London, 29 March 2006
Product name: **Keppra**
Procedure No. **EMEA/H/C/277/X/46**

SCIENTIFIC DISCUSSION

1. Introduction

UCB S.A. applied for the Marketing Authorisation of Keppra concentrate for solution for infusion, containing 500 mg levetiracetam per vial (5 ml) through a line-extension procedure.
Levetiracetam is indicated as adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy. In adults and adolescents weighing 50 kg or more, the starting dose corresponds to 500 mg twice daily. Depending on clinical response and tolerance, the daily dose can be increased up to 1,500 mg twice daily. Adjustment to lower doses is recommended for some patients with impaired renal function, down to 250 mg twice daily or 500 mg once daily. In children aged 4 to 11 years and adolescents weighing less than 50 kg, the starting dose corresponds to 10 mg/kg twice daily. Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily.
Products containing levetiracetam for oral administration were previously authorised, namely Keppra film-coated tablets (250 mg, 500 mg, 750 mg and 1,000 mg) and Keppra 100 mg/ml oral solution.
The purpose of the new proposed formulation is to allow the use of levetiracetam in medical situations where patients are unable to take oral medication. The use of a concentrate for solution for infusion ensures that seizure control could be maintained, avoiding any risk of destabilising the patient. A strength of 500 mg levetiracetam per vial (5 ml concentrate) is selected. However, doses of 500 mg, 1000 mg or 1500 mg can be obtained by diluting 1, 2 or 3 vials of drug product in a 100 ml infusion bag. Due to the high solubility of levetiracetam in water and its stability in aqueous media, the sterile concentrate can be presented as an aqueous solution that is terminally steam sterilised.

2. Quality aspects

Drug Substance (to be changed in the EPAR to "Active Substance")
Module 3.2.S of the dossier corresponds to the currently approved documentation for the oral dosage forms, except for the addition of tests for microbiological quality and bacterial endotoxins to the drug substance specification and the stability programme. All variations that were approved after the original registration are included in the drug substance documentation.

Manufacture
General information such as nomenclature, structure, and physico-chemical properties have been adequately detailed for the active substance. Levetiracetam has one chiral centre and exists as the S enantiomer.

Levetiracetam can be synthesised following two routes, namely the "tartaric acid resolution route of synthesis" or the "synthesis route including a chiral Multicolumn Continuous Chromatography (MCC) separation step".

The tartaric acid resolution route of synthesis takes place in 7 steps. Appropriate specification and description of the test methods are presented for the starting materials as well as for reagents, solvents and processing aids used in the synthesis. Adequate control of critical steps and intermediates have been presented as well as method description and validation reports.

The MCC route of synthesis takes place in 7 steps. Appropriate specification is presented for the starting materials as well as for reagents, solvents and processing aids used in the active substance synthesis. In-process controls are described for the critical steps and for relevant intermediates. Analytical methods have been described and validated.
No differences were observed neither for physical properties (differential scanning algometry, NMR, X-Ray powder diffraction and optical rotation) nor chemical properties (IR, MS, HPLC for assay and impurities, GC for residual solvents, sulphated ash and heavy metals) between levetiracetam obtained by the tartaric acid route and the MCC route

Specification

The structure of levetiracetam has been fully characterised by IR, NMR, MS, elemental analysis, X-ray diffraction analysis, optical rotation. Polymorphism has not been observed regardless of the conditions tested.

Impurities have been sufficiently described and justified. Specifications for both synthetic routes are the same, except for the residual solvents (as the solvents used are different) and the residual reagent test for one reagent (not used in the MCC synthesis). The proposed specifications are equivalent to those already approved for the oral formulations, except for the addition of bacterial endotoxin and microbiological quality tests. Analytical methods have been described and validated.

Batch analyses demonstrate that the results are fully in compliance with the proposed specification, including microbiological quality and endotoxins. Residual solvents limits comply with the ICH requirements.

Stability

In the long term and accelerated studies conducting according to ICH requirements, there were no significant changes observed and all the results are in compliance with the specifications. Related substances remain below the limit of quantification. Microbiological quality and bacterial endotoxins were satisfactorily tested.

A satisfactory retest period has been agreed for levetiracetam when stored below 25°C.

Other ingredients

Certificates of Analysis, in compliance with the current version of the Ph.Eur., are presented for all excipients. There are no excipients of human or animal origin used.

Medicinal Product

Pharmaceutical Development

Keppra concentrate for solution for injection is a sterile clear and colourless solution without preservative added. It is an aqueous solution containing 500 mg of levetiracetam per 5 ml.

The manufacturing process is conventional for this type of product and satisfactorily described. The process development has been satisfactorily accounted for.

Compatibility of the drug product with perfusion materials has been demonstrated.

Manufacture of the finished product

A detailed description of the manufacturing process and controls has been provided. Since a standard manufacturing process with terminal steam sterilisation is used, process validation is sufficiently documented.

Product Specification

Specification (identical at release and the end of shelf life) is appropriate for this pharmaceutical form (concentrate for solution for infusion) and includes description, identification, assay, related substance, pH, sterility, bacterial endotoxins, particulate contamination and extractable volume.
All non-compendial methods have been satisfactorily detailed and validated.

Batch analyses on industrial-scale batches are in compliance with the proposed specifications. Impurities remain below the limit of quantitation.

Stability

Three full-scale batches placed in the proposed marketing container have been stored at 25°C/60%RH, 30°C/65%RH and 40°C/75%RH, both in upright and inverted position for 9 months, 12 months and 6 months respectively. No significant change has been observed and all results remain within specification.

Photostability studies have demonstrated that the sterile concentrate is neither light-sensitive, nor thermal sensitive (freeze-thaw cycle). These results support the shelf-life and storage conditions stated in the SPC.

Discussion on chemical, pharmaceutical and biological aspects

Levetiracetam is already approved in two oral dosage forms. Module 3.2.S of the submitted dossier corresponds to the currently approved documentation for the oral dosage forms, except for the addition of microbiological quality and bacterial endotoxins tests to the drug substance specifications and stability programme.

The drug product is a concentrate for solution for infusion. The manufacturing process is conventional for this type of product. It is an aqueous solution, containing standard pharmacopoeial excipients, which is terminal steam sterilised in its final container. The proposed specification is based on the general requirements for this type of products and the approved specifications for the oral dosage forms. The currently available stability data do not indicate degradation during storage.

3. Non-clinical aspects

Introduction

For this application, additional non-clinical safety studies have been conducted to assess the short-term use of the drug via IV infusion, as this is the way of administration that is being applied for. The data were supported, where considered necessary, by previously submitted studies, which also included studies conducted on the oral formulation. The CHMP endorsed the justification for using oral studies, based on the complete oral bioavailability of the drug. Only studies not previously submitted have been assessed in the context of this procedure. These new studies are listed below.

Topic	Study title	UCB Code
4.2.1.3 - Safety pharmacology	Study PSM0833 ucb L059. Evaluation of effects on human blood viscosity and erythrocyte deformability.	RRLE02C1102
4.2.2 - Pharmacokinetics	Validation of an analytical assay for the determination of ucb L057 in plasma samples by LC-ESI/MS. Boulanger P.-Kestelyn C.	RRLE04M0201
	Validation of an analytical assay for the determination of ucb L057 in urine samples by LC-ESI/MS. Boulanger P.-Kestelyn C.	RRLE04M0202
4.2.3 - Toxicology	Study PSM1143 ucb L059. Single dose toxicity study by the oral route in the Sprague-Dawley rat	RRLE04A1207

	Study PSM1144 - ucb L059. Acute toxicity study by the oral route in the Beagle-dog	RRLE04A1209
	Study PSM0819 - ucb L059 - 2-week 15-minute (b.i.d) intravenous infusion toxicity study in the rat	RRLE02C1501
	Study PSM0908 - ucb L059 - 4-week 15-minute (b.i.d.) intravenous infusion toxicity study in the Sprague-Dawley rat.	RRLE02B2202
	Study PSM0814 - ucb L059 - 4-week 15-minute (b.i.d.) intravenous infusion toxicity study in the Beagle dog	RRLE02C1504

The strategy used in the development programme was to demonstrate the similar exposure between the levetiracetam intravenous formulation and the marketed oral formulations, and to evaluate the safety profile for intravenous administration. As the pharmacokinetic profiles and indication are the same for the oral and the intravenous formulations, the MAH has not performed any evaluation of efficacy of the intravenous formulation as such.

General comments on compliance with GLP/GMP

The newly performed non-clinical studies were conducted in compliance with GLP. There are no GMP inspection issues identified in the dossier.

Pharmacology

Levetiracetam has previously been shown to exhibit potent protection in a broad range of animal models of chronic epilepsy reflecting both partial and primary generalised seizures. The new data from the submitted new *in vitro* safety pharmacology study showed that levetiracetam reduced red cell deformability and aggregation at 100 mg/mL but not at 30 mg/mL in human volunteer blood. However in man, the concentration of levetiracetam is rapidly diluted in the circulating blood and the clinical effect is therefore assessed to be negligible.

Pharmacokinetics

The pharmacokinetic profile of levetiracetam is uncomplicated and similar in all species investigated, including man. The absorption of levetiracetam after oral administration is rapid and complete, with 100% bioavailability. The AUC values after IV and oral administration were similar, but $t_{1/2}$ values are missing after oral administration. The metabolism is minor, and approximately 60% of the substance is excreted unchanged in urine, which is the main route of excretion in both humans and animals. The level of the major metabolite, L057, is somewhat lower in animals compared to man. Two new validated methods were submitted in support of the toxicokinetic measurements.

Toxicology

According to the knowledge of levetiracetam deriving from the assessment of previous applications, kidney, liver and CNS were identified in toxicity studies as main target organs. In the rat kidney, mechanistic and histopathology data demonstrated that levetiracetam induced nephropathy in male rats. However, it was demonstrated that the treatment-related accumulation of hyaline droplets was caused by α2μ-globulin accumulation. This accumulation is specific for the male rat and is reversible upon cessation of treatment. It is considered, however, to have no relevance for man. In the rodent liver, the treatment-related changes consisted of increased weight, centrilobular hypertrophy, fatty infiltration, and increased serum enzymes. After long-term repeat dosing in the rat, effects were observed at dose/exposure levels similar to the clinical exposure and dose. The cause of these effects was not established, but could possibly be due to an adaptive change associated with microsomal enzyme induction. However, no liver cell damage was reported and no treatment related proliferative

or neoplastic changes were found in the liver in the carcinogenicity studies. The possible relevance for man of the observed liver changes was considered unknown and the findings are reflected in the proposed SPC for this application.

Acute toxicity of levetiracetam has been studied in mice, rats and dogs after both IV and oral administration. The maximum non lethal dose after IV dosing was 750 mg/kg in mice, 1000 mg/kg in rats and ≥ 1200 mg/kg in dogs whereas after oral administration the maximum non lethal dose was > 5000 mg/kg in mice and rats and ≥ 2400 mg/kg in dogs. The difference in mortality indices between IV and oral administration may be related to Cmax plasma concentrations. Based on these studies, the acute toxicity of levetiracetam is considered low.

Three new repeat dose IV toxicity studies, including toxicokinetics, were submitted in support of this application. Levetiracetam was administered in rats as a 15-minute IV infusion twice daily 10 hours apart for 2-and 4-weeks at doses ranging from 225 to 1800 mg/kg/day. There were no treatment-related deaths or effects on body weight, food consumption, ophthalmology, haematology or clinical chemistry parameters. Urinary specific gravity increased in males dosed 1800 mg/kg/day and females from 900 mg/kg/day. At the1800 mg/kg/day dose, liver and kidney weights were increased. Hyaline droplets were seen in the proximal tubules of males from 450 mg/kg/day along with basophilic tubules. Minimal centrilobular hypertrophy was seen in the liver of all males and some females dosed 1800 mg/kg/day. Three males also showed these effects at 630 mg/kg/day. The nephropathy (hyaline droplets in the proximal tubules) and the minimal centrilobular hypertrophy are expected findings (see above). The No Observed Adverse Effect Level (NOAEL) was 225 mg/kg/day in the 2-week rat study and given the lack of toxicological concern associated with the kidney findings, 225 mg/kg/day may also be considered a NOAEL in the 4-week rat study. The rats were exposed to levetiracetam and its primary metabolite, ucb L057, throughout the studies. The extent of exposure to levetiracetam remained unchanged over the two weeks of treatment. In the 4-week study, concentrations were slightly higher in males than in females and at the end of the infusion were proportional to the dose administered. For man, the exposure relevant for safety evaluation is Cmax 72±21 µg/mL and AUCτ 372± µg·h/mL. At NOAEL, rats were exposed 2-3 times (AUC) or 0.1-0.2 times the human exposure (Cmax, C10h) in the 2-week IV study. At the highest dose level, rats were exposed to 18-24 times (AUC) and approximately at the human exposure. In the 4-week study at 225 mg/kg/day, the rats were exposed to 3-4 times the human exposure. At the highest tested dose level, rats were exposed to 4-6 times the predicted human exposure.

In dogs, levetiracetam was administered a 15-minute IV infusion twice daily 10 hours apart for 4-weeks at doses ranging from 150 to 600 mg/kg/day. There were no treatment-related effects on body weight, food consumption, ophthalmology, ECG parameters or urinary parameters. At the end of the treatment period, a slight decrease occurred in red blood cell count, haemoglobin, packed cell volume and in the erythroid series from the bone marrow smears examination for both sexes at the 600 mg/kg/day dose level. Slight increases in plasma chloride concentration were detected among females treated at and above 300 mg/kg/day. Given the minor and non-adverse nature of the finding at 300 mg/kg/day, this level may be considered the study NOAEL. Measured plasma concentrations showed that rats and Beagle dogs were exposed to levetiracetam and its primary metabolite, ucb L057, throughout the study, and there was no evidence of a difference between males and females. At NOAEL, dogs were exposed 4-6 times the human exposure. At the highest dose level, dogs were exposed to 7-9 times the predicted human exposure.

The results from the performed IV repeat-dose toxicity studies showed that treatment-related effects were observed at the injection sites in rats but not in dogs (dosed up to 600 mg/kg/day). Venous and perivenous fibroplasia and intimal proliferation occurred at the injection site in rats treated with 1800 mg/kg for 2 weeks and was further associated with minimal arterial thrombi in the lungs, probably reflecting changes occurring at the injection site. An increased incidence of injection site damage was also seen in both sexes from 630 mg/kg/day following 4-weeks of treatment. These findings may indicate a vaso-irritative potential. Additionally, information on possible extravasal tissue damage at mis-dosing was not included in the submission dossier.

Discussion on the non-clinical aspects

The CHMP considered that changing the administration route from oral to IV had not caused any additional toxicity, apart from the local effects indicating a vaso-irritative potential observed at the injection sites, which needed to be further addressed.

In the light of this initial assessment, as part of a consolidated List of questions sent to the MAH on 28 July 2005 (day 120), this concern led to the inclusion of this issue as a topic to be addressed in writing by the MAH.

Further to this request, UCB reviewed the data on the vaso-irritation potential of levetiracetam and in order to fully address the concerns of the CHMP, conducted a 5-day vasal tissue irritation study. These results were submitted on 11 October 2005, and are outlined below.

In summary, the findings showed that administration of the Keppra formulation by the intravenous route either as the concentrate (100 mg/ml) or diluted as described in the SPC (15 mg/ml) to the right ear of rabbits for 5 days resulted in at most minimal injection site reactions (grades 0 to 1.0) in terms of erythema, oedema, induration and infiltration. Similar findings were also recorded for the vehicle and saline controls. After repeated administrations, only minimal infiltration was noted with the diluted vehicle or test item.

After subcutaneous injection, there were no local reactions except oedema (grade 1) and a slight (grade 1) or marked (grade 3) hematoma in 2/3 animals with the concentrated vehicle.

Intra-arterial administration resulted in slightly higher responses with grades of 1-2 for erythema, oedema, induration, and infiltration. These effects were noted in all groups, including controls, without dose or concentration relationship.

After perivenous injection, local effects were limited to very slight erythema and minimal infiltration in a limited number of animals distributed evenly within control, vehicle and treated groups.

No adverse effects were seen at any of the injection sites at necropsy. Histopathological examination of the injection sites and surrounding tissues, performed 5 days later, is currently ongoing. It can provisionally be concluded that the reactions seen at the injection site were the consequence of administration procedures with no specific drug related contribution to the effects seen. Based on these interim findings, the MAH claimed that it was reasonable to conclude that the infusion of the Keppa IV as proposed in the SPC would not pose an undue hazard in clinical practice.

The CHMP considered the provisional conclusion of the MAH concerning the local tolerance study that was carried out to be agreeable. Both repeat dose intravenous effects and single misdosing effects were addressed in the study design.

However, before any final conclusions can be drawn the histopathological data should be awaited. These should be provided in the form of a Follow-up Measure to this procedure, worded as follows: "*Submission of the final QC released report of study NCD1341 ("ucb L059: A local tolerance study by intravenous, perivenous, intra-arterial and subcutaneous routes in male New Zealand White rabbits"), including. histopathological examinations, by March 2006.*"

4. Clinical aspects

Introduction

Levetiracetam is provided in 5 ml glass vials containing 500 mg levetiracetam (500 mg/5 ml). Between one to three vials are used for any single administration, *i.e.*, doses of 500 to 1500 mg, (twice daily), consistent with the recommended adult oral dose of 1000 to 3000 mg/day. Before administration, 100 ml of compatible diluent is added. The dose should be infused over 15 minutes.
Since the indication is identical for the oral and the IV formulations, the MAH had not planned any evaluation of efficacy for the IV formulation. The clinical studies therefore primarily concern the evaluation of bioequivalence with oral levetiracetam, and the safety of the intravenous formulation.

GCP

Three recent pharmacokinetic clinical studies (N01077, N01065 and N01066) were conducted between 2003 and 2004 specifically to support the registration of the intravenous formulation. These studies were performed in accordance with the ICH E6 GCP: Consolidated Guidance (April 1996). Four early biopharmaceutics or clinical pharmacology studies (N058, N060, N069 and N204) and one pilot study (N099) were conducted in the 1980s in Belgium or Italy with earlier intravenous formulations of levetiracetam. These studies were conducted in accordance with the guidelines of the Declaration of Helsinki. There are no GCP inspection issues identified in the dossier.

Pharmacokinetics

Levetiracetam has a rather uncomplicated pharmacokinetic profile. The substance is highly soluble, it is well absorbed and has an absolute bioavailability of almost 100%. Levetiracetam is not bound to plasma proteins (< 10 %). The elimination is to a large extent by renal excretion, with 50-65% excreted as unchanged drug and approximately 25% as an inactive acidic metabolite, ucb L057. The half-life of levetiracetam is 7-8 hours. The pharmacokinetics is dose- and time-independent and the inter-individual variability is low. Metabolism to the major metabolite occurs in whole blood and its formation does not seem dependent on the cytochrome P450 enzymes.

Methods
The most relevant pharmacokinetic study to the proposed new drug product is Study N01077, in which levetiracetam IV was administered at the highest recommended dose of 1500 mg and over a 15-minute infusion rate, in line with the proposed SPC. In the other studies, a different infusion rate/dose was used. The following assessment is therefore primarily focused on study N01077.
Study N01077 was divided in two parts. The first part was a single dose bioavailability comparison between levetiracetam 1500 mg 15-min IV infusion (3 ampoules in 100 mL of sterile saline 0.9% solution) and oral levetiracetam (1500 mg as 3 x 500 mg tablets).

The second part was a study of the pharmacokinetic profile of levetiracetam 1500 mg 15-min IV infusion during repeated dosing (4 days b.i.d). The study included 18 healthy male and female volunteers. Seventeen subjects were included in the part I pharmacokinetic analysis (one subject excluded due to incorrect IV dosing) and 18 were included in the analysis of part II (12 on active drug, 6 on placebo). After oral administration, the sampling times were at: pre-dose, 15 min, 30 min, 45 min, 1 h, 1.5 h, 2 h, 3 h, 6 h, 9 h, 12 h, 24 h and 36 h post-dose; after IV administration, the sampling times were at: pre-dose, 5 min, 10 min, 15 min, 30 min, 1 h, 2 h, 3 h, 6 h, 9 h, 12 h, 24 h and 36 h post-dose (until 12 h only for sampling on Day 7 of part II). Levetiracetam was determined in plasma samples using a validated gas chromatographic method with nitrogen-phosphorus detection. Concentrations of ucb L057 in plasma were measured by LC/ESI/MS.

Results
Intravenous versus oral administration
The plasma concentrations of levetiracetam, including Cmax, was similar when levetiracetam was administered as a 15 minute IV infusion and as oral tablets (See table 1 below)

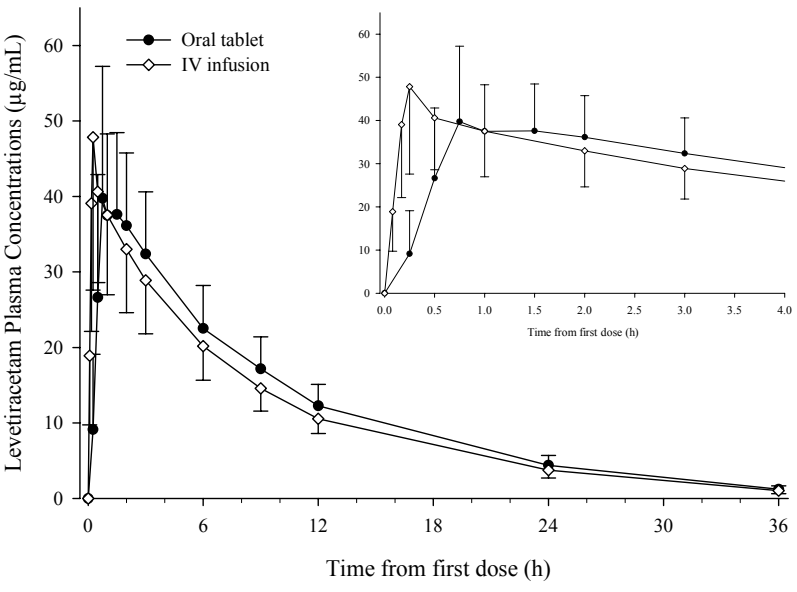
Table 1. Pharmacokinetic Parameters of Levetiracetam after a Single Administration of a 3 × 500 mg Oral Tablet (Reference) or a 1500 mg IV Infusion (Test) in 17 Healthy Subjects – Per Protocol Population (Study N01077 Part I)

PK Parameter (units)	Reference[a]: Levetiracetam 3 × 500 mg tablet	Test[a]: Levetiracetam 1500 mg I.V.	CV[b] (%)	Test versus Reference[c]	
				Point Estimate	90% CI
$AUC_{(0-t)}$ (µg·h/ml)	414.7 ± 88.6	378.6 ± 73.2	6.4	91.7	88.3 - 95.3
AUC (µg·h/ml)	427.9 ± 89.6	392.4 ± 71.2	5.9	92.2	89.0 - 95.6
C_{max} (µg/ml)	47.7 ± 13.5	50.5 ± 18.8	20.8	103.7	91.6 - 117.4
tmax (h)	0.75 (0.50 - 2.0)	0.25 (0.22 - 2.0)	NA	NA	NA

[a] Values are arithmetic means ± SD.
[b] Intra-individual CV (%).
[c] Point estimate and 90% 2-sided CI for the expected test/reference geometric mean ratio (%), derived from ANOVA for continuous parameters.
NA = not applicable.

Following IV administration, the majority of subjects showed time to peak values at the end of infusion. However, in 7 subjects tmax occurred later than the end of the IV infusion. The entire administration process as well as the duration of the infusion (maximum 15 min) has been verified and no deviations were observed. This increase of tmax was not observed following multiple doses where only the position during the IV infusion has changed (sitting position in single dose and decubitus position in multiple doses.

Figure 1 Average Plasma Concentrations of Levetiracetam Over Time after a Single Administration of Levetiracetam 3 x 500 mg Oral Tablet (Reference) or Levetiracetam 1500 mg IV Infusion (Test) in 17 Healthy Subjects – Per Protocol Population. Values are Arithmetic Means ± SD. Inset: 0-4 Hour Interval (Study N01077 Part A)



Average AUC(0-t) and AUC of ucb L057 were very similar after oral and IV administration AUC averaged 19.1 ± 4.34 and 18.3 ± 5.33 µg Eq levetiracetam *h/mL, after oral and IV administration, respectively. Average Cmax were also similar (1.02 and 0.946 µg/mL, respectively). Tmax after infusion was somewhat shorter than after oral administration.

Multiple dose exposure as IV infusion
The pharmacokinetics of levetiracetam was as expected. AUCτ tended to be lower than AUC day 1 although the confidence interval included 100. The observed pharmacokinetic parameters are summarised below (Table 2). For ucb L057 median time to peak was 3.0 h and Cmax averaged 1.66 ±0.45 µg Eq LEV/mL. Minimal concentration at steady-state averaged 0.89 ±0.34 µg Eq LEV/mL.

Table 2. Pharmacokinetic Parameters of Levetiracetam after a Single Administration of a 1500 mg IV Single Dose (Part A) or a 1500 mg IV Multiple Doses (Part B) Infused over 15 Minutes in 12 Healthy Subjects – Per Protocol Population (Study N01077)

PK Parameter[(d)] (units)	**Levetiracetam[(a)] 1500 mg I.V. Single dose (Day 1)**	**Levetiracetam[(a)] 1500 mg I.V. Multiple dose (Day 7)**	**CV[(b)] (%)**	**Day 7 versus Day 1[(c)]**	
				Point estimate	**90% CI**
AUC or AUCτ (µg·h/ml)	389.4 ± 77.6	371.9 ± 80.9	8.3	95.2	89.6 – 101.2
C_{max} (µg/ml)	52.4 ± 22.3	71.7 ± 21.3	NA	NA	NA
C_{min} (µg/ml)	NA	14.1 ± 3.75	NA	NA	NA
R_{max}	NA	1.51 ± 0.48	NA	NA	NA
R_{AUC}	NA	1.43 ± 0.23	NA	NA	NA
LF	NA	0.96 ± 0.11	NA	NA	NA

[(a)] Values are arithmetic means ± SD.
[(b)] Intra-individual CV (%).
[(c)] Point estimate (PE) and 90% 2-sided CI for the expected Day 7/Day 1 geometric mean ratio (%), derived from ANOVA for continuous parameters.
[(d)] R_{AUC} = AUC ratio; R_{max} = C_{max} ratio; LF = linearity factor.
NA = not applicable.

In Study N01165, single-doses of 1500 to 2500 mg were infused over 5 minutes and 2000 to 4000 mg were infused over 15 minutes. Mean Cmax was approximately 10% higher after administration of 2000 mg over 5 minutes as compared to over 15 minutes (60.6 vs 55.6 ug/ml).

Exposure relevant for safety evaluation
The exposure relevant for safety evaluation (Cmax 72±21 µg/ml and AUCτ 372±81 µg·h/ml), was considered by CHMP to be similar to the exposure obtained with oral administration of the same dose.

CHMP overall conclusions on pharmacokinetics

The pharmacokinetic documentation shows that an IV 15 min infusion of levetiracetam results in similar Cmax and AUC of levetiracetam as the same dose administered orally as tablets. Similar exposure of the metabolite ucb L057 is also obtained with the two modes of administration. Tmax after IV infusion is shorter than after oral administration, due to higher rate of systemic input and lack of lag time.

Pharmacodynamics

The mechanism of action for levetiracetam is still not completely known. Levetiracetam induces seizure protection in a broad range of animal models of partial and primarily generalised seizures without having a pro-convulsant effect. In man, an activity in both partial and generalised epilepsy conditions (epileptiform discharge/photoparoxysmal response) has been demonstrated. Two studies were conducted with the intravenous formulation of levetiracetam to investigate the effect on cerebral perfusion and quantitative electroencephalogram (EEG) in adult healthy volunteers or elderly healthy volunteers. No effects of levetiracetam on regional cerebral blood flow or quantitative EEG were detected.

Clinical efficacy

The therapeutic efficacy of levetiracetam as adjunctive treatment in epileptic patients has been evaluated in a large number of studies with the *oral* formulation. These studies were included in the original Keppra film-coated tablets application (EMEA/H/C/277.) However, the MAH has not performed any new efficacy studies with the *intravenous* formulation. As the daily exposure to levetiracetam is route independent, and the pharmacokinetics of levetiracetam are linear and time independent, the MAH's position is that the efficacy conclusions should apply also to the intravenous formulation for levetiracetam. The MAH's position that no new efficacy studies are required with the intravenous formulation was endorsed by the CHMP.

Clinical safety

Introduction

The systemic safety profile of the levetiracetam intravenous formulation is based on the safety experience with the oral tablet formulation and the more recently approved levetiracetam oral solution. Additional data recommendations or requirements for intravenous levetiracetam were requested by the Division of Neuropharmacological Drug Products of the FDA, who suggested that UCB explored the clinical safety of giving the intravenous formulation at higher doses and faster infusion rates than recommended in the proposed draft labeling, in order to better describe the safety margin of this formulation. This study (N01165) has been conducted using infusions of 1500 to 2500 mg over 5 minutes and 2000 to 4000 mg over 15 minutes.

Overall, the MAH conducted eight studies involving 117 levetiracetam-exposed subjects using levetiracetam intravenous formulations. The three recent studies (N01077, N01065 and N01066), conducted between 2003 and 2004, specifically intended to support the registration of the intravenous formulation. These studies used the proposed formulation and were performed in accordance with the ICH E6 Good Clinical Practice: Consolidated Guidance (April 1996).

In addition to the three recent studies, UCB conducted four early biopharmaceutics or clinical pharmacology studies (N058, N060, N069 and N204) and one pilot study (N099) in the 1980s in Belgium or Italy with earlier intravenous formulations of levetiracetam in accordance with the guidelines of the Declaration of Helsinki. These studies included 38 adult subjects exposed to at least one intravenous infusion of levetiracetam undiluted at doses ranging from 25 to 1600 mg and with varying durations of IV administration.

A list of clinical studies conducted with levetiracetam intravenous formulations is provided below in Table 3.

Table 3. Clinical Studies Conducted in the Development Program for Keppra Sterile Concentrate

Study Number (Country) Year Conducted	**Objective**	**Number of Subjects exposed to LEV IV (M/F) Mean age [Age range]**	**Status**
Clinical Pharmacology Studies (Healthy Volunteers)			
N058 (Belgium) 1985	Maximal Tolerated Dose	6 (4/2) 35.3 years [27 to 47]	Completed (Final Report)
N069 (Belgium) 1986	Bioavailability IV vs. capsules and oral solution	12 (12/0) 26 years [22 to 28]	Completed (Final Report)
N01077 (Belgium) 2003	Bioavailability IV vs. tablet (Part A) PK, safety, tolerability at repeat dose (Part B)	18 (9/9) 35 years [19-52]	Completed (Final Report)
N01165 (Belgium) 2004	Pharmacokinetics and tolerability of LEV with higher doses and faster infusion rate	36 (18/18) 37.8 years [21-52]	Completed (Final Report)
Pharmacodynamic Studies (Non-Epilepsy)			
N060 (Italy) 1985	Regional cerebral blood flow	9 (5/4) 73.3 years [59 to 84]	Completed (Final Report)
N099 (Belgium) 1989	Deep venous thrombosis (DVT) prevention	3 (1/2) 62.3 years [47 to 80]	Completed (Final Report)
N204 (Italy) 1985	Regional cerebral blood flow	8 (8/0) 23 years [21 to 25]	Completed (Final Report)
Studies in Patients with Epilepsy			
N01166 (Germany, France, UK) 2004	Safety and tolerability of LEV in subjects with partial onset seizures	25 (12/13) 40.8 years [20.2 to 65.2]	Completed (Final Report)

Patient exposure
The number of subjects exposed, durations of the intravenous infusion, and doses of levetiracetam administered are summarised below.

Overall, across all eight studies, 117 subjects (92 healthy volunteers and non-epileptic patients and 25 adults with partial onset seizures) were exposed to intravenous levetiracetam. In these studies, 79 subjects have been exposed to the proposed intravenous formulation administered as an infusion (over 15 minutes in 36 healthy subjects and 25 epilepsy patients and over 5 minutes in 18 subjects) and 38 subjects following injection of earlier intravenous formulations during older studies conducted in Europe in the mid- to late 1980s. Single doses used in all studies range from 25 to 4000 mg.
A total of 36 individuals (healthy subjects) have received doses in the range of 1500 to 4000 mg over 15 minutes, with 12 of these having received additional dosing of 1500 mg twice a day for 4 days.

Another 36 subjects received single doses of 25 to 2500 mg over 2 to 5 minutes. Finally, 20 subjects received slow infusions of relatively low doses of 250 to 1000 mg given over 3 to 4 hours.
In study N01166, volunteer patients who were already being treated orally with levetiracetam in doses ranging from 1000 to 3000 mg/day had their oral maintenance dose of levetiracetam replaced with an intravenous dose on a mg-for-mg basis for the 4-day intravenous treatment period.

Adverse events
The adverse events reported in the eight studies with intravenous levetiracetam are summarised below. The adverse events are first summarised for studies using the proposed infusion time, and then studies using faster than recommended infusion times. Finally, studies for which the infusion time is slower or unknown are considered.

a) Studies using the proposed infusion time

Three studies were conducted where levetiracetam was administered as a 15-minute intravenous infusion. These studies (N01077, N01166 and N01165) are summarised below.

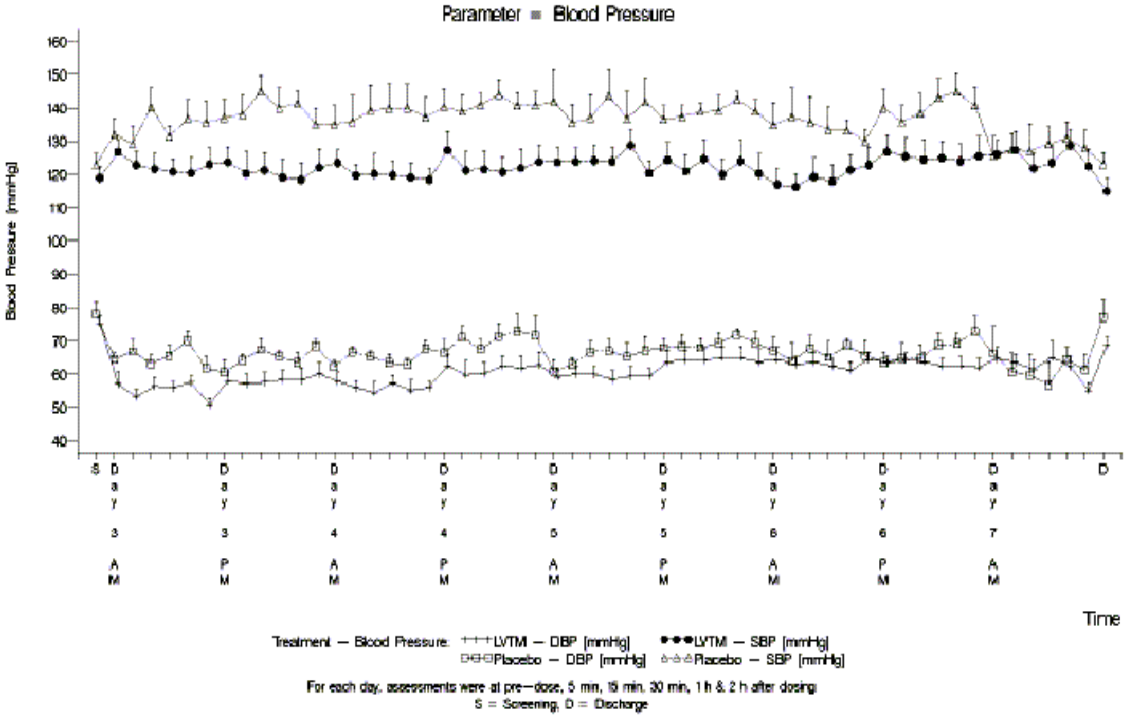
Study N01077

This study was divided in two parts, the first part (Part A) was an open-label, randomised single-dose, two-period crossover trial, whereas the second part (Part B) was a double-blind, randomised, placebo-controlled, parallel group study of twice daily infusions given for 4 days.

During Part A, subjects received single doses of levetiracetam 1500 mg, given as a 15-minute intravenous infusion (diluted in 100 ml 0.9% sodium chloride) and as an oral dose. The two single administrations were separated by a 7-day washout period. After administration of the oral tablet, 13/18 experienced a treatment emergent AE as compared with 16/18 for IV infusion. Gastrointestinal disorders were experienced by 2/18 in the IV infusion group vs. none in the oral tablet group. Nervous system disorders were reported by 15/18 in the IV group vs. 12/18 in the oral tablet group. Among nervous system disorders, somnolence was more frequent in the IV group (61 % vs. 28 %, respectively, whereas dizziness and dizziness postural was more common in the oral tablet group. Two subjects in the IV group experienced pruritus at the injection site following intravenous infusion.

During Part B, subjects were assigned to levetiracetam 1500 mg twice daily for 4 days by IV infusion (n=12) or placebo (N=6). Eight of 12 subjects (66.7%) randomized to levetiracetam experienced adverse events during the multiple dose part as compared to 2 of 6 subjects (33.3%) randomized to placebo. The most common adverse events for levetiracetam were somnolence, headache, postural dizziness, dizziness, and decreased blood pressure (BP). There were two subjects who had low blood pressure. The lowest on treatment value for one of these patients was 85/48 mmHg measured 2 hours following the day 5 evening dose. This subject had tendency to low BP also at screening. For the other patient, the lowest screening recording was 100/67 mmHg, whereas the lowest on-treatment measurement occurred following the evening dose on Day 3 (84/41 mmHg) and Day 4 (90/29 mm Hg and 84/38 MM Hg, retest value). Both patients were otherwise asymptomatic. A graphical illustration of mean systolic and diastolic blood pressure for the multiple-dose Part B of study N01077 shows that there is a decrease of primarily systolic but also diastolic BP during intravenous administration of levetiracetam compared with administration of placebo (Fig.2)

Figure 2. Mean (± SEM) Blood pressure changes over time following multiple doses of intravenous Levetiracetam (Study N01077 Part B)



In study N01077, ECG measurements were made pre-dose and at 5, 15, 30, 60 and 120 minutes after each drug administration. Ventricular rate and PR, QRS, QT and QTc intervals were recorded. No relevant effects on ECG were found with single and multiple doses of 1500 mg levetiracetam infused over 5 minutes. The mean baseline (screening) QTc values were between 390 to 415 msec. The mean changes from baseline were small decreases or small increases (1.2 msec at 5 minutes post-dose). Three of 18 subjects had single isolated recordings > 450 msec (Subjects 001/0006, 001/0010, and 001/0011); the longest of the values was 461 msec.

The CHMP considered that, during part A of study N01077, the frequency of treatment emergent AEs was higher for the IV group than for the tablet group. Somnolence was more common in the IV group, and two subjects reported pruritus at the injection site during intravenous infusion. The MAH was therefore requested to clarify the risk for tissue damage in case of extravasal deposition of levetiracetam. In addition, the risk for injection site damage during long-term intravenous administration of levetiracetam was also requested to be discussed, considering also the results from preclinical studies. In the placebo-controlled Part B, somnolence, dizziness postural and headache were more common in the levetiracetam group, and decreased blood pressure was reported for 2/12 patients (none in the placebo group). In Part B, the systolic and diastolic blood pressure decreased in the levetiracetam group compared with the placebo group.

Study N01165

The second study compared adverse events with single ascending doses and with faster infusion times. The IV doses of levetiracetam were 2000 mg, 3000 mg and 4000 mg as 15-minute infusions and 1500 mg, 2000 mg and 2500 mg as 5 minutes infusions. The incidence of subjects with treatment-emergent adverse events was 25.0% (3/12 subjects) for placebo, 88.9% (16/18 subjects) in the levetiracetam 15-minute infusion group, and 86.1% (31/36 subjects) for all levetiracetam IV groups. For all doses of intravenous levetiracetam combined, the most frequently reported treatment-emergent adverse events, as well as drug related treatment-emergent adverse events, were related to nervous system disorders (dizziness, somnolence, postural dizziness and headache).

Two subjects in Study N01165 experienced cardiac events; sinus bradycardia (1500 mg/5 minutes) and first degree AV block (3000 mg/15 minutes) in 1 subject each:

- Subject No. 001/0016 (41.4-year old male, 1500 mg/5 minutes) consistently showed heart rate values below 50 bpm at screening (49 bpm) and during the study (range 42 to 40 from the end of the infusion to 24 hours post-dose). Twelve hours post-dose, a heart rate of 35 bpm was reported as clinically significant sinus bradycardia; the subject was asymptomatic. Moreover, this subject had prolongation of the QRS interval to 128 msec at 24 hours post-dose (screening (≥ 109 msec). This was not judged by the Investigator as related to study treatment;

- Subject No. 001/0032 (38.4-year old female, 3000 mg/15 minutes) had intermittent first degree atrioventricular block reported as an adverse event during the treatment period. She had a slight prolongation of PR interval at baseline (screening 200 msec with heart rate 61 bpm; pre-dose 205 msec with heart rate 57 bpm), with a maximum prolongation of PR interval to 239 msec (heart rate 56 bpm) at 1 hour post-dose. The PR interval prolongation was also present at discharge (220 msec with heart rate 62 bpm). The subject was asymptomatic. The event was considered unrelated to study medication by the Investigator.

The number and percentage of subjects with treatment-emergent adverse events are presented in Table 4.

Table 4. Number (%) of Subjects with Treatment-Emergent Adverse Events Overall and for Each Dose of Levetiracetam IV and Placebo – Study N01165 ITT Population

Primary System Organ Class Preferred term (MedDRA)	Placebo N = 12	LEV IV 15 min (mg)			LEV IV 5 min (mg)			All LEV doses N = 36
		2000 N = 6	3000 N = 6	4000 N = 6	1500 N = 6	2000 N = 6	2500 N = 6	
Number of subjects with at least one TE AE:	3 (25)	5 (83.3)	5 (83.3)	6 (100)	6 (100)	3 (50.0)	6 (100)	31 (86.1)
Infections and infestations	0	0	0	1 (16.7)	0	0	0	1 (2.8)
Herpes simplex	0	0	0	1 (16.7)	0	0	0	1 (2.8)
Psychiatric disorders	0	0	0	1 (16.7)	0	0	0	1 (2.8)
Irritability	0	0	0	1 (16.7)	0	0	0	1 (2.8)
Nervous system disorders	2 (16.7)	4 (66.7)	4 (66.7)	6 (100)	5 (83.3)	3 (50.0)	6 (100)	28 (77.8)
Balance disorder	0	0	0	0	1 (16.7)	0	0	1 (2.8)
Dizziness	0	2 (33.3)	1 (16.7)	5 (83.3)	4 (66.7)	2 (33.3)	5 (83.3)	19 (52.8)
Dizziness postural	0	0	3 (50.0)	1 (16.7)	1 (16.7)	2 (33.3)	0	7 (19.4)
Dysgeusia	1 (8.3)	0	0	0	0	0	0	0
Headache	1 (8.3)	1 (16.7)	1 (16.7)	1 (16.7)	0	1 (16.7)	1 (16.7)	5 (13.9)
Somnolence	0	1 (16.7)	1 (16.7)	2 (33.3)	2 (33.3)	3 (50.0)	3 (50.0)	12 (33.3)
Eye disorders	0	0	0	0	0	0	1 (16.7)	1 (2.8)
Vision blurred	0	0	0	0	0	0	1 (16.7)	1 (2.8)
Cardiac disorders	0	0	1 (16.7)	0	1 (16.7)	0	0	2 (5.6)
Atrioventricular block first degree	0	0	1 (16.7)	0	0	0	0	1 (2.8)
Sinus bradycardia	0	0	0	0	1 (16.7)	0	0	1 (2.8)
Gastrointestinal disorders	1 (8.3)	0	0	1 (16.7)	0	1 (16.7)	0	2 (5.6)
Dry mouth	0	0	0	0	0	1 (16.7)	0	1 (2.8)
Nausea	1 (8.3)	0	0	1 (16.7)	0	0	0	1 (2.8)
Vomiting	0	0	0	1 (16.7)	0	0	0	1 (2.8)
Musculoskeletal and connective	0	1 (16.7)	0	0	0	1 (16.7)	0	2 (5.6)
tissue disorders								
Back pain	0	0	0	0	0	1 (16.7)	0	1 (2.8)
Sensation of heaviness	0	1 (16.7)	0	0	0	0	0	1 (2.8)
General disorders and	0	1 (16.7)	2 (33.3)	0	0	1 (16.7)	1 (16.7)	5 (13.9)
administration site conditions								
Fatigue	0	1 (16.7)	2 (33.3)	0	0	0	1 (16.7)	4 (11.1)
Feeling drunk	0	0	1 (16.7)	0	0	0	0	1 (2.8)
Thirst	0	0	0	0	0	1 (16.7)	0	1 (2.8)

The CHMP considered that in Study N01165, one subject had clinically significant sinus bradycardia and prolongation of the QRS-interval after administration of 1500 mg levetiracetam during 5 minutes. The MAH was therefore requested to submit more detailed data about this subject and discuss the relation to the administration of study drug (see below).

Study N01166

In this study, levetiracetam was administered intravenously as adjunctive treatment to patients with partial onset seizures as a 15-minute infusion in doses ranging from 1000 mg to 3000 mg/day, administered *b.i.d.* Twenty-five patients were enrolled; all patients completed the study. A total of 11 (44%) subjects experienced at least one treatment emergent AE (TEAE).

The primary system organ class that was reported with the highest overall incidence was in nervous system disorders (28%, 7/25 subjects), and general disorders and administration site conditions (16%, 4/25 subjects). The most frequently reported adverse events were headache (5 subjects) and fatigue (3 subjects). A total of 5 subjects (20%) experienced TE AEs considered by the Investigator as related to the study drug. The TE AEs related to the study medication were dizziness, vision blurred, ear pain, dysuria and blood pressure diastolic decrease. The Investigator judged all events mild or moderate in severity. With exception of two TE AEs, all adverse events reported during the trial had resolved by the end of the trial. In both cases which had not resolved (disturbance in attention, subject No. 001/0006 and fatigue, subject No. 001/0003), the TE AEs were considered not related to study drug.

With regard to vital signs, one subject presented intermittent diastolic blood pressure decreases below normal range (<40 mm Hg). The Investigator assessed the event as 'possibly related' to the study drug. Three ECG abnormalities were reported (sinus bradycardia, incomplete bundle branch block, and right axis deviation). The Investigator did not consider them as clinically significant. One 51-year old female patient showed QT-prolongation (>470 ms) after correction by Bazett, Fridericia and Framingham formulas at pre-dose morning of Day 4. At 15-minute post-dose the subject showed QTc values after correction within the normal range. The investigator reported no seizure worsening during the clinical trial period and during the brief follow-up.

The CHMP considered that the MAH had to submit supplementary information with regard to the time relationship between administration of study drug and diastolic blood pressure decreases in one patient in Study N01166, and between the occurrences of ECG abnormalities (three reports) and the administration of levetiracetam in the same study (see below).

b) Studies using faster than recommended infusion times

In the three studies described below, single intravenous doses of levetiracetam over 2 to 5 minutes were administered.

Study N058

This is an early dose-escalating study, conducted in Belgium, to determine the maximum tolerated dose. Six healthy volunteers participated, 4 men and 2 women. Age ranged from 27 to 47 years, weight from 51 to 93 kg. An initial open-label, dose escalation phase (25 mg to 1600 mg) was followed by a double-blind, crossover phase during which each subject received a single dose of either the active drug (1600 mg levetiracetam) or placebo with a 1-week washout between doses. Levetiracetam was administered in a 5-minute intravenous infusion without dilution of the 100mg/ml product prior to administration.

During the dose escalation phase, no adverse events were reported until the 400 mg dose. At 800 mg, 1 subject reported dizziness 1 hour after injection. With a dose of 1600 mg, adverse effects developed at 15 or 30 minutes post-administration and lasted 2 to 4 hours. 4/6 subjects reported feeling tipsy and dizziness at 1600 mg. The other 2 subjects reported euphoria. Static and dynamic equilibrium were assessed following the 1600-mg dose by various means, including the use of the Romberg test. There was a dose-related increase in equilibrium and motor coordination adverse events. The Romberg test showed highly positive results in 2 of the 6 subjects at 15 to 90 minutes post-dose, leading to a fall in 1 subject. Spontaneously reported adverse events reported with levetiracetam 1600 mg IV during the crossover phase are shown in Table 5.

Table 5. Number of Spontaneously Reported Adverse Events (Verbatim Terms) in 6 Healthy Subjects Following Levetiracetam 1600 mg Administered Intravenously Over 5 Minutes versus Placebo (Study N058)

Adverse Event (Verbatim Terms)	**LEV 1600 mg No. of Reports**	**Placebo No. of Reports**
Drunken gait	4	0
Difficulty in concentrating	2	0
Drunken feeling	2	0
Dry mouth	2	1
Spinning head, dizziness	2	0
Tiredness, drowsiness	2	0
Tripping feeling	2	0
Deep sleep (slept very soundly)	1	0
Euphoria	1	0
Feeling in great form	1	0
Heavy headedness	1	0
Impaired equilibrium	1	0
Inefficacy	1	0
Sluggish ideation	1	0
Blurred vision	0	1

Note: the study report does not include a complete listing of events by subject; therefore, the denominator is not known.

Study N069

This was a three-way cross-over study with a 1-week interval between doses. The primary goal of the study was an assessment of bioavailability/bioequivalence. The study included 12 healthy volunteers (aged 22-28 years). They received levetiracetam 1000 mg either intravenous (5 ml injection in 2 minutes without dilution of the 200 mg/ml product prior to administration) or as an oral solution (1000 mg/50 ml) or as capsules (2 x 500 mg capsules).

Two subjects in all three session reported moderate drowsiness and dizziness that lasted for 3 hours after drug intake. All volunteers complained of a burning feeling at the site of the intravenous injection during the injection and up to a few seconds post injection.

The CHMP considered that in study N069, all subjects reported a burning feeling at the injection site after intravenous administration of 1000 mg of levetiracetam at a faster infusion rate than recommended in the SPC. The MAH was therefore requested to clarify if there is risk for tissue damage in case of extravasal deposition of levetiracetam. Moreover, as in the submitted clinical studies, levetiracetam had not been administered for longer periods than 4 days, the MAH was also asked to discuss the risk for injection site damage during long-term intravenous administration of levetiracetam, considering also the results from preclinical studies (see below).

c) Studies where the infusion times are longer or unknown

Study N204

This was a single-blind Phase I study conducted in Italy between November 1985 and April 1986. The aim was to investigate the effects of levetiracetam on cerebral blood flow, quantitative EEG and neuropsychological status. Eight healthy male volunteers with age range 21-25 years were included. A single dose of levetiracetam 1000 mg or placebo was administered intravenously over 3 hours without dilution of the 200 mg/ml product prior to administration. No adverse events were reported during the study.

Study N060

N060 was a single-blind trial conducted in Italy in 1985. The primary aim was to evaluate the effect of levetiracetam on cerebral blood blow. Nine healthy volunteers (age 59-84 years) received a single intravenous dose of 500 mg levetiracetam administered in 3 to 4 hours (500 mg/5 ml) without dilution prior to administration. All subjects completed the study. No adverse events were reported.

Study N099

The study was conducted in Belgium in 1989. It was a pilot study to compare the efficacy and safety of two treatments, calcium heparin and levetiracetam, for deep venous thrombosis in patients undergoing major elective chest and/or abdominal surgery or orthopaedic surgery of the lower limbs. Patients were randomized to levetiracetam or calcium heparin in an open-label fashion. Levetiracetam was administered as two 250-mg oral doses (capsules) twice on the day prior to surgery, with 250 mg levetiracetam given intravenously (250 mg/5ml, undiluted prior to administration) starting on the day of surgery and continuing for up to 3 days (duration of administration not stated). Post-operatively, levetiracetam was to be continued for up to Day 7 or 14, depending on the nature of the surgery. The trial was terminated after the enrolment of 6 patients, 3 of whom received levetiracetam, when the results of other levetiracetam double-blind studies demonstrated that orally administered levetiracetam had no effect on bleeding time. Two patients received 250 mg levetiracetam intravenously once a day for 2 days post-operatively. No adverse events were reported. The third patient received two oral doses (capsules) of levetiracetam 250 mg pre-operatively and 250 mg intravenously post-operatively. The patient underwent resection of an aortic aneurysm and, approximately 12 hours post-operatively, she had a massive hemiplegia (side and cause unknown) and died. This case is described further in the section below, entitled 'Serious adverse events and deaths'.

Serious adverse events and deaths
Among the studies submitted for this application, there was one reported serious adverse event that resulted in death. In Study N099, a 79-year old female was scheduled to have a resection of an aortic aneurysm and randomized to levetiracetam treatment. The day before surgery, the patient received two oral 250-mg doses of levetiracetam (*b.i.d.*) and, preoperatively on the morning of surgery, one dose of 250 mg IV levetiracetam. She then underwent resection of an aortic aneurysm and approximately 12 hours post-operatively sustained a massive cerebrovascular hemorrhage (coded as hemiplegia) (side and cause unknown) and died 4 days later. The investigator concluded that accidental puncturing of a possibly highly atherosclerotic carotid had led to a thromboembolism in the arteria cerebri media, causing the massive hemiplegia and ensuing death 4 days after the event. According to the investigator, there was no relationship with the study medication.

With the exception of the death described above, there were no other serious adverse events reported with the intravenous use of levetiracetam in any study.

CHMP considered that an association between the reported death and exposure to levetiracetam is to be considered unlikely.

Laboratory findings
In the submitted studies with the intravenous formulation, there were no apparent effects of levetiracetam on clinical laboratory parameters. In study N01166, where multiple doses were administered in epileptic patients, there were no clinically significant changes in laboratory results except for one high blood glucose level at screening. One subject presented with an abnormally low level of platelets at the final visit. However, this abnormality was classified as 'not clinically significant' since there were technical problems with the laboratory analysis (EDTA-tube insufficiently filled). In three of the older European studies (N058, N069 and N099), haematology and blood chemistry tests and urinalysis were performed. There were no clinically significant effects on laboratory parameters in these studies. Clinical laboratory tests were not performed in the other two older European studies N204 and N060.

The CHMP considered that, due to the short duration of the treatment, any clinically significant effects on laboratory parameters are unlikely.

Safety in special populations
Subjects in the studies of intravenous levetiracetam are primarily adult Caucasian, but the overall numbers of both males and females enrolled in the studies are rather small. Additionally, the CHMP considered that no new information has been made available in this Extension application concerning safety in special populations.

Post marketing experience/Risk management
No spontaneous reports of adverse events with an intravenous formulation of levetiracetam have been received by the MAH.

The MAH has performed a review of the literature. Three abstracts from international meetings were retrieved. These described preliminary open-label trials in 27 patients with acute intractable migraine or cluster headache conducted by the same primary investigator. Levetiracetam was compounded into an intravenous solution and administered by intravenous bolus injection in each study. Limited safety data were described in the abstracts, with transient nausea and drowsiness reported in 1 and 2 patients, respectively.

Discussion on the clinical aspects
Overall, eight studies including 117 levetiracetam-exposed subjects had been conducted with the intravenous formulation. In these studies, 92 healthy volunteers and non-epileptic patients, and 25 adults with partial onset seizures were exposed to intravenous levetiracetam. Seventy-nine subjects have been exposed in studies with the proposed intravenous formulation administered as an infusion (over 15 minutes in 36 healthy subjects and 25 epilepsy patients, and over 5 minutes in 18 subjects) and 38 subjects following injection of earlier intravenous formulations in studies conducted in Europe in the mid- to late 1980s. Single doses used in all studies range from 25 to 4000 mg.

The safety data from studies with intravenous levetiracetam indicate a similar safety profile as with the oral formulation, although a slightly higher incidence of CNS-related adverse events was reported after administration of 1500 mg levetiracetam as infusion compared with the same dose as oral tablet. The results from studies with the intravenous formulation indicate a potential for blood pressure decrease, which has not been reported for the oral formulations. When administered intravenously as a more concentrated solution than recommended in the proposed SPC, all patients reported a burning sensation at the administration site. There are two reports on local irritation at the injection site also when levetiracetam is administered as recommended in the SPC. A potential for injection site damage is supported by findings in the preclinical studies, where venous and perivenous fibroplasia and intimal proliferation occurred at the injection site in rats. In the light of all the above-described initial assessment of clinical data, the CHMP considered that it would be desirable to clarify whether extravasal deposition of levetiracetam may cause tissue damage in humans, discussing the risk for injection site damage during long-term administration of levetiracetam. Supplementary information would also need to be provided with regard to reports of ECG abnormalities and blood pressure decrease in Study N01166, and one report of clinically significant sinus bradycardia in Study N01165.

Therefore, as part of a consolidated List of Questions sent to the MAH on 28 July 2005 (day 120), these concerns led to the inclusion of the following four topics in the list of issues to be addressed in writing by the MAH (see text in italics).

1. In study N069, all subjects reported a burning feeling at the injection site after intravenous administration of 1000 mg of levetiracetam at a faster infusion rate than recommended in the SPC. The applicant should clarify if there is risk for tissue damage in case of extravasal deposition of levetiracetam. In the submitted clinical studies, levetiracetam has not been administered for longer periods than 4 days. The risk for injection site damage during long-term intravenous administration of levetiracetam should be discussed, considering also the results from preclinical studies.

2. The applicant should submit supplementary information with regard to the time relationship between administration of study drug and diastolic blood pressure decreases in one patient in Study N01166, and between the occurrences of ECG abnormalities (three reports) and the administration of levetiracetam in the same study.

3. In Study N01165, one subject had clinically significant sinus bradycardia and prolongation of the QRS-interval after administration of 1500 mg levetiracetam during 5 minutes. The applicant should present more detailed data about this subject and discuss the relation to administration of study drug.

4. The tendency to hypotension with the IV formulation does merit further attention, because it could be particularly pertinent to the patient group likely to receive this intravenous preparation. The Applicant should describe what kind of post marketing surveillance should be envisaged in this regard.

Further to these requests, on 11 October 2005, UCB submitted their response, outlined below point by point.

<u>Point 1:</u> *(…risk for tissue damage in case of extravasal deposition and long-term intravenous administration of levetiracetam…)*

In summary, UCB stated that the IV formulation used in Study N069 was different from the formulation that was subsequently developed, and intended to be marketed. The IV formulation used in Study N069 was prepared as a 200 mg/mL levetiracetam solution without a pH buffering system and was administered undiluted as a bolus injection within 2 minutes. The current IV levetiracetam formulation is 100 mg/mL and is buffered. Therefore, it is understandable that local irritation occurred in Study N069, where highly concentrated and unbuffered drug was rapidly administered to subjects. This would be the same situation as in the pre-clinical rat repeat-dose studies where levetiracetam (as a concentrated 200 mg/mL solution) was rapidly administered. It is UCB's belief that, in these preclinical studies, the injection site effects were the direct result of rapid bolus administration together with the high concentration of the drug, particularly as at lower concentrations there were no injection site effects. Based on the observations, seen both pre-clinically and clinically in Study N069, dilution of the formulation and a slower infusion rate were adopted in further clinical development and are the proposed dosing regime outlined in the SPC proposed.
In three studies (N01077, N01165, and N01166) that used the levetiracetam IV formulation intended to be marketed as recommended in the proposed SPC, following proper dilution, only 2 (2.5%) of 79 individuals experienced mild local pruritus at the injection site. In these two cases, pruritus was transient (lasting 5 and 20 minutes respectively) and judged to be mild in severity by the investigator. Both cases were in the single-dose administration (Part A) of Study N01077. These two subjects continued in the study and received repeat-dose IV infusion of 1500 mg levetiracetam b.i.d for 4 days in Part B of the Study, without reporting any local injection site effects. None of the subjects in Studies N01166 or N01165 reported adverse events related to the injection procedure, including 30 subjects who received a higher dose (and faster infusion rate) than recommended by the proposed SPC. Therefore, the clinical data available would suggest that the risk of tissue damage should be minimal if the levetiracetam IV formulation is administered after proper dilution, as stated in the proposed SPC.

Currently, UCB has no clinical data with the proposed commercial levetiracetam IV formulation to assess longer-term use (>4 days). However, the objective of developing levetiracetam IV formulation is to allow it to be used in medical situations where patients are unable to take oral medications. Such situations should only exceptionally last longer than 4 days.
In order to further address the concerns of the CHMP regarding the risk for the injection site damage due to accidental mis-dosing with IV administration of levetiracetam and its long-term use, UCB has conducted a non-clinical study to assess local tolerance of levetiracetam concentrate for solution for injection. The results (described above in section 3.3 - Non-Clinical aspects) are reassuring.

The CHMP agreed with the explanation that the solution used in study N069 was more concentrated and infused during a shorter time than currently recommended, is likely to explain the common occurrences of local irritating effects in that study. As already mentioned above in this document (section 3.3 - Non-Clinical aspects), the results of a new non-clinical study are reassuring, pending the results of the histopathological examination. The MAH stated that situations where Keppra IV would be used should only exceptionally last longer than 4 days. However, there could be situations where longer-term use is necessary.

Therefore, the CHMP considered that the SPC should mention (in Section 4.2 – Posology) the lack of clinical experience of IV administration for periods longer than 4 days.

The MAH agreed with this request from the CHMP, and provided Product Information documents amended as requested.

Point 2: (supplementary information on the time relationship between drug administration and diastolic blood pressure decreases in Study N01166, and between occurrences of ECG abnormalities)

In summary, UCB response stated that one subject (005/0030), a 48 year old male patient with partial onset epilepsy, received 1000 mg bid levetiracetam IV infusion (over 15 minutes) for 4 days in Study N01166. This subject reported an adverse event of "decrease of diastolic blood pressure" initiating from Day 1 pre-dose. To respond to the question from CHMP, the vital signs of subject 005/0030 were reviewed and summarised. Subject 005/0030 had a low but normal diastolic blood pressure at screening (61 mmHg). The diastolic blood pressure before the first dose of levetiracetam IV infusion for this subject was also low (46 mmHg). During the 4-day administration, the diastolic blood pressure for this subject fluctuated between 32 to 71 mmHg, with the majority of the values less than 55 mmHg. At the final visit, the diastolic blood pressure for the subject was 52 mmHg. A similar observation can be made for systolic blood pressure: the subject had a relatively low systolic blood pressure before and throughout the study. A table was provided, illustrating that the blood pressure profiles remain largely unchanged throughout the administration and subsequent monitoring phases of the study and they do not appear to suggest a time relationship with the administration of levetiracetam intravenous infusion. In addition, heart rate remained stable with the administration of levetiracetam. If there had been a time relationship between the infusion of levetiracetam and blood pressure decrease, one would expect to observe a baroreceptor reflex mediated parallel increase in heart rate for adjustment of blood pressure. UCB pointed therefore out that it may be concluded that it is unlikely that there was a time relationship between the intravenous administration of levetiracetam and diastolic blood pressure decreases for subject 005/0030 in Study N01166.
In this Study, 7 subjects reported at least one ECG abnormality, which consisted of sinus bradycardia, incomplete right bundle branch block and right axis deviations. All ECG abnormalities in Study N01166 were reviewed. The majority of these abnormalities already existed in the baseline (during screening or at pre-dose on Day 1). There were no significant ECG changes after administration of levetiracetam intravenous infusion. None of the ECG abnormalities were considered to be clinically significant by the Investigator. Compared to baseline, no clinically relevant modifications were observed in the ECG parameters after administration of levetiracetam intravenous infusion.
In the light of the supplementary information summarised above, the CHMP considered the issue resolved, as the additional analysis did not provide any clear evidence for a time relationship between intravenous administration of levetiracetam and decreases of blood pressure. Moreover, no clinically significant ECG changes were recorded after levetiracetam intravenous infusion.

Point 3: (Presentation of more detailed data about one subject in Study N01165 who had clinically significant sinus bradycardia and prolongation of the QRS-interval after administration of 1500 mg levetiracetam during 5 minutes.)

In summary, UCB response stated that subject 001/0016 (a 41 year old healthy male subject) received 1500 mg levetiracetam single dose, via a 5 minutes infusion in Study N01165. This subject had a clinically significant sinus bradycardia post dose and a not clinically significant prolongation of QRS interval during the study.

This subject's heart rate was low at screening and pre-dose (VR = 40 – 49 bpm) and low heart rate values were also recorded at different time points during the trial, namely 40 – 44 bpm with the exception of a ventricular rate of 35 bpm at 12 h post-dose. The subject was clinically asymptomatic but the Investigator judged the observation to be clinically significant. Sinus bradycardia was recorded as an AE and was assessed by the Investigator as 'not related' to the study drug.

In subject 001/0016 the QRS duration varied between 109 and 118 msec at screening and pre-dosing. From the end of levetiracetam infusion up to 12 hours post-dosing the duration of the QRS complex remained in a similar range, namely 107-114 msec. At 24 hours post-dosing the QRS complex increased to 128 msec, but returned to 118 msec at discharge.

In conclusion, subject 001/0016 had already reported bradycardia and prolongation of QRS complex at baseline. Following the administration of levetiracetam 5-minute IV infusion, limited fluctuations were recorded for heart rate and duration of QRS complex. Bradycardia was reported as adverse event at 12 hour post dosing, which, in the context of the continuous observations was not attributed to the study drug administration. There appears to be no time relationship between bradycardia, prolongation of QRS – complex, and the administration of the study drug.

The CHMP considered UCB's response satisfactory, and the issue resolved.

Point 4: (Attention to tendency to hypotension with the IV formulation and description of post marketing surveillance envisaged.)

In summary, UCB's response stated that vital signs (heart rate, blood pressure and respiratory rate) were recorded in the two recently completed studies N01077 and N01165 at screening, on-treatment, and discharge in supine position after a 5-minute rest and in the dorsal decubitus position during infusion. In the multiple-dose portion of Study N01077, 2 subjects (No. 001/0013 and 001/0014) had low systolic blood pressure measurements (≤ 100 mmHg). The lowest on-treatment blood pressure value for 001/0013, recorded in the supine position, was 85/48 mmHg, measured 2 hours following the Day 5 evening dose; this subject had repeated measurements made at screening as a result of similarly low recordings (lowest 94/33 mmHg). For 001/0014, the lowest screening recording (in a supine position) was 100/67 mmHg. The lowest on treatment measurements occurred 5 minutes following the evening dose on Day 3 (84/41 mmHg) and Day 4 (90/29 mmHg and 84/38 mmHg, retest value). Both were reported as adverse events. The patients were otherwise asymptomatic. As these values were present pre- and post-dose, they are not clearly attributable to treatment. There were no other individual clinically significant changes, including no observations of orthostatic hypotension.

Vital sign measurements (including blood pressure) were also obtained following treatment in the five older studies conducted in the mid- to late-1980s in Europe. There were no reported alterations in vital sign measurements.

In study N01166 vital sign values remained relatively stable during the study, and within normal ranges. Nevertheless, one patient (005/0030) presented diastolic blood pressure decreases. Additional data with regard to the time relationship between administration of study drug and diastolic blood pressure decrease in this patient were submitted as response to the CHMP question. Since peak and trough diastolic blood pressure values were similar, there appears to be no relationship between the diastolic blood pressure and the administration of levetiracetam intravenous infusion. Low values were

present pre- and post-dose, the patient already presented a decreased diastolic blood pressure at baseline just before study drug administration, and moreover, peak and trough diastolic blood pressure values were similar, therefore the decreases in diastolic blood pressure are not clearly attributable to treatment.

With reference to the above-mentioned data, UCB's position is that there does not seem to be a tendency to hypotension with the IV formulation. Therefore no specific post-marketing surveillance is envisaged in regard to hypotension. However, because hypotension might be particularly pertinent to the patient group likely to receive the intravenous preparation, events of hypotension will be closely monitored during routine post marketing surveillance.

The CHMP considered UCB's response satisfactory, and the issue resolved.

Therefore, at day 150 of the procedure, UCB had answered in a satisfactory way to all clinical questions. Most of the concerns in the initial assessment report (local irritation, ECG changes, potential QT prolongation, hypotension) were not confirmed by a closer examination of the data.
The only remaining point of concern (lack of safety data for IV administrations that would be longer than 4 days) will be addressed by the inclusion of adequate wording in the SPC.

In addition to the 4 points above, a report of a simulation model in children for intravenous administration of Keppra concentrate was submitted (in an addendum to module 5 to the answers to the CHMP Day 120 Request for Supplementary Information on clinical aspects). This report establishes that the PK model supports extrapolations from children to adults for oral administration and from adults to children for intravenous administration. Based on the similarity of the predicted C_{max} and AUC following oral dosing and simulations for IV dosing in children, and to facilitate the appropriate dosing of Keppra 100 mg/ml concentrate for solution for infusion in the paediatric population, UCB proposed to include the wording of the newly approved paediatric information of Keppra oral formulations (Ref: EMEA/H/C/277/II/44, approval that took place during this procedure) in the proposed PI of Keppra 100 mg/ml concentrate for solution for infusion and to include information on the results of the PK simulation model in children (section 5.2).

In summary, although no clinical data are available from IV dosing to paediatric patients, UCB's proposed that dosing recommendations for children from the age of 4 years should be inserted in the SPC. To support these IV dosing recommendations in children, the MAH submitted a population pharmacokinetic analysis. In this report, the information from the population PK analysis of oral levetiracetam in children and of the bioavailability study between the intravenous solution and the oral tablet in healthy adult subjects was merged into one simulation model in order to evaluate an optimal intravenous dosing regimen in children 4 years of age and older as a function of the relevant covariates. There was an underprediction of C_{max} obtained after IV administration in adults. This was suggested to be caused by the drug not being fully distributed in the body at the end of an intravenous infusion resulting in a short period of time with higher concentrations than those predicted by a one-compartment model. The volume of the central compartment relative to body weight was stated to be higher in young infants than in adults but rapidly approaching adult values with increasing age, so that a similar transient elevation could be expected. Based on the observations in adults, it was stated that the initial concentration following the end of the infusion in children (C_{max}) may be as much as 75% higher than that predicted. Except for this short period, these results indicate that the current simulation model of levetiracetam obtained with oral data in children and using the relative bioavailability measured in adults can be utilised to predict the exposure after intravenous administration of levetiracetam in epileptic children and adults.

The CHMP considered that, since the bioavailability of oral levetiracetam is 100% and since the plasma concentrations obtained with the solution for infusion are very similar to the levels after oral administration, the main unknown factor is whether the product has a similar initial distribution in paediatric and adult patients. In the analysis, similar distribution is assumed. No paediatric IV data is available and as such, the resulting one-compartment model could not be validated in paediatric patients administered IV levetiracetam.

If the initial distribution of levetiracetam is different in children than in adults, the C_{max} obtained in children with the proposed IV dose recommendation may differ from the C_{max} in children after oral administration. The magnitude of this difference is difficult to predict. If the obtained C_{max} is higher, a prolongation of the infusion time (reduction of the infusion rate) may be needed. The AUC obtained in children after IV administration will be the same as after oral administration. The possibly higher C_{max} after IV administration should therefore be assessed by the MAH in light of the available clinical documentation in children with orally administered levetiracetam.

The safety of levetiracetam is relatively good and much higher concentrations have been well tolerated in children, e.g. in studies N159 and N157. Furthermore, the inter-subject variability for the different parameters of the model leads to a range of concentrations of at least 2 fold whatever the dose. Therefore, a potential increase in C_{max} after IV administration in children above 40 kg does not appear to raise serious risks. Nevertheless, the MAH should investigate whether the model could be adjusted in order to provide more realistic estimates of the bolus effect and of Cmax (e.g. by a two-compartmental mode). Based on these results, the need for a reduction of the infusion rate in children when there is a risk of unacceptably high C_{max} should be discussed.

In essence, the MAH was requested by CHMP to evaluate the possibility to slow down the infusion rate to 30 min in children if there are safety concerns (the latter could be assessed using an appropriate PK model).

To this end, UCB initiated additional PK simulations using a two-compartment model in order to improve the accuracy on peak plasma concentrations at the end of infusion. The impact of slowing down the infusion rate of Keppra 100 mg/ml concentrate for solution for infusion is also explored. UCB informed the CHMP that a final report could be expected by March 2006.
In order to avoid additional delays in the approval of this procedure for Keppra 100 mg/ml concentrate for solution for infusion, UCB therefore proposed to provide the CHMP with the report as a Follow-up Measure (FUM) by 1 March 2006.

CHMP considered this proposal acceptable: the MAH will therefore provide additional information as a FUM about the potential risks of higher Cmax in children than in adults following IV administration. This FUM will be worded as follow:

"Amendment to Study report RXCE05F1305 "Simulations for evaluation of dose adaptation rules of intravenous levetiracetam in children". This amendment will assess the risk of high Cmax in children after IV administration. PK models could be used to better delineate this risk. If the risk is substantial, the MAH will discuss the need for a reduction of the infusion rate in (some) children. Longer infusion times may better mimic the oral pharmacokinetic profile, and this may be investigated by data simulation."

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system
All new applications and relevant post-authorisation procedures for which a European Commission Decision will be granted after 20 November 2005 will have to comply with relevant provisions set out in the new legislation. Therefore, during assessment of this procedure, UCB was requested to provide documents that set out a detailed description of the system of pharmacovigilance, as requested by Art 8.3 (ia) and n) of the amended Directive. A statement signed by the applicant and the qualified person for pharmacovigilance, indicating that the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country was also requested.

Further to the above request, the MAH has provided a signed statement from the Qualified Person Responsible for Pharmacovigilance. The location of the description in the MAA, and updating of the information, post authorisation has been provided. The EU/EEA Qualified Person Responsible for Pharmacovigilance has been identified. The organisation of the pharmacovigilance activities and written policies and procedures in Global Drug Safety have been described. Databases, training and documentation systems, and quality management systems have been identified.

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

Risk Management Plan
Not applicable

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

6. Overall conclusions, risk/benefit assessment and recommendation

No major deficiencies have been identified in the quality part of the application. The MAH has correctly addressed all major Quality Issues and has finally committed to 2 minor quality-related FUMs, which have no impact on the benefit/risk balance.

In the non-clinical studies, changing the administration route from oral to IV has not caused any additional toxicity besides the local effects seen at the injection sites, which need to be further addressed. The CHMP agrees with the provisional conclusion of the Applicant concerning the local tolerance study that was carried out. Both repeat dose intravenous effects and single misdosing effects were addressed in the study design.

However, before any final conclusions can be drawn the histopathological data should be provided. The CHMP considered that these should be provided as post-marketing authorisation in the form of FUMs.

The pharmacokinetic documentation shows that a 15-min IV infusion of levetiracetam in adults results in similar C_{max} and AUC values of levetiracetam as the same dose administered orally as tablets. However, the rate of input of levetiracetam is higher after IV infusion. Similar data were not available for children, so the MAH is requested to evaluate the possibility to slow down the infusion rate to 30 min in children if there are safety concerns (the latter could be assessed using an appropriate PK model).

The safety data from studies with intravenous levetiracetam indicate a similar safety profile as with the oral formulation, with a predominance of CNS-related adverse events. In the studies with the intravenous formulation some subjects were noted to have transient decreases in blood pressure. When administered intravenously as a more concentrated solution than recommended in the proposed SPC, all patients reported a burning sensation at the administration site. There are two reports on local irritation at the injection site with the recommended concentration and infusion rate. Further post-marketing non-clinical histopathological data should clarify whether extravasal deposition of levetiracetam may cause tissue damage. In addition, the SPC will mention that there are no safety data for IV administrations for periods longer than 4 days.

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Keppra 100 mg/ml concentrate for solution for infusion in the treatment of "*adjunctive therapy in the treatment of partial onset seizures with or without secondary generalisation in adults and children from 4 years of age with epilepsy*" was favourable and therefore recommended the granting of the extension to the marketing authorisation.

Further to the approval of Keppra 100 mg/ml concentrate for solution for infusion, the MAH will submit PSURs annually until the next Renewal of the Marketing Authorisation for Keppra.