Inovelon

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Inovelon 100 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

100 mg
Each film-coated tablet contains 100 mg rufinamide.
Excipient: 20 mg lactose monohydrate/film coated tablet.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

100 mg
Pink, 'ovaloid', slightly convex, scored on both sides, embossed '€261' on one side and blank on the other side.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Inovelon is for oral use. It should be taken twice daily with water in the morning and in the evening, in two equally divided doses. As a food effect was observed, it will preferable to administer Inovelon 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.

Use in children four years of age or older and less than 30 kg
Patients <30 kg not receiving valproate:
Treatment should be initiated at a daily dose of 200 mg. According to clinical response and tolerability, the dose may be increased by 200 mg/day increments, as frequently as every two days, up to a maximum recommended dose of 1000 mg/day. Doses of up to 3600 mg/day have been studied in a limited number of patients.

Patients <30 kg also receiving valproate medication:
As valproate significantly decreases clearance of Inovelon, 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 400 mg/day.

Use in adults and children four years of age or older of 30 kg or over
Treatment should be initiated at a daily dose of 400 mg. According to clinical response and tolerability, the dose may be increased by 400 mg/day increments, as frequently as every two days, up to a maximum recommended dose as indicated in the table below.

Weight range	30.0 – 50.0 kg	50.1 – 70.0 kg	≥70.1 kg
Maximum recommended dose (mg/day)	1800	2400	3200

Doses of up to 4000 mg/day (in the 30-50 kg range) or 4800 mg/day (over 50 kg) have been studied in a limited number of patients.

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

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

Patients with hepatic impairment
Use in patients with hepatic impairment has not been studied. Caution and careful dose titration is recommended when treating patients with mild to moderate hepatic impairment. Therefore, use in patients with severe hepatic impairment is not recommended.

Effect of food
Inovelon should preferably be taken with food (see Section 5.2).

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

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.

4.3 Contraindications

Hypersensitivity to the active substance, triazole derivatives or to any excipients.

4.4 Special warnings and precautions for use

Status epilepticus cases have been observed during clinical development studies, under rufinamide whereas no such cases have been observed under placebo. These events led to rufinamide discontinuation in 20 % of the cases. If patients develop new seizure types and/or experience an increased frequency of status epilepticus that is different from the patient's baseline condition, then the benefit risk ratio of the therapy should be reassessed.

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

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.

Serious antiepileptic drug hypersensitivity syndrome has occurred in association with rufinamide therapy. Signs and symptoms of this disorder were diverse; however, patients typically, although not exclusively, presented with fever and rash associated with other organ system involvement. Other associated manifestations included lymphadenopathy, liver function tests abnormalities, and haematuria. Because the disorder is variable in its expression, other organ system signs and symptoms not noted here may occur. This 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.

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect Inovelon

Other anti-epileptic medicinal products
Rufinamide concentrations may be decreased by co-administration with carbamazepine, phenobarbital, phenytoin, vigabatrin or primidone.

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

The addition or withdrawal of these drugs or adjusting of the dose of these drugs during Inovelon therapy may require an adjustment in dosage of Inovelon.

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

Potential for Inovelon to affect other medicinal products

Other anti-epileptic medicinal products
The pharmacokinetic interactions between rufinamide and other anti-epileptic drugs have been evaluated in patients with epilepsy using population pharmacokinetic modelling. Rufinamide appears not to have clinically relevant effect on carbamazepine, lamotrigine, phenobarbital, topiramate or valproate steady state concentrations. Since rufinamide may decrease phenytoin clearance and increase average steady state plasma concentrations of co-administered phenytoin, consideration should be given to reducing the dose of phenytoin.

Oral contraceptives
Co-administration of rufinamide 800 mg b.i.d. and a combined oral contraceptive (ethinyloestradiol 35 µg and norethindrone 1 mg) for 14 days resulted in a mean decrease in the ethinyl estradiol AUC_{0-24} of

22% and in norethindrone AUC_{0-24} of 14%. Studies with other oral or implant contraceptives have not been conducted. Women of child-bearing potential using hormonal contraceptives are advised to use an additional safe and effective contraceptive method (see Section 4.4 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 drugs which are metabolised by this enzyme. The effect was modest to moderate. The mean CYP3A activity, assessed as clearance of triazolam, was increased by 55% after 11 days of treatment with rufinamide 400 mg b.i.d. The exposure of triazolam was reduced by 36%. Higher rufinamide doses may result in a more pronounced induction. It may not be excluded that rufinamide may decrease the exposure also of drugs metabolized by other enzymes, or transported by transport proteins such as P-glycoprotein.

It is recommended that patients treated with drugs that are metabolised by the CYP3A enzyme system are to be carefully monitored for two weeks at the start of, or after the end of treatment with Inovelon, or after any marked change in the dose. A dose adjustment of the concomitantly administered drug may need to be considered. These recommendations should also be considered when rufinamide is used concomitantly with drugs with a narrow therapeutic window such as warfarin and digoxin.

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

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

4.6 Pregnancy and lactation

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

Moreover, effective anti-epileptic therapy must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Risk related to rufinamide:
Studies in animals revealed no teratogenic effect but foetotoxicity in presence of maternal toxicity (see Section 5.3). The potential risk for humans is unknown.

For rufinamide, no clinical data on exposed pregnancies are available

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

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

If women treated with rufinamide plan to become pregnant, the indication of this product should be carefully weighed. During pregnancy, an effective antiepileptic rufinamide treatment must not be interrupted, since the aggravation of the illness is detrimental to both the mother and the foetus.

Is not known if rufinamide is excreted in human breast milk. Due to the potential harmful effects for the breast fed infant, the lactation should be avoided during maternal 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, Inovelon may have a mild to severe influence on the ability to drive or 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

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

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

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

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		

System Organ Class	Very Common	Common	Uncommon	Rare
Ear and Labyrinth disorders		Vertigo		
Respiratory, thoracic and mediastinal disorders		Epistaxis		
Gastrointestinal disorders	Nausea Vomiting	Abdominal pain upper Constipation Dyspepsia Diarrhoea		
Hepato-biliary disorders			Hepatic enzyme increase	
Skin and subcutaneous tissue disorders		Rash* Acne		
Musculoskeletal and connective tissue and bone disorders		Back pain		
Reproductive system and breast disorders		Oligomenorrhoea		
General disorders and administration site conditions	Fatigue	Gait disturbance*		
Investigations		Weight decrease		
Injury, poisoning		Head injury Contusion		

*Cross refer to Section 4.4.

4.9 Overdose

After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for Inovelon. Treatment should be supportive and may include haemodialysis (see Section 5.2).

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-epileptics, carboxamide derivatives; ATC-code: N03AF03.

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

Clinical experience
Inovelon 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 or female patients (between 4 and 30 years of age) were included if they were being treated with 1 to 3 concomitant fixed-dose antiepileptic drugs. Each patient had to have at least 90 seizures in the month prior to study entry. A significant improvement was observed for all three primary variables: the percentage change in total seizure frequency per 28 days during the maintenance phase relative to baseline (-35.8% on Inovelon vs. –1.6% on placebo, p= 0.0006), the number of tonic-atonic seizures (-42.9% on Inovelon vs. 2.2% on placebo, p = 0.0002), and the seizure severity rating from the Global Evaluation performed by the parent/guardian at the end of the double-blind phase (much or very much improved in 32.2% on Inovelon vs. 14.5% on the placebo arm, p=0.0041).

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

5.2 Pharmacokinetic properties

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

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

Children (2-12 years)

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

Elderly

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

5.3 Preclinical safety data

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

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

In reproductive and developmental toxicity studies, there were reductions in foetal growth and survival, and some stillbirths secondary to maternal toxicity. However, no effects on morphology and function, including learning or memory, were observed in the offspring. Inovelon was not teratogenic in mice, rats or rabbits.

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

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Cellulose, microcrystalline
Maize starch
Croscarmellose sodium
Hypromellose
Magnesium stearate
Sodium laurilsulfate
Silica colloidal, anhydrous

Film coating:
Opadry 00F44042 [consists of hypromellose, macrogols (8000), titanium dioxide (E171), talc and ferric oxide red (E172)].

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

100 mg
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.

7. MARKETING AUTHORISATION HOLDER

Eisai Limited, 3 Shortlands, London W6 8EE, UK

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

1. NAME OF THE MEDICINAL PRODUCT

Inovelon 200 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

200 mg
Each film-coated tablet contains 200 mg rufinamide.
Excipient: 40 mg lactose monohydrate/film coated tablet.

For a full list of excipients, see Section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

200 mg
Pink, 'ovaloid', slightly convex, scored on both sides, embossed '€262' on one side and blank on the other side.

The tablet can be divided into equal halves.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

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

Inovelon is for oral use. It should be taken twice daily with water in the morning and in the evening, in two equally divided doses. As a food effect was observed, it will preferable to administer Inovelon 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.

Use in children four years of age or older and less than 30 kg
Patients <30 kg not receiving valproate:
Treatment should be initiated at a daily dose of 200 mg. According to clinical response and tolerability, the dose may be increased by 200 mg/day increments, as frequently as every two days, up to a maximum recommended dose of 1000 mg/day. Doses of up to 3600 mg/day have been studied in a limited number of patients.

Patients <30 kg also receiving valproate medication:
As valproate significantly decreases clearance of Inovelon, 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 400 mg/day.

Use in adults and children four years of age or older of 30 kg or over
Treatment should be initiated at a daily dose of 400 mg. According to clinical response and tolerability, the dose may be increased by 400 mg/day increments, as frequently as every two days, up to a maximum recommended dose as indicated in the table below.

Weight range	30.0 – 50.0 kg	50.1 – 70.0 kg	≥70.1 kg
Maximum recommended dose (mg/day)	1800	2400	3200

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

Patients with hepatic impairment
Use in patients with hepatic impairment has not been studied. Caution and careful dose titration is recommended when treating patients with mild to moderate hepatic impairment. Therefore, use in patients with severe hepatic impairment is not recommended.

Effect of food
Inovelon should preferably be taken with food (see Section 5.2).

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

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.

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Hypersensitivity to the active substance, triazole derivatives or to any excipients.

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concomitant antiepileptic medicinal products once seizure control has been achieved with the addition of Inovelon.

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

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.

4.5 Interaction with other medicinal products and other forms of interaction

Potential for other medicinal products to affect Inovelon

Other anti-epileptic medicinal products
Rufinamide concentrations may be decreased by co-administration with carbamazepine, phenobarbital, phenytoin, vigabatrin or primidone.

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

The addition or withdrawal of these drugs or adjusting of the dose of these drugs during Inovelon therapy may require an adjustment in dosage of Inovelon.

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

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Other anti-epileptic medicinal products
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Oral contraceptives

Co-administration of rufinamide 800 mg b.i.d. and a combined oral contraceptive (ethinyloestradiol 35 µg and norethindrone 1 mg) for 14 days resulted in a mean decrease in the ethinyl estradiol AUC_{0-24} of 22% and in norethindrone AUC_{0-24} of 14%. Studies with other oral or implant contraceptives have not been conducted. Women of child-bearing potential using hormonal contraceptives are advised to use an additional safe and effective contraceptive method (see Section 4.4 and 4.6).

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It is recommended that patients treated with drugs that are metabolised by the CYP3A enzyme system are to be carefully monitored for two weeks at the start of, or after the end of treatment with Inovelon, or after any marked change in the dose. A dose adjustment of the concomitantly administered drug may need to be considered. These recommendations should also be considered when rufinamide is used concomitantly with drugs with a narrow therapeutic window such as warfarin and digoxin.

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

4.6 Pregnancy and lactation

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.

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

For rufinamide, no clinical data on exposed pregnancies are available

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

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Is not known if rufinamide is excreted in human breast milk. Due to the potential harmful effects for the breast fed infant, the lactation should be avoided during maternal 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, Inovelon may have a mild to severe influence on the ability to drive or 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

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

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

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

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		

System Organ Class	Very Common	Common	Uncommon	Rare
Eye Disorders		Diplopia Vision blurred		
Ear and Labyrinth disorders		Vertigo		
Respiratory, thoracic and mediastinal disorders		Epistaxis		
Gastrointestinal disorders	Nausea Vomiting	Abdominal pain upper Constipation Dyspepsia Diarrhoea		
Hepato-biliary disorders			Hepatic enzyme increase	
Skin and subcutaneous tissue disorders		Rash* Acne		
Musculoskeletal and connective tissue and bone disorders		Back pain		
Reproductive system and breast disorders		Oligomenorrhoea		
General disorders and administration site conditions	Fatigue	Gait disturbance*		
Investigations		Weight decrease		
Injury, poisoning		Head injury Contusion		

*Cross refer to Section 4.4.

4.9 Overdose

After an acute overdose, the stomach may be emptied by gastric lavage or by induction of emesis. There is no specific antidote for Inovelon. Treatment should be supportive and may include haemodialysis (see Section 5.2).

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: anti-epileptics, carboxamide derivatives; ATC-code: N03AF03.

Mechanism of action

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

Clinical experience
Inovelon 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 or female patients (between 4 and 30 years of age) were included if they were being treated with 1 to 3 concomitant fixed-dose antiepileptic drugs. Each patient had to have at least 90 seizures in the month prior to study entry. A significant improvement was observed for all three primary variables: the percentage change in total seizure frequency per 28 days during the maintenance phase relative to baseline (-35.8% on Inovelon vs. –1.6% on placebo, p= 0.0006), the number of tonic-atonic seizures (-42.9% on Inovelon vs. 2.2% on placebo, p = 0.0002), and the seizure severity rating from the Global Evaluation performed by the parent/guardian at the end of the double-blind phase (much or very much improved in 32.2% on Inovelon vs. 14.5% on the placebo arm, p=0.0041).

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

5.2 Pharmacokinetic properties

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

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

Children (2-12 years)
Children generally have lower clearance of rufinamide than adults, and this difference is related to body size. Studies in new-born infants or infants and toddlers under 2 years of age have not been conducted.

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

5.3 Preclinical safety data

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

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

In reproductive and developmental toxicity studies, there were reductions in foetal growth and survival, and some stillbirths secondary to maternal toxicity. However, no effects on morphology and function, including learning or memory, were observed in the offspring. Inovelon was not teratogenic in mice, rats or rabbits.

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

Regarding the immunotoxic potential, small thymus and thymic involution were observed in dogs in a 13 week study with significant response at the high dose in male. In the 13 week study, female bone

marrow and lymphoid changes are reported at the high dose with a weak incidence.-In rats decreased cellularity of the bone marrow and thymic atrophy were observed only in the carcinogenicity study.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Lactose monohydrate
Cellulose, microcrystalline
Maize starch
Croscarmellose sodium
Hypromellose
Magnesium stearate
Sodium laurilsulfate
Silica colloidal, anhydrous

Film coating:
Opadry 00F44042 [consists of hypromellose, macrogols (8000), titanium dioxide (E171), talc and ferric oxide red (E172)].

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Do not store above 30°C.

6.5 Nature and contents of container

200 mg
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.

7. MARKETING AUTHORISATION HOLDER

Eisai Limited, 3 Shortlands, London W6 8EE, UK

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT