▼ This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION - INOVELON® RUFINAMIDE FILM COATED TABLETS

1 NAME OF THE MEDICINE

Rufinamide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each INOVELON 100 mg tablet contains 100 mg rufinamide

Each INOVELON 200 mg tablet contains 200 mg rufinamide

Each INOVELON 400 mg tablet contains 400 mg rufinamide

Excipients with known effects:

Each 100 mg film coated tablet contains 20 mg lactose monohydrate

Each 200 mg film coated tablet contains 40 mg lactose monohydrate

Each 400 mg film coated tablet contains 80 mg lactose monohydrate

For the full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

INOVELON 100 mg film coated tablets: Pink, oval, slightly convex, scored on both sides, embossed ‘Є261’ on one side and blank on the other side. The tablet can be divided into equal doses.

INOVELON 200 mg film coated tablets: Pink, oval, slightly convex, scored on both sides, embossed ‘Є262’ on one side and blank on the other side. The tablet can be divided into equal doses.

INOVELON 400 mg film coated tablets: Pink, oval, slightly convex, scored on both sides, embossed '€263' on one side and blank on the other side. The tablet can be divided into equal doses.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

INOVELON is indicated as adjunctive therapy in the treatment of seizures associated with Lennox Gastaut syndrome in patients 4 years of age and older

4.2 DOSE AND METHOD OF ADMINISTRATION

Treatment with INOVELON should be initiated by a physician specialised in paediatrics or neurology with experience in the treatment of epilepsy.

INOVELON should be taken twice daily in two equally divided doses, one in the morning and one in the evening.

Use in children four years of age or older and less than 30 kg

Patients not receiving valproate:

Treatment should be initiated at a total daily dose of 200 mg. According to clinical response and tolerability, the total daily dose may be increased by 200 mg/day increments, as frequently as every third day up to a maximum recommended total daily dose of 1000 mg/day.

Total daily doses of up to 3600 mg/day have been studied in a limited number of patients.

Patients also receiving valproate:

As valproate significantly decreases clearance of rufinamide, a lower maximum total daily dose of INOVELON is recommended for patients <30 kg being co-administered valproate. Treatment should be initiated at a total daily dose of 200 mg. According to clinical response and tolerability, after a minimum of two days the total daily dose may be increased by 200 mg/day, to the maximum recommended total daily dose of 600 mg/day.

Use in adults, adolescents and children four years of age or older and 30 kg or over

Patients not receiving valproate:

Treatment should be initiated at a total daily dose of 400 mg. According to clinical response and tolerability, the total daily dose may be increased by 400 mg/day increments, as frequently as every other day up to a maximum recommended total daily dose as indicated in the table below.

Weight range	30.0 – 50.0 kg	50.1 – 70.0 kg	[3] 70.1 kg
Maximum recommended total daily dose	1,800 mg/day	2,400 mg/day	3,200 mg/day

Total daily doses of up to 4,000 mg/day (in the 30 -50 kg range) or 4,800 mg/day (in the over 50 kg range) have been studied in a limited number of patients.

Patients receiving valproate:

As valproate significantly decreases clearance of rufinamide, a lower maximum total daily dose of INOVELON is recommended for patients ≥30 kg being co-administered valproate. Treatment should be initiated at a total daily dose of 400 mg. According to clinical response and tolerability, the total daily dose may be increased by 400 mg/day increments, as frequently as every other day up to a maximum recommended total daily dose as indicated in the table below

Weight range	30.0 – 50.0 kg	50.1 – 70.0 kg	≥70.1 kg
Maximum recommended total daily dose	1,200 mg/day	1,600 mg/day	2,200 mg/day

Dosage adjustment in renal impairment

A study in patients with severe renal impairment indicated that no dose adjustments are required for these patients (see Section 5.2 Pharmacokinetic properties).

Dosage adjustment in hepatic impairment

Use in patients with hepatic impairment has not been studied. Caution and careful dose titration is recommended when treating patients with mild to moderate hepatic impairment. INOVELON should not be used in patients with severe hepatic impairment.

Discontinuation of treatment

When INOVELON treatment is to be discontinued, it should be withdrawn gradually. In clinical trials INOVELON discontinuation was achieved by reducing the dose by approximately 25% every two days (see Section 4.4 Special warnings and precautions for use).

In the case of one or more missed doses, individualised clinical judgement is necessary.

Recent uncontrolled, open-label studies have suggested that treatment may provide long-term efficacy over a two year period.

Paediatric population

The population PK analysis of INOVELON in a total of 115 patients, including 85 paediatric patients (24 patients ages 1 to 3 years, 40 patients ages 4 to 11 years, and 21 patients ages 12 to 17 years) indicated that no dose adjustment is required for paediatric patients because of age.

The efficacy of INOVELON in children aged 4 years and less has not yet been established. Currently available data are described in Section 4.8 Adverse Effects and 5.1 Pharmacodynamic properties but no recommendation on a posology can be made.

Method of administration

INOVELON is for oral use. INOVELON should be taken twice daily in the morning and in the evening, in two equally divided doses. INOVELON should be administered with food (see Section 5.2 Pharmacokinetic properties). If the patient has difficulty with swallowing, tablets can be crushed and administered in half a glass of water.

4.3 CONTRAINDICATION

Hypersensitivity to the active substance, triazole derivatives or to any of the excipients (see Section 6.1 List of excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Status epilepticus

Status epilepticus cases have been observed during treatment with INOVELON in clinical development studies, whereas no such cases were observed with placebo. These events led to INOVELON discontinuation in approximately 20% of the cases of status epilepticus (2 out of 11 patients). If patients develop new seizure types and/or experience an increased frequency

of status epilepticus that is different from the patient's baseline condition, then the benefit-risk ratio of the therapy should be reassessed.

Withdrawal of INOVELON

INOVELON should be withdrawn gradually to reduce the possibility of seizures on withdrawal. In clinical studies discontinuation was achieved by reducing the dose by approximately 25% every two days. There are insufficient data on the withdrawal of concomitant antiepileptic medicinal products once seizure control has been achieved with the addition of INOVELON.

Central Nervous System reactions

INOVELON treatment has been associated with dizziness, somnolence, ataxia and gait disturbances, which could increase the occurrence of accidental falls in this population (see Section 4.8 Adverse effects). Patients and carers should exercise caution until they are familiar with the potential effects of this medicinal product.

Hypersensitivity reactions

Serious antiepileptic medicinal product hypersensitivity syndrome including DRESS (Drug Reaction with Eosinophilia and Systemic Symptoms) and Stevens-Johnson syndrome have occurred in association with INOVELON therapy. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included lymphadenopathy, liver function tests abnormalities, and haematuria. Because the disorder is variable in its expression, other organ system signs and symptoms not noted here may occur. The antiepileptic drug hypersensitivity syndrome occurred in close temporal association to the initiation of INOVELON therapy and in the paediatric population. If this reaction is suspected, INOVELON should be discontinued and alternative treatment started. All patients who develop a rash while taking INOVELON must be closely monitored.

QT shortening

In a thorough QT study, INOVELON produced a decrease in QTc interval proportional to concentration. Although the underlying mechanism and safety relevance of this finding is not known, clinicians should use clinical judgment when assessing whether to prescribe INOVELON to patients at risk from further shortening their QTc duration (e.g. Congenital Short QT Syndrome or patients with a family history of such a syndrome).

Women of childbearing potential

Women of childbearing potential must use contraceptive measures during treatment with INOVELON. Physicians should try to ensure that appropriate contraception is used, and should use clinical judgement when assessing whether oral contraceptives, or the doses of the oral contraceptive components, are adequate based on the individual patients clinical situation (see Section 4.6 Fertility, pregnancy and lactation – Use in Pregnancy and Section 4.5 Interactions with other medicines).

Lactose

INOVELON film coated tablets contain lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take the film coated tablets.

Suicidal ideation

Suicidal ideation and behaviour have been reported in patients treated with antiepileptic agents in several indications. A meta-analysis of randomised placebo-controlled trials of anti-epileptic medicinal products has also shown a small increased risk of suicidal ideation and behaviour. The mechanism of this risk is not known and the available data do not exclude the possibility of an increased risk for INOVELON.

Therefore patients should be monitored for signs of suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of suicidal ideation or behaviour emerge.

Use in the elderly

There is limited information on the use of INOVELON in older people. Since the pharmacokinetics of INOVELON are not altered in older people (see Section 5.2 Pharmacokinetic properties), dosage adjustment is not required in patients over 65 years of age.

Paediatric use

The efficacy of INOVELON in children aged 4 years and less has not yet been established. Currently available data are described in Section 4.8 Adverse Effects and 5.1 Pharmacodynamic properties but no recommendation on a posology can be made.

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Potential for other medicinal products to affect INOVELON

Other antiepileptic medicinal products

Rufinamide concentrations are not subject to clinically relevant changes on co-administration with known enzyme inducing antiepileptic medicinal products.

For patients on INOVELON treatment who have administration of valproate initiated, significant increases in rufinamide plasma concentrations may occur. Population modelling predicted increased concentrations of 55-70% in children, 23-26% in adolescents and <16% in adults. Therefore, consideration should be given to a dose reduction of INOVELON in patients who are initiated on valproate therapy (see Section 4.2 Dose and method of administration).

In a population pharmacokinetic model, analyses of rufinamide administration and concurrent administration of phenytoin, phenobarbital or primidone identified increased rufinamide clearance, which would result in a decrease in rufinamide concentrations of 43-46% in children, 30-32% in adolescent and 25-26% in adults. The clinical significance of this modelling is unknown.

In a population pharmacokinetic model, analyses of rufinamide administration and concurrent administration of carbamazepine or vigabatrin resulted in increased rufinamide clearance, which would be expected to lead to a decrease in rufinamide concentrations of < 30%. The clinical significance of this modelling is unknown.

The addition or withdrawal of these medicinal products or adjusting of the dose of these medicinal products during INOVELON therapy may require an adjustment in dosage of INOVELON (see Section 4.2 Dose and method of administration).
No significant changes in rufinamide concentration are observed following co-administration with lamotrigine, topiramate or benzodiazepines.

Potential for INOVELON to affect other medicinal products

Other antiepileptic medicinal products

The pharmacokinetic interactions between rufinamide and other antiepileptic medicinal products have been evaluated in patients with epilepsy, using population pharmacokinetic modelling. Rufinamide appears not to have a clinically relevant effect on carbamazepine, lamotrigine, phenobarbital, topiramate, phenytoin or valproate steady state concentrations.

Oral contraceptives

Co-administration of rufinamide 800 mg b.i.d. and a combined oral contraceptive (ethinyloestradiol 35 µg and norethindrone 1 mg) for 14 days resulted in a mean decrease in the ethinyl estradiol AUC_{0-24} of 22% and in norethindrone AUC_{0-24} of 14%. Studies with other oral or implant contraceptives have not been conducted. Women of child-bearing potential using hormonal contraceptives are advised to use an additional safe and effective contraceptive method (see Section 4.4 Special warnings and precautions for use).

Cytochrome P450 enzymes

Rufinamide is metabolised by hydrolysis, and is not metabolised to any notable degree by cytochrome P450 enzymes. Furthermore, rufinamide does not inhibit the activity of cytochrome P450 enzymes (see Section 5.2 Pharmacokinetic properties). Thus, clinically significant interactions mediated through inhibition of cytochrome P450 system by rufinamide are unlikely to occur. Rufinamide has been shown to induce the cytochrome P450 enzyme CYP3A4 and may therefore reduce the plasma concentrations of substances which are metabolised by this enzyme. The effect was modest to moderate. The mean CYP3A4 activity, assessed as clearance of triazolam, was increased by 55% after 11 days of treatment with INOVELON 400 mg b.i.d. The exposure of triazolam was reduced by 36%. Higher INOVELON doses may result in a more pronounced induction. It may not be excluded that INOVELON may also decrease the exposure of substances metabolized by other enzymes, or transported by transport proteins such as P-glycoprotein.

It is recommended that patients treated with substances that are metabolised by the CYP3A4 enzyme system are to be carefully monitored for two weeks at the start of, or after the end of treatment with INOVELON, or after any marked change in the dose. A dose adjustment of the concomitantly administered medicinal product may need to be considered. These recommendations should also be considered when INOVELON is used concomitantly with substances with a narrow therapeutic window such as warfarin and digoxin.

A specific interaction study in healthy subjects revealed no influence of INOVELON at a dose of 400 mg bid on the pharmacokinetics of olanzapine, a CYP1A2 substrate.

No data on the interaction of INOVELON with alcohol are available.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

No data are available on the effects on human fertility following treatment with INOVELON. Rats exposed to clinical concentrations of INOVELON and above showed decreased fertility, reduced fertility index in females and decreased spermatozoa counts in males at 3 times

clinical exposure and decreases in implants and live embryos at approximately 2 times clinical exposure.

Use in Pregnancy (Category B3)

Risk related to epilepsy and antiepileptic medicinal products in general

It has been shown that in the offspring of women with epilepsy, the prevalence of malformations is two to three times greater than the rate of approximately 3% in the general population. In the treated population, an increase in malformations has been noted with polytherapy; however, the extent to which the treatment and/or the illness is responsible has not been elucidated.

Moreover, effective antiepileptic therapy should not be abruptly interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus. Anti Epileptic Drug (AED) treatment during pregnancy should be carefully discussed with the treating physician.

Risk related to INOVELON

Studies in animals revealed no teratogenic effect, but foetotoxicity in the presence of maternal toxicity was observed. In reproductive and developmental toxicity studies, there were reductions in foetal growth and survival, and some stillbirths secondary to maternal toxicity at exposures that were several-fold greater than clinical. However, no effects on morphology and function, including learning or memory, were observed in the offspring. Rufinamide was not teratogenic in mice, rats or rabbits. The potential risk for humans is unknown.

For INOVELON, no clinical data on exposed pregnancies are available.

Taking these data into consideration, INOVELON should not be used during pregnancy, or in women of childbearing age not using contraceptive measures, unless clearly necessary.

Women of childbearing potential must use contraceptive measures during treatment with INOVELON. Physicians should try to ensure that appropriate contraception is used, and should use clinical judgement when assessing whether oral contraceptives, or the doses of the oral contraceptive components, are adequate based on the individual patients clinical situation (see Section 4.4 Special warnings and precautions for use and Section 4.5 Interactions with other medicines).

If women treated with INOVELON plan to become pregnant, the continued use of this product should be carefully weighed. During pregnancy, interruption of an effective

antiepileptic such as INOVELON can be detrimental to both the mother and the foetus if it results in aggravation of illness.

Should any patients taking INOVELON become pregnant, it is encouraged to register the patient on the Australian Pregnancy Register for Women on Antiepileptic Medication by calling 1800 069 722.

Use In Lactation

Animal studies suggest that rufinamide is likely to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from rufinamide, a decision should be made whether to discontinue nursing or discontinue the drug taking into account the importance of the drug to the mother

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

INOVELON may cause dizziness, somnolence and blurred vision. Depending on the individual sensitivity, INOVELON may have a minor to major influence on the ability to drive and use machines. Patients must be advised to exercise caution during activities requiring a high degree of alertness, e.g., driving or operating machinery.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

Summary of the safety profile

The clinical development program has included over 1,900 patients, with different types of epilepsy, exposed to INOVELON. The most commonly reported adverse reactions overall were headache, dizziness, fatigue, and somnolence. The most common adverse reactions observed at a higher incidence than placebo in patients with Lennox-Gastaut syndrome were somnolence and vomiting. Adverse reactions were usually mild to moderate in severity. The discontinuation rate in Lennox-Gastaut syndrome due to adverse reactions was 8.2% for patients receiving INOVELON and 0% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from the INOVELON treatment group were rash and vomiting.

Tabulated list of adverse reactions

Adverse reactions reported with an incidence greater than placebo, during the Lennox-Gastaut syndrome double-blind studies or in the overall INOVELON-exposed population, are listed in the table below by MedDRA preferred term, system organ class and by frequency.

Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥1/10,000 to <1/1,000),

Table 1 Adverse reactions reported in patients in clinical trials

System Organ Class	Very Common	Common	Uncommon
Infections and infestations		Pneumonia Influenza Nasopharyngitis Ear infection Sinusitis Rhinitis	
Immune system disorders			Hypersensitivity*
Metabolism and nutrition disorders		Anorexia Eating disorder Decreased appetite	
Psychiatric disorders		Anxiety Insomnia	
Nervous system disorders	Somnolence* Headache Dizziness*	Status epilepticus* Convulsion Coordination abnormal* Nystagmus Psychomotor hyperactivity Tremor	
Eye Disorders		Diplopia Vision blurred	
Ear and Labyrinth disorders		Vertigo	
Respiratory, thoracic and mediastinal disorders		Epistaxis	
Gastrointestinal disorders	Nausea Vomiting	Abdominal pain upper Constipation Dyspepsia Diarrhoea	
Hepatobiliary disorders			Hepatic enzyme increase
Skin and subcutaneous tissue disorders		Rash* Acne	
Musculoskeletal and connective tissue and bone disorders		Back pain	
Reproductive system and breast disorders		Oligomenorrhoea	
General disorders and administration site conditions	Fatigue	Gait disturbance*	

System Organ Class	Very Common	Common	Uncommon
Investigations		Weight decrease	
Injury, poisoning and procedural complications		Head injury Contusion	

*Cross reference to Section 4.4 Special warnings and precautions for use

Adverse events that were reported in at least 2% of patients with LGS treated with INOVELON or placebo as adjunctive therapy in double-blind trials and were numerically more common in the patients treated with any dose of INOVELON are summarised in Table 2.

Table 2 Percentage of Patients with Adverse Events that Occurred in more than 2.0% of INOVELON-treated Patients at Higher Incidences with INOVELON than Placebo, listed by MedDRA Preferred Term (Double-blind, adjunctive therapy study in LGS)

	INOVELON	Placebo
Total number of patients studied	N=74 (%)	N=64 (%)
Percentage of patients with any adverse event	81.1	81.3
Somnolence	24.3	12.5
Vomiting	21.6	6.3
Fatigue	9.5	7.8
Decreased appetite	9.5	4.7
Nasopharyngitis	9.5	3.1
Headache	6.8	4.7
Rash	6.8	1.6
Rhinitis	5.4	4.7
Ataxia	5.4	0
Psychomotor hyperactivity	4.1	3.1
Convulsion	4.1	1.6
Ear infection	4.1	1.6
Epistaxis	4.1	0
Nystagmus	4.1	0
Status epilepticus	4.1	0
Contusion	2.7	1.6
Head injury	2.7	1.6
Loose stools	2.7	1.6
Sinusitis	2.7	1.6
Acne	2.7	0
Dizziness	2.7	0
Eating disorder	2.7	0
Exanthema	2.7	0
Influenza	2.7	0
Oligomenorrhea	2.7	0
Pneumonia	2.7	0

Other special populations

Paediatric Population (age 1 to less than 4 years)

In a multicentre, open-label study comparing the addition of INOVELON to the addition of any other AED of the investigator's choice in paediatric patients, 1 to less than 4 years of age with inadequately controlled LGS, 25 patients of which 10 subjects were age 1 to 2 years, were exposed to INOVELON as adjunctive therapy for 24 weeks at a dose of up to 45 mg/kg/day, in 2 divided doses. The most frequently reported TEAEs in the INOVELON treatment group (occurring in ≥10% of subjects) were upper respiratory tract infection and vomiting (28.0% each), pneumonia and somnolence (20.0% each), sinusitis, otitis media, diarrhoea, cough, and pyrexia (16.0% each), and bronchitis, constipation, nasal congestion, rash, irritability, and decreased appetite (12.0% each). The frequency, type and severity of these adverse reactions were similar to that in children 4 years of age and older, adolescents and adults. Age characterisation in patients less than 4 years was not identified in the limited safety database due to the small number of patients in the study.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at http://www.tga.gov.au/reporting-problems.

4.9 OVERDOSE

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

There is no specific antidote for INOVELON. Treatment should be supportive and may include haemodialysis (see Section 5.2 Pharmacokinetic properties).

Multiple dosing of 7,200 mg/day was associated with no major signs or symptoms.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: antiepileptics, carboxamide derivatives; ATC code: N03AF03.

Mechanism of action

Rufinamide modulates the activity of sodium channels, prolonging their inactive state. Rufinamide is active in a range of animal models of epilepsy.

Clinical trials

INOVELON (rufinamide tablets) was administered in a double blind, placebo-controlled study, at total daily doses of up to 45 mg/kg/day in 2 divided doses for 84 days, to 139 patients with inadequately controlled seizures associated with Lennox-Gastaut Syndrome (including both atypical absence seizures and drop attacks). Male or female patients (between 4 and 30 years of age) were included if they were being treated with 1 to 3 concomitant fixed-dose antiepileptic medicinal products; a minimum of 90 seizures in the month before the 28-day baseline period; an EEG within 6 months of study entry demonstrating a pattern of slow spike-and-wave complexes (2.5 Hz); a weight of at least 18 kg; and a CT scan or MRI study confirming the absence of a progressive lesion. All seizures were classified according to the International League Against Epilepsy Revised Classification of Seizures. Because it is difficult for caregivers to precisely separate tonic and atonic seizures, the international expert panel of child neurologists agreed to group these seizure types and call them tonic–atonic seizures or "drop attacks". As such, drop attacks were used as one of the primary end points. A significant improvement was observed for all three primary variables: the percentage change in total seizure frequency per 28 days during the maintenance phase relative to baseline (-35.8% on INOVELON vs. –1.6% on placebo, p= 0.0006), the number of tonic-atonic seizures (-42.9% on INOVELON vs. 2.2% on placebo, p = 0.0002), and the seizure severity rating from the Global Evaluation performed by the parent/guardian at the end of the double-blind phase (much or very much improved in 32.2% on INOVELON vs. 14.5% on the placebo arm, p=0.0041).

Additionally, INOVELON was administered in a multicentre, open-label study comparing the addition of INOVELON to the addition of any other AED of the investigator's choice to the existing regimen of 1 to 3 AEDs in paediatric patients, 1 to less than 4 years of age with inadequately controlled LGS. In this study, 25 patients were exposed to INOVELON as adjunctive therapy for 24 weeks at a total daily dose of up to 45 mg/kg/day, in 2 divided doses. A total of 12 patients received any-other AED at the investigator's discretion in the control arm. The study was mainly designed for safety and not adequately powered to show a difference with regards to the seizure efficacy variables. The adverse event profile was similar to that in children 4 years of age and older, adolescents, and adults. In addition, the study investigated the cognitive development, behaviour, and language development of subjects treated with INOVELON compared to subjects receiving any-other-AED. The Least Square mean change of the Child Behaviour Checklist (CBCL) Total Problems score after 2 years of treatment were 53.75 for the any other AED group and 56.35 for the INOVELON group (LS mean difference [95% CI] +2.60 [-10.5,15.7]; P=0.6928), and the difference between treatments was -2.776 (95% CI: -13.3, 7.8, P=0.5939). However, due to the limitations of the available data the study was inconclusive in respect of efficacy.

Population pharmacokinetic/pharmacodynamic modelling demonstrated that the reduction of total and tonic-atonic seizure frequencies, the improvement of the global evaluation of seizure severity and the increase in probability of reduction of seizure frequency were dependent on rufinamide concentrations.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Maximum plasma levels are reached approximately 6 hours after administration. Peak concentration (C_{max}) and plasma AUC of rufinamide increase less than proportionally with dose in both fasted and fed healthy subjects and in patients, probably due to dose-limited absorption behaviour. After single doses, food increases the bioavailability (AUC) of rufinamide by approximately 34% and the peak plasma concentration by 56%.

Distribution

In *in-vitro* studies, only a small fraction of rufinamide (34%) was bound to human serum proteins with albumin accounting for approximately 80% of this binding. This indicates minimal risk of drug-drug interactions by displacement from binding sites during concomitant administration of other substances. Rufinamide was evenly distributed between erythrocytes and plasma.

Metabolism

Rufinamide is almost exclusively eliminated by metabolism. The main pathway of metabolism is hydrolysis of the carboxylamide group to the pharmacologically inactive acid derivative CGP 47292. Cytochrome P450-mediated metabolism is very minor. The formation of small amounts of glutathione conjugates cannot be completely excluded.

Rufinamide has demonstrated little or no significant capacity *in-vitro* to act as a competitive or mechanism-based inhibitor of the following human P450 enzymes: CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4/5 or CYP4A9/11-2.

Excretion

The plasma elimination half-life is approximately 6-10 hours in healthy subjects and patients with epilepsy. When given twice daily at 12-hourly intervals, rufinamide accumulates to the extent predicted by its terminal half-life, indicating that the pharmacokinetics of rufinamide are time-independent (i.e. no autoinduction of metabolism).

In a radiotracer study in three healthy volunteers, the parent compound (rufinamide) was the main radioactive component in plasma, representing about 80% of the total radioactivity, and the metabolite CGP 47292 constituting only about 15%. Renal excretion was the

predominant route of elimination for active substance related material, accounting for 84.7% of the dose.

Linearity/non-linearity

Dose proportionality

The bioavailability of rufinamide is dependent on dose. As dose increases, the bioavailability decreases.

Special populations

Hepatic impairment

No studies have been performed in patients with hepatic impairment. Caution and careful dose titration is recommended when treating patients with mild to moderate hepatic impairment. INOVELON should not be used in patients with severe hepatic impairment (see Section 4.2 Dose and method of administration).

Renal impairment

The pharmacokinetics of a single 400 mg dose of INOVELON was not altered in subjects with chronic and severe renal failure compared to healthy volunteers. However, plasma levels were reduced by approximately 30% when haemodialysis was applied after administration of INOVELON, suggesting that this may be a useful procedure in case of overdose (see Section 4.2 Dose and method of administration and Section 4.9 Overdose).

Age, sex, weight, race

Population pharmacokinetic modelling has been used to evaluate the influence of sex on the pharmacokinetics of rufinamide. Such evaluations indicate that sex does not affect the pharmacokinetics of rufinamide to a clinically relevant extent.

A pharmacokinetic study in older healthy volunteers did not show a significant difference in pharmacokinetic parameters compared with younger adults.

Paediatric Population

Children generally have lower clearance of rufinamide than adults, and this difference is related to body size with rufinamide clearance increasing linearly with body weight. The population PK analysis of rufinamide on data pooled from 1182 subjects, including 287 paediatric patients (11 patients ages 1 to <2 years, 19 patients ages 2 to <4 years, 59 patients ages 4 to <8 years, 80 patients ages 8 to <12 and 118 patients ages 12 to <18 years) indicated

that when rufinamide is dosed on a mg/kg basis, comparable exposure is achieved in all age groups and no dose adjustment is required for paediatric patients because of age.

Studies in new-born infants or infants and toddlers under 1 year of age have not been conducted.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Rufinamide showed no evidence for mutagenicity in assays using bacterial or mammalian cells. Similarly, rufinamide showed no evidence for clastogenicity in an in vitro assay with mammalian cells or in a micronucleus assay using rats.

These results suggest that rufinamide is not of genotoxic concern.

Carcinogenicity

Mice and rats received dietary rufinamide for two years at exposure ratios up to about 2-and 4-fold, respectively. The mouse study indicated dosing-related increases in the incidences of osteoma and of hepatocellular adenoma and carcinoma. The osteomas were correlated with the induction of murine oncogenic viruses and the hepatic tumours with hepatic microsomal enzyme induction. The induction of these tumours was not considered relevant to the clinical safety of rufinamide. Male rats showed a treatment-related increase in the incidence of thyroid follicular adenomas. This tumour is produced by an effect on the pituitary-thyroid axis and is a well-known, rat-specific phenomenon of no relevance to clinical use.

These results, in combination with those for genotoxicity, suggest that rufinamide is not of carcinogenic concern for human use.

Paediatric Use

The toxicity profile of rufinamide in juvenile animals was similar to that in adult animals. Decreased body weight gain was observed in both juvenile rats and dogs. In juvenile rats, adaptive centrilobular hepatocellular hypertrophy was observed at 150 mg/kg (exposure ratio of 2), and pituitary cytoplasmic vacuolation was observed at 50 (exposure ratio of 1) and 150 mg/kg. These findings are unlikely to be relevant to humans. Findings in juvenile dogs included elevated serum alanine aminotransferase values, and deposition of brown pigment in the liver. These findings are also unlikely to be relevant to humans as hepatotoxicity and formation of insoluble metabolites has not been detected in humans. Additional findings at 200 mg/kg in juvenile dogs in which dosing initiated at 6 weeks of age included increased liver weights and slightly lower growth measurements and food intake compared with controls. Reversibility of all findings was demonstrated during the 4- or 10-week recovery

periods. There was no indication from the dog study that rufinamide dosing affects neural development or responses in various neurological tests.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

The tablets contain sodium lauryl sulfate, maize starch, hypromellose, lactose monohydrate, microcrystalline cellulose, croscarmellose sodium, colloidal anhydrous silica and magnesium stearate. The film coating contains hypromellose, macrogol 8000, titanium dioxide, purified talc and iron oxide red.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

INOVELON 100 mg film coated tablets are available in cold-formed polyamide/aluminium/PVC foil laminate blisters in packs of 10, 30, 50, 60 and 100 film-coated tablets.

INOVELON 200 mg film coated tablets are available in cold-formed polyamide/aluminium/PVC foil laminate blisters in packs of 10, 30, 50, 60 and 100 film-coated tablets.

INOVELON 400 mg film coated tablets are available in cold-formed polyamide/aluminium/PVC foil laminate blisters in packs of 10, 30, 50, 60 and 100 film-coated tablets.

Not all pack sizes may be marketed.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

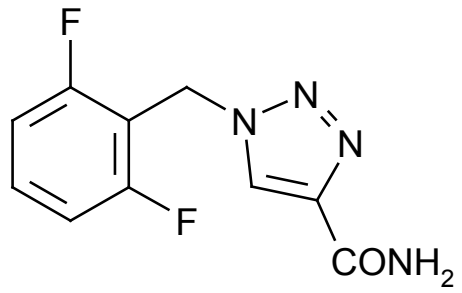
6.7 PHYSICOCHEMICAL PROPERTIES

Rufinamide is a white, crystalline, odourless and slightly bitter tasting neutral powder. Rufinamide is practically insoluble in water, slightly soluble in tetrahydrofuran and in methanol, and very slightly soluble in ethanol and acetonitrile.

Chemical Structure

Chemical Name: 1-[(2,6-Difluorophenyl)methyl]-1*H*-1,2,3-triazole-4-carboxamide.

The empirical formula of rufinamide is $C_{10}H_8F_2N_4O$



CAS number

CAS Number: 106308-44-5

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription only medicine

8 SPONSOR

Eisai Australia Pty. Ltd.
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9 DATE OF FIRST APPROVAL

22 June 2018