Rufinamide

Inovelon®

200 mg
Film-Coated Tablets
Anti-epileptic

1. NAME OF THE MEDICINAL PRODUCT(S)

Rufinamide (Inovelon®) 200 mg film-coated tablets

2. FORMULATION

Each film-coated tablet contains 200 mg of rufinamide.
For excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Oral Film-Coated Tablet
Pink, 'ovaloid' slightly convex, film-coated tablets, scored on both sides, embossed 'E262' on one side and blank on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Rufinamide is indicated as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in children 4 years of age and older and in adults.

4.2 Posology and Method of Administration

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

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

Patients <30 kg not receiving valproate:
Treatment should be initiated at a daily dose of 200 mg. According to clinical response and tolerability, the dose may be increased by 200 mg/day increments, as frequently as every two days, up to a maximum recommended dose of 1,000 mg/day. Doses of up to 3600 mg/day have been studied in a limited number of patients.

Patients <30 kg also receiving valproate:
As valproate significantly decreases clearance of rufinamide, a lower maximum dose of Inovelon is recommended for patients <30 kg being co-administered valproate. Treatment should be initiated at a daily dose of 200 mg. According to clinical response and tolerability, after a minimum of 2 days the dose may be increased by 200 mg/day, to the maximum recommended dose of 600 mg/day.

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

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

Weight range	30.0-50.0 kg	50.1 -70.0 kg	≥70.1 kg
Maximum recommended dose	1,800 (mg/day)	2,400 (mg/day)	3,200 (mg/day)

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

Elderly
There is limited information on the use of rufinamide in the elderly. Since the pharmacokinetics of rufinamide are not altered in the elderly (see Section 5.2), dosage adjustment is not required in patients over 65 years of age.

Renal Impairment
A study in patients with severe renal impairment indicated that no dose adjustments are required for these patients. (See section 5.2)

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. Use in patients with severe hepatic impairment is not recommended.

Discontinuation of treatment
When rufinamide treatment is to be discontinued, it should be withdrawn gradually. In clinical trials rufinamide discontinuation was achieved by reducing the dose by approximately 25% every two days (see section 4.4).

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

Uncontrolled open-label studies suggest sustained long-term efficacy, although no controlled study has been conducted for longer than three months.

Paediatric population

The safety and efficacy of rufinamide in children aged 4 years and less has not yet been established. No data are available.

Method of Administration

Rufinamide is for oral use. It should be taken twice daily with water in the morning and in the evening, in two equally divided doses. As a food effect was observed, rufinamide should be administered with food (see section 5.2). If the patient has difficulty with swallowing, tablets can be crushed and administered in half a glass of water.

4.3 Contraindications

Rufinamide is contraindicated in patients with known hypersensitivity to rufinamide, triazole derivatives, or to any excipients used in the formulation.

4.4 Special Warnings and Special Precautions for Use

Status epilepticus

Status epilepticus cases have been observed during clinical development studies, under rufinamide whereas no such cases have been observed under placebo. These events led to rufinamide discontinuation in 20 % of the cases. 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

Rufinamide 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 rufinamide.

Central Nervous System Reactions

Rufinamide 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). Patients and caretakers should exercise caution until they are familiar with the potential effects of the medication.

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 rufinamide 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 rufinamide therapy and in the paediatric population. If this reaction is suspected, rufinamide should be discontinued and alternative treatment started. All patients who develop a rash while taking rufinamide must be closely monitored.

QT shortening

In a thorough QT study, rufinamide 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 rufinamide 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 effective contraception during treatment with rufinamide. Physicians should try to ensure that appropriate contraception is used, and should use clinical judgment when assessing whether oral contraceptives, or the doses of the oral contraceptive components, are adequate based on the individual patient clinical situation (Section 4.5 and 4.6).

Lactose

Rufinamide contains lactose, therefore patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Suicidal ideation

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

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 behavior emerge.

4.5 Interaction with Other Medicinal Products

Potential for other medicinal products to affect rufinamide

Other Anti-Epileptic Drugs

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

For patients on rufinamide treatment who have administration of valproate initiated, significant increases in rufinamide plasma concentrations may occur. The most pronounced increases were observed in patients of low body weight (<30 kg). Therefore, consideration should be given to a dose reduction of rufinamide in patients <30 kg who are initiated on valproate therapy (see section 4.2).

The addition or withdrawal of these medicinal products or adjusting of the dose of these medicinal products during rufinamide therapy may require an adjustment in dosage of rufinamide (see section 4.2).

No significant changes in rufinamide concentration are observed following co-administration with lamotrigine, topiramate or benzodiazepines.

Potential for rufinamide to affect other medicinal products

Other Anti-Epileptic Drugs

The pharmacokinetic interactions between rufinamide and other anti-epileptic drugs have been evaluated in patients with epilepsy using population pharmacokinetic modelling. Rufinamide appears not to have 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 AUC0-24 of 22% and in norethindrone AUC0-24 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 sections 4.4 and 4.6).

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). 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 CYP3A activity, assessed as clearance of triazolam, was increased by 55% after 11 days of treatment with rufinamide 400 mg b.i.d. The exposure of triazolam was reduced by 36%. Higher rufinamide doses may result in a more pronounced induction. It may not be excluded that rufinamide may also decrease the exposure of substances metabolised 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 rufinamide, 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 rufinamide 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 rufinamide at a dose of 400 mg bid on the pharmacokinetics of olanzapine, a CYP1A2 substrate.

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

4.6 Fertility, Pregnancy and Lactation

Fertility

No data are available on the effects on fertility following treatment with rufinamide.

Pregnancy

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 are 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. AED treatment during pregnancy should be carefully discussed with the treating physician.

Risk Related to Rufinamide:

Studies in animals revealed no teratogenic effect but fetotoxicity in the presence of maternal toxicity (see Section 5.3). The potential risk for humans is unknown.

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

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

Women of childbearing potential must use contraceptive measures during treatment with rufinamide. 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 sections 4.4 and 4.5).

If women treated with rufinamide plan to become pregnant, the continued use of this product should be carefully weighed. During pregnancy, interruption of an effective antiepileptic can be detrimental to both the mother and the foetus if it results in aggravation of the illness.

Lactation

It is not known if rufinamide is excreted in human breast milk. Due to the potential harmful effects for the breast fed infant, breast-feeding should be avoided during maternal treatment with rufinamide.

4.7 Effects on Ability to Drive and Use Machines

Rufinamide may cause dizziness, somnolence and blurred vision. Depending on the individual sensitivity, rufinamide 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 Undesirable Effects

Summary of the safety profile

The clinical development program has included over 1,900 patients, with different types of epilepsy, exposed to rufinamide. 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 rufinamide and 0% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from the rufinamide 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 rufinamide-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 < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥1/10,000 to <1/1,000).

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

*Cross reference to section 4.4.

4.9 Overdose

After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis.
There is no specific antidote for rufinamide. Treatment should be supportive and may include haemodialysis (see section 5.2).
Multiple dosing of 7,200 mg/day was associated with no major signs or symptoms.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: anti-epileptics, 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 Experience

Rufinamide was administered in a double blind, placebo-controlled study, at doses of up to 45 mg/kg/day for 84 days, to 139 patients with inadequately controlled seizures associated with Lennox-Gastaut Syndrome (including both atypical absence seizures and drop attacks). Male and female patients (between 4 to 30 years of age) were eligible if they had a history of multiple seizure types, which had to include atypical absence seizures and drop attacks (i.e., tonic-atonic or astatic seizures); 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).

Population pharmacokinetic/pharmacodynamic modeling 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 doses in both fasted and fed healthy subjects and in patients, probably due to dose-limited absorption behavior. 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.

Biotransformation

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.

Elimination

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).

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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, with 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

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

Pharmacokinetics in special patient groups

Hepatic Impairment

No studies have been performed in patients with hepatic impairment and therefore rufinamide should not be administered to patients with severe hepatic impairment. (Section 4.2)

Renal Impairment

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

Gender

Population pharmacokinetic modeling 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.

Pediatric Population

Children generally have lower clearance of rufinamide than adults, and this difference is related to body size. Studies in newborn infants or infants and toddlers under 2 years of age have not been conducted.

Elderly

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

5.3 Preclinical Safety Data

Conventional safety pharmacology studies revealed no special hazards at clinically relevant doses.

Toxicities observed in dogs at exposures similar to human exposure at the maximum recommended dose were liver changes, including bile thrombi, cholestasis and liver enzyme elevations thought to be related to increased bile secretion in this species. No evidence of an associated risk was identified in the rat and monkey repeat dose toxicity studies.

In reproductive and developmental toxicity studies, there were reductions in foetal growth and survival, and some stillbirths secondary to maternal toxicity. 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 toxicity profile of rufinamide in juvenile animals was similar to that in adult animals. Decreased body weight gain was observed in both juvenile and adult rats and dogs. Mild toxicity in the liver was observed in juvenile as well as in adult animals at exposure levels lower than or similar to those reached in patients. Reversibility of all findings was demonstrated after stopping treatment.

Rufinamide was not genotoxic and had no carcinogenic potential. Adverse effects not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to human use, was myelofibrosis of the bone marrow in the mouse carcinogenicity study. Benign bone neoplasms (osteomas) and hyperostosis seen in mice were considered a result of the activation of a mouse specific virus by fluoride ions released during the oxidative metabolism of rufinamide.

Regarding the immunotoxic potential, small thymus and thymic involution were observed in dogs in a 13-week study with significant response at the high dose in male. In the 13-week study, female bone marrow and lymphoid changes are reported at the high dose with a weak incidence. In rats, decreased cellularity of the bone marrow and thymic atrophy were observed only in the carcinogenicity study.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

The excipients used for the rufinamide film-coated tablets are all of pharmacopoeial quality:

Core: Sodium laurylsulfate, Colloidal anhydrous silica / Colloidal silicon dioxide, Magnesium stearate, Croscarmellose sodium, Hypromellose / Hydroxypropyl Methylcellulose, Maize starch / Corn starch, Lactose monohydrate, Microcrystalline Cellulose, Purified water.

Coat: Red iron oxide / Ferric oxide (red), Titanium dioxide, Macrogol / Polyethylene glycol, Talc, Hypromellose / Hydroxypropyl Methylcellulose, Purified water.

6.2 Incompatibilities

None

6.3 Shelf Life

Rufinamide should be used before the expiration date indicated in the package.

6.4 Storage Condition

Store at temperatures not exceeding 30°C.

6.5 Availability

Aluminum /Aluminum blister pack of 10's (box of 60 film-coated tablets)

6.6 Instructions for Use and Handling

No special requirements.

Manufactured by:

Bushu Pharmaceuticals Ltd. Misato Factory
950, Hiroki, Ohaza, Misato-machi, Kodama-gun,
Saitama-ken, Japan
Under License of Eisai Co., Ltd.

PRODUCT REGISTRATION HOLDER

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47400 Petaling Jaya,
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DATE OF REVISION OF PACKAGE INSERT

July 2019

End

2004211

Item No.	2004211	EML	EML-INOVTAB-1900005		Colours		
Description	Inovelon Tablets				Black		
Strength	ALL				Keyline (Non-Printing)		
Change Description	REG Change of Product Reg Holder Address				Text Free Area (Tech)		
Component Type	Leaflet				Cirrus_Info_Box		
Dimensions	945 x 185 mm						
Keyline Reference	LEAF004	V 07					
Varnish							
Market(s)	Non EU	MALAYSIA					
Language(s)	English						
Barcode Type							
Pharmacode	3477						
Proof By	EBR						
Proof No.	1	Main Body Font Size	9pt				
Date	02/08/2019	Printed Colours	1				

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