily without there being evidence of loss of efficacy during a 12-month follow-up.

1. Koller WC, Royse VL. Efficacy of primidone in essential tremor. *Neurology* 1986; **36:** 121–4.
2. Sasso E, *et al.* Primidone in the long-term treatment of essential tremor: a prospective study with computerized quantitative analysis. *Clin Neuropharmacol* 1990; **13:** 67–76.
3. Serrano-Dueñas M. Use of primidone in low doses (250 mg/day) versus high doses (750 mg/day) in the management of essential tremor: double-blind comparative study with one-year follow-up. *Parkinsonism Relat Disord* 2003; **10:** 29–33.

Preparations

BP 2008: Primidone Oral Suspension; Primidone Tablets;
USP 31: Primidone Oral Suspension; Primidone Tablets.

Proprietary Preparations (details are given in Part 3)
Arg.: Mysoline; ***Austral.:*** Mysoline; ***Austria:*** Cyral; Mysoline; ***Belg.:*** Mysoline†; ***Braz.:*** Epidona†; Mysoline; ***Canad.:*** Mysoline†; ***Chile:*** Mysoline†; ***Cz.:*** Liskantin; ***Denm.:*** Mysoline†; ***Fin.:*** Mysoline†; ***Fr.:*** Mysoline†; ***Ger.:*** Liskantin; Mylepsinum; Resimatil; ***Gr.:*** Mysoline; ***Hung.:*** Sertan; ***India:*** Mysoline†; ***Irl.:*** Mysoline; ***Israel:*** Prysoline; ***Ital.:*** Mysoline; ***Mex.:*** Mysoline; ***Neth.:*** Mysoline; ***Norw.:*** Mysoline†; ***Pol.:*** Mizodin; ***Port.:*** Mysoline; ***Rus.:*** Hexamidin (Гексамидин); ***S.Afr.:*** Mysoline; ***Spain:*** Mysoline; ***Swed.:*** Mysoline†; ***Switz.:*** Mysoline; ***Turk.:*** Mysoline; ***UK:*** Mysoline; ***USA:*** Mysoline; ***Venez.:*** Mutigan†.

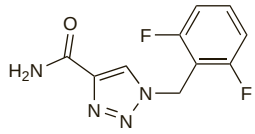
Multi-ingredient: ***Cz.:*** Mysoline†.

Rufinamide *(BAN, USAN, rINN)*

60231/4; CGP-33101; E-2080; RUF-331; Rufinamida; Rufinamidum. 1-(2,6-Difluorobenzyl)-1*H*-1,2,3-triazole-4-carboxamide.

Руфинамид

$C_{10}H_8F_2N_4O$ = 238.2.
CAS — 106308-44-5.
ATC — N03AF03.
ATC Vet — QN03AF03.



Adverse Effects and Precautions

The most common adverse effects with rufinamide include headache, dizziness, fatigue, somnolence, nausea, and vomiting. Other reported adverse effects include anorexia, weight loss, anxiety, insomnia, vertigo, nystagmus, tremor, dyspepsia, constipation, and diarrhoea. Convulsions, including status epilepticus, have occurred. Lymphadenopathy, abnormal liver function tests, and haematuria, as well as fever and rash, have been reported as part of a hypersensitivity syndrome.

Rufinamide can reduce the QT interval and should be used with caution in those with a shortening of their QT interval or with a family history of congenital short QT syndrome.

Care is required when withdrawing rufinamide therapy—see Uses and Administration, below.

Breast feeding. For comment on antiepileptic therapy and breast feeding, see p.467.

Driving. For a comment on antiepileptic drugs and driving, see p.468.

Pregnancy. For comments on the management of epilepsy during pregnancy, see p.468.

Interactions

There are complex interactions between antiepileptics, and toxicity may be enhanced without a corresponding increase in antiepileptic activity. Such interactions are very variable and unpredictable and plasma monitoring is often advisable with combination therapy. Rufinamide plasma concentrations are reportedly decreased by carbamazepine, phenobarbital, phenytoin, vigabatrin, or primidone. In contrast, significant increases in rufinamide plasma concentrations can occur with valproate and dosage adjustments may be necessary (see Uses and Administration, below).

Rufinamide induces the cytochrome P450 isoenzyme CYP3A4 and may be expected to decrease plasma concentrations of drugs metabolised by this route, such as oral contraceptives. Rufinamide reportedly increases steady-state plasma concentrations of phenytoin.

Pharmacokinetics

Rufinamide is well absorbed after oral doses; peak plasma concentrations are reached after about 6 hours. Food increases the bioavailability of rufinamide by about 34 to 40%. It is 34% bound to serum proteins, mainly to albumin.

Rufinamide is hydrolysed to an inactive metabolite and has a plasma elimination half-life of about 6 to 10 hours, although clearance in children is reported to be slower. It is mainly excreted in urine as the inactive metabolite.

◊ References

1. Cardot JM, *et al.* The influence of food on the disposition of the antiepileptic rufinamide in healthy volunteers. *Biopharm Drug Dispos* 1998; **19:** 259–62.

Uses and Administration

Rufinamide is an antiepileptic used as an adjunct in the treatment of seizures associated with the Lennox-Gastaut syndrome (p.465) in patients aged 4 years and over. Rufinamide is given orally in 2 divided doses daily with food. The initial daily dose in patients weighing less than 30 kg is 200 mg, increased according to response in increments of 200 mg every 2 days to a usual maximum of 1 g daily; the recommended maximum dose in those taking *valproate* is 600 mg daily. In patients weighing more than 30 kg, the initial daily dose is 400 mg, increased according to response in increments of 400 mg every 2 days to a maximum daily dose of 1.8 g in those weighing up to 50 kg, 2.4 g in those weighing up to 70 kg, and 3.2 g in those over 70 kg.

As with other antiepileptics, withdrawal of rufinamide therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures. UK licensed product information recommends reducing the daily dose by about 25% every 2 days. For a discussion on whether or not to withdraw antiepileptic therapy in seizure-free patients, see p.465.

Rufinamide has also been investigated as adjunctive therapy in the treatment of partial and primary generalised tonic-clonic seizures.

◊ References.

1. Jain KK. An assessment of rufinamide as an anti-epileptic in comparison with other drugs in clinical development. *Expert Opin Invest Drugs* 2000; **9:** 829–40.
2. Pålhagen S, *et al.* Rufinamide: a double-blind, placebo-controlled proof of principle trial in patients with epilepsy. *Epilepsy Res* 2001: **43:** 115–24.
3. Deeks ED, *et al.* Rufinamide. *CNS Drugs* 2006; **20:** 751–60.
4. Cheng-Hakimian A, *et al.* Rufinamide: pharmacology, clinical trials, and role in clinical practice. *Int J Clin Pract* 2006; **60:** 1497–501.
5. Glauser T, *et al.* Rufinamide for generalized seizures associated with Lennox-Gastaut syndrome. *Neurology* 2008; **70:** 1950–8.

Preparations

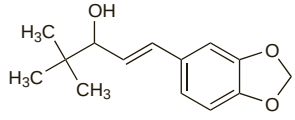
Proprietary Preparations (details are given in Part 3)
Cz.: Inovelon; ***Port.:*** Inovelon; ***UK:*** Inovelon.

Stiripentol *(USAN, rINN)*

BCX-2600; Estiripentol; Stiripentolum. 4,4-Dimethyl-1-[(3,4-methylenedioxy)phenyl]-1-penten-3-ol.

Стирипентол

$C_{14}H_{18}O_3$ = 234.3.
CAS — 49763-96-4.
ATC — N03AX17.
ATC Vet — QN03AX17.



Adverse Effects and Precautions

The most common adverse effects of stiripentol include anorexia, weight loss, insomnia, drowsiness, ataxia, hypotonia, and dystonia. Other common adverse effects include nausea, vomiting, and aggressiveness, and other mood or behavioural disorders. Neutropenia is also reported to be common; persistent severe neutropenia usually resolves spontaneously when stiripentol is stopped. Photosensitivity, rash, and urticaria have occurred. Patients may exhibit altered liver enzyme values.

Growth rates, blood counts, and hepatic function should be monitored periodically in patients given stiripentol.

Interactions

Stiripentol is a potent inhibitor of several cytochrome P450 isoenzymes, including CYP1A2, CYP2C19, and CYP3A4, and may markedly reduce clearance of drugs metabolised by these enzymes. The possibility of an effect on stiripentol metabolism by other inhibitors or inducers of these enzymes should also be borne in mind.

For interactions of stiripentol with other antiepileptics, see under Carbamazepine, p.474, Diazepam, p.990, and Phenytoin, p.498.

Uses and Administration

Stiripentol is used with clobazam and valproate as adjunctive therapy in the treatment of refractory generalised tonic-clonic seizures in severe myoclonic epilepsy in infancy. It is thought to be less potent than some conventional antiepileptics, but may reduce their adverse effects when used adjunctively.

Stiripentol is given orally and should be started at a low dose, gradually increased over 3 days, to the recommended dose of 50 mg/kg daily given in 2 or 3 divided doses with food (but not with dairy products, carbonated drinks, fruit juice, or food and drinks that contain caffeine or theophylline). After starting adjunctive stiripentol therapy, the daily dose of clobazam may be reduced by 25% every week if there are signs of adverse effects or overdosage with clobazam. The daily dose of valproate is not usually adjusted, however, it may be reduced by 30% every week if there are signs of gastrointestinal adverse effects.

Epilepsy. A 24-week study[1] in 10 children found that stiripentol might be effective as adjunctive therapy for the treatment of atypical absence seizures (p.465). Further studies suggested benefit from adjunctive use in children with partial epilepsy[2] and severe myoclonic epilepsy.[2-4]

1. Farwell JR, *et al.* Stiripentol in atypical absence seizures in children: an open trial. *Epilepsia* 1993; **34:** 305–11.
2. Perez J, *et al.* Stiripentol: efficacy and tolerability in children with epilepsy. *Epilepsia* 1999; **40:** 1618–26.
3. Chiron C, *et al.* Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. *Lancet* 2000; **356:** 1638–42.
4. Chiron C. Stiripentol. *Expert Opin Invest Drugs* 2005; **14:** 905–11.

Preparations

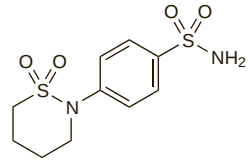
Proprietary Preparations (details are given in Part 3)
Cz.: Diacomit; ***Fr.:*** Diacomit; ***Port.:*** Diacomit.

Sultiame *(BAN, rINN)*

Riker-594; Sulthiame *(USAN)*; Sultiaami; Sultiam; Sultiamo; Sultiamum. 4-(Tetrahydro-2*H*-1,2-thiazin-2-yl)benzenesulphonamide *S,S*-dioxide.

Сультиам

$C_{10}H_{14}N_2O_4S_2$ = 290.4.
CAS — 61-56-3.
ATC — N03AX03.
ATC Vet — QN03AX03.



Pharmacopoeias. In *Jpn.*

Profile

Sultiame is a carbonic anhydrase inhibitor that has been used as an antiepileptic in most forms of epilepsy (p.465) except absence seizures. It has usually been given with other antiepileptics and it is believed that much of its activity is due to the inhibition of metabolism of the other drugs.

Sultiame has been given orally in initial doses of 100 mg twice daily or 50 mg three times daily gradually increased according to response to 200 mg three times daily. A dose of 5 to 10 mg/kg daily, adjusted according to response, has been recommended in Rolandic epilepsy.

Interactions. For the effect of sultiame on *phenytoin*, see p.498.

Porphyria. Sultiame has been associated with acute attacks of porphyria and is considered unsafe in porphyric patients.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Ospolot; ***Austral.:*** Ospolot; ***Austria:*** Ospolot; ***Cz.:*** Ospolot; ***Ger.:*** Ospolot; ***Gr.:*** Ospolot; ***Hung.:*** Ospolot; ***Israel:*** Ospolot; ***Switz.:*** Ospolot.