SUMMARY OF THE RISK MANAGEMENT PLAN

Active substance	Rufinamide (E2080)
Product(s) concerned (brand name):	Inovelon®
Company	Eisai Europe Ltd. European Knowledge Centre Mosquito Way Hatfield AL10 9SN United Kingdom

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v1.0

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DISCLAIMER:

Marketing Authorisation Holder: Eisai Pharma AG, Zurich

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them.

The RMP summary of Inovelon® (Rufinamide) is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation/Information sur le médicament" approved and published in Switzerland, eg, by mentioning risks occurring in populations or indications not included in the Swiss authorisation.

Please note that the reference document which is valid and relevant for the effective and safe use of INOVELON in Switzerland is the "Arzneimittelinformation/Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Eisai Pharma AG is fully responsible for the accuracy and correctness of the content of the published summary RMP of INOVELON.

Public Summary of the Risk Management Plan

1 Overview of Disease Epidemiology

In children and adolescents younger than 15 years of age, the incidence of Lennox-Gastaut Syndrome (LGS) is approximately 1 to 2 per 100,000. Boys tend to have a higher risk than girls, but there are no differences by country. The mean age at which LGS symptoms become apparent is typically between 2 and 6 years; in most cases, physical and cognitive development is usually normal before LGS onset. Symptoms in young children include personality disturbance and arrest of psychomotor and educational development; in older children, symptoms include psychosis. The main cognitive deficits are reaction time and information processing. The mean age of onset for LGS is usually between 2 and 6 years. There is an early onset type of LGS that is associated with retardation of development, and a late-onset type known as juvenile LGS. Patients with LGS have a high rate of injuries due to seizures and falls.

2 Summary of Treatment Benefits

Study 3310101022 (hereafter termed "Study -022") is the pivotal study which led to approval of rufinamide. Patients in the rufinamide group experienced a 33% median reduction from baseline in the total seizure frequency over a 28-day interval, compared to a 12% median reduction for the placebo group. The rufinamide group had a 43% median reduction (compared to baseline) in the frequency of tonic-atonic seizures over a 28-day interval. The placebo group showed no improvement for this type of seizure. Seizures became less severe in 53% of rufinamide-treated patients as compared with 31% of placebo-treated patients.

3 Unknowns Relating to Treatment Benefits

The majority of the subjects in Study -022 were between the ages of 4 and 12 years (41.9%), 25.7% of subjects were between the ages of 12 and 17 years, and 32.4% of subjects were older than 17 years. Treatment benefits in older subjects have not been assessed in clinical studies.

Most of the subjects in Study -022 were Caucasian, probably due to the race distribution in the countries where the study took place. However, treatment benefits were also seen in Study 304, which was conducted in Japanese patients with LGS. Although other ethnicities have not been comprehensively evaluated, there is no evidence to suggest that results would differ according to ethnicity.

4 Summary of Safety Concerns

Important Identified Risks

A summary of safety concerns under important identified risks for rufinamide therapy in the treatment of LGS is provided in Table 1.

Table 1. Important Identified Risks

Risk	What is Known	Preventability
One continuous, nonstopping seizure lasting longer than 5 minutes (Status epilepticus)	Status epilepticus is a condition in which seizures occur repeatedly at short intervals. This condition can be life-threatening if not promptly and appropriately treated. Status epilepticus was been reported to occur in approximately 4% (1 of 25) patients with LGS who were treated with rufinamide. It can also occur during treatment with other antiepileptic drugs.	Factors that contribute to onset of status epilepticus have not been identified. Status epilepticus is treatable if detected early.
Rash and allergy (Rash and hypersensitivity including DRESS and SJS)	Rash and hypersensitivity are not more likely to occur after treatment with rufinamide as compared with placebo.	No factor has been identified that might increase the likelihood of rash or hypersensitivity to rufinamide.
Decreased desire to eat and weight loss (Decreased appetite and weight loss)	Decreased appetite associated with or without weight loss was reported in approximately 9.5 % of subjects treated with rufinamide.	No factor has been identified that might increase the likelihood of decreased appetite and weight loss.
Abnormal coordination	Ataxia and gait disturbance occurred in up to 5.4% of patients who were treated with rufinamide in clinical studies.	No factor has been identified that would predispose to ataxia or gait disturbance after treatment with rufinamide.
Somnolence	Somnolence (sleepiness) occurred in approximately ¼ of subjects with LGS who were treated with rufinamide, as compared with approximately 1 in 8 of subjects treated with placebo.	No factor has been identified that would predispose to somnolence after treatment with rufinamide.
Dizziness and vertigo	Dizziness occurred with a frequency of approximately 1 in 30 in patients with LGS who were treated with rufinamide. This side effect was not considered to be severe.	No factors have been identified that would predispose to dizziness.
Diplopia and blurred vision	Diplopia (double vision) and blurred vision each occurred in a single subject who had LGS and treated with rufinamide in clinical studies.	No factors have been identified that would predispose to diplopia or blurred vision.
Vomiting	Vomiting occurred in approximately 1 in 5 subjects with LGS as compared with approximately 1 in 17 subjects who received placebo.	Drugs in the antiemetic class may prevent vomiting or make it less likely to occur.

DRESS = Drug Rash with Eosinophilia and Systemic Symptoms; LGS = Lennox-Gastaut Syndrome.

Important Potential Risks

A summary of safety concerns under important potential risks for rufinamide in the treatment of LGS is provided in Table 2.

Table 2. Important Potential Risks

Risk	What is Known (Including Reason Why it is Considered a Potential Risk)
Pregnancy and associated birth defects.	Studies in animals have shown that high doses of rufinamide may damage fetal development. Thus far, rufinamide has not been associated with birth defects or any other instances of harm to pregnancy. Nonetheless, a pregnancy registry has been set up to keep track of any such events should they occur. Rufinamide may make certain types of birth control less effective. Patients should notify their physicians if they are pregnant or plan to become pregnant.
Blood cell abnormalities	Abnormalities in blood cells have occasionally been reported in patients treated with other AEDs. Relatively few events of this type have occurred in patients treated with rufinamide. No factors have been identified that would predispose to blood cell abnormalities.
Developmental and maturation impairment in children and adolescents	The effects of AEDs on development and maturation in children and adolescents have not been fully studied. Patients with LGS are usually significantly mentally retarded, physical disabled, and suffer from behavioural disorders. The assessment of normal "development" in these patients is complex. No factors have been identified that would predispose to impairment of development and maturation.
Adverse effects on cognition	In rufinamide-treated patients, with the exception of somnolence, there was no clear difference between the individual adverse effects on cognition or their overall incidence. In a controlled study, there were only 2 of these events in the LGS population, 1 in the rufinamide group, and 1 in the placebo group. No factors have been identified that would predispose to adverse effects on cognition.
Shortened QT interval on ECG	In a study of the QT interval, which is related to the electrical system of the heart and is measured by ECGs, rufinamide was associated with a small decrease in QT. To date, no association has been seen between proarrhythmia (an abnormal heartbeat pattern) and treatment with rufinamide. Patients with congenital Short QT syndrome or a family history of such a syndrome should not take rufinamide.
Suicidality	Suicide is considered to be a potential risk associated with treatment with AEDs. LGS patients, due to the mental and physical impairment associated with the disease, are likely to be highly dependent and to be supervised by a caregiver, which would lower the risk of suicide. No specific risk has been identified with rufinamide
Worsening of seizures and changes in seizure type including withdrawal seizure	There is a potential risk with antiepileptic drugs, including rufinamide, of increased seizure activity soon after the withdrawal of medication. In clinical studies, discontinuation was achieved by reducing the dose by approximately 25% every 2 days.
Medication errors especially those associated with the oral suspension formula	Inovelon® is a coloured (pink) scored tablet that is identified by '€', and a number embossed on 1 side. The number is specific to each tablet strength. Medication errors have been identified with the use of Inovelon tablets; however, the incidence has been very low. Rufinamide oral suspension is a white, slightly viscous, liquid suspension. It is contained in a fully labelled bottle, with a graduated dosing syringe and a PIBA. Until administration, the suspension is to remain within the labelled primary packaging unit. It is anticipated that administration of the suspension will occur immediately after the filling of the dosing syringe.

Table 2. Important Potential Risks

Risk	What is Known (Including Reason Why it is Considered a Potential Risk)
	The medication is presented in mL units. Given the oral solution formulation, there is potential for confusion to arise if patients are prescribed in mg.

AED = antiepileptic drug, ECG = electrocardiogram, LGS = Lennox-Gastaut Syndrome, PIBA = push in bottle adaptor, QT = Time interval from the onset of the QRS complex to the end of the T wave on an ECG tracing.

Missing Information

Missing information for rufinamide therapy in the treatment of LGS is provided in Table 3.

Table 3. Missing Information

Risk	What is Known (Including Reason Why it is Considered a Potential Risk)
People older than age 65 (Elderly population)	There have been a limited number of elderly patients who have taken rufinamide. The pharmacokinetics of rufinamide are not altered in the elderly, dosage adjustment is not required in patients over 65 years of age. Given there are a large number of more suitable medications for these patients to use, it is unlikely that rufinamide will be used in this group of patients.
Taking other medicines with rufinamide (Concomitant medications)	Most patients take other drugs with rufinamide. It is not possible to characterize fully all of the side effects that may occur as a result of these drug combinations.
Liver damage (Hepatic impairment)	The risks of rufinamide in patients with liver damage are not known. It is recommended that rufinamide not be used in patients with severe liver damage and used cautiously in patients with mild to moderate liver damage.

5 Summary of Risk Minimisation Measures by Safety Concern

All medicines have a Product Information Sheet, which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet. The measures in these documents are known as routine risk minimisation measures.

The product information for Inovelon® (active substance rufinamide) can be found on the Swissmedic website (www.swissmedicinfo.ch).

6 Planned Postauthorisation Development Plan

List of Studies in Postauthorisation Development Plan

There are no studies planned for postauthorisation development.

Studies that are a Condition of the Marketing Authorisation

There are no studies planned that are a condition of the Marketing Authorisation.

7 Summary of Changes to the Risk Management Plan Over Time

Table 4. Major Changes to the Risk Management Plan over Time

Version	Date	Safety Concerns	Comment
1.0	Feb 2007	None	Finalised as part of the Post Approval Commitments Includes Safety Specification Version 4.0 (Feb 2007) and Pharmacovigilance Plan 3.0 (Feb 2007)
2.0	Sep 2007	'QT Shortening' included as a potential risk	Updated as requested by CHMP to include 'QT shortening' as a potential risk Includes Safety Specification Version 5.0 (September)
3.0	Mar 2008	None	Updated to be included with PSUR #2 Includes Safety Specification Version 6.0 (March 2008) and Pharmacovigilance Plan 5.0 (Mar 2008)
4.0	Sep 2008 and Mar 2009	None	Updated to be included with PSUR #3 and #4. Includes Safety Specification Version 7.0 (Jul 2008) and Pharmacovigilance Plan 6.0 (Jul 2008)
5.0	Mar 2010	None	Updated to be included with PSUR #5. Includes Safety Specification Version 9.0 (Jan 2010) and Pharmacovigilance Plan 8.0 (Jan 2010)
6.0	Mar 2011	None	Updated to full EU-RMP template as requested in PSUR Assessment Report (28 May 2010) and to be included with PSUR #6.
7.0	Mar 2012	'Medication Errors' added as an Important Potential Risk. Added in risks which were previously removed: coordination abnormal, somnolence, dizziness and vertigo, immune system disorders including infections and infestations, status epilepticus, worsening of seizures/changes in seizure type	Added in 'Medication errors' as an important potential risk in Sections 1.10, 2, and 5; and added in risks which were previously removed. Both as requested in PSUR #6 Assessment Report (16 Jun 2011).

Table 4. Major Changes to the Risk Management Plan over Time

Version	Date	Safety Concerns	Comment
		and withdrawal seizures.	
8.0		None	Reformatted to fit the changed RMP template and updated with new studies.
9.0	Dec 2016	Infections removed as an Important Potential Risk	Updated due to completion of a registry study and 2 paediatric studies
			Updated based on the Rapporteur's comments that the types of infections currently described in the PI have not had an impact on the risk/benefit balance of the product and could be well managed by routine RM activities, and thus proposes Infections be removed from the RMP.
10.0	Aug 2017	None	Updated indication to include patients from 1 to less than 4 years of age Posology updated

CHMP = Committee for Medicinal Products for Human Use; EU = European Union; PSUR = periodic safety update report; QT = time interval from the onset of the QRS complex to the end of the T wave on an ECG tracing; RMP = risk management plan,