Risk Management Plan

Levetiracetam 100mg/ml concentrate for solution for infusion

Intrapharm Laboratories Ltd
The Granary, The Courtyard Barns,
Choke Lane, Cookham Dean
Maidenhead, Berkshire
SL6 6PT
United Kingdom

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(v1.0)

Administrative information on the RMP

Part	Module/Annex	Date last updated for submission (sign off date)	Version number of RMP when last submitted
Part I	**Product Overview**	-	1.0
Part II	**Safety Specification** SV.1 - Post authorisation experience SVIII – Summary of the safety concerns	-	1.0
Part III	**Pharmacovigilance Plan**	Not applicable	Not applicable
Part IV	**Plan for post-authorisation efficacy studies**	Not applicable	Not applicable
Part V	**Risk Minimisation Measures**	-	1.0
Part VI	**Summary of activities in the risk management plan by product**	-	1.0
Part VII	**Annex 1** Interface between EU-RMP and Eudravigilance	Not applicable	Not applicable
	Annex 2 Tabulated summary of planned, ongoing and completed pharmacovigilance study programme	Not applicable	Not applicable
	Annex 3 Protocols for proposed, on-going and completed studies from Pharmacovigilance Plan	Not applicable	Not applicable
	Annex 4 Specific adverse event follow-up forms	-	1.0
	Annex 5 Protocols for proposed and on-going studies in RMP Part IV	Not applicable	Not applicable
	Annex 6 Details of proposed additional risk minimisation activities (if applicable)	Not applicable	Not applicable
	Annex 7 Other supporting data (including reference material)	Not applicable	Not applicable
	Annex 8 Summary of changes to the risk management plan over time	-	1.0

RMP version to be assessed as part o this application:

Version number of last agreed RMP: Not applicable

Data lock point for EU–RMP:	31/08/2017	RMP Version number:	1.0
Date of final sign off:	15/08/2017		

Other RMP versions under evaluation:

Version number	Submitted on	Procedure number
Not applicable	Not applicable	

Details of the currently approved RMP:

Version number	Approved with procedure	Date of approval
Not applicable	Not applicable	

Contact Person for this RMP

QPPV Name : [redacted]

QPPV Signature : …… [redacted] ……

Qualifications : BPhar [redacted] PGDip (Pharmacovigilance)

E-mail address : [redacted]

Telephone : [redacted]

The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV.

Table of Contents

List of Annexes

Part I: PRODUCT OVERVIEW

Active substance (s) (INN/common name)	Levetiracetam
Pharmaco-therapeutic group (ATC Code):	Antiepileptics, other antiepileptics (ATC Code: N03AX14)
Authorisation procedure (s) (central, mutual recognition, decentralised, national)	Decentralised
Name of Marketing Authorisation Holder or Applicant	Intrapharm Laboratories Ltd
Medicinal product(s) to which this RMP refers	Levetiracetam 100mg/ml concentrate for solution for infusion
Invented name(s) of the medicinal product) in the European Economic Area (EEA)	Levetiracetam 100mg/ml Concentrate for Solution for Infusion
Marketing Authorisation Procedure	Decentralised: UK/H/6789/001/DC UK (RMS), IE (CMS)
Brief description of product (chemical class, mode of action etc)	Levetiracetam is a pyrorolidone derivative (S-enantiomer of α-ethyl-2-oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active substances. The mechanism of action of levetiracetam still remains to be fully elucidated. In vitro and in vivo experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission. In-vitro studies show that levetiracetam affects intraneuronal Ca^{2+} levels by partial inhibition of N-type Ca^{2+} currents and by reducing Ca^{2+} from intraneuronal stores. It partially reverses reductions in GABA- and glycine-gated currents induced by zinc and β-carbolines. It binds to a specific site in reodent brain tissue, which is the synaptic vescicle protein 2A, believed to be involved in vesicle fusion and neurotransmitter exocytosis. Levetiracetam and related analoges show a rank order of affinity for binding to

	the synaptic vesicle protein 2A which correlates with the potency of their anti-seizure protection in the mouse audiogenic model of epilepsy. These findings suggests the interaction between levetiracetam and the synaptic vesicle protein 2A seems to contribute to the antiepileptic mechanism of action of the medicinal product.
Hyperlink to the Product Information	
Indication (s) in the EEA	Levetiracetam concentrate for solution for infusion is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy. Levetiracetam is indicated as adjunctive therapy • In the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy. • In the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy. • In the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy. Levetiracetam concentrate for solution for infusion is an alternative treatment for patients when oral administration is temporarily not feasible.
Dosage in the EEA	Levetiracetam therapy can be initiated with either intravenous or oral administration. Conversion to or from oral to intravenous administration can be done directly without titration. The total daily dose and frequency of administration should be maintained. *Monotherapy for adults and adolescents from 16 years of age*: The recommended starting dose is 250 mg twice daily which should be increased to an initial therapeutic dose of 500 mg twice daily after two weeks. The dose

	can be further increased by 250 mg twice daily every two weeks depending upon the clinical response. The maximum dose is 1500 mg twice daily. *Add-on therapy for a adults (≥18 years) and adolescents (12 to 17 years weighing 50kg or more*: The initial therapeutic dose is 500 mg twice daily. This dose can be started on the first day of treatment. Depending upon the clinical response and tolerability, the daily dose can be increased up to 1,500 mg twice daily. Dose changes can be made in 500 mg twice daily increases or decreases every two to four weeks. <u>Duration of Treatment</u> There is no experience with administration of intravenous levetiracetam for longer period than 4 days. <u>Special populations</u> *Elderly (65 years and older):* Adjustment of the dose is recommended in elderly patients with compromised renal function. *Renal impairment:* The daily dose must be individualised according to renal function. *Hepatic impairment*: No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73 m^2. <u>Paediatric population</u> The physician should prescribe the most appropriate pharmaceutical form, presentation and strength according to age, weight and dose. *Add-on therapy for children aged 4 to 11 years and adolescents (12 to 17 years) weighing less than 50kg:* The initial therapeutic dose is 10 mg/kg twice daily.

<table>
<tr><td></td><td>Depending upon the clinical response and tolerability, the dose can be increased up to 30 mg/kg twice daily. Dose changes should not exceed increases or decreases of 10 mg/kg twice daily every two weeks. The lowest effective dose should be used.

Dose in children 50 kg or greater is the same as in adults.

Dose recommendations for children and adolescents:

<table>
<tr><th>Group</th><th>Starting Dose: 10mg/kg twice daily</th><th>Maximum dose: 30mg/kg twice daily</th></tr>
<tr><td>15 kg (1)</td><td>150 mg twice daily</td><td>450 mg twice daily</td></tr>
<tr><td>20 kg (1)</td><td>200 mg twice daily</td><td>600 mg twice daily</td></tr>
<tr><td>25 kg</td><td>250 mg twice daily</td><td>750 mg twice daily</td></tr>
<tr><td>From 50 kg (2)</td><td>500 mg twice daily</td><td>1500 mg twice daily</td></tr>
<tr><td colspan="3">(1) Children 25 kg or less should preferably start the treatment with Levetiracetam 100 mg/ml oral solution.
(2) Dose in children and adolescents 50 kg or more is the same as in adults</td></tr>
</table>
</td></tr>
<tr><td>Pharmaceutical form (s) and strength (s)</td><td>Concentrate for solution for infusion

100mg/ml presented in a 5ml glass vial.</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU</td><td>No</td></tr>
</table>

PART II: SAFETY SPECIFICATION

SV. POST AUTHORISATION EXPERIENCE

No post authorisation experience is available yet for Levetiracetam 100mg/ml concentrate for solution for infusion, as the current RMP is presented at the time of the application for marketing approval. Post marketing experience for the past 18 years is available for Keppra 100mg/ml concentration for solution for infusion.

SV.1 Post-authorisation exposure

1.1 Method used to calculate exposure

Not applicable, since this is the initial RMP submitted in respect of a marketing authorization for the applicant product.

1.2 Exposure

Not applicable, since this is the initial RMP submitted in respect of a marketing authorization for the applicant product.

SVIII. SUMMARY OF THE SAFETY CONCERNS

The adverse events listed in the SPC of Levetiracetam 100mg/ml concentrate for solution for infusion are in accordance with the most recently approved Product Information of the reference product.

The following safety concerns have been collected from clinical data and during post authorisation experience with the reference product in the approved indications for Flucloxacillin:

Table SVIII.1 Summary of safety concerns

Important identified risks	• Anaphylaxis and hypersensitivity • Haemotological abnormalities • Suicide and behaviour disorders • Renal impairment • Hepatic impairment
Important potential risks	• Fertility, Pregnancy and Lactation • Interaction with other medicinal products • Medication error

Missing information	• Long term effects on children > 4 years • Use in children <4 years

PART III. PHARMACOVIGILANCE PLAN

Not applicable – Additional imposed mandatory pharmacovigilance activities are not required at this time.

PART IV. PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

Not applicable.

PART V. RISK MINIMISATION MEASURES (incl. evaluation of the effectivess of risk minimsation activities)

Risk Minimisation Plan

The safety information in the proposed product information is aligned to the reference material product.

Legal status:
Prescription only medicine (POM)

Pack size:
Levetiracetam 100mg/ml concentrate for solution for infusion in colourless 5ml glass vials sealed with a bromobutyl rubber stopper, sealed with an aluminium blue flip off cap. The product is supplied in cartons containing 1x5ml vial or 10x5ml vials.

At the present time, routine pharmacovigilance activities, such as the product information provided in the Summary of Product Characteristics and Patient Leaflets, are deemed sufficient to manage the safety risks outline in this RMP. For important potential risks and those safety areas where clinical information is missing, additional targeted follow up investigations for special interest cases will be conducted.

All identified and potential risks are reported in the summary of product characteristics (SmPC) and the package leaflet for the reference product and the applicant product. The frequency of the adverse events has been derived from those reported in clinical studies (adults, adolescents, children and infants >1 month) and from 18 years of post-marketing reports experience.

The following convention has been used for the classification of undesirable effects: -

Very common	>1/10
Common	>1/100; <1/10
Uncommon	>1/1000; <1/100
Rare	>1/10,000; <1/1000
Very rare	<1/10,000

- *Educational material:*
  Not applicable.

Updates to the EU-RMP:

An update to the RMP will be provided upon the request of any Competent Authority. In addition, updates to the RMP will be submitted within 60 days of any important milestone being reached or where new information is received that may impact on the current safety specification or risk minimisation activities.

Aggregate Reporting Requirements:

In line with the new pharmacovigilance legislation Dir 2010/84/EC a Risk Management Plan (RMP) is provided in this application. The need for updates to the RMP will be reviewed annually. The PSUR schedule will align with that as proposed by the EURD List provided for under Article 107c(7) of Directive 2001/83/EC as published by the EMA, as follows:

Active substances and combinations of active substances	**European Union reference date (EURD)**	**PSUR Submission Frequency**	**DLP**	**Submission date (According to the timelines defined in GVP Module VII, Section A)**	**Are PSURs required for products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended?**	**Publication Date (in accordance with Article 107c(7) of Directive 2001/83/EC as amended)**
levetiracetam	29/09/2000	3 years	30/11/18	28/02/19	No	16/07/15

If the dates of submission of a PSUR and the update of an RMP coincide, they shall be submitted at the same time.

V.1 Routine Risk Minimisation Measures

Table V.1.1 Description of routine risk minimisation measures by safety concern

Safety concern	**Anaphylaxis and hypersensitivity**
Objectives of the risk minimisation measures.	None proposed
Routine risk minimization activities	The following information is included in the SPC: **Section 4.3 Contraindications** Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients. **Section 4.8 Undesirable effects:** ***Immune system disorders*** Rare: Drug reaction with eosinophilia symptoms (DRESS), Hypersensitivity (including angioedema and anaphylaxis) **Section 6.1 List of excipients** Sodium acetate trihydrate Glacial acetic acid Sodium chloride Water for injection

Safety concern	**Haematological abnormalities**
Objectives of the risk minimisation measures.	None proposed
Routine risk minimization activities	The following information is included in the SPC: **Section 4.3 Contraindications** Hypersensitivity to the active substance or other pyrrolidone derivatives or to any of the excipients. **Section 4.4 Special warnings and precautions for use** <u>Blood cell counts</u> Rare cases of decreased blood cell counts (neutropenia, agranulocytosis, leucopenia, thrombocytopenia and pancytopenia) have been described in association with levetiracetam administration, generally at the beginning of the treatment. Complete blood cell counts are advised in patients experiencing important weakness, pyrexia, recurrent infections

	or coagulation disorders. **Section 4.8 Undesirable effects:** ***Blood and lymphatic system disorders*** Uncommon: Thrombocytopenia, leukopenia Rare: Pancytopenia, neutropenia, agranulocytosis Description of selected adverse reactions Bone marrow suppression was identified in some of the cases of pancytopenia.

Safety concern	**Suicide and behaviour disorders**
Objectives of the risk minimisation measures.	None proposed
Routine risk minimization activities	The following information is included in the SPC: **Section 4.4 Special warnings and precautions for use** Suicide Suicide, suicide attempt, suicidal ideation and behaviour have been reported in patients treated with anti-epileptic agents (including levetiracetam. A meta-analysis of randomized placebo-controlled trials of anti-epileptic medicinal products has shown a small increased risk of suicidal thoughts and behaviour. The mechanism of this risk is not known. Therefore patients should be monitored for signs of depression and/or suicidal ideation and behaviours and appropriate treatment should be considered. Patients (and caregivers of patients) should be advised to seek medical advice should signs of depression and/or suicidal ideation or behaviour emerge **Section 4.8 Undesirable effects:** ***Psychiatric disorders*** Common: Depression, hostility/aggression, anxiety, insomnia, nervousness/irritability Uncommon: Suicide attempt, suicidal ideation, psychotic disorder, abnormal

		behaviour, hallucination, anger, confusional state, panic attack, affect lability/mood swings, agitation	
		Rare: Completed suicide, personality disorder, thinking abnormal	

Safety concern	**Renal impairment**
Objectives of the risk minimisation measures.	None proposed
Routine risk minimization activities	The following information is included in the SPC: **Section 4.2 Posology and method of administration** *Renal impairment:* The daily dose must be individualised according to renal function. For adult patients, refer to the following table and adjust the dose as indicated. To use this dosing table, an estimate of the patient's creatinine clearance (CLcr) in ml/min is needed. The CLcr in ml/min may be estimated from serum creatinine (mg/dl) determination, for adults and adolescents weighting 50 kg or more, the following formula: $$\text{CLcr (ml/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dl)}} \text{ (x 0.85 for women)}$$ **Then CLcr is adjusted for body surface area (BSA) as follows:** $$\text{CLcr (ml/min/1.73 m}^2\text{)} = \frac{\text{CLcr (ml/min)}}{\text{BSA subject (m}^2\text{)}} \times 1.73$$ Dosing adjustment for adult and adolescents patients weighing more than 50 kg with impaired renal function:

Group	**Creatinine Clearance (ml/min/1.73m^2)**	**Dose and Frequency**
Normal	>80	500 to 1,500mg twice daily
Mild	50-79	500 to 1,000mg twice daily
Moderate	30-49	250 to 750mg twice daily
Severe	<30	250 to 500mg twice daily
End-stage renal disease patients undergoing	-	500 to 1,000mg once daily(2)

dialysis[1]		

(1) A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.
(2) Following dialysis, a 250 to 500 mg supplemental dose is recommended.

For children with renal impairment, levetiracetam dose needs to be adjusted based on the renal function as levetiracetam clearance is related to renal function. This recommendation is based on a study in adult renally impaired patients.

The CLcr in ml/min/1.73 m^2 may be estimated from serum creatinine (mg/dl) determination, for young adolescents and children using the following formula (Schwartz formula):

$$\text{Clcr (ml/min/1.73m}^2\text{)} = \frac{\text{Height (cm)} \times \text{ks}}{\text{Serum Creatinine (mg/dl)}}$$

ks= 0.55 in Children to less than 13 years and in adolescent female; ks= 0.7 in adolescent male

Dosing adjustment for children and adolescents patients weighing less than 50 kg with impaired renal function:

Group	**Creatinine Clearance (ml/min/1.73m^2)**	**Dose and Frequency**
Normal	>80	10 to 30 mg/kg (0.10 to 0.30 ml/kg) twice daily
Mild	50-79	10 to 20 mg/kg (0.10 to 0.20 ml/kg) twice daily
Moderate	30-49	5 to 15 mg/kg (0.05 to 0.15 ml/kg) twice daily
Severe	<30	5 to 10 mg/kg (0.05 to 0.10 ml/kg) twice daily
End-stage renal disease patients undergoing dialysis	-	10 to 20 mg/kg (0.10 to 0.20 ml/kg) once daily [1] [2]

(1) A 15 mg/kg (0.15 ml/kg) loading dose is recommended on the first day of treatment with levetiracetam.
(2) Following dialysis, a 5 to 10 mg/kg (0.05 to 0.10 ml/kg) supplemental dose is recommended.

Section 4.5 Special warnings and precautions for use

Renal impairment

The administration of levetiracetam to patients with renal impairment may require dose adjustment. In patients with severely impaired hepatic function, assessment of renal function is recommended before dose selection.

Acute Kidney injury

The use of levetiracetam has been very rarely associated with acute kidney injury, with a time to onset ranging from a few days to several months.

	Excipients This medicinal product contains 2.5 mmol (or 57mg) sodium per maximum single dose [0.8 mmol (or 19mg) per vial]. To be taken into consideration by patients on a controlled sodium diet. **Section 4.8 Undesirable effects:** ***Renal and urinary disorders*** Rare: Acute kidney injury **Section 5.2 Pharmacokinetic properties** Renal impairment The apparent body clearance of both levetiracetam and of its primary metabolite is correlated to the creatinine clearance. It is therefore recommended to adjust the maintenance daily dose of Levetiracetam concentrate for solution for infusion, based on creatinine clearance in patients with moderate and severe renal impairment (see section 4.2). In anuric end-stage renal disease adult subjects the half-life was approximately 25 and 3.1 hours during interdialytic and intradialytic periods, respectively. The fractional removal of levetiracetam was 51 % during a typical 4-hour dialysis session.

Safety concern	**Hepatic Impairment**
Objectives of the risk minimisation measures.	None proposed
Routine risk minimization activities	The following information is included in the SPC: **Section 4.2 Posology and method of administration** *Hepatic impairment*: No dose adjustment is needed in patients with mild to moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is recommended when the creatinine clearance is < 60 ml/min/1.73 m^2. **Section 4.8 Undesirable effects:**

	Hepatobiliary disorders Uncommon: Liver function test abnormal. Rare: Hepatic failure, hepatitis. **Section 5.2 Pharmacokinetic properties** Hepatic impairment In subjects with mild and moderate hepatic impairment, there was no relevant modification of the clearance of levetiracetam. In most subjects with severe hepatic impairment, the clearance of levetiracetam was reduced by more than 50 % due to a concomitant renal impairment.

Safety concern	**Fertility, Pregnancy and Lactation**
Objectives of the risk minimisation measures.	None proposed
Routine risk minimization activities	The following information is included in the SPC: **Section 4.6 Fertility, pregnancy and lactation** Pregnancy Postmarketing data from several prospective pregnancy registries have documented outcomes in over 1,000 women exposed to levetiracetam monotherapy during the first trimester of pregnancy. Overall, these data do not suggest a substantial increase in the risk for major congenital malformations, although a teratogenic risk cannot be completely excluded. Therapy with multiple antiepileptic medicinal products is associated with a higher risk of congenital malformations than monotherapy and, therefore, monotherapy should be considered. Studies in animals have shown reproductive toxicity. Levetiracetam concentrate for solution for infusion is not recommended during pregnancy and in women of childbearing potential not using contraception unless clinically necessary. Physiological changes during pregnancy may affect levetiracetam concentration. Decrease in levetiracetam plasma concentrations has been observed during pregnancy. This decrease is more pronounced during the third trimester (up to 60% of baseline concentration before pregnancy). Appropriate clinical management of pregnant women treated with levetiracetam should be ensured. Discontinuation of antiepileptic treatments may result in exacerbation of the disease which could be harmful to the mother and the foetus. Breastfeeding Levetiracetam is excreted in human breast milk. Therefore, breast-feeding is not recommended.

	However, if levetiracetam treatment is needed during breastfeeding, the benefit/risk of the treatment should be weighed considering the importance of breastfeeding Fertility No impact on fertility was detected in animal studies. No clinical data are available, potential risk for human is unknown. **Section 5.3 Preclinical safety data** No adverse reactions on male or female fertility or reproduction performance were observed in rats at doses up to 1800 mg/kg/day (x 6 the MRHD on a mg/m2 or exposure basis) in parents and F1 generation. Two embryo-foetal development (EFD) studies were performed in rats at 400, 1200 and 3600 mg/kg/day. At 3600 mg/kg/day, in only one of the 2 EFD studies, there was a slight decrease in foetal weight associated with a marginal increase in skeletal variations/minor anomalies. There was no effect on embryomortality and no increased incidence of malformations. The NOAEL (No Observed Adverse Effect Level) was 3600 mg/kg/day for pregnant female rats (x 12 the MRHD on a mg/m2 basis) and 1200 mg/kg/day for inimiza. Four embryo-foetal development studies were performed in rabbits covering doses of 200, 600, 800, 1200 and 1800 mg/kg/day. The dose level of 1800 mg/kg/day induced a marked maternal toxicity and a decrease in foetal weight associated with increased incidence of inimiza with cardiovascular/skeletal anomalies. The NOAEL was <200 mg/kg/day for the dams and 200 mg/kg/day for the fetuses (equal to the MRHD on a mg/m2 basis). A peri- and post-natal development study was performed in rats with levetiracetam doses of 70, 350 and 1800 mg/kg/day. The NOAEL was ≥ 1800 mg/kg/day for the F0 females, and for the survival, growth and development of the F1 offspring up to weaning.(x 6 the MRHD on a mg/m2 basis). Neonatal and juvenile animal studies in rats and dogs demonstrated that there were no adverse effects seen in any of the standard developmental or maturation endpoints at doses up to 1800 mg/kg/day (x 6-17 the MRHD on a mg/m2 basis).

Safety concern	**Interaction with other medicinal products**
Objectives of the risk minimisation measures.	None proposed
Routine risk minimization activities	The following information is included in the SPC: **Section 4.5 Interaction with other medicinal products and other forms of interaction** Antiepileptic medicinal products Pre-marketing data from clinical studies conducted in adults indicate that levetiracetam did not influence the serum concentrations of existing

	antiepileptic medicinal products (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) and that these antiepileptic medicinal products did not influence the pharmacokinetics of levetiracetam. As in adults, there is no evidence of clinically significant medicinal product interactions in paediatric patients receiving up to 60 mg/kg/day levetiracetam. A retrospective assessment of pharmacokinetic interactions in children and adolescents with epilepsy (4 to 17 years) confirmed that adjunctive therapy with orally administered levetiracetam did not influence the steady-state serum concentrations of concomitantly administered carbamazepine and valproate. However, data suggested a 20 % higher levetiracetam clearance in children taking enzyme-inducing antiepileptic medicinal products. Dose adjustment is not required. Probenecid Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been shown to inhibit the renal clearance of the primary metabolite, but not of levetiracetam. Nevertheless, the concentration of this metabolite remains low. Methotrexate Concomitant administration of levetiracetam and methotrexate has been reported to decrease methotrexate clearance, resulting in increased/prolonged blood methotrexate concentration to potentially toxic levels. Blood methotrexate and levetiracetam levels should be carefully monitored in patients treated concomitantly with the two drugs Oral contraceptives and other pharmacokinetics interactions Levetiracetam 1,000 mg daily did not influence the pharmacokinetics of oral contraceptives (ethinyl-estradiol and levonorgestrel); endocrine parameters (luteinizing hormone and progesterone) were not modified. Levetiracetam 2,000 mg daily did not influence the pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-administration with digoxin, oral contraceptives and warfarin did not influence the pharmacokinetics of levetiracetam.

Safety concern	**Medication error**
Objectives of the risk minimisation measures.	None proposed
Routine risk minimization activities	The following information is included in the SPC: **Section 4.2 Posology and method of administration** Method of administration Levetiracetam concentrate for solution for infusion is for intravenous use only and the recommended dose must be diluted in at least 100 ml of a compatible diluent and administered intravenously as a 15-minute intravenous infusion (see section 6.6).

Section 6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except thos mentioned in section 6.6.

Section 6.3 Shelf life

2 years.

From a microbiological point of view, the product should be used immediately after dilution. If not used immediately, in-use storage time and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

Section 6.6 Special precautions for disposal and other handling
See Table 1 for the recommended preparation and administration of Levetiracetam concentrate for solution for infusion to achieve a total daily dose of 500 mg, 1,000 mg, 2,000 mg, or 3,000 mg in two divided doses.

Table 1. Preparation and administration of Levetiracetam concentrate for solution for infusion

Dose	Withdrawal Volume	Volume of Diluent	Infusion Time	Frequency of Administration	Total Daily Dose
250mg	2.5ml (half 5ml vial)	100ml	15 minutes	Twice daily	500mg/day
500mg	5ml (one 5ml vial)	100ml	15 minutes	Twice daily	1000mg/day
1000mg	10ml (two 5ml vials)	100ml	15 minutes	Twice daily	2000mg/day
1500mg	15ml (three 5ml vials)	100ml	15 minutes	Twice daily	3000mg/day

This medicinal product is for single use only, any unused solution should be discarded.

Levetiracetam concentrate for solution for infusion was found to be chemically and physically stable and compatible when mixed with the following diluents for at least 24 hours and stored in PVC bags or PP bottles under controlled temperature of 25 °C.

Diluents:
• Sodium chloride 9 mg/ml (0.9%) solution for injection
• Hartmann’s or Ringer’s lactate solution for injection
• Dextrose 50 mg/ml (5%) solution for injection

Medicinal product with particulate matter or discoloration should not be used.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Safety concern	**Long term use in children > 4 years**
Objectives of the risk minimisation measures.	None proposed
Routine risk minimisation activities	The following information is included in the SPC: **Section 4.4 Special warnings and precautions for use** <u>Paediatric population</u> Available data in children did not suggest impact on growth and puberty. However, long term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children remain unknown.

Safety concern	**Use in children < 4 years**
Objectives of the risk minimisation measures.	None proposed
Routine risk minimization activities	The following information is included in the SPC: **Section 4.2 Posology and method of administration** *Add-on therapy for infants and children less than 4 years:* The safety and efficacy of Levetiracetam concentrate for solution for infusion in infants and children less than 4 years have not been established. Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made. **Section 4.8 Undesirable effects** <u>Paediatric population</u> In patients aged 1 month to less than 4 years, a total of 190 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. Sixty of these patients were treated with levetiracetam in placebo-controlled studies. In patients aged 4-16 years, a total of 645 patients have been treated with levetiracetam in placebo-controlled and open label extension studies. 233 of these patients were treated with levetiracetam in placebo-controlled studies. In both these paediatric age ranges, these data are supplemented with the post-marketing experience of the use of levetiracetam. In addition, 101 infants aged less than 12 months have been exposed in a post authorization safety study. No new safety concerns for levetiracetam were identified for infants less than 12 months of age with epilepsy.

V.2 Additional Risk Minimisation Measures

Routine risk minimization activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary table of risk minimisation measures

Table V.3 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Table V.3.1 Important identified risks

Safety concern	Routine risk minimisation activities sufficient	Additional risk minimisation measures
Anaphylaxis and hypersenstivity	Information is included in the product labelling (SPC sections 4.3, 4.8 and 6.1)	None proposed
Haematological abnormalities	Information is included in the product labelling (SPC sections 4.3, 4.4 and 4.8)	Non proposed
Suicide and behaviour disorders	Information is included in the product labelling (SPC sections 4.4 and 4.8)	None proposed
Renal impairment	Information is included in the product labelling (SPC sections 4.2, 4.5, 4.8 and 5.2)	None proposed
Hepatic impairment	Information is included in the product labelling (SPC section 4.3, 4.8 and 5.2)	None proposed

V.3.2 Important potential risks

Safety concern	Routine risk minimisation activities sufficient	Additional risk minimisation measures
Fertility, pregnancy and lactation	Information is included in the product labelling (SPC sections 4.6 and 5.3) Routine pharmacovigilance activities, which include targeted follow up of	None proposed

	spontaneous, literature and, where applicable, clinical trial case reports.	
Interaction with other medicinal products	Information included in the Product labelling (SPC sections 4.5). Routine pharmacovigilance activities, which include additional follow up of spontaneous, literature and, where applicable, clinical trial case reports.	None proposed
Medication error	Information included in the Product labelling (SPC sections 4.2, 6.2, 6.3 and 6.6). Routine pharmacovigilance activities, which include targeted follow up of spontaneous, literature and, where applicable, clinical trial case reports.	None proposed

V.3.3 Missing information

Safety concern	**Routine risk minimisation activities sufficient**	**Additional risk minimisation measures**
Long term use in children > 4 years	Information is included in the product labelling (SPC sections 4.4) Routine pharmacovigilance activities, which include targeted follow up of spontaneous, literature and, where applicable, clinical trial case reports.	None proposed
Use in children < 4 years	Information is included in the product labelling (SPC sections 4.2 and 4.8) Routine pharmacovigilance activities, which include targeted follow up of spontaneous, literature and, where applicable, clinical trial case reports.	None proposed

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Levetiracetam 100mg/ml concentrate for solution for infusion

This is a summary of the risk management plan (RMP) for Levetiracetam 100mg/ml concentrate for solution for infusion. The RMP details important risks of Levetiracetam 100mg/ml concentrate for solution for infusion, how these risks can be minimised, and how more information will be obtained about Levetiracetam 100mg/ml concentrate for solution for infusion 's risks and uncertainties (missing information).

Levetiracetam 100mg/ml concentrate for solution for infusion's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Levetiracetam 100mg/ml concentrate for solution for infusion should be used.

I. The medicine and what it is used for

Levetiracetam concentrate for solution for infusion is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in adults and adolescents from 16 years of age with newly diagnosed epilepsy.

Levetiracetam is indicated as adjunctive therapy

- In the treatment of partial onset seizures with or without secondary generalisation in adults, adolescents and children from 4 years of age with epilepsy.
- In the treatment of myoclonic seizures in adults and adolescents from 12 years of age with Juvenile Myoclonic Epilepsy.
- In the treatment of primary generalised tonic-clonic seizures in adults and adolescents from 12 years of age with Idiopathic Generalised Epilepsy.

Levetiracetam concentrate for solution for infusion is an alternative treatment for patients when oral administration is temporarily not feasible. It contains Levetiracetam as the active substance and it is given by intravenous infusion.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Levetiracetam 100mg/ml concentrate for solution for infusion, together with measures to minimise such risks and the proposed studies for learning more about

Levetiracetam 100mg/ml concentrate for solution for infusion's risks, are outlined below.

- Specific reference safety information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC is used to address patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size as a sterile, single use vial requiring dilution and reconstitution prior to use is chosen to ensure that the medicine is used correctly;
- The medicine's legal status — the medicine is supplied to the patient with a prescription and can only be administered by a suitably qualified healthcare professional.

Together, these measures constitute *routine risk minimisation* measures.

If important information that may affect the safe use of Levetiracetam 100mg/ml concentrate for solution for infusion is not yet available, it is listed under 'missing information' below

II.A List of important risks and missing information

Important risks of Levetiracetam 100mg/ml concentrate for solution for infusion are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Levetiracetam 100mg/ml concentrate for solution for infusion. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the longterm use of the medicine).

List of important risks and missing information	
Important identified risks	• Anaphylaxis and hypersensitivity • Haemotological abnormalities • Suicide and behaviour disorders • Renal impairment • Hepatic impairment
Important potential risks	• Fertility, Pregnancy and Lactation • Interaction with other medicinal products • Medication error
Important missing information	• Long term effects on children > 4 years • Use in children <4 years

II.B Summary of important risks

The safety information in the proposed Product Information is aligned to the reference product.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Levetiracetam 100mg/ml concentrate for solution for infusion.

II.C.2 Other studies in the Post authorisation development plan

There are no studies required for Levetiracetam 100mg/ml concentrate for solution for infusion.

ANNEXES

Annex 1: Interface with EudraVigilance

Not applicable

Annex 2: Tabulated summary of planned, on-going and completed pharmacovigilance study programme

Not applicable

Annex 3: Protocols for proposed, ongoing and completed studies in the pharmacovigilance plan

Not applicable

Annex 4: Specific adverse event follow up forms

EXAMPLE LETTER – ATYPICAL FRACTURES

INITIAL HEALTHCARE PROFESSIONAL LETTER

For the attention of the reporter

dd-mmm-yyyy

[Dr]
[Address]

[Postcode]

Our Ref: [AE Reference Number]

Dear Dr/Sirs/Ms,

Re: [PRODUCT DETAILS]

We have been informed of a suspected adverse event/adverse drug reaction **[(AE/ADR)]** which occurred whilst your patient **[PATIENT'S NAME (identifier)],** was receiving therapy with **[PRODUCT]**. As you may be aware we have a legal and professional obligation to update and maintain safety data on our product and where appropriate to report this information to the Regulatory authority as soon as possible.

In view of this, we would very much like to receive details of this case and would be grateful if you could spare the time to complete the enclosed Adverse Event Form. The reverse of the form can be used for additional case related information, if required.

We would appreciate the provision of any additional information such as, **[INSERT TARGETED INFORMATION, such as fractures site, radiographic features, bone mineral density scans]** or other relevant information which would enable a full medical assessment of this case.

If however you feel that the suspected ADR is/was not related to **[PRODUCT]**, we would appreciate confirmation below. Completion of the attached Adverse Event form is not required in this instance.

Page 2./…..

STATEMENT TO REFUTE PRODUCT ASSOCIATED WITH ADVERSE EVENT:

Our Ref: **[AE Reference Number]**

I now feel that this event is/was NOT related to ……

Signed:…… Qualifications:……..

Print Name:……..……...…… Date:……..

Reason
(s)……..……

……..……...……

Please be assured that any information provided will be treated in the strictest confidence.

Thank you in advance for your co-operation.

Kind regards,

[NAME]
Drug Safety Officer

Encl. *Adverse Drug Reaction Form*

Page 2./…..

RED LINE
PHARMACOVIGILANCE

SUSPECT ADVERSE DRUG REACTION REPORT

Date Received:	Adverse Event Ref:

PATIENT DETAILS:

Initials	Age	Sex:	Weight	Date of Birth	Hospital Ref.

If female, is the patient pregnant?	If yes, Date of Last Menstrual Period:	Expected Delivery Date:

SUSPECTED DRUG(S):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					

SUSPECTED ADVERSE REACTION(S):

Please describe the reaction and any treatment given.	Outcome: ○ Recovered ○ Recovering ○ Continuing ○ Unknown

Do you consider the reaction to be serious?	Date reaction started:	Date reaction stopped:

Reason for Seriousness:

○ Patient Died ○ Life Threatening ○ Congenital Abnormality
○ Involved/Prolonged Hospitalisation ○ Disability/Incapacity ○ Medically Significant

CONCOMITANT MEDICATION (incl. herbal or self medication):

Drug/Brand Name	Route of Admin	Daily Dosage	Indication	Date Started	Date Stopped
1.					
2.					
3.					
4.					

ADDITIONAL INFORMATION RELEVANT TO THIS EVENT:

PLEASE USE THE REVERSE OF THIS PAGE FOR ADDITIONAL NOTES.

REPORTER DETAILS:

Title, Name & Surname	Speciality	Signature	Date

Postal Address: Postcode:	Email:	Tel No.

*PLEASE RETURN THIS FORM IN THE STAMPED, SELF-ADDRESSED ENVELOPE PROVIDED.

RL/PV-1/6.2010/v1.0

Annex 5: Protocols for proposed and on-going studies in RMP part IV

Not applicable

Annex 6: Details of proposed additional risk minimisation activities

Not applicable

Annex 7: Other supporting data

Not applicable

Annex 8: Summary of changes to the risk management plan over time

Version	**Approval date** **Procedure**	**Change**
1.0	<date of auth> UK/H/6789/001/DC	Initial RMP –Initial submission with the Marketing Autorisation Application.