SOC	Preferred term	Rufinamide (N=1,248) N (%)	Placebo (N=635) N (%)
Any		100 (8.1)	27 (4.3)
Ear and labyrinth disorders	Vertigo	7 (0.6)	0
Eye disorders	Diplopia	12 (1.0)	1 (0.2)
	Vision blurred	3 (0.2)	1 (0.2)
	Accommodation disorder	2 (0.2)	0
Gastrointestinal disorders	Nausea	13 (1.0)	0
	Vomiting	5 (0.4)	1 (0.2)
	Abdominal pain upper	4 (0.3)	1 (0.2)
	Diarrhea	2 (0.2)	1 (0.2)
General disorders and administration site conditions	Fatigue	20 (1.6)	3 (0.5)
	Asthenia	4 (0.3)	0
	Malaise	4 (0.3)	0
	Gait disturbance	3 (0.2)	1 (0.2)
Metabolism and nutrition disorders	Anorexia	5 (0.4)	0
Nervous system disorders	Dizziness	22 (1.8)	3 (0.5)
	Headache	14 (1.1)	4 (0.6)
	Ataxia	11 (0.9)	0
	Convulsion	10 (0.8)	4 (0.6)
	Somnolence	8 (0.6)	2 (0.3)
	Nystagmus	5 (0.4)	1 (0.2)
	Paresthesia	4 (0.3)	0
	Disturbance in attention	3 (0.2)	0
	Sedation	3 (0.2)	0
	Tremor	2 (0.2)	2 (0.3)
	Hemiparesis	2 (0.2)	1 (0.2)
	Sensory disturbance	2 (0.2)	1 (0.2)
	Lethargy	2 (0.2)	0
	Grand mal convulsion	1 (0.1)	3 (0.5)
	Memory impairment	1 (0.1)	2 (0.3)
Psychiatric disorders	Anxiety	4 (0.3)	1 (0.2)
	Irritability	4 (0.3)	1 (0.2)
	Confusional state	3 (0.2)	1 (0.2)
	Apathy	3 (0.2)	0
	Aggression	2 (0.2)	1 (0.2)
	Affect lability	2 (0.2)	0
Skin and subcutaneous tissue disorders	Rash	6 (0.5)	1 (0.2)
	Face edema	2 (0.2)	0
	Rash papular	2 (0.2)	0
	Urticaria	2 (0.2)	0

Note: Patient-years of exposure = 291.51 for rufinamide and 149.60 for placebo.

All treated patients with epilepsy (n=1,978)

In the population of all treated patients with epilepsy, 259 (13.1%) of 1,978 patients treated with rufinamide discontinued study drug due to adverse events. The events most often leading to discontinuation of rufinamide were fatigue (38 patients), headache (32 patients), nausea (31 patients), dizziness (31 patients), rash (17 patients), convulsion (24), diplopia (19), somnolence (18), vomiting (13).

- Laboratory findings

Clinical laboratory data were summarized using descriptive statistics for values obtained at baseline and at the last post-baseline visit, and for the difference between those two evaluations.

Hepatic laboratory parameters

In the double-blind studies, increases in hepatobiliary parameters occurred in $\leq$ 3.4 % of the rufinamide-treated patients and in $\leq$ 6.0 % of the placebo-treated patients. For most individual parameters, the percentages of patients with upward of downward shifts were similar for rufinamide and placebo. A total of 22 cases reporting of increased liver enzymes with a value over 3N were

analysed. Although the causal role of rufinamide is difficult to establish due to confounding factors this adverse reaction will be mention inn the SPC. There were no serious adverse events related to hepatobiliary laboratory tests or the hepatobiliary system in either treatment group. One rufinamide-treated patient (in Study 022) discontinued due to hepatic enzymes increased. In other studies, one patient had a serious adverse event related to the hepatobiliary system (cholecystitis, Study 0101) and another patient in Study 021PE discontinued due to suspicion of hepatitis toxic, the origin of which was not confirmed later on.

Renal laboratory parameters
Mean changes between baseline and the last post-baseline evaluation were small for all renal parameters, and were comparable in the rufinamide and placebo groups in the double-blind studies.

Adverse events related to renal laboratory tests or renal disorders occurred in less than 1% of all rufinamide-treated patients. One patient had a serious adverse event of renal failure acute after a prolonged seizure, which resulted in rhabdomyolysis and dehydration. Renal experts at the hospital attributed the event to the prolonged seizure, which resulted in dehydration. The patient was subsequently restarted on rufinamide.

Haematology laboratory parameters
Mean changes between baseline and the last post-baseline evaluation were small for every parameter, and were comparable in the rufinamide and placebo groups for every population that compared results from the double-blind studies.

Thyroid laboratory parameters
Rufinamide does not appear to have a clinically or statistically significant effect on thyroid although there were individual cases of changes of T3 or TSH and individual cases of hypothyroidism.

- Other adverse effects of interest

Status epilepticus
Status epilepticus did not occur in any patient who received placebo in any of the double-blind studies in the rufinamide clinical development program. As shown in the following table, status epilepticus was an adverse event in 1.4% of all patients who received at least 1 dose of rufinamide, a serious adverse event in 1.0%, and an event that led to discontinuation of treatment in 0.3%. The incidence of status epilepticus as an adverse event was higher in patients with LGS (3.7%) and in paediatric patients (2.6%) than in adult patients (1.1%). Serious status epilepticus occurred in ≤2.0% of the patients in any subgroup, and this event led to the discontinuation of <1.0% of those in any subgroup. No patient had a status epilepticus that lead to death.

Table 7. Overview of Occurrence of Status Epilepticus in Rufinamide Clinical Studies

	Double-blind plus open-label			
	All patients with epilepsy (N=1978)	**Patients with LGS (N=135)**	**Paediatric patients (N=391)**	**Adults patients (N=1561)**
Incidence of status epilepticus	27 (1.4%)	5 (3.7%)	10 (2.6%)	17 (1.1%)
Discontinuation due to status epilepticus	6 (0.3%)	1 (0.7%)	2 (0.5%)	4 (0.3%)
Status epilepticus as non-fatal serious adverse event	19 (1.0%)	2 (1.5%)	8 (2.0%)	11 (0.7%)

Note: he population "all patients with epilepsy" includes all patients who received at least 1 dose of rufinamide in any Phase II or III double-blind study, open-label extension of a double-blind study, or open-label study. The remaining 3 populations shown in this table include all patients who received at least 1 dose of rufinamide in a Phase II or III double-blind study or its open-label extension (patients enrolled only in Phase II or III open-label studies are not included). Patients included in the population "patients with LGS" are also included in the populations "paediatric patients" and "adult patients" depending on whether their age at baseline was ≤16 years (paediatric patients) or >16 years (adult patients).
Cross reference: Appendix 3, Tables 2.2.2, 2.2.4, 2.2.6, 3.1.2, 3.2.4, 3.2.6, 5.1.1, 22.2.1, 22.4.1, 22.6.1

According to the literature, status epilepticus is a relatively frequent occurrence in paediatric patients with epilepsy. A review of the occurrence of status epilepticus in 4 epidemiologic cohorts in presented in the table below:

Incidence of Status Epilepticus in Different Epidemiologic Cohorts

	Incidence of status epilepticus	References
Rufinamide clinical trials	1.4% (27/1978)	
Rochester	9% (7/74)	Hauser 1993 Hesdorffer 1998
Finland	9% (5/53)	Sillanpaa, Jalava, Kaleva 1998 Sillanpaa, Jalava, Shinnar 1998
Bronx	11% (18/171)	Shinnar 1996
New Haven	6% (9/136)	Berg 1992 Berg 1996 Berg 1997

A review in the literature showed that status epilepticus develops in more than 60% of patients with LGS [Shorvon 1994].
As rufinamide was studied as an adjuvant therapy, the majority of exposed patients were on multiple other anti-epileptic medications. However, analysis of data shows that there is no association of any particular concomitant AED with the occurrence of status epilepticus. Except when the concomitant antiepileptic is stopped or had a dose modification, the concurrent AED could not be considered as a confounding factor in patients without a previous medical history of status epilepticus. In this particular population, rufinamide causal role in status epilepticus onset could not neither be excluded nor established. Furthermore, status epilepticus was not notified in the placebo group.
Consequently, status epilepticus is mentioned in the SPC of rufinamide, section 4.4. In addition, the applicant committed to perform a post-approval safety study (registry) which would include a sufficient number of patients to allow the estimation of adverse effects including this one.

Rash/hypersensitivity
Rash occurred in similar percentages of rufinamide-treated patients (3.1%) and placebo-treated patients (3.3%), even when the incidence was not corrected for duration of exposure. Rash was a serious adverse event in 3 (0.2%) and 1 (0.2%) patients, respectively. Rash led to discontinuation of treatment in 10 (0.8%) and 1 (0.2%) patients, respectively. Consequently, and as the majority of anti-epileptic medications are associated with rash, the mention of "Rash" in the SPC (in sections 4.4 and 4.8) and as an identified potential risk of the Pharmacovigilance plan have been included.
In all treated patients with epilepsy, rash was a serious adverse event in 5 (0.3%) patients and led to the discontinuation of treatment in 24 (1.2%) patients. None of the 1,978 patients experienced erythema multiforme, Stevens-Johnson syndrome, or toxic epidermal necrolysis.

In the pivotal study 022 in the Lennox-Gastatut syndrome, rash occurred more frequently in the rufinamide group than in the placebo group (6.8% for rufinamide, and 1.6% for placebo). One report of rash was classified as serious, and rash caused discontinuation of treatment in 2 patients.

In addition, a photosensitivity rash has been reported in 2 cases. These cases do not provide sufficient data to establish relationship between rufinamide therapy and the onset of photosensitivity. However, photosensitivity skin reaction could be suspected for all antiepileptic drugs.
Consequently, a warning has been included in the SPC, section 4.4 "all patients who develop a rash while taking rufinamide must be closely supervised".

Antiepileptic drug hypersensitivity syndrome
Upon review of patient narratives, the applicant suspects that a total of 5 patients (2 with serious adverse events coded as hypersensitivity and 3 others with serous adverse events coded as pyrexia or rash) might have suffered an antiepileptic drug hypersensitivity syndrome characterised by fever, rash,

and evidence of internal organ involvement. In all cases, the reaction occurred during the first 4 weeks of treatment. All patients were children. None of them had mucosal involvement or blistering of the skin. All patients recovered after discontinuation of rufinamide. After thorough analysis, the relationship with rufinamide therapy has been suspected for two of them (≈2/2000 exposed patients), which is higher than reported in the literature (≈1 per 3000 exposures). Consequently, a warning is included in the SPC in section 4.8 and a cumulative review of hypersensitivity reports will be carried out in the PSUR. The incidence of hypersensitivity will be also monitored during a post marketing safety study and included in the Pharmacovigilance plan.

Effects on weight
Rufinamide seems to induce notable weight decrease (more than 7%) in a limited number of patients under the age of 12 years. The mean weight in adult patients has not been significantly modified under rufinamide. This is mentioned as an undesirable effect in SPC and is part of the safety parameters to be monitored in the risk management plan.
The adverse event"eating disorder" which has been observed in the LGS group, is also mentioned in the SPC.

- Safety in special populations

Age
There were some differences noted between age groups. Headache, dizziness, and nausea occurred at lower rates in the youngest #group, and at comparable rates in the older groups. This was trued in both the rufinamide and placebo groups for headache and nausea, but not dizziness. Somnolence occurred at the highest rate in the youngest group of rufinamide-treated patients; rates were comparable by age in placebo-treated patients.

Gender
The incidence of common adverse events was similar for the two groups, except for nausea, which was more common in females.

Renal or hepatic impairment
A study in patients with severe renal impairment indicated that no dose adjustments are required for these patients.
Use in patients with hepatic impairment has not been studied. Therefore, use in patients with severe hepatic impairment is not recommended. Caution should be exercised in treating patients with mild to moderate hepatic impairment.

- Post marketing experience

No post-marketing data are available.

- Discussion on clinical safety

The majority of adverse events reported with rufinamide and assessed as possibly related to treatment were neurological disorders (with headache, somnolence, dizziness and fatigue) and gastro intestinal disorders, with vomiting and nausea. No relationship with dose has been identified. CNS-related adverse events and gastrointestinal disorders were a common cause for treatment discontinuation.
There were no indications of ECG abnormalities or QTc prolongation associated with rufinamide exposure.

The occurrence of serious status epilepticus in the whole population of rufinamide treated patients as no case has been reported in placebo treated patients is considered a particular safety issue. Even if Status epilepticus is very frequent in patients with LGS and that 12 of the 27 patients with status epilepticus had potential triggering factors, the other cases had no obvious explanation.
This risk will be monitored in post-authorisation on long-term therapy and on a more important number of patients under rufinamide. This issue is included in the SPC and the pharmacovigilance plan.

Anticonvulsant hypersensitivity syndrome was reported in 5 patients and for 2 cases the relationship with rufinamide is suspected. A warning was introduced in the SPC. This point will be followed within each PSUR and assessed in the registry study.

At this stage, there is no strong argument for a safety issue in human regarding the risk of myelofibrosis, but we consider that this should be monitored and that a specific section in PSUR on all haematological disorders reported is deemed necessary.

Both, myelofibrosis and immunotoxic potential risks are included in the pharmacovigilance plan.

According to the CHMP guidance document concerning development of AEDs in children, short term and long-term studies should be designed to detect possible impact on learning, intelligence, growth, endocrine function and puberty. This safety aspect will be monitored as described in the risk management plan.

Pharmacovigilance

Detailed description of the Pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan that was assessed and was considered satisfactory provided that revisions are submitted to the rapporteur in the post-opinion phase (see follow-up measures)

Table Summary of the risk management plan

Safety Concern	Proposed Pharmacovigilance Activities	Proposed Risk Minimization Activities (routine and additional)
Status Epilepticus	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Reported Spontaneous Serious Adverse Events of seizure, or associated terms, will be followed up to exclude additional cases of status epilepticus. ▪ The registry study will evaluate the occurrence, severity and character of seizures during the use of rufinamide, and contrast these with seizures seen with other anti-epileptic drugs in patients with LGS. ▪ Seizures experienced in the registry study that are considered medically significant (require urgent change in medication, medical intervention, or hospitalization) will be reported as a serious adverse event. Therefore the diagnosis of 'status epilepticus' can be made on both historical and	▪ Status epilepticus will be described in all product labelling. ▪ In the proposed SPC status epilepticus will be described in the warning section (4.4)[1]: "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". ▪ Status epilepticus will be

[1] As changed in SPC version 07, 8 Nov 2006

	modern criteria. Information of these events, and the full impact on the patient, will be collected through structured questions. ▪ Status epilepticus will be reviewed on a cumulative basis, and discussed in the PSUR.	included as an adverse event in Section 4.8 as a common adverse event
Hypersensitivity	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Spontaneous reported events of hypersensitivity, or associated terms, will be followed up to exclude additional cases of the Anticonvulsant Hypersensitivity Syndrome. ▪ The incidence and character of hypersensitivity reactions will be monitored during the registry study where symptoms of hypersensitivity will explicitly captured using a structured questionnaire. ▪ Assessment of the character of hypersensitivity should allow for a more accurate incidence of the 'Anticonvulsant Hypersensitivity Syndrome' during the use of rufinamide being determined. ▪ Reports of hypersensitivity reactions will be reviewed on a cumulative basis within the PSUR.	▪ Hypersensitivity will be described in the safety information. In the SPC this will be in the warning section (4.4) as: "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". ▪ The event of hypersensitivity will be included as an uncommon adverse event in Section 4.8.
Decreased Appetite and Weight Loss	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Weight changes (when provided), compared to baseline, will be monitored during rufinamide use. Unexpected changes in weight due to confounding factors will be identified during this study, such as concomitant medications, or concurrent infections.	• Decreased appetite and weight decreased are included in Section 4.8 of the SPC as common adverse events.
Coordination Abnormal	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports ▪ Soliciting of adverse events through the registry study.	• Coordination abnormal is included Section 4.8 of the SPC as a common adverse event.
Somnolence	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports	• Somnolence is included in Section 4.8 of the SPC as a very common adverse event.

	▪ Soliciting of adverse events through the registry study.	
Dizziness and vertigo	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports ▪ Soliciting of adverse events through the registry study.	▪ Dizziness is included in Section 4.8 of the SPC as a very common adverse event. Vertigo is included in Section 4.8 of the SPC as a common adverse event.
Diplopia and blurred vision	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports ▪ Soliciting of adverse events through the registry study.	▪ Diplopia and vertigo are included in Section 4.8 of the SPC as common adverse events.
Vomiting	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Soliciting of adverse events through the registry study.	▪ Vomiting is included in Section 4.8 of the SPC as a very common adverse event.
The risk of birth defects during pregnancy	▪ A pregnancy registry will be maintained by EURAP (European and International Registry of Anti-epileptic drugs in Pregnancy). ▪ Pregnancies will be reported in the appropriate section of the PSUR.	▪ A warning is included in Section 4.6 of the SPC. The text includes the following: "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".
Potential for haematological blood dyscrasias	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Review of provided laboratory values provided during the registry study. ▪ Soliciting of adverse events through the registry study. ▪ Haematological adverse events will be addressed in the PSUR.[2]	▪ Pre-clinical findings are discussed in Section 5.3 of the SPC: "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".

[2] As requested by the CHMP

Potential for immuno-toxicity	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Review of provided laboratory values provided during the registry study. ▪ Soliciting of adverse events through the registry study. ▪ Immune disorders and associated haematological adverse events will be addressed in the PSUR.	▪ Pre-clinical findings are discussed in Section 5.3 of the SPC: "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". ▪ Infections frequently experienced during the LGS study are included in the SPC as common adverse events in Section 4.8 (Pneumonia, influenza, nasopharyngitis, ear infection, sinusitis and rhinitis)
Potential for the developmental and maturation impairment in children and adolescents	▪ Review of basic growth measurements, when provided, during the registry study. ▪ Soliciting of adverse events through the registry study.	
Potential for adverse effect on cognition	▪ Routine pharmacovigilance practices for spontaneous and clinical study adverse events reports. ▪ Soliciting of adverse events through the registry study. ▪ Analysis of discontinuations form the registry study for events associated with cognitive impairment.	▪ Somnolence and dizziness are included as very common adverse events in Section 4.8 of the SPC.

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

Additionally, further safety information will be collected in a post-marketing safety study (registry) of anti-epileptic drugs in LGS.

5 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology

In vitro, rufinamide is involved in modulation of sodium channels probably by prolonging their inactive state and has demonstrated efficacy in relevant *in vivo* models of seizure disorders.
The behavioural and safety pharmacology studies carried out show that rufinamide is without unwanted pharmacological effects at doses exceeding those which confer anti-convulsant protection.

Rufinamide shows a low acute toxicity. In the repeated-dose toxicity studies, the main target organ was the liver. Rufinamide did not show genotoxic potential. There is no evidence of teratogenic potential in either rat or rabbit, but showed reproductive toxicity at doses where maternal toxicity was seen.
The juvenile toxicity data for rat and dog indicate that the juvenile is not more sensitive than the mature animal to the toxicity of rufinamide. In addition, the rat study showed no effects on behavioral and physical development.

Regarding the immunotoxic potential, decreased bone marrow cellularity (dogs/rats), lymph nodes (dogs/baboons) and spleen (baboon) were observed inconsistently in repeat-dose toxicity and carcinogenicity studies. No relevant findings have been detected in the clinical trials. However, clinical hematological adverse events will be monitored in post-authorisation as part of the pharmacovigilance risk management plan.

Concerning the carcinogenicity aspects, in the mouse, increases in hepatocellular adenomas and carcinomas and in incidence of osteomas in both sexes at the high dose were observed. Treatment-related myelofibrosis was also seen at mid and high dose in both females and males in mice.
The mechanism of this myelofibrosis remains unknown. Nevertheless, this is regarded as part of fibro-osseous lesions (FOL), which is thought to be age dependent. In this particular case, regarding the hyperostosis and osteomas, the increased exposure to fluoride and mouse-specific retro-virus are contributing factors. Therefore it is probably not predictive of development of myelofibrosis in human. In any case, the potential risk of myelofibrosis will be monitored in the risk management plan

Rufinamide shows no physical or overt psychological dependence liability in cynomolgus monkey.
Rufinamide showed no skin irritation, corrosive or sensitization potential in the skin irritation study in rabbit and in the contact hypersensitivity study performed in guinea pigs.
There are no safety-related concerns with respect to impurities, degradation products and excipients.
The environmental exposure resulting from the limited use of the product will be low.

Efficacy
For efficacy, the results of the single pivotal study to assess the safety and efficacy of rufinamide as adjunctive therapy relative to placebo in patients with inadequately controlled Lennox-Gastaut syndrome showed positive results in LGS as compared to placebo.
The patient population, as chosen on the basis of the inclusion/exclusion criteria, was appropriate and representative of patients with LGS, in particular due to the substantial proportion of children included in the present trial (more than 2/3).
Patients who received rufinamide in this trial showed:

- a significant median reduction in total seizure and tonic-atonic seizure frequency compared to placebo;
- a significant improvement in the severity of the seizures compared to placebo;
- significantly greater (50% and 75%) responder rates for tonic-atonic seizure frequency per 28 days versus placebo;
- greater reductions in all seizure types associated with LGS (absence, tonic-clonic, myoclonic, tonic, atonic, partial) compared to placebo.

The sensitivity analysis performed confirmed the robustness of the results.

Nevertheless, the assessment of the impact of the baseline imbalance on the total seizure frequency could not be totally excluded.
Uncontrolled open-label studies suggest sustained long-term efficacy, although no controlled study has been conducted for longer than three months.
Supportive studies with rufinamide permitted to collect data about titration, maintenance dose, dose-response relationship, pharmacokinetics and short term safety.

Safety
From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics
The majority of adverse events reported with rufinamide and assessed as possibly related to treatment were neurological disorders (headache, somnolence, dizziness and fatigue) and gastro intestinal disorders (vomiting and nausea). No relationship with dose has been identified.

Status epilepticus and anticonvulsant hypersensitivity syndrome will be followed up in the pharmacovigilance plan.

At this stage, there is no strong argument for a safety issue in human regarding the potential risk of myelofibrosis, the CHMP considers that this should be monitored and a specific section on all haematological disorders will be reported in the PSUR.

Immunotoxic potential risk is included in the pharmacovigilance plan. (see follow-up measures)

Having considered the safety concerns listed in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

- User consultation

The results of the user testing were assessed and a number of insufficiencies were noted. Consequently, the applicant proposed to implement several improvements to the package leaflet.

Risk-benefit assessment

For efficacy, the results of the single pivotal study to assess the safety and efficacy of rufinamide as adjunctive therapy relative to placebo in patients with inadequately controlled Lennox-Gastaut syndrome showed positive results in LGS as compared to placebo.
Supportive studies with rufinamide permitted to collect data about titration, maintenance dose, dose-response relationship, pharmacokinetics and short term safety.
The sensitivity analysis performed confirmed the robustness of the results.
Nevertheless, the assessment of the impact of the baseline imbalance on the total seizure frequency could not be totally excluded.
Uncontrolled open-label studies suggest sustained long-term efficacy, although no controlled study has been conducted for longer than three months.
On the safety aspects, the majority of adverse events reported with rufinamide and assessed as possibly related to treatment were neurological disorders (headache, somnolence, dizziness and fatigue) and gastro intestinal disorders (vomiting and nausea). No relationship with dose has been identified.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns

Since effects on skeletal, behavioural, sexual, immune maturation and development in the population of young patients suffering Lennox Gastaut syndrome could induce more consequences on their general vulnerable state and that rufinamide will be used as add-on drug, monitoring of body weight, height , general growth including puberty, cognitive state before and after drug initiation will be addressed as outlined in the planned post-approval study that is integrated in the risk management plan.
The following safety issues will be specifically monitored:

- Status epilepticus
- Hypersensitivity
- Decreased appetite and weight loss

    - Coordination abnormal
    - Somnolence
    - Dizziness and vertigo
    - Diplopia and blurred vision
    - Vomiting
    - The risk of birth defects with anti-epileptic drugs
    - Potential for haematological blood dyscrasias
    - Potential for immuno-toxicity
    - Potential for developmental and maturation impairment in children and adolescents
    - Potential for adverse effect on cognition
    - The risk of suicide with anti-epileptic drugs
- no additional risk minimisation activities were required beyond those included in the product information.

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Inovelon, in the treatment of "seizures associated with Lennox-Gastaut syndrome as adjunctive therapy in patients 4 years and older", was favourable and therefore recommended the granting of the marketing authorisation.