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Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Inovelon

rufinamide

Procedure No.: EMEA/H/C/000660/X/0017

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.



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List of abbreviations

AEDs	Anti Epileptic drugs
AUC	Area Under the Curve
CGP	Good Clinical Practice
CHMP	Committee for Medicinal Products for Human Use
Cmax	Concentration maximum
CPPs	Critical process parameters
EC	European Commission
ECG	Electrocardiogram
EEG	Electroencephalogram
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EU	European Union
	European and International Registry of Anti-epileptic drugs in Pregnancy
EURAP	
EU-RMP	EU Risk Management Plan
GCP	Good Clinical Practice
HPLC	High Performance Liquid Chromatography
PDA	Photodiode Array
ITT	Intent To Treat
LGS	Lennox-Gastaut syndrome
	Organization of Economic Co-operation and Development
OECD	
PARs	Proven acceptable ranges
PEC	Predicted-environmental-concentration
PET	Polyethylene Terephthalate
pH	Measure of acidity
Ph Eur	European Pharmacopoeia
PIBA	Press-in bottle adapter
PIP	Paediatric Investigation Plan
PKs	Pharmacokinetics
PP	Per-protocol
PSURs	Periodic Safety Update Report
RH	Relative Humidity
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics
TEAEs	Treatment-Emergent Adverse Event
TLC	Thin Layer Chromatography

1 Background information on the procedure

1.1 Submission of the dossier

The applicant Eisai Ltd submitted on 23 September 2010 an application for an extension of the Marketing Authorisation to the European Medicines Agency (EMA) for Inovelon, pursuant to Article 19 of Commission Regulation (EC) No 1234/2008, Annex I.

Inovelon was designated as an orphan medicinal product EU/3/04/240 on 20 October 2004. Inovelon was designated as an orphan medicinal product in the following indication: treatment of Lennox-Gastaut Syndrome.

Information on Paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/153/2010 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice/Protocol Assistance

The applicant did not seek scientific advice or Protocol Assistance at the CHMP.

1.2 Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was: Pierre Demolis.

- The application was received by the EMA on 23 September 2010.
- The procedure started on 20 October 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 13 January 2011 (Annex 1).
- During the meeting on 17 February 2011, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 17 February 2011 (Annex 2).
- The applicant submitted the responses to the CHMP consolidated List of Questions on 27 April 2011.

- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 17 June 2011 (Annex 3).
- During the CHMP meeting on 20-23 June 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant (Annex 4).
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 22 August 2011.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the list of outstanding issues to all CHMP members on 14 September 2011 (Annex 5).
- During the meeting on 19-22 September 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion the extension of Marketing Authorisation to Inovelon on 22 September 2011.

2 Scientific discussion

2.1 Introduction

Lennox-Gastaut syndrome (LGS) is rare and is one of the most severe forms of childhood epilepsy. The syndrome usually affects children between the ages of 1 and 8 years (typically between 3 and 5 years), but occasionally has its onset in children who are more than 8 years old. LGS begins in childhood but continues to manifest into adulthood in a large number of patients and has a significant morbidity and mortality. The hallmarks of the disease include the following triad:

- The presence of multiple seizure types: the most characteristic are tonic-atonic seizures and atypical absences, but tonic-clonic, myoclonic, and partial seizures are also frequently present. Tonic-atonic seizures often provoke sudden falls (commonly called drop attacks) and result in injuries.
- The presence of generalized discharges with slow spike-and-wave complexes in the EEG.
- The presence of mental retardation or a learning disability. In general, this is represented by a static encephalopathy, although the mental status may worsen in the course of the disease due to multiple causes, such as very frequent occurrence of seizures, sometimes subclinical, frequent head trauma from the falls associated with seizures (drop attacks), and undesirable cognitive effects of the high doses of antiepileptic drugs (AEDs) used to treat this very refractory type of epilepsy.

Patients with LGS often receive polytherapy due to the lack of full response to any single AED.

Inovelon (rufinamide) tablets were authorised in the EU on 16 January 2007 for use as "*adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years of age and older and adults.*"

The dose of Inovelon depends on the patient's age and weight and whether the patient is also taking valproate. Treatment generally starts with a daily dose of 200 or 400 mg and may be increased as frequently as every other day (up to the maximum recommended dose) according to the patient's response to treatment.

As a post-approval commitment Eisai agreed to develop a "child-friendly" formulation.

Eisai Limited submitted an application for Inovelon 40 mg/mL, oral suspension as a line extension to the already marketed Inovelon 100, 200 and 400 mg, film-coated tablets.

Inovelon oral suspension is intended to be used for treatment in the same indication and the same dose range to the film-coated tablets, but affords a more convenient presentation for administration to young children and for those who cannot swallow tablets.

Aspects on the product and its development

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

In the European Union, Rufinamide is currently available as tablets, with three strengths being on the market: 100 mg, 200 mg and 400 mg. For this new pharmaceutical form under review, a marketing authorization is sought for a unique strength (40 mg/mL). Since the oral suspension is intended for use at the same dose amounts as already approved for tablets, no specific characterization of rufinamide PKs is needed except the demonstration of bioequivalence of the currently used tablets and the proposed oral suspension.

The proposed dose range is similar to the film-coated tablets given daily in two divided doses. This dosage form affords compliance and flexibility of dosing from 100 mg (2.5 mL) administered by a graduated oral syringe to 2000 mg (50mL) (5 ml of suspension is equivalent to one 200 mg tablet).

No new non-clinical data were submitted.

The RMP has been revised in conformity with the EU-RMP template, to include both forms (tablets and oral suspension).

2.2 Quality aspects

2.2.1 Introduction

The drug substance rufinamide, is a triazole derivative used as an antiepileptic drug (AED), structurally unrelated to currently marketed AEDs.

This is an extension to include an additional dosage form developed for children and for those who are unable or prefer not to swallow a tablet. The product is formulated as a preserved, non-sterile multidose orange flavoured liquid suspension formulation containing rufinamide 40 mg/mL.

The product is presented as a 460 mL fill into a 500 mL o-PET bottle with a child-resistant PP closure together with an oral dosing syringe with a press-in bottle adaptor (PIBA) to deliver 200 mg of rufinamide as a 5 mL dose (or increments thereof).

For a full list of excipients refer to the SmPC.

2.2.2 Active Substance

The drug substance, rufinamide, used to manufacture the oral suspension is identical in all respects (synthesis, manufacturer, specification including bulk density etc) to that used in the manufacture of the currently registered Inovelon film-coated tablets 100 mg, 200 mg and 400 mg. A new reference standard has been established and this is the only additional information provided.

2.2.3 Finished Medicinal Product

Pharmaceutical Development

The active substance is chemically stable and neutral - rufinamide does not act as a base or acid in aqueous solution (not dissociating). It is insoluble in aqueous solvent with low solubility in water and in gastric and intestinal fluid. Because of the low solubility of rufinamide, a suspension formulation was selected as the candidate formulation.

Rufinamide is not hygroscopic and does not absorb water up to 95% relative humidity (at 25°C). There are four known polymorphic forms. The same thermodynamically stable form is used in all batches for process development studies and clinical investigations. The presence of rufinamide does not significantly impact the pH of the suspension formulation.

No compatibility issues with the excipients have been found. The choice of excipients is based on pharmaceutical technological experience gained from development of similar products. The excipients selected are of pharmacopoeial grade except for the orange flavour which is supplied by a global vendor. All excipients are well accepted for use in pharmaceuticals and are standard ingredients in suspension formulations.

The preservative system comprises methylparaben, propylparaben and potassium sorbate and was designed to secure an in-use shelf life of 90 days after first opening of the bottle. The preservative system has been developed taking into account the anti microbial and physicochemical properties as well as manufacturing aspects. Although the exact quantities used were not fully justified, the mixture of the preservatives is commonly used to achieve preservative efficacy and the preservative effectiveness has been shown. An expert statement on the safety of parabens species in oral formulations was provided. However propylparaben is no longer permitted in the EU for use in food products. Therefore, the applicant has committed to develop a paraben free formulation post-approval. It is considered that the requested reformulation could be done post-approval without compromising the safety of the product or otherwise affecting the benefit / risk balance. A change management protocol has been submitted and an agreeable time frame was proposed.

Inovelon oral suspension contains propylene glycol as a solvent for parabens since parabens are relatively difficult to dissolve in water. An expert statement on the safety of propylene glycol was also presented.

Anhydrous citric acid is added to the formulation to maintain the pH at approximately 4.0 where the performance of these preservatives is optimal.

It was demonstrated that the oral suspension has satisfactory performance of preservative efficacy according to Ph Eur acceptance criteria.

The artificial orange flavour is added in consideration of palatability in younger children. Samples of different flavours were evaluated and orange was finally selected. An expert statement on the safety of the orange flavour was provided. The orange flavour consists of limonene, maize maltodextrin, alpha tocopherol and benzyl alcohol.

Non-crystallizing sorbitol solution, 70% is added as a sweetening agent in consideration of palatability in younger children. Sorbitol is commonly used in paediatric formulations as a sweetener. The safety of sorbitol in paediatric formulations was properly discussed.

The container closure system intended for marketing was evaluated using both development and commercial bottles and it was shown that the bottle provided adequate protection against moisture and light. The compatibility of the container closure system and press-in bottle adapter (PIBA) was

demonstrated showing adequate protection without any potential contamination from extractables or leachables. Inovelon oral suspension compatibility with the oral syringe and with a measuring cup for up to 6 hours at ambient conditions has also been shown.

A critical aspect in product manufacture is product homogeneity throughout the whole manufacturing process and for administration (dose uniformity) of the dosage form. A relative bioavailability study confirmed bioequivalence between 400 mg tablets and 10 mL of suspensions with different particle sizes and dissolution rates. These results indicated that particle size and dissolution rate is not critical to the bioavailability. The dissolution method has been optimised and shown to be discriminatory. Further, a correlation between particle size and dissolution has been established and only dissolution testing will be used as a finished product control method. Particle size will be checked at the end of the drug substance homogenization process by laser diffraction as an in-process test.

Specific gravity is also employed as another in-process test. The specific gravity data are used to adjust the filling operation. The criteria for the specific gravity was determined based on the results from the process development batches.

Adventitious agents

None of the excipients are derived from animal and/or human sources.

Manufacture of the product

Inovelon oral suspension is manufactured using a conventional process for oral suspension products comprising four main steps.

A risk assessment was performed for the manufacturing process. Risk levels were assigned by process development studies. Proven acceptable ranges (PARs) and proposed operating conditions for the homogenization process, final mixing, filtration process and mixing before filling were evaluated and established. The risk levels were mitigated by setting PARs for each critical process parameters (CPPs) or by setting the CPPs to constant values based on the process development studies. Results of the comparative bioavailability study with the tablets also contributed to mitigate the risk level by a decrease of the severity level of particle size and dissolution rate. Bulk holding time was determined by an appropriate study.

Process validation has been performed on three consecutive commercial scale batches manufactured by the proposed manufacturer using the proposed manufacturing conditions.

In addition to in-process controls, additional tests were conducted to compliment the information on the reproducibility and robustness of the manufacturing process.

The manufacturing process is satisfactorily described and the proposed in-process controls are adequate. The results demonstrate that the manufacturing process established throughout the process development studies is able to consistently yield product with desirable quality.

Product specification

The release and shelf life specifications for Inovelon oral suspension include tests and limits for appearance (visual), identification (TLC, HPLC-PDA), pH (Ph. Eur.), dissolution (Ph. Eur.), related substances (HPLC), assay (HPLC), assay for preservatives (HPLC), viscosity (viscometer) and microbial limits (Ph. Eur.).

Batch analysis data are provided from seven batches of Inovelon oral suspension manufactured by the proposed manufacturer and three batches manufactured by another manufacturer. The batches were

tested according to the specification with an additional test for particle size. All batches met the requirement for each acceptance criteria and demonstrated good batch-to-batch consistency.

Stability of the product

Stability studies have been performed on six full scale batches, and three supportive stability batches.

Studies on development batches include those studied under long-term conditions (30°C / 65% RH) for up to 12 months and accelerated conditions (40°C / 75% RH) for six months stored in the upright and inverted position. There was no significant change in any of the analytical test results except the assay for potassium sorbate. Potassium sorbate was found to decrease, but complies with the shelf life specification. There was no difference between the stability results of the samples stored in the upright orientation and the inverted orientation. It was found that the cap with liner did not affect the stability.

Photostability studies were conducted on samples in the upright position in bottles without a cover or covered with aluminium foil (dark control). No changes were observed and all results met the acceptance criteria. Photostability testing results showed that light had no influence on the quality; hence no special storage precautions are required in relation to light.

In-use stability was conducted on samples in the upright position. No significant change was observed during storage for 90 days at 30°C / 65% RH except for a decreasing trend for potassium sorbate. The decrease of potassium sorbate did not affect the preservative efficacy.

The supportive stability studies were performed under long-term conditions (30°C / 65% RH) for up to 36 months and accelerated conditions (40°C / 75% RH) for six months, stored in the upright and inverted position. There was no significant change in any of the analytical test results except the assay for potassium sorbate, but microbial limits and preservatives efficacy results remained unchanged.

Photostability studies were conducted in the upright position, performed using 1.2 million lux hours on bottles without a cover. No changes were observed in the suspension exposed to light.

In-use stability was conducted on samples stored in the upright position. No significant change was observed during storage for 90 days. There was no difference between using PIBA and not using PIBA.

Freeze-thaw and temperature cycling studies have been conducted. These conditions had no impact on the quality of the drug product. In addition, an 18 month refrigerated stability study has been conducted.

Based on the results from all of the stability studies, the proposed shelf life and in-use shelf life when stored in the original container under the proposed storage conditions is accepted.

2.2.4 Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the drug substance and drug product has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in the clinic.

2.2.5 Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6 Recommendation for future quality development

In the context of the obligation of the applicant to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The applicant has committed to develop a paraben free formulation post-approval. It is considered that the requested reformulation could be done post-approval. A change management protocol has been submitted and an agreeable time frame was proposed.

2.3 Non-clinical aspects

2.3.1 Introduction

No new non-clinical data have been submitted in the application, which was considered acceptable by the CHMP.

2.3.2 Ecotoxicity/environmental risk assessment

The applicant has provided an ERA including a Phase I with calculation of a PEC_{surfacewater} based on a refined F_{pen}. Moreover the ERA includes parts of a Phase II assessment.

The F_{pen} refinement and the resulting PEC calculation provided by the applicant is based on prevalence data of the disease (number of patients) and on additional data (number of average treatment days per year per patient, Eisai product market share). Taking into consideration all these data together, the refined PEC_{surfacewater} results in a value below the action limit of 0.01µg/l. However, this approach was not considered acceptable. According to the Guideline on the environmental risk assessment of medicinal products for human use EMEA/CHMP/4447/00, only prevalence data of the disease are acceptable for a PEC refinement in Phase I. If only the prevalence data are taken into consideration the refined PEC_{surfacewater} will exceed the action limit for a Phase II assessment.

In the context of technical and scientific progress, the CHMP recommends that the applicant completes the Phase II assessment as described below.

The currently provided sludge respiration test, the modified Sturm test and the fresh water algal test are acceptable for risk assessment. The tests were already assessed during the authorisation procedure for Inovelon tablets. Nevertheless, because the active substance rufinamide was not readily biodegradable in the provided modified Sturm test (OECD 301 B) a test on Transformation in aquatic sediment systems (OECD 308) is necessary. Thus, the applicant should update the ERA by completing a Phase II assessment according to the requirements of the guideline EMEA/CHMP/4447/00, by a Daphnia reproduction test (OECD 211) and a Fish early life stage test (OECD 210).

Table 1 Summary of main study results

Substance (INN/Invented Name): rufinamide (INOVELON)					
CAS-number (if available):					
<i>PBT screening</i>		<i>Result</i>	<i>Conclusion</i>		
Bioaccumulation potential- log K_{ow}	OECD 107	0.65	Potential PBT N		
<i>PBT-assessment</i>					
Parameter	Result relevant for conclusion		Conclusion		
Bioaccumulation	log K_{ow}	0.65	not B		
	BCF	not available			
Persistence	DT50 or ready biodegradability	7-9% at Day 29 in Modified Sturm Test	P		
PBT-statement :	The compound is not considered as PBT nor vPvB				
<i>Phase I</i>					
Calculation	Value	Unit	Conclusion		
PEC _{surfacewater} , default or refined (e.g. prevalence, literature)	Default (Refined F_{pen} approach used in the ERA was not accepted)	$\mu\text{g/L}$	> 0.01 threshold Y		
Other concerns (e.g. chemical class)			N		
<i>Phase II Physical-chemical properties and fate</i>					
Study type	Test protocol	Results	Remarks		
Ready Biodegradability Test	OECD 301B	7-9% at Day 29	Modified Sturm Test		
<i>Phase IIa Effect studies</i>					
Study type	Test protocol	Endpoint	value	Unit	Remarks
Algae, Growth Inhibition Test/ <i>Species</i>	OECD 201	NOEC	>33 000	$\mu\text{g/L}$	Species <i>Selenastrum capricornutum</i>
<i>Daphnia</i> sp. ("static test")	OECD 202	NOEC immobilisation	>100 000	$\mu\text{g/L}$	Conducted at max solubility in water
<i>Activated Sludge, Respiration Inhibition Test</i>	OECD 209	EC		$\mu\text{g/L}$	No toxicity to wastewater bacteria at concentration of 100 000 $\mu\text{g/L}$

2.3.3 Conclusion on the non-clinical aspects

No new non-clinical data have been submitted in the application, which was considered acceptable by the CHMP.

The applicant has provided a revised ERA including a Phase I with calculation of a PEC surface water. Despite the request from the CHMP to conduct additional studies to complete the Phase II assessment, it was considered that Inovelon oral suspension will be interchangeable with the currently marketed form, but will not lead to an increased consumption of this orphan drug.

In the context of technical and scientific progress, the CHMP recommends that the applicant completes the Phase II assessment.

The results from the additional studies were not considered required by the Committee before the adoption of the positive CHMP opinion and it is confirmed that this application complies with Article 6 of Regulation (EC) No 726/2004 having regard to the requirements of Article 8(3) (ca) of Directive 2001/83.

2.4 Clinical aspects

2.4.1 Introduction

The marketing approval for Inovelon oral suspension is being sought on the basis of bioequivalence with the current marketed tablets. The primary data to support bioequivalence comes from the single clinical study, E2080-E044-003, as the final market image suspension was tested in this study.

A second study (study CRUF331-0102) was also submitted. In this latter study performed in 1999 by NOVARTIS (the former owner of the rufinamide patent) a prototype of an oral suspension earlier developed for the US market had been tested versus a comparator also developed for the US market. This study could not be considered relevant for the application under review.

To support the safety package the applicant submitted also a double-blind, placebo-controlled, parallel-group study of the rufinamide tablet (E2080-A001-301; referred to as Study 301) in subjects with partial onset seizures currently inadequately treated with a maximum of three AEDs.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that the studies conducted in support of this application were carried out inside the European Union in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2 Pharmacokinetics

The Pharmacokinetics of the product are described below, as reflected in the Product Information:

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 auto induction 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.

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.

Overview of the bioequivalence studies

Two bioequivalence studies are provided by the applicant: Study E2080-E044-003 and CRUF331-0102.

Study E2080-E044-003 is a randomized, open-label, 4-period crossover trial to compare the bioavailability of single 400 mg doses of rufinamide administered as the marketed tablet with 3 suspension formulations manufactured using different homogeneity speeds. Results are shown in Table 2.

From this study it could be concluded that each suspension is bioequivalent to the 400 mg tablet when administered under fed conditions. Therefore, the particles size appears not to be critical for the bioavailability of the oral suspension. The applicant reassured the Committee that rufinamide pharmacokinetics is still linear within the therapeutic range 100 to 400 mg and the non linearity linked to the low solubility of the drug would occur for higher doses.

Table 2: Statistical Analysis of PK Parameters from Study E2080-E044-003

Parameter		Test Suspension Formulations		
		1800 rpm	2100 rpm	3000 rpm
C_{max} (ng/mL)	Suspension least square mean (test)	4254.87	4204.29	4418.44
	Tablet least square mean (reference)	4840.24	4840.24	4840.24
	Ratio of treatment means (suspension/tablet)	0.88	0.87	0.91
	90% Confidence Interval of ratio	(0.84-0.92)	(0.83-0.91)	(0.88-0.95)
AUC_(0-72h) (ng.h/mL)	Suspension least square mean (test)	74279.02	73746.03	73701.17
	Tablet least square mean (reference)	75960.48	75960.48	75960.48
	Ratio of treatment means (suspension/tablet)	0.98	0.97	0.97
	90% Confidence Interval of Ratio	(0.95-1.00)	(0.95-1.00)	(0.95-0.99)
AUC_(0-inf) (ng.h/mL)	Suspension least square mean (test)	74668.44	74101.81	74085.66
	Tablet least square mean (reference)	76374.48	76374.48	76374.48
	Ratio of treatment means (suspension/tablet)	0.98	0.97	0.97
	90% Confidence Interval of ratio	(0.95-1.00)	(0.95-0.99)	(0.95-0.99)

The second Study CRUF331-0102 evaluated the relative bioavailability of a single 400 mg dose of rufinamide tablet under fed conditions, a single 400 mg dose of rufinamide oral suspension under fed conditions, or a single dose of 400 mg rufinamide oral suspension under fasted conditions. This study showed that the rufinamide oral suspension administered with food was bioequivalent to the rufinamide tablet administered with food. Food significantly increases the systemic exposure of rufinamide suspension by 31%.

However, in this study 102, performed in 1999 by the former owner of the rufinamide patent (Novartis), the Test product was an oral suspension prototype developed for the US market and the comparator was a tablet manufactured by wet granulation and a pre-densification step also formulated for the US market. Therefore, this study could not be considered relevant for the current application in the EU.

2.4.3 Conclusions on clinical pharmacokinetics

Given that rufinamide delivered as 10 mL of a 40 mg/mL oral suspension formulation has been demonstrated to be bioequivalent to the 400 mg oral tablet formulation, the dosing recommendations for the oral suspension are the same as those approved for the marketed tablet.

2.5 Clinical efficacy

Efficacy of rufinamide was established in the original marketing authorisation application. There is no new pertinent efficacy information in the authorised indication, which is the use of rufinamide oral suspension as adjunctive therapy in subjects with LGS.

The applicant submitted a report from a clinical study E2080-A001-301 (referred to as Study 301). In this clinical trial, rufinamide has been evaluated for the treatment of refractory partial-onset seizures in a population of adolescents and adults. The formulation used in this study is however a tablet and the assessment of this data does not affect the assessment of the oral suspension nor is a new indication opted for, however the study is described below.

2.5.1 Study E2080-A001-301 Summary of main study results

Study 301 was a double-blind, placebo-controlled, parallel-group study of rufinamide given as adjunctive therapy in adolescent and adult patients (12 to 80 years inclusive) with refractory partial seizures.

Three hundred and fifty-seven subjects were randomly assigned to receive rufinamide (N=176) or placebo (N=181). Three hundred and fifty-six subjects (176 in the rufinamide group and 180 in the placebo group) received at least 1 dose of double-blind medication and were included in the safety population. Three hundred and thirty-five subjects (160 in the rufinamide group and 175 in the placebo group) were included in the Intent-to-Treat (ITT) population.

For the ITT population, the median percentage change in total partial seizure frequency per 28 days during the Maintenance Phase relative to the Baseline Phase (the primary efficacy variable) was -23.25 in the rufinamide group and -9.80 in the placebo group ($p=0.007$). For the per-protocol (PP) population, the median percentage change was -25.35 for the rufinamide group and -10.45 for the placebo group ($p=0.005$). Thus, the magnitude and direction of the results were consistent for the ITT and PP populations. The results for subgroups of the subjects based on age, sex, race, and dose achieved at the end of the Titration Phase were consistent with those for the ITT population.

The results for the secondary efficacy variables supported the results for the primary variable. A higher percentage of subjects in the rufinamide group (32.5%) than the placebo group (14.3%) experienced at least a 50% reduction in partial seizure frequency per 28 days during the Maintenance Phase relative to the Baseline Phase (odds ratio: 2.889; $p<0.001$).

2.5.2 Conclusions on clinical efficacy

Efficacy of rufinamide was established in the original marketing authorisation application. There is no new pertinent efficacy information in the authorised indication.

The usefulness of the efficacy evaluation of this study for the current application is however limited as the formulation used in this study is a tablet and is conducted in a different indication.

2.6 Clinical safety

The clinical safety data package to support this application came from:

- a double-blind, placebo-controlled, parallel-group study of the rufinamide tablet (E2080-A001-301; referred to as Study 301) in subjects with partial onset seizures currently inadequately treated with a maximum of three AEDs.
- a primary randomized, open-label, 4-period crossover trial to compare bioavailability of the rufinamide oral suspension (E2080-E044-003; hereafter referred to as Study 003), and PK of rufinamide administered as a tablet formulation with three suspension formulations manufactured under different conditions of homogenization speeds).
- and a supporting randomized, open-label, 3-way, crossover trial to compare the relative bioavailability of the rufinamide oral suspension single 400 mg doses of rufinamide oral suspension and single 400 mg doses of rufinamide tablet under fed conditions, and to evaluate the effect of food on the bioavailability of the rufinamide oral suspension (CRUF331 0102; hereafter referred to as Study 102).

Safety results in Study 301 were consistent with the known safety profile of rufinamide tablets. Nevertheless, the absolute lymphocyte count decreased in 15 subjects (9.3%) in the rufinamide group, compared to 4 subjects (2.3%) in the placebo group. The applicant reassured the Committee performing an additional search of the safety database (excluding study -301) that reported no incidences of lymphocytopenia and there have been no lymphocytopenia related safety signals in the post-marketing reports after marketing of rufinamide for 4 years in the EU and for 2 years in the US. The applicant was however requested to closely monitor lymphocytopenia and discuss any possible event in future PSURs.

For Study 003, TEAEs and treatment-related TEAEs were frequent (54.2% of all subjects and 37.5% of all subjects, respectively), mild to moderate in severity, and manageable or reversible with concomitant medication. Only two subjects experienced TEAEs that led to withdrawal; both were urinary tract infections and were considered not related to treatment. TEAEs and treatment-related TEAEs did not appear more frequent with a particular treatment and therefore, there appears to be no effect of homogeneity on safety. As exposure is the same for the three suspension formulations and the 400 mg tablet, there was no impact of the manufacturing conditions on safety.

No new safety information emerged from the adverse events reported in study 102 in the healthy volunteers who received one dose of 400 mg rufinamide (tablet or oral suspension) under fasted or fed conditions. Adverse events reported with the oral suspension and with the tablet were comparable.

2.6.1 Conclusions on clinical safety

In summary, rufinamide was safe and well tolerated when administered as an oral suspension in both Study 003 and Study 102. However, those two studies were bioequivalent studies, open label and performed with single doses in low number of healthy volunteers. The data in Study 301 were consistent with those previously reported for rufinamide tablets.

2.7 Risk Management Plan

The applicant submitted an updated risk management plan.

Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization Activities (routine and additional)
Identified Risk: Rash and Hypersensitivity	Routine pharmacovigilance Registry Study	Warning in section 4.4 of the SmPC that 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. Information on incidence also in Undesirable effects in section 4.8 of SmPC.
Identified Risk: Decreased Appetite and Weight Loss	Routine pharmacovigilance	Information on incidence in Undesirable effects in section 4.8 of SmPC
Identified Risk: Vomiting	Routine pharmacovigilance Registry Study	Information on incidence in Undesirable effects in section 4.8 of SmPC
Potential Risk: Pregnancy and Associated Birth Defects	Routine pharmacovigilance Pregnancy Registry	Warning in section 4.4 of the SmPC that 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 judgment when assessing whether oral contraceptives, or the doses of the oral contraceptive components, are adequate based on the individual patient's clinical situation (see Section 4.5). Warning to avoid rufinamide in pregnancy unless benefit outweighs the risks in section 4.6 of the SmPC.
Potential Risk: Developmental and Maturation Impairment in	Routine pharmacovigilance Registry Study	Changes will be made to the SmPC if warranted.

Safety concern	Proposed pharmacovigilance activities (routine and additional)	Proposed risk minimization Activities (routine and additional)
Children and Adolescents		
Potential Risk: Adverse Effects on Cognition	Routine pharmacovigilance Registry Study	Changes will be made to the SmPC if warranted.
Potential Risk: Shortened QT interval on ECG	Routine pharmacovigilance	Warning in section 4.4 of the SmPC that 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).
Potential Risk: Suicide	Routine pharmacovigilance Registry Study	Changes will be made to the SmPC if warranted.
Medication Errors	Routine pharmacovigilance Registry Study	Changes will be made to the SmPC if warranted.
Missing Information: Elderly population	Routine pharmacovigilance	Since the pharmacokinetics of rufinamide are not altered in the elderly, dosage adjustment is not required in patients over 65 years of age. (Section 4.2 and Section 5.2 in SmPC).
Missing Information: Concomitant Medications	Routine pharmacovigilance Registry Study	Warning in section 4.5 of the SmPC about interactions.
Missing Information: Pregnancy	Routine pharmacovigilance Pregnancy registry	Warning in section 4.4 and section 4.5 of the SmPC that women of childbearing potential must use contraceptive measures
Missing Information: Hepatic Impairment	Routine pharmacovigilance	Section 4.2 of the SmPC notes that 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. Also noted in section 5.2 of SmPC.

The CHMP, having considered the data submitted for the new pharmaceutical form, was of the opinion that the pharmacovigilance activities in addition to the use of routine Pharmacovigilance, agreed for the currently marketed formulation were to be maintained to investigate further some of the safety concerns:

- **Registry Study:** European Registry of Anti-Epileptic Drug Use in Patients with LGS (E2080-E044-401). Ongoing study. Planned Date for Submission of Final Data: December 2013.
- **Pregnancy registry:** A pregnancy registry is being maintained by EURAP (European and International Registry of Anti-epileptic drugs in Pregnancy). Eisai provide financial support to EURAP in return for details of pregnancy cases collected and the reported outcomes.

No additional risk minimisation activities were required beyond those included in the product information in relation to the new formulation.

In addition, the MAH is requested to submit an updated version of the RMP in order to discuss and reflect the potential risk of the propylparaben contained in Inovelon on the reproductive system.

PSUR cycle

The CHMP considered that the PSUR cycle should be amended based on the data submitted in the application and requested an additional yearly PSUR.

The next PSUR will cover the period from 16 January 2011 to 15 January 2012 and should be submitted no later than 15 March 2012.

2.8 Update of the Product information

Inovelon oral suspension is intended to be used for treatment in the same indication and the same dose range to the film-coated tablets, which has been reflected in the new presentations incorporated in the product information.

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

3 Benefit-Risk Assessment

Benefits

Beneficial effects

Inovelon oral suspension is intended to be used for treatment in the same indication and the same dose range to the film-coated tablets, but affords a more convenient presentation for administration to young children and for those with difficulties in swallowing and increases the treatment options for patients who prefer to not swallow a solid oral dosage form.

Uncertainty in the knowledge about the beneficial effects

Rufinamide was safe and well tolerated in the 3 studies submitted to support the safety profile of the product and the results of the findings were consistent with the known safety profile of Rufinamide tablets. However, Study 301 has been performed with rufinamide tablets, and not oral suspension; and in patients with partial onset seizures, whereas rufinamide is currently authorized in the treatment of seizures associated with Lennox-Gastaut syndrome. In addition, safety data coming from the other 2 bioequivalence studies 003 and 102 have a limited significance, since these were bioequivalence studies, open label and performed in a low number of healthy volunteers.

Risks

Unfavourable effects

Based on the favourable outcome of the Bioequivalence study comparing the new oral solution with the established tablet formulation, the same safety profile as the tablet presentation is expected.

Uncertainty in the knowledge about the unfavourable effects

Although at present many medicinal products contain propylparabens, propylparaben is no longer permitted in the EU for use in food products. It has been shown to exhibit an oestrogenic potential *in vitro* and effects on male fertility parameters have been observed in rat studies. Thus, considering that the product is intended for the paediatric population, the use of propylparaben represents a concern, which needs to be further elucidated.

While a consortium of companies is working with the AFSSAPS to assess the potential risk of propylparaben on the reproductive system of the neonatal rat, the MAH has committed to develop a paraben free formulation post-approval, which was acceptable, in the light of the clinical need for the product in the small target population.

Benefit-risk Balance

Importance of favourable and unfavourable effects

The benefit-risk balance is considered positive.

Benefit-risk balance

Lennox-Gastaut syndrome (LGS) is rare and is one of the most severe forms of childhood epilepsy and patients with LGS often receive polytherapy due to the lack of full response to any single AED.

Inovelon oral suspension provides additional treatment options for patients who have not sufficiently responded to other AEDs, and rufinamide has shown to be efficacious as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children 4 years of age and older and adults.

The development of a suitable oral suspension formulation of rufinamide increases the treatment options for patients, particularly young children, with LGS. The oral suspension would also address the needs of older patients who are unable to or prefer not to swallow a solid oral dosage form. Patient compliance would also be expected to improve, especially in young children.

Inovelon oral suspension has been shown to be bioequivalent to the marketed 400 mg tablet. Based on these results, rufinamide oral suspension confers all the benefits of the tablets with respect to seizure control but offers an alternative oral formulation for ease of use in young children and a potential increase in patient compliance.

As there are potential risks associated to the use of the preservative propylparaben that cannot be excluded, the applicant has committed to develop a paraben free formulation after adoption of the positive CHMP opinion, which was acceptable in the light of the clinical need for the product.

Overall, having considered the benefits of the new formulation and its comparable safety profile to the marketed tablets the CHMP considered that the benefit-risk balance of rufinamide oral solution was favourable.

4 Recommendations

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the benefit-risk balance of Inovelon oral suspension as adjunctive treatment of seizures associated with Lennox-Gastaut syndrome was favourable and therefore recommended the granting of the extension of the Marketing Authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

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

Conditions and requirements of the Marketing Authorisation

Risk Management System

The MAH must ensure that the system of pharmacovigilance, presented in Module 1.8.1 of the marketing authorisation, is in place and functioning before and whilst the product is on the market.

The MAH shall perform the pharmacovigilance activities detailed in the Pharmacovigilance Plan of the Risk Management Plan (RMP) presented in Module 1.8.2 of the marketing authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- at the request of the EMA

PSUR cycle

The PSUR cycle for the product will follow a yearly cycle until otherwise agreed by the CHMP.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Not applicable

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.