Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT

INOVELON 100 MG TABLETS
INOVELON 200 MG TABLETS
INOVELON 400 MG TABLETS

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 100 mg rufinamide.
Excipients with known effect: 20 mg lactose monohydrate/film coated tablet.

Each film-coated tablet contains 200 mg rufinamide.
Excipients with known effect: 40 mg lactose monohydrate/film coated tablet.

Each film-coated tablet contains 400 mg rufinamide.
Excipients with known effect: 80 mg lactose monohydrate/film coated tablet.

For the full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

Pink, 'ovaloid', slightly convex and scored on both sides.

Inovelon 100 mg tablets is embossed 'Є261' on one side and blank on the other side
Inovelon 200 mg tablets is embossed 'Є262' on one side and blank on the other side
Inovelon 400 mg tablets is embossed 'Є263' on one side and blank on the other side

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Inovelon tablets is indicated as adjunctive therapy in the treatment of seizures associated with Lennox-Gastaut syndrome in patients 1 year of age and older.

4.2 Posology and method of administration

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

Posology

Use in children from one year to less than four years of age

Patients not receiving valproic acid (as sodium):
Treatment should be initiated at a dose of 10 mg/kg/day administered in two equally divided doses separated by approximately 12 hours. According to clinical response and tolerability, the dose may be increased by up to 10 mg/kg/day every third day to a target dose of 45 mg/kg/day administered in two equally divided doses separated by approximately 12 hours. For this patient population, the maximum recommended dose is 45 mg/kg/day.

Patients receiving valproic acid (as sodium):
As valproic acid (as sodium) significantly decreases clearance of rufinamide, a lower maximum dose of Inovelon tablets is recommended for patients being co-administered valproic acid (as sodium). Treatment should be initiated at a dose of 10 mg/kg/day administered in two equally divided doses separated by approximately 12 hours. According to clinical response and tolerability, the dose may be increased by up to 10 mg/kg/day every third day to a target dose of 30 mg/kg/day administered in two equally divided doses separated by approximately 12 hours.
For this patient population, the maximum recommended dose is 30 mg/kg/day.

If the recommended calculated dose of Inovelon tablets is not achievable, the dose should be given to the nearest whole 100 mg tablet.

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

Patients <30 kg not receiving valproic acid (as sodium):
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 third day, up to a maximum recommended dose of 1000 mg/day.

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

Patients <30 kg also receiving valproic acid (as sodium):
As valproic acid (as sodium) significantly decreases clearance of Inovelon tablets, a lower maximum dose of Inovelon tablets is recommended for patients <30 kg being co-administered valproic acid (as sodium). 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

Patients >30 kg not receiving valproic acid (as sodium):
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 other day, 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 (in the over 50 kg) have been studied in a limited number of patients.

Patients >30 kg also receiving valproic acid (as sodium):
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 other day, 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	1,200 mg/day	1,600 mg/day	2,200 mg/day

Elderly
There is limited information on the use of **Inovelon tablets** in older people. Since, the pharmacokinetics of rufinamide are not altered in older people (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. Therefore, use in patients with severe hepatic impairment is not recommended.

Discontinuation of **Inovelon tablets**
When **Inovelon tablets** treatment is to be discontinued, it should be withdrawn gradually. In clinical trials **Inovelon tablets** 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 new-born infants or infants and toddlers aged less than 1 year have not been established. No data are available. (see section 5.2)

Method of administration
Rufinamide is for oral use. The tablet should be taken twice daily with water in the morning and in the evening, in two equally divided doses., **Inovelon tablets** 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. Alternatively, use the score line to break the tablet into two equal halves.

4.3 Contraindications

Hypersensitivity to the active substance, triazole derivatives or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Status epilepticus
Status epilepticus cases have been observed during treatment with rufinamide in clinical development studies, whereas no such cases were observed with 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 of rufinamide

Inovelon tablets 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 is insufficient data on the withdrawal of concomitant antiepileptic medicinal products once seizure control has been achieved with the addition of **Inovelon tablets**.

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 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 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. As the disorder is variable in its expression, other organ system signs and symptoms not noted here may occur. The antiepileptic drug (AED) 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 contraceptive measures during treatment with **Inovelon tablets**. 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 4.5 and 4.6).

Lactose

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

Sodium content

This medicine contains less than 1 mmol sodium (23 mg) per daily dose, i.e. is essentially 'sodium-free'.

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 tablets**.
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.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect **Inovelon tablets**

Other anti-epileptic 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 tablets** treatment who have administration of valproic acid (as sodium) initiated, significant increases in rufinamide plasma concentrations may occur. Therefore, consideration should be given to a dose reduction of **Inovelon tablets** in patients who are initiated on valproic acid (as sodium) therapy (see Section 4.2).

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

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

Potential for **Inovelon tablets** to affect other medicinal products

Other anti-epileptic medicinal products
The pharmacokinetic interactions between rufinamide and other anti-epileptic 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 valproic acid (as sodium) steady state concentrations.

Oral contraceptives
Co-administration of rufinamide 800 mg twice daily 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 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 CYP3A4 activity, assessed as clearance of triazolam, was increased by 55% after 11 days of treatment with rufinamide 400 mg twice daily. 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 **Inovelon tablets**, 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 twice daily 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

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 is responsible has not been elucidated.

Moreover, effective anti-epileptic therapy should not be interrupted abruptly, 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 foetotoxicity in the presence of maternal toxicity was observed (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 contraceptive measures, unless clearly necessary.

Women of childbearing potential must use contraceptive measures during treatment with **Inovelon tablets**. 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.

Breast-feeding
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.

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

4.7 Effects on ability to drive and use machines

Inovelon tablets may cause dizziness, somnolence and blurred vision. Depending on the individual sensitivity, **Inovelon tablets** 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 **Inovelon tablets** and 0% for patients receiving placebo. The most common adverse reactions resulting in discontinuation from the **Inovelon tablets** 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 to < 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 disorder	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		
Hepato-biliary 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.

Additional information on special populations

Paediatric Population (age 1 to less than 4 years)

In a multicentre, open-label study comparing the addition of rufinamide to 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, 25 patients, of which 10 subjects were aged 1 to 2 years, were exposed to rufinamide 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 rufinamide 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 small number of patients in the study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form https://sideeffects.health.gov.il.

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 **Inovelon tablets**. 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

Inovelon tablets 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 and 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.
As 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 tablets** vs. –1.6% on placebo, p= 0.0006), the number of tonic-atonic seizures (-42.9% on **Inovelon tablets** 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 tablets** vs. 14.5% on the placebo arm, p=0.0041).

Additionally, Inovelon **tablets** (rufinamide oral suspension) was administered in a multicentre, open-label study comparing the addition of rufinamide 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 rufinamide as adjunctive therapy for 24 weeks at a 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 rufinamide 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 rufinamide 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).

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 doses 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.

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).

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:

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

Pharmacokinetics in special patient groups

Sex

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.

Renal impairment

The pharmacokinetics of a single 400 mg dose of rufinamide were 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 rufinamide, suggesting that this may be a useful procedure in case of overdose (see sections 4.2 and 4.9).

Hepatic impairment

No studies have been performed in patients with hepatic impairment and therefore **Inovelon tablets** should not be administered to patients with severe hepatic impairment (see section 4.2).

Elderly

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

Children (1-12 years)

Children generally have lower clearance of rufinamide than adults, and this difference is related to body size with rufinamide clearance increasing with body weight.

A recent population PK analysis of rufinamide on data pooled from 139 subjects (115 LGS patients and 24 healthy subjects), including 83 paediatric LGS patients (10 patients aged 1 to < 2 years, 14 patients aged 2 to < 4 years, 14 patients aged

4 to < 8 years, 21 patients aged 8 to < 12 years and 24 patients aged 12 to < 18 years) indicated that when rufinamide is dosed on a mg/kg/day basis in LGS subjects aged 1 to < 4 years, comparable exposure to that in LGS patients aged ≥ 4 years, in which efficacy has been demostrated, is achieved.

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

5.3 Preclinical safety data

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

Toxicities observed in dogs at levels 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.
Inovelon tablets 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. An adverse effect 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.

Environmental Risk Assessment (ERA):
Environmental risk assessment studies have shown that rufinamide is very persistent in the environment (see section 6.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Cellulose, microcrystalline (E460), Lactose monohydrate, Maize starch,

Croscarmellose sodium (E468), Hypromellose (E464), Magnesium stearate (E470b), Silica colloidal, anhydrous, Sodium laurilsulfate

Film coating:
Hypromellose (E464), Macrogols (8000), Titanium dioxide (E171), Talc, Ferric oxide red (E172)].

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Aluminium/aluminium blisters, packs of 10 (100 mg), 60 (200mg and 400 mg) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements for disposal.
This medicinal product could have potential risk for the environment. Any unused medicinal product or waste material should be disposed of in accordance with local requirements (see section 5.3).

7. Manufacturing

Eisai Manufacturing Limited, European Knowledge Centre, Mosquito Way, Hatfield, HERTFORDSHIRE, AL10 9SN, UK

8. Registration Numbers

100 mg – 145-35-33202
200 mg – 145-36-33204
400 mg - 145-37-33205

9. Registration Holder and importer

Eisai Israel ltd, PO Box 3393, Petah Tikva, 4951600, Israel.

Revised in February 2024 according to MOHs guidelines.