ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Inovelon 100 mg film-coated tablets
Inovelon 200 mg film-coated tablets
Inovelon 400 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Oral Tablet

Each film-coated tablet contains 100 mg rufinamide.
Each film-coated tablet contains 200 mg rufinamide.
Each film-coated tablet contains 400 mg rufinamide.

Excipients with known effect:

Each 100 mg film-coated tablet contains 20 mg lactose (as monohydrate).
Each 200 mg film-coated tablet contains 40 mg lactose (as monohydrate).
Each 400 mg film-coated tablet contains 80 mg lactose (as monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

100 mg: Pink, 'ovaloid', slightly convex, approximately 10.2 mm in length, scored on both sides, embossed 'Є261' on one side and blank on the other side. The tablet can be divided into equal halves.

200 mg: Pink, 'ovaloid', slightly convex, approximately 15.2 mm in length, scored on both sides, embossed 'Є262' on one side and blank on the other side. The tablet can be divided into equal halves.

400 mg: Pink, 'ovaloid', slightly convex, approximately 18.2 mm in length, scored on both sides, embossed 'Є263' 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 (LGS) in patients 1 year of age and older.

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.

Inovelon oral suspension and Inovelon film-coated tablets may be interchanged at equal doses. Patients should be monitored during the switch over period.

Posology

Use in children from 1 year to less than 4 years of age

Patients not receiving valproate:
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 valproate:
As valproate significantly decreases clearance of rufinamide, a lower maximum dose of Inovelon is recommended for patients being co-administered valproate. 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 is not achievable, the dose should be given to the nearest whole 100 mg tablet.

Use in children 4 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 third day, up to a maximum recommended dose of 1,000 mg/day.

Doses of up to 3,600 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 4 years of age or older of 30 kg or over

Patients > 30 kg not receiving valproate:
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 valproate:
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 rufinamide 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. Use in patients with severe hepatic impairment is not recommended.

Discontinuation of rufinamide
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 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 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

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 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. 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 4.5 and 4.6).

Lactose

Inovelon 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.

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 rufinamide

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. Therefore, consideration should be given to a dose reduction of Inovelon in patients 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 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 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 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 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 antiepileptic 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 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.

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 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 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 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		

System Organ Class	Very Common	Common	Uncommon	Rare
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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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: 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 experience

Inovelon (rufinamide 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 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 (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%.

Inovelon oral suspension and Inovelon film-coated tablets have been demonstrated to be bioequivalent.

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 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. 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. 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

Lactose monohydrate
Cellulose, microcrystalline (E460)
Maize starch
Croscarmellose sodium (E468)
Hypromellose (E464)
Magnesium stearate (E470b)
Sodium laurilsulfate
Silica colloidal, anhydrous

Film coating

Hypromellose (E464)
Macrogols (8000)
Titanium dioxide (E171)
Talc
Ferric oxide red (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

Do not store above 30ºC.

6.5 Nature and contents of container

Aluminium/aluminium blisters, packs of 10, 30, 50, 60 and 100 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. MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany
e-mail: medinfo_de@eisai.net

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/378/001-005
EU/1/06/378/006-010
EU/1/06/378/011-016

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2007
Date of latest renewal: 09 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Inovelon 40 mg/ml oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml of oral suspension contains 40 mg rufinamide.

1 bottle of 460 ml contains 18400 mg rufinamide.

Excipients with known effect:

Each ml of oral suspension contains:
175 mg sorbitol (E420)
1.2 mg methyl parahydroxybenzoate (E218),
0.3 mg propyl parahydroxybenzoate),
less than 0.01 mg benzoic acid (E210)

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Oral suspension.

White, slightly viscous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

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.

Inovelon oral suspension and Inovelon film-coated tablets may be interchanged at equal doses. Patients should be monitored during the switch over period.

Posology

Use in children from 1 year to less than 4 years of age

Patients not receiving valproate:
Treatment should be initiated at a dose of 10 mg/kg/day (0.25 ml/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 (0.25 ml/kg/day) every third day to a target dose of 45 mg/kg/day (1.125 ml/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 (1.125 ml/kg/day).

Patients receiving valproate:
As valproate significantly decreases clearance of rufinamide, a lower maximum dose of Inovelon is recommended for patients being co-administered valproate. Treatment should be initiated at a dose of 10 mg/kg/day (0.25 ml/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 (0.25 ml/kg/day) every third day to a target dose of 30 mg/kg/day (0.75 ml/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 (0.75 ml/kg/day).

If the recommended calculated dose of Inovelon is not achievable, the dose should be given to the nearest 0.5 ml of rufinamide.

Use in children 4 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 (5 ml dosing suspension given as two 2.5 ml doses, one in the morning and one in the evening). 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 1,000 mg/day (25 ml/day).

Doses of up to 3,600 mg/day (90 ml/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 (15 ml/day).

Use in adults, adolescents and children 4 years of age or older of 30 kg or over

Patients > 30 kg not receiving valproate:
Treatment should be initiated at a daily dose of 400 mg (10 ml dosing suspension given as two 5 ml doses). 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 or 45 ml/day	2,400 mg/day or 60 ml/day	3,200 mg/day or 80 ml/day

Doses of up to 4,000 mg/day (100 ml/day) in the 30 -50 kg range or 4,800 mg/day (120 ml/day) in the over 50 kg category have been studied in a limited number of patients.

Patients > 30 kg also receiving valproate:
Treatment should be initiated at a daily dose of 400 mg (10 ml dosing suspension given as two 5 ml doses). 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 or 30 ml/day	1,600 mg/day or 40 ml/day	2,200 mg/day or 55 ml/day

Elderly
There is limited information on the use of rufinamide 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. Use in patients with severe hepatic impairment is not recommended.

Discontinuation of rufinamide
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 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 suspension 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).

The oral suspension should be shaken vigorously before every administration. See section 6.6 for further details.

The prescribed dose of Inovelon oral suspension can be administered via an enteral feeding tube. Follow the manufacturer's instructions for the feeding tube to administer the medicine. To ensure adequate dosing, after administration of the oral suspension, the enteral feeding tube must be flushed at least once with 1 ml of water.

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

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 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. 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 4.5 and 4.6).

Parahydroxybenzoates

Inovelon oral suspension contains parahydroxybenzoates which may cause allergic reactions (possibly delayed).

Sorbitol (E420)
Each mL of Inovelon oral suspension contains 175 mg sorbitol (E420).
Patients with hereditary fructose intolerance (HFI) should not take this medicinal product.
Caution should be exercised when combining Inovelon oral suspension with other antiepileptic medications containing sorbitol, since a combined intake of over 1 gram of sorbitol may affect absorption of some drugs.

Benzoic Acid (E210)

Each mL of Inovelon oral suspension contains less than 0.01 mg benzoic acid (E210).
Benzoic acid can displace bilirubin from albumin, leading to increase in bilirubinaemia. This may increase neonatal jaundice which may develop into kernicterus (non-conjugated bilirubin deposits in the brain tissue).

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.

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 rufinamide

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. Therefore, consideration should be given to a dose reduction of Inovelon in patients 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 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 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 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 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 antiepileptic 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 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.

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 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 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 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		

System Organ Class	Very Common	Common	Uncommon	Rare
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. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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: 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 experience

Inovelon (rufinamide 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 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 (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%.

Inovelon oral suspension and Inovelon film-coated tablets have been demonstrated to be bioequivalent.

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 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. 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. 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

Microcrystalline cellulose (E460)
Carmellose sodium (E466)

Citric acid, anhydrous (E330)
Simethicone emulsion, 30% containing purified water, silicone oil, polysorbate 65 (E436), methylcellulose (E461), silica gel, polyethylene glycol stearate, sorbic acid (E200), benzoic acid (E210) and sulfuric acid (E513).
Poloxamer 188
Orange flavour
Hydroxyethylcellulose
Methyl parahydroxybenzoate (E218)
Potassium sorbate (E202)
Propyl parahydroxybenzoate
Propylene glycol (E1520).

Sorbitol (E420), liquid (non-crystallising)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.
After first opening: 90 days.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Oriented-polyethylene terephthalate (o-PET) bottle with a child-resistant polypropylene (PP) closure; each bottle contains 460 ml of suspension in an outer cardboard carton.

Each carton contains one bottle, two identical calibrated oral dosing syringes and a press-in-bottle adapter (PIBA). The oral dosing syringes are graduated in 0.5 ml increments.

6.6 Special precautions for disposal and other handling

Preparation: The press-in-bottle adapter (PIBA) which is supplied in the product carton should be inserted firmly into the neck of the bottle before use and remain in place for the duration of the usage of the bottle. The dosing syringe should be inserted into the PIBA and the dose withdrawn from the inverted bottle. The cap should be replaced after each use. The cap fits properly when the PIBA is in place.

Nasogastric tube (NG): Polyvinyl chloride (PVC) tube of not greater than 40 cm in length and diameter of tube 5 Fr. To ensure adequate dosing, after administration of the oral suspension, the enteral feeding tube must be flushed at least once with 1 ml of water.
No special requirements for disposal.

This medicinal product could have potential risk for the environment. Any unused medicinal product to waste material should be disposed of in accordance with local requirements (see section 5.3).

7. MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany
e-mail: medinfo_de@eisai.net

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/378/017

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 16 January 2007
Date of latest renewal: 09 January 2012

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

Periodic Safety Update Reports

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Inovelon 100 mg film-coated tablets
Rufinamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 100 mg rufinamide.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10
10 film-coated tablets
30
30 film-coated tablets
50
50 film-coated tablets
60
60 film-coated tablets
100
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/378/001-005

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inovelon 100 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Inovelon 100 mg film-coated tablets
Rufinamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Inovelon 200 mg film-coated tablets
Rufinamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg rufinamide.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10
10 film-coated tablets
30
30 film-coated tablets
50
50 film-coated tablets
60
60 film-coated tablets
100
100 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/378/006-010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inovelon 200 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Inovelon 200 mg film-coated tablets
Rufinamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Inovelon 400 mg film-coated tablets
Rufinamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 400 mg rufinamide.

3. LIST OF EXCIPIENTS

Contains lactose. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

10
10 film-coated tablets
30
30 film-coated tablets
50
50 film-coated tablets
60
60 film-coated tablets
100
100 film-coated tablets
200
200 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP (MM/YYYY)

9. SPECIAL STORAGE CONDITIONS

Do not store above 30ºC.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/378/011-016

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inovelon 400 mg tablets

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:

NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Inovelon 400 mg film-coated tablets
Rufinamide

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Eisai

3. EXPIRY DATE

EXP:

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING AND THE IMMEDIATE PACKAGING

1. NAME OF THE MEDICINAL PRODUCT

Inovelon 40 mg/ml oral suspension
Rufinamide

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml of Inovelon oral suspension contains 40 mg rufinamide.
1 bottle contains 18400 mg rufinamide.

3. LIST OF EXCIPIENTS

Also contains methyl parahydroxybenzoate (E218)
propyl parahydroxybenzoate
sorbitol (E420) and benzoic acid (E210)

See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Oral suspension 460 ml.
Each carton contains 1 bottle, 2 syringes and 1 press-in-bottle adapter (PIBA).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Shake well before use.

Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:
After first opening: use within 90 days.

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/378/017

13. BATCH NUMBER<, DONATION AND PRODUCT CODES>

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Inovelon 40 mg/ml

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Inovelon 100 mg film-coated tablets
Inovelon 200 mg film-coated tablets
Inovelon 400 mg film-coated tablets
Rufinamide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask the doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to the doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Inovelon is and what it is used for

Inovelon contains a medicine called rufinamide. It belongs to a group of medicines called antiepileptics, which are used to treat epilepsy (a condition where someone has seizures or fits).

Inovelon is used with other medicines to treat seizures associated with Lennox-Gastaut syndrome in adults, adolescents and children from 1 year of age. Lennox-Gastaut syndrome is the name given to a group of severe epilepsies in which you may experience repeated seizures of various types.
Inovelon has been given to you by your doctor to reduce the number of your seizures or fits.

2. What you need to know before you take Inovelon

Do not take Inovelon:

- if you are allergic to rufinamide or triazole derivatives or any of the other ingredients of Inovelon (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist if:

- you have Congenital Short QT Syndrome or a family history of such a syndrome (electrical disturbance of the heart), as taking rufinamide could make it worse.

- you suffer from liver problems. There is limited information on the use of rufinamide in this group, so the dose of your medicine may need to be increased more slowly. If your liver disease is severe the doctor may decide Inovelon is not recommended for you.

- you get a skin rash or fever. These could be signs of an allergic reaction. See the doctor immediately as very occasionally this may become serious.

- you suffer an increase in the number or severity or duration of your seizures, you should contact the doctor immediately if this happens.

- you experience difficulty walking, abnormal movement, dizziness or sleepiness inform the doctor, if any of these happen.

- if you take this medicine and have thoughts of harming or killing yourself at any time, **contact your doctor or go to a hospital straight away** (see section 4).

Consult the doctor, even if these events occurred at any time in the past.

Children
Inovelon should not be given to children younger than 1 year of age since there is not enough information on its use in this age group.

Other medicines and Inovelon

Tell the doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. If you are taking the following medicines: phenobarbital, fosphenytoin, phenytoin or primidone, you may need 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 change in the dose of the other medicines may be needed as they may become slightly less effective when given with rufinamide.

Antiepileptic medicines and Inovelon

If the doctor prescribes or recommends an additional treatment for epilepsy (e.g., valproate) you must tell the doctor you are taking Inovelon as the dose may need adjusting.

Adults and children taking valproate at the same time as rufinamide will result in high levels of rufinamide in the blood. Tell your doctor if you are taking valproate as the dose of Inovelon may need to be reduced by your doctor.

Tell the doctor if you are taking hormonal/oral contraceptives, e.g., "The pill". Inovelon may make the pill not effective at preventing pregnancy. Therefore, it is recommended that you use an additional safe and effective contraceptive method (such as a barrier method, e.g., condoms) when taking Inovelon.

Tell the doctor if you are taking the blood thinner – warfarin. The doctor may need to adjust the dose.

Tell the doctor if you are taking digoxin (a medicine used to treat heart conditions). The doctor may need to adjust the dose.

Inovelon with food and drink

See section 3 – 'How to use Inovelon' for advice on taking Inovelon with food and drink.

Pregnancy, breast-feeding and fertility

If you are pregnant, or think you might be pregnant, or are planning to get pregnant, ask the doctor or pharmacist for advice before taking Inovelon. You must only take Inovelon during your pregnancy if the doctor tells you to.

You are advised not to breast-feed while taking Inovelon, as it is not known if rufinamide will be present in breast milk.

If you are a woman of childbearing age, you must use contraceptive measures while taking Inovelon.

Ask the doctor or pharmacist for advice before taking any medicine at the same time as Inovelon.

Driving and using machines

Inovelon may make you feel dizzy, drowsy and affect your vision, particularly at the beginning of treatment or after a dose increase. If this happens to you, do not drive or operate machinery.

Inovelon contains lactose

If you have been told by the doctor that you have an intolerance to some sugars, contact the doctor before taking this medicinal product.

Inovelon contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per daily dose, that is to say essentially 'sodium-free'.

3. How to use Inovelon

Always take this medicine exactly as your doctor has told you. Check with the doctor or pharmacist if you are not sure.

It may take a while to find the best dose of Inovelon for you. The dose will be calculated for you by the doctor and will depend on your age, weight and whether you are taking Inovelon with another medicine called valproate.

Children aged between 1 and 4 years of age

The recommended starting dose is 10 mg for each kilogram of body weight, each day. Taken in two equal doses, half in the morning and the other half in the evening. The dose will be calculated for you by the doctor and may be increased by 10 mg for each kilogram of body weight, every third day.

The maximum daily dose will depend on whether or not you are also taking valproate. Maximum daily dose not taking valproate is 45 mg for each kilogram of body weight, each day. Maximum daily dose taking valproate is 30 mg for each kilogram of body weight, each day.

Children 4 years of age or older weighing less than 30 kg

The recommended starting dose is 200 mg a day. Taken in two equal doses, half in the morning and the other half in the evening. The dose will be calculated for you by the doctor and may be increased by 200 mg every third day.

The maximum daily dose will depend on whether or not you are also taking valproate. Maximum daily dose not taking valproate is 1,000 mg each day. Maximum daily dose taking valproate is 600 mg each day.

Adults, adolescents and children weighing 30 kg or over

The recommended starting dose is 400 mg a day. Taken in two equal doses, half in the morning and the other half in the evening. The dose will be calculated for you by the doctor and may be increased by 400 mg every other day.

The maximum daily dose will depend on whether or not you are also taking valproate. Maximum daily dose not taking valproate is no more than 3,200 mg, depending on body weight. Maximum daily dose taking valproate is no more than 2,200 mg, depending on body weight.

Some patients may respond to lower doses and your doctor may adjust the dose depending on how you respond to the treatment.

If you experience side effects, your doctor may increase the dose more slowly.

Inovelon tablets must be taken twice daily with water, in the morning and in the evening. Inovelon should be taken with food. If you have difficulty swallowing, you can crush the tablet, then mix the powder in about half a glass (100 ml) of water and drink immediately. You can also break the tablets into two equal halves and swallow with water.

Do not reduce the dose or stop this medicine unless the doctor tells you to.

If you take more Inovelon than you should

If you may have taken more Inovelon than you should, tell the doctor or pharmacist immediately, or contact your nearest hospital casualty department, taking the medicine with you.

If you forget to take Inovelon

If you forget to take a dose, continue taking the medicine as normal. Do not take a double dose to make up for forgotten dose. If you miss taking more than one dose, seek advice from the doctor.

If you stop taking Inovelon

If the doctor advises stopping treatment, follow their instructions concerning the gradual reduction of Inovelon in order to lower the risk of an increase in seizures.

If you have any further questions on the use of this product, ask the doctor or pharmacist.

4. Possible side effects

Like all medicines, Inovelon can cause side effects, although not everybody gets them.

The following side effects can be very serious:

Rash and/or fever. These could be signs of an allergic reaction. If they happen to you tell your doctor or go to a hospital immediately:

Change in the types of seizures you experience/more frequent seizures which last a long time (called status epilepticus). Tell your doctor immediately.

A small number of people being treated with antiepileptics such as Inovelon have had thoughts of harming or killing themselves. If at any time you have these thoughts contact your doctor immediately (see section 2).

You may experience the following side effects with this medicine. Tell the doctor if you have any of the following:

Very common (more than 1 in 10 patients) side effects of Inovelon are:

Dizziness, headache, nausea, vomiting, sleepiness, fatigue.

Common (more than 1 in a 100 patients) side effects of Inovelon are:

Problems associated with nerves including: difficulty walking, abnormal movement, convulsions/seizures, unusual eye movements, blurred vision, trembling.

Problems associated with the stomach including: stomach pain, constipation, indigestion, loose stools (diarrhoea), loss or change in appetite, weight loss.

Infections: ear infection, flu, nasal congestion, chest infection.

In addition, patients have experienced: anxiety, insomnia, nose bleeds, acne, rash, back pain, infrequent periods, bruising, head injury (as a result of accidental injury during a seizure).

Uncommon (between 1 in a 100 and 1 in a 1000 patients) side effects of Inovelon are:

Allergic reactions and an increase in markers of liver function (hepatic enzyme increase).

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Inovelon

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton. The expiry date refers to the last day of that month.

Do not store above 30°C.

Do not use this medicine if you notice that the appearance of the medicine has changed.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Inovelon contains

- The active substance is rufinamide.

  Each 100 mg film-coated tablet contains 100 mg of rufinamide.
  Each 200 mg film-coated tablet contains 200 mg of rufinamide.
  Each 400 mg film-coated tablet contains 400 mg of rufinamide.

- The other ingredients are lactose monohydrate, microcrystalline cellulose (E460), maize starch, croscarmellose sodium (E468), Hypromellose (E464), magnesium stearate, sodium laurilsulfate and colloidal anhydrous silica. The film-coating consists of Hypromellose (E464), macrogols (8000), titanium dioxide (E171), talc and ferric oxide red (E172).

What Inovelon looks like and contents of the pack

- Inovelon 100 mg tablets are pink, oval, slightly convex film-coated tablets, scored on both sides, embossed ‘€261’ on one side and blank on the other side.

They are available as packs of 10, 30, 50, 60 and 100 film-coated tablets.

- Inovelon 200 mg tablets are pink, oval, slightly convex film-coated tablets, scored on both sides, embossed ‘Є262’ on one side and blank on the other side.

They are available as packs of 10, 30, 50, 60 and 100 film-coated tablets.

- Inovelon 400 mg tablets are pink, oval, slightly convex film-coated tablets, scored on both sides, embossed ‘Є263’ on one side and blank on the other side.

They are available as packs of 10, 30, 50, 60,100 and 200 film-coated tablets.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany
e-mail: medinfo_de@eisai.net

Manufacturer:
Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Eisai SA/NV
Tél/Tel: +32 (0)800 158 58

Lietuva
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Vokietija)

България
Eisai GmbH
Тел.: + 49 (0) 69 66 58 50
(Германия)

Luxembourg/Luxemburg
Eisai SA/NV
Tél/Tel: +32 (0)800 158 58
(Belgique/Belgien)

Česká republika
Eisai GesmbH organizační složka
Tel: + 420 242 485 839

Magyarország
Ewopharma Hungary Ltd.
Tel.: +36 1 200 46 50

Danmark
Eisai AB
Tlf: + 46 (0) 8 501 01 600
(Sverige)

Malta
Cherubino LTD
Tel.: +356 21343270

Deutschland
Eisai GmbH
Tel: + 49 (0) 69 66 58 50

Nederland
Eisai B.V.
Tel: + 31 (0) 900 575 3340

Eesti
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Saksamaa)

Norge
Eisai AB
Tlf: + 46 (0) 8 501 01 600
(Sverige)

Ελλάδα
Arriani Pharmaceutical S.A.
Τηλ: + 30 210 668 3000

España
Eisai Farmacéutica, S.A.
Tel: + (34) 91 455 94 55

France
Eisai SAS
Tél: + (33) 1 47 67 00 05

Hrvatska
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Njemačka)

Ireland
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Germany)

Ísland
Eisai AB
Sími: + 46 (0)8 501 01 600
(Svíþjóð)

Italia
Eisai S.r.l.
Tel: + 39 02 5181401

Κύπρος
Arriani Pharmaceuticals S.A.
Τηλ: + 30 210 668 3000
(Ελλάδα)

Latvija
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Vācija)

Österreich
Eisai GesmbH
Tel: + 43 (0) 1 535 1980-0

Polska
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Niemcy)

Portugal
Eisai Farmacêtica, Unipessoal Lda
Tel: + 351 214 875 540

România
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Germania)

Slovenija
Ewopharma d.o.o.
Tel: +386 590 848 40

Slovenská republika
Eisai GesmbH organizačni složka
Tel.: + 420 242 485 839
(Česká republika)

Suomi/Finland
Eisai AB
Puh/Tel: + 46 (0) 8 501 01 600
(Ruotsi)

Sverige
Eisai AB
Tel: + 46 (0) 8 501 01 600

United Kingdom (Northern Ireland)
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Germany)

This leaflet was last revised in {MM/YYYY}.

Detailed information on this product is available on the European Medicines Agency website http://www.ema.europa.eu

Package leaflet: Information for the user

Inovelon 40 mg/ml oral suspension
Rufinamide

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask the doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to the doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Inovelon is and what it is used for

Inovelon contains a medicine called rufinamide. It belongs to a group of medicines called antiepileptics, which are used to treat epilepsy (a condition where someone has seizures or fits).

Inovelon is used with other medicines to treat seizures associated with Lennox-Gastaut syndrome in adults, adolescents and children from 1 year of age. Lennox-Gastaut syndrome is the name given to a group of severe epilepsies in which you may experience repeated seizures of various types.

Inovelon has been given to you by your doctor to reduce the number of your seizures or fits.

2. What you need to know before you take Inovelon

Do not take Inovelon:

- if you are allergic to rufinamide or triazole derivatives or any of the other ingredients of Inovelon (listed in section 6).

Warnings and precautions

Talk to your doctor or pharmacist if:

- you have Congenital Short QT Syndrome or a family history of such a syndrome (electrical disturbance of the heart), as taking rufinamide could make it worse.
- you suffer from liver problems. There is limited information on the use of rufinamide in this group, so the dose of your medicine may need to be increased more slowly. If your liver disease is severe the doctor may decide Inovelon is not recommended for you.
- you get a skin rash or fever. These could be signs of an allergic reaction. See the doctor immediately as very occasionally this may become serious.
- you suffer an increase in the number or severity or duration of your seizures, you should contact the doctor immediately if this happens.
- you experience difficulty walking, abnormal movement, dizziness or sleepiness inform the doctor, if any of these happen.

- if you take this medicine and have thoughts of harming or killing yourself at any time, **contact your doctor or go to a hospital straight away** (see section 4).

Consult the doctor, even if these events occurred at any time in the past.

Children

Inovelon should not be given to children younger than 1 year of age since there is not enough information on its use in this age group.

Other medicines and Inovelon

Tell the doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. If you are taking the following medicines: phenobarbital, fosphenytoin, phenytoin or primidone, you may need 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 change in the dose of the other medicines may be needed as they may become slightly less effective when given with rufinamide.

Antiepileptic medicines and Inovelon

If the doctor prescribes or recommends an additional treatment for epilepsy (e.g., valproate) you must tell the doctor you are taking Inovelon as the dose may need adjusting.

Adults and children taking valproate at the same time as rufinamide will result in high levels of rufinamide in the blood. Tell your doctor if you are taking valproate as the dose of Inovelon may need to be reduced by your doctor.

Tell the doctor if you are taking hormonal/oral contraceptives, e.g., "The pill". Inovelon may make the pill not effective at preventing pregnancy. Therefore, it is recommended that you use an additional safe and effective contraceptive method (such as a barrier method, e.g., condoms) when taking Inovelon.

Tell the doctor if you are taking the blood thinner – warfarin. The doctor may need to adjust the dose.

Tell the doctor if you are taking digoxin (a medicine used to treat heart conditions). The doctor may need to adjust the dose.

Inovelon with food and drink

See section 3 – 'How to use Inovelon' for advice on taking Inovelon with food and drink.

Pregnancy, breast-feeding and fertility

If you are pregnant, or think you might be pregnant, or are planning to get pregnant, ask the doctor or pharmacist for advice before taking Inovelon. You must only take Inovelon during your pregnancy if the doctor tells you to.

You are advised not to breast-feed while taking Inovelon, as it is not known if rufinamide will be present in breast milk.

If you are a woman of childbearing age, you must use contraceptive measures while taking Inovelon.

Ask the doctor or pharmacist for advice before taking any medicine at the same time as Inovelon.

Driving and using machines

Inovelon may make you feel dizzy, drowsy and affect your vision, particularly at the beginning of treatment or after a dose increase. If this happens to you, do not drive or operate machinery.

Inovelon contains sorbitol (E420)

Inovelon contains 175 mg sorbitol (E420) in each mL. Sorbitol is a source of fructose. If your doctor has told you that you (or your child) have an intolerance to some sugars or if you have been diagnosed with hereditary fructose intolerance (HFI), a rare genetic disorder in which a person cannot break down fructose, talk to your doctor before you (or your child) take or receive this medicine.

Sorbitol may cause gastrointestinal discomfort and mild laxative effect.

Taking Inovelon with other anti-epileptic medicine which contains sorbitol, may affect how much they work. Tell your doctor or pharmacist if you are taking any other anti-epileptic medicine(s) with sorbitol.

Inovelon contains benzoic acid (E210)

Inovelon contains less than 0.01 mg benzoic acid (E210) in each mL. Benzoic acid may increase jaundice (yellowing of the skin and eyes) in newborn babies up to 4 weeks old.

Inovelon contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per daily dose, that is to say essentially 'sodium-free'.

Inovelon contains methyl parahydroxybenzoate (E218) and propyl parahydroxybenzoate

These ingredients may cause allergic reactions (possibly delayed).

3. How to use Inovelon

Always take this medicine exactly as your doctor has told you. Check with the doctor or pharmacist if you are not sure.

It may take a while to find the best dose of Inovelon for you. The dose will be calculated for you by the doctor and will depend on your age, weight and whether you are taking Inovelon with another medicine called valproate.

<u>Children aged between 1 and 4 years of age</u>

The recommended starting dose is 10 mg (0.25 ml) for each kilogram of body weight, each day. Taken in two equal doses, half in the morning and the other half in the evening. The dose will be calculated for you by the doctor and may be increased by 10 mg (0.25 ml) for each kilogram of body weight, every third day.

The maximum daily dose will depend on whether or not you are also taking valproate. Maximum daily dose not taking valproate is 45 mg (1.125 ml) for each kilogram of body weight, each day. Maximum daily dose taking valproate is 30 mg (0.75 ml) for each kilogram of body weight, each day.

Children 4 years of age or older weighing less than 30 kg

The recommended starting dose is 200 mg (5 ml) a day. Taken in two equal doses, half in the morning and the other half in the evening. The dose will be calculated for you by the doctor and may be increased by 200 mg (5 ml) every third day.

The maximum daily dose will depend on whether or not you are also taking valproate. Maximum daily dose not taking valproate is 1,000 mg (25 ml) each day. Maximum daily dose taking valproate is 600 mg (15 ml) each day.

Adults, adolescents and children weighing 30 kg or over

The recommended starting dose is 400 mg (10 ml) a day. Taken in two equal doses, half in the morning and the other half in the evening. The dose will be calculated for you by the doctor and may be increased by 400 mg (10 ml) every other day.

The maximum daily dose will depend on whether or not you are also taking valproate. Maximum daily dose not taking valproate is no more than 3,200 mg (80 ml), depending on body weight.
Maximum daily dose taking valproate is no more than 2,200 mg (55 ml), depending on body weight.

Some patients may respond to lower doses and your doctor may adjust the dose depending on how you respond to the treatment.

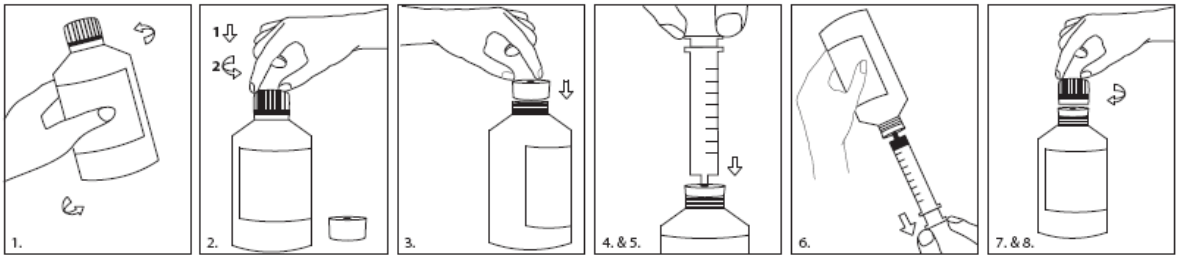
If you experience side effects, your doctor may increase the dose more slowly.

Inovelon oral suspension must be taken twice every day, once in the morning and once in the evening. Inovelon should be taken with food.

Method of administration

For dosing, please use the syringe and adaptor provided.

Instructions on how to use the syringe and adaptor are provided below:



1. Shake well before use.
2. Push down (1) and turn cap (2) to open bottle
3. Insert adaptor into the neck of the bottle until a tight seal is made
4. Push plunger of syringe completely down
5. Insert the syringe into the opening of the adaptor as far as possible.
6. Turn upside down and withdraw the prescribed amount of Inovelon from the bottle.
7. Turn upright and remove the syringe
8. Leave the adaptor in place and replace cap on bottle.
9. After dose administration, separate barrel and plunger, and fully immerse both components in HOT soapy water.
10. Immerse the barrel and plunger in water to remove any residual detergent, shake off excess water and leave components to air dry. Do not wipe dry the dispensers.
11. Do not clean and reuse the syringe after 40 uses, or if the markings on the syringe wash off.

Do not reduce the dose or stop this medicine unless the doctor tells you to.

If you take more Inovelon than you should

If you may have taken more Inovelon than you should, tell the doctor or pharmacist immediately, or contact your nearest hospital casualty department, taking the medicine with you.

If you forget to take Inovelon

If you forget to take a dose, continue taking the medicine as normal. Do not take a double dose to make up for forgotten dose. If you miss taking more than one dose, seek advice from the doctor.

If you stop taking Inovelon

If the doctor advises stopping treatment, follow their instructions concerning the gradual reduction of Inovelon in order to lower the risk of an increase in seizures.

If you have any further questions on the use of this product, ask the doctor or pharmacist.

4. Possible side effects

Like all medicines, Inovelon can cause side effects, although not everybody gets them.

The following side effects can be very serious:

Rash and/or fever. These could be signs of an allergic reaction. If they happen to you tell your doctor or go to a hospital immediately:

Change in the types of seizures you experience/more frequent seizures which last a long time (called status epilepticus). Tell your doctor immediately.

A small number of people being treated with antiepileptics such as Inovelon have had thoughts of harming or killing themselves. If at any time you have these thoughts contact your doctor immediately (see section 2).

You may experience the following side effects with this medicine. Tell the doctor if you have any of the following:

Very common (more than 1 in 10 patients) side effects of Inovelon are:

Dizziness, headache, nausea, vomiting, sleepiness, fatigue.

Common (more than 1 in a 100 patients) side effects of Inovelon are:

Problems associated with nerves including: difficulty walking, abnormal movement, convulsions/seizures, unusual eye movements, blurred vision, trembling.

Problems associated with the stomach including: stomach pain, constipation, indigestion, loose stools (diarrhoea), loss or change in appetite, weight loss.

Infections: ear infection, flu, nasal congestion, chest infection.

In addition, patients have experienced: anxiety, insomnia, nose bleeds, acne, rash, back pain, infrequent periods, bruising, head injury (as a result of accidental injury during a seizure).

Uncommon (between 1 in a 100 and 1 in a 1000 patients) side effects of Inovelon are:

Allergic reactions and an increase in markers of liver function (hepatic enzyme increase).

Reporting of side effects

If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store Inovelon

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the bottle label and carton. The expiry date refers to the last day of that month.

If you have any suspension left in the bottle more than 90 days after it was first opened, do not use it.

Do not use the suspension if you notice that the appearance or smell of your medicine has changed. Return the medicine to the pharmacist.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Inovelon contains

- The active substance is rufinamide. Each millilitre contains 40 mg of rufinamide. 5 ml contains 200 mg rufinamide.

- The other ingredients are microcrystalline cellulose and carmellose sodium, anhydrous citric acid, simethicone emulsion 30% (containing purified water, silicone oil, polysorbate 65, methylcellulose, silica gel, polyethylene glycol stearate, sorbic acid, benzoic acid (E210) and sulfuric acid), poloxamer 188, orange flavour, hydroxyethylcellulose, methyl parahydroxybenzoate (E218), potassium sorbate (E202), propyl parahydroxybenzoate, propylene glycol (E1520), sorbitol (E420), liquid (non-crystallising), and purified water.

What Inovelon looks like and contents of the pack

- Inovelon is a white slightly viscous suspension. It comes in a bottle of 460 ml with two identical syringes and a push in bottle adaptor (PIBA). The syringes are graduated in 0.5 ml increments.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany
e-mail: medinfo_de@eisai.net

Manufacturer:
Eisai GmbH
Edmund-Rumpler-Straße 3
60549 Frankfurt am Main
Germany

For any information about this medicinal product, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Eisai SA/NV
Tél/Tel: +32 (0)800 158 58

Lietuva
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Vokietija)

България
Eisai GmbH
Тел.: + 49 (0) 69 66 58 50
(Германия)

Luxembourg/Luxemburg
Eisai SA/NV
Tél/Tel: +32 (0)800 158 58
(Belgique/Belgien)

Česká republika
Eisai GesmbH organizačni složka
Tel: + 420 242 485 839

Magyarország
Eisai GmbH
Tel.: + 49 (0) 69 66 58 50
(Németország)

Danmark
Eisai AB
Tlf: + 46 (0) 8 501 01 600
(Sverige)

Malta
Cherubino LTD
Tel.: +356 21343270

Deutschland
Eisai GmbH
Tel: + 49 (0) 69 66 58 50

Eesti
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Saksamaa)

Ελλάδα
Arriani Pharmaceutical S.A.
Τηλ: + 30 210 668 3000

España
Eisai Farmacéutica, S.A.
Tel: + (34) 91 455 94 55

France
Eisai SAS
Tél: + (33) 1 47 67 00 05

Hrvatska
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Njemačka)

Ireland
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Germany)

Ísland
Eisai AB
Sími: + 46 (0)8 501 01 600
(Svíþjóð)

Italia
Eisai S.r.l.
Tel: + 39 02 5181401

Κύπρος
Arriani Pharmaceuticals S.A.
Τηλ: + 30 210 668 3000
(Ελλάδα)

Latvija
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Vācija)

Nederland
Eisai B.V.
Tel: + 31 (0) 900 575 3340

Norge
Eisai AB
Tlf: + 46 (0) 8 501 01 600
(Sverige)

Österreich
Eisai GesmbH
Tel: + 43 (0) 1 535 1980-0

Polska
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Niemcy)

Portugal
Eisai Farmacêtica, Unipessoal Lda
Tel: + 351 214 875 540

România
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Germania)

Slovenija
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Nemčija)

Slovenská republika
Eisai GesmbH organizačni složka
Tel.: + 420 242 485 839
(Česká republika)

Suomi/Finland
Eisai AB
Puh/Tel: + 46 (0) 8 501 01 600
(Ruotsi)

Sverige
Eisai AB
Tel: + 46 (0) 8 501 01 600

United Kingdom (Northern Ireland)
Eisai GmbH
Tel: + 49 (0) 69 66 58 50
(Germany)

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Detailed information on this product is available on the European Medicines Agency website http://www.ema.europa.eu