24 October 2013
EMA/777160/2013
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Levetiracetam Hospira

International non-proprietary name: LEVETIRACETAM

Procedure No. EMEA/H/C/002783/0000

Note

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

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1. Background information on the procedure

1.1. Submission of the dossier

The applicant Hospira UK Limited submitted on 29 November 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Levetiracetam Hospira, through the centralised procedure under Article 3 (3) of Regulation (EC) No. 726/2004– 'Generic of a centrally authorised product'. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 19 July 2012.

The application concerns a generic medicinal product as defined in Article 10(2)(b) of Directive 2001/83/EC and refers to a reference product for which a Marketing Authorisation is or has been granted in in the Union on the basis of a complete dossier in accordance with Article 8(3) of Directive 2001/83/EC.

The applicant applied for the following indication:

Levetiracetam Hospira 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 Hospira 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 Hospira concentrate is an alternative for patients when oral administration is temporarily not feasible.

The legal basis for this application refers to a Generic application (Article 10(1) of Directive No 2001/83/EC).

The application submitted is composed of administrative information and complete quality data.

Information on paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

The chosen reference product is:

■ Medicinal product which is or has been authorised in accordance with Community provisions in accordance with Community provisions in force for not less than 6/10 years in the EEA:

- Product name, strength, pharmaceutical form: Keppra 250 mg Film-coated tablets
- Marketing authorisation holder: UCB Pharma S.A.
- Date of authorisation: 29/09/2000
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/00/146/001-005

  EU/1/00/146/029 and EU/1/00/146/034

■ Medicinal product authorised in the Community/Members State where the application is made or European reference medicinal product:

- Product name, strength, pharmaceutical form: Keppra 100 mg/ml Concentrate for solution for infusion.
- Marketing authorisation holder: UCB Pharma S.A.
- Date of authorisation: 29/03/2006
- Marketing authorisation granted by: Community
- Community Marketing authorisation number: EU/1/00/146/030

■ Medicinal product which is or has been authorised in accordance with Community provisions in force and to which bioequivalence has been demonstrated by appropriate bioavailability studies:

- Not applicable

Scientific advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was licensed in the USA at the time of submission of the application.

1.2. Manufacturers

Manufacturer(s) responsible for batch release

Hospira UK Limited
Queensway, Royal Leamington Spa
Warwickshire, CV31 3RW
United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Juris Pokrotnieks

- The application was received by the EMA on 29 November 2012.
- The procedure started on 26 December 2012.
- The Rapporteur's initial Assessment Report was circulated to all CHMP members on 15 March 2013.
- During the meeting on 22-25 April 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 26 April 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 16 July 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 19 August 2013.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 05 September 2013.
- During the CHMP meeting on 16-19 September 2013, the CHMP agreed on a list of outstanding issues to be addressed by the applicant.
- The applicant submitted the responses to the CHMP consolidated List of Outstanding Issues on 26 September 2013.
- The Rapporteur circulated the Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 01 October 2013.
- During the meeting on 21-24 October 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Levetiracetam Hospira.

2. Scientific discussion

2.1. Introduction

The Marketing Authorization Application of Levetiracetam Hospira 100 mg/ml concentrate for solution for infusion is a generic of the centrally authorised product Keppra which exists as film-coated tablets of 250 mg, 500 mg, 750 mg and 1000 mg as oral solution (100 mg/ml) and as concentrate for solution for infusion (100 mg/ml).

The mechanism of action of levetiracetam still remains to be fully elucidated but appears to be different from the mechanisms of current antiepileptic medicinal products. In vitro and in vivo experiments suggest that levetiracetam does not alter basic cell characteristics and normal neurotransmission.

Levetiracetam is indicated for the treatment of Epilepsy.

The efficacy and safety of levetiracetam has been demonstrated in several well-controlled studies. A summary of these studies can be found in the EPAR of the reference product Keppra.

A summary of the literature with regard to clinical data of Levetiracetam Hospira was provided and was accepted by the CHMP. This is in accordance with the relevant guideline and additional clinical studies were not considered necessary.

Bioequivalence testing with the reference product was not required under the provisions of the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1: "Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product."

The therapeutic indication of Levetiracetam Hospira is:

Levetiracetam Hospira 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 Hospira 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 Hospira concentrate for solution for infusion is an alternative for patients when oral administration is temporarily not feasible. This generic application has one more pack size than the reference product, which is consistent with the posology and treatment duration as approved in the SmPC.

2.2. Quality aspects

2.2.1. Introduction

The finished product is available as a 100 mg/ml concentrate for solution for infusion of levetiracetam as active substance.

Other ingredients are: sodium acetate trihydrate, glacial acetic acid, sodium chloride and water for injections.

The product is available in 5 ml glass vial (type I) with bromobutyl rubber stoppers and an aluminium flip-off seal as described in section 6.5 of the SmPC.

2.2.2. Active substance

Levetiracetam is a white to off-white crystalline powder soluble in methanol, acetonitrile and water. It presents one single asymmetric centre being the S-enantiomer the active one. According to the synthetic process described in this application the active substance is consistently obtained as the S-enantiomer and is routinely controlled by a chiral purity test. From the presented literature and patents, it is evident that there is no designated polymorphic form described for Levetiracetam.

The specification of the active substance and finished product are in accordance with the European Pharmacopoeia.

The chemical name of Levetiracetam is (S)-2-(2-oxopyrrolidin-1-yl)butanamide and has the following structure:

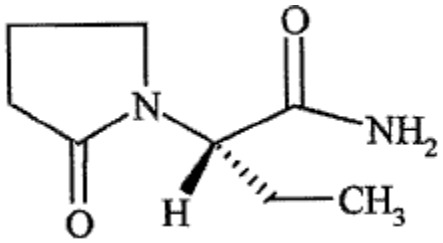

Figure 1: Chemical structure of levetiracetam

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

The chemical structure elucidation has been performed by infrared spectroscopy, ultraviolet spectroscopy, ^{1}H NMR spectroscopy, ^{13}C NMR spectroscopy, X-ray powder difractogram and mass spectrometry.

Manufacture

The active substance is synthesised in three steps using commercially available and well defined starting materials. The final active substance is purified by crystallisation.

The designation of the starting materials for the synthesis of the active substance has been justified with respect to their impurity profiles, their potential for a carry-over into the final active substance, their structural complexity and with respect to their proximity to the final intermediate and the drug substance, respectively.

Information provided describes adequately the manufacturing including reactions conditions, quantities of raw materials and yields.

The characterisation of the active substance and its impurities is in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origins and characterised. The carry-over of impurities, reagents, solvents and catalysts from the starting material into the final active substance has been also discussed.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediates, starting materials and reagents have been presented.

The active substance is packaged in double polyethylene bag and sealed. The materials in contact with the active substance comply with the EC directive 2002/72/EC and EC 10/2011.

Specification

The active substance specification includes tests for appearance, solubility, identification (specific optical rotation, IR; HPLC), assay (HPLC appearance of solution, enatiomeric purity (HPLC), impurities (HPLC), heavy metals (Ph Eur), water content (Ph Eur), sulphated ash (Ph Eur), residual solvents (GC), microbiological quality (Ph Eur).

A detailed description for all analytical methods was provided. Full method validation data was also provided for the in-house analytical methods in accordance with the relevant ICH Guidelines. The analytical methods proposed are suitable to control the quality of the active substance. The impurity limits are acceptable and there is no concern from the point of view of safety.

Batch analysis data are provided on three production batches produced by the proposed synthetic route, and the batch analysis data show that the active ingredient can be manufactured reproducibly. All results are within the specifications and consistent from batch to batch.

Stability

Three production scale batches of the active substance packed in the intended commercial packaging from the proposed manufacturers were put on stability testing as per ICH conditions: under long term (25°C/60%RH) for up 48 months and accelerated (40°C/75%RH) for up 6 months. The active substance used in the primary stability studies was manufactured according to the commercial process.

The following parameters were tested: appearance, loss on drying, impurities (HPLC), assay (HPLC) and chiral purity (HPLC).

Forced degradation studies were conducted by exposing the active substance to *u.v* radiation, high temperature, aqueous hydrolysis, acid, base and oxidative conditions. Based on these studies it is observed that Levetiracetam is sensitive to acidic, basic, oxidation and aqueous conditions.

Photostability testing following ICH guidelines Q1B was performed on one batch of the active substance. The results showed that there are no significant changes for any of the evaluated parameters established for the stability studies.

The stability results indicate that the active substance is stable at controlled room temperature. The results justify the proposed retest period in the proposed container.

2.2.3. Finished medicinal product

Pharmaceutical development

The concentrate for solution for infusion has been developed with the objective of developing a pharmaceutical form similar to the innovator's product Keppra concentrate for solution for infusion. The formulation development was based on the reference medicinal product, and Levetiracetam Hospira contains the same excipients (qualitatively) as in Keppra parenteral formulation.

The excipients used in the manufacturing of Levetiracetam Hospira are commonly used in this type of pharmaceutical medicinal products and especially in solutions for infusion. All excipients are described in the European Pharmacopoeia and its specifications and analytical procedures are also in accordance with the European Pharmacopoeia standards. The list of excipients is included in section 6.1 of the SmPC.

Based on the results of the compatibility studies between the active substance and the different excipients, it was concluded that there are no compatibility issues.

Levetiracetam Hospira is administered intravenously and is 100% bioavailable. Therefore, a bioequivalence study versus the reference product Keppra was not required. In order to demonstrate equivalence between Levetiracetam Hospira and the reference product (Keppra) a pharmaceutical equivalence testing was conducted. This Testing included evaluation of appearance, identification, pH, assay of Levetiracetam, impurities and enatiomeric purity. Based on the results, the Applicant demonstrated that both formulations are equivalent.

Physical and chemical in-use stability studies for diluted solutions stored in PVC bags were conducted during the drug development. Based on the results it was concluded that the diluted solution is stable when stored up to 24 hours at 30°C.

The primary packaging is described as stated in the SmPC. The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data. This container was selected on the basis of compatibility and container-closure integrity studies and is adequate for the intended use of the medicinal product.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process consists of the following main steps: weighing of raw materials and volumetric determination of water for injection, preparation of the Levetiracetam solution, aseptic filtration, filling, sealing of the vials, final sterilization and packaging. Satisfactory flow-chart with in-Process Controls of the manufacturing process has been included.

Terminal sterilisation process by autoclave is used with validated parameters to achieve overkill cycle. Validation data concerning product terminal sterilisation (heat distribution and penetration) and sterility of bulk solution (microbial efficacy of the cycle) is provided.

The validation of the manufacturing process has been evaluated on three consecutive production scale batches. The quality of the production batches was evaluated through the results of in process testing as well as the results of finished product testing. The validation protocol was enclosed in the dossier.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form: appearance (visual), identification (specific optical rotation and HPLC), pH (Ph Eur), extractable volume (Ph Eur), particulate contamination (Ph Eur), sterility (Ph Eur), bacterial endotoxins (Ph Eur), assay (HPLC), impurities (HPLC), enantiomeric purity (HPLC), residual solvents (GC) and Osmolality (Ph Eur).

Batch analysis data of three scale batches of the finished product are provided. The results confirm the consistency of the process and its ability to manufacture a product complying with the product specification.

Stability of the product

Stability data of three scale batches of finished product stored under long term conditions for twenty four months at 25 ºC / 60% RH and for up to six months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of medicinal product are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for: appearance (visual), pH (Ph Eur), particulate contamination (Ph Eur), bacterial endotoxins (Ph Eur), sterility, assay (HPLC), impurities (HPLC) and enantiomeric purity (HPLC).

One batch was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. In addition stress stability studies were performed on one fully representative batch under various extreme conditions including acid, base, heat and oxidation. The data demonstrate that the medicinal product is not affected by light and is susceptible to degradation under acid, base, and oxidative conditions.

Based on the available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, and pharmaceutical aspects

Levetiracetam is described in the European Pharmacopoeia. Where applicable, specifications applied by both the active substance and the finished product manufacturers are in-line with the monograph.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The manufacturing flow-chart was provided with suitable in-process controls. The manufacturing process is adequately validated at full scale at the proposed manufacturing site and a validation protocol has been presented.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the data provided the quality of this medicinal product is considered to be acceptable. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendations for future quality development

None

2.3. Non-clinical aspects

2.3.1. Introduction

A non-clinical overview on the pharmacology, pharmacokinetics and toxicology has been provided, which is based on up-to-date and adequate scientific literature. The overview justified why there is no need to generate additional non-clinical pharmacology, pharmacokinetics and toxicology data. The non-clinical aspects of the SmPC were in line with the SmPC of the reference product. The impurity profile has been discussed and was considered acceptable.

Therefore, the CHMP agreed that no further non-clinical studies were required.

2.3.2. Ecotoxicity/environmental risk assessment

No environmental risk assessment was submitted. This was justified by the applicant as the introduction of Levetiracetam Hospira is considered unlikely to result in any significant increase in the combined sales volumes for all levetiracetam containing products and the

exposure of the environment to the active substance. Thus, the environmental risk was expected to remain unchanged and not to increase.

2.3.3. Conclusion on the non-clinical aspects

The CHMP considered the absence of non-clinical data adequately justified considering that the pharmacodynamic, pharmacokinetic and toxicological properties of levetiracetam are well known in light of the experience gained over more than 10 years of marketing of levetiracetam containing medicinal products in the EU/EEA.

2.4. Clinical aspects

2.4.1. Introduction

This is an application for a concentrate for solution for infusion containing levetiracetam in an aqueous solution in the same amount as the reference product Keppra (100mg/ml). The intended use and route of administration is also identical to the reference product.

In line with the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1 in its current version, bioequivalence studies are generally not required for parenteral solutions if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product. Hence, the applicant has not conducted any bioequivalence studies in support of this application.

2.4.2. Pharmacokinetics and Pharmacodynamics

No new pharmacodynamic studies were presented by the applicant and no such studies are required for this application. However, the applicant provided a clinical overview in support of this application, including references to scientific literature on the pharmacokinetic and pharmacodynamic properties of levetiracetam injectable formulations.

2.4.3. Clinical efficacy and safety

The applicant provided an overview of the scientific literature with regards to the clinical safety and efficacy of levetiracetam.

2.4.4. Post marketing experience

No post-marketing data are available. The medicinal product has not been marketed in any country.

2.4.5. Conclusions on clinical aspects

The CHMP considered the lack of additional clinical data adequately justified by the applicant. The applicant provided a clinical overview based on up-to-date scientific literature, which was considered acceptable by the CHMP.

2.5. Pharmacovigilance

Detailed description of the pharmacovigilance system

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

Risk management plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

Based on the PRAC review of the Risk Management Plan version 2.0, the PRAC considers by consensus that the risk management system for Levetiracetam (Levetiracetam Hospira) in the treatment of the proposed indications is acceptable.

Advice on conditions of the marketing authorisation

Risk management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

Additional risk minimisation measures

The PRAC considers that no additional risk minimisation measures will be necessary for the safe and effective use of the medicinal product in the proposed indication.

Obligation to conduct post-authorisation measures

None

Safety concerns

The applicant identified the following safety concerns in the RMP in line with the reference product Keppra (100mg/ml solution for infusion):

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Abnormal behaviour and suicide
	Blood dyscrasias
	Interactions with Carbamazepine, Phenobarbital, Phenytoin and Primidone, Probenecid
Important potential risks	Seizure worsening
Missing information	Long-term effects on learning, intelligence, growth, endocrine function, puberty and childbearing potential in children
	Limited data available on safety in patients with different epilepsy syndrome younger than 12 months and those younger than 4 years

Pharmacovigilance plans

The PRAC, having considered the data submitted, was of the opinion that routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

The PRAC also considered that routine pharmacovigilance is sufficient to monitor the effectiveness of the risk minimisation measures.

Risk minimisation measures

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

PSUR submission

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

User consultation

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

3. Benefit-risk balance

This application concerns a generic version of levetiracetam concentrate for solution for infusion. The reference product Keppra 100 mg/ml concentrate for solution for infusion is indicated as monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy.

Keppra 100 mg/ml concentrate for solution for infusion is also 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.

Keppra concentrate is an alternative for patients when oral administration is temporarily not feasible.

No nonclinical studies have been provided for this application but an adequate summary of the available nonclinical information for the active substance was presented and considered sufficient.

From a clinical perspective, this application does not contain new data on the pharmacokinetics and pharmacodynamics as well as the efficacy and safety of the active substance; the applicant's clinical overview on these clinical aspects based on information from published literature was considered sufficient.

Bioequivalence testing with the reference product is not required under the provisions of the Guideline on the Investigation of Bioequivalence CPMP/EWP/QWP/1401/98 Rev.1: "Bioequivalence studies are generally not required if the test product is to be administered as an aqueous intravenous solution containing the same active substance as the currently approved product."

The overall benefit-risk assessment is considered to be positive, since no new indication or population is claimed and reference is made to the innovator product for the benefits and risks of levetiracetam. Levetiracetam is considered an antiepileptic drug with well known safety and efficacy profile for the treatment of various forms of epilepsy, this being supported by experience with marketed levetiracetam in a large number of patients.

The CHMP, having considered the data submitted in the application and available on the chosen reference medicinal product, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information. The CHMP furthermore considered that there is sufficient support for concluding on a benefit/risk ratio comparable to the reference product.

4. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Levetiracetam Hospira as a monotherapy in the treatment of partial onset seizures with or without secondary generalisation in patients from 16 years of age with newly diagnosed epilepsy; 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 is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal products subject to medical prescription.

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

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

- **Additional risk minimisation measures**

None