LÄKEMEDELSVERKET
SWEDISH MEDICAL PRODUCTS AGENCY

Public Assessment Report
Scientific discussion

Fosphenytoin Eugia
(fosphenytoin sodium)

SE/H/2123/01/DC

This module reflects the scientific discussion for the approval of Fosphenytoin Eugia. The procedure was finalised on 2022-09-20. For information on changes after this date please refer to the module 'Update'.

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I. INTRODUCTION

Based on the review of the quality, safety and efficacy data, a marketing authorisation has been granted for Fosphenytoin Eugia, 75 mg/ml (50 mg PE/ml), Concentrate for solution for injection/infusion.

The active substance is fosphenytoin sodium. A comprehensive description of the indication and posology is given in the SmPC.

For recommendations to the marketing authorisation not falling under Article 21a/22a/22 of Directive 2001/83/EC and conditions to the marketing authorisation pursuant to Article 21a/22a/ 22 of Directive 2001/83/EC to the marketing authorisation, please see section VI.

The application for Fosphenytoin Eugia, 75 mg/ml, concentrate for solution for injection/infusion, is a generic application made according to Article 10(1) of Directive 2001/83/EC. The applicant, RPH Pharmaceuticals AB, applies through the Decentralised Procedure with Sweden acting as reference member state (RMS) and FR as concerned member state (CMS).

The reference medicinal product chosen for the purposes of establishing the expiry of the data protection period is Pro-Epanutin, 75 mg/ml, concentrate for solution for injection/infusion authorised in Sweden since 1998, with Pfizer AB as marketing authorisation holder.

Potential similarity with orphan medicinal products
According to the application form and a check of the Community Register of orphan medicinal products there is no medicinal product designated as an orphan medicinal product for a condition relating to the indication proposed in this application.

II. QUALITY ASPECTS

II.1 Drug Substance

The structure of the drug substance has been adequately proven and its physico-chemical properties are sufficiently described.

The manufacture of the drug substance has been adequately described and satisfactory specifications have been provided for starting materials, reagents and solvents.

The drug substance specification includes relevant tests and the limits for impurities and degradation products have been justified. The analytical methods applied are suitably described and validated.

Stability studies confirm the retest period.

II.2 Medicinal Product

The medicinal product is formulated using excipients listed in section 6.1 in the Summary of Product Characteristics.

The manufacturing process has been sufficiently described and critical steps identified.

The tests and limits in the specification are considered appropriate to control the quality of the finished product in relation to its intended purpose.

Stability studies have been performed and data presented support the shelf life and special precautions for storage claimed in the Summary of Product Characteristics, sections 6.3 and 6.4.

III. NON-CLINICAL ASPECTS

Pharmacodynamic, pharmacokinetic and toxicological properties of fosphenytoin sodium are well known. As fosphenytoin sodium is a widely used, well-known active substance, no further studies are required and the applicant provides none. Overview based on literature review is, thus, appropriate.

Environmental Risk Assessment (ERA)
Since Fosphenytoin Eugia are generic products, it will not lead to an increased exposure to the environment. An environmental risk assessment is therefore not deemed necessary.

There are no objections to approval of Fosphenytoin Eugia from a non-clinical point of view.

IV. CLINICAL ASPECTS

Pharmacokinetics
To support the marketing authorisation application the applicant has not conducted any bioequivalence studies but applies for a biowaiver.

Pharmacokinetic properties of the active substance
Fosphenytoin is a pro-drug of phenytoin. When fosphenytoin is administered by IV infusion, maximum plasma fosphenytoin concentrations are achieved at the end of the infusion. Fosphenytoin is completely bioavailable following IM administration of fosphenytoin. Peak concentrations occur at approximately 30 minutes postdose. Plasma fosphenytoin concentrations following IM administration are lower but more sustained than those following IV administration due to the time required for absorption of fosphenytoin from the injection site.

The pharmacokinetics of phenytoin following IV administration of fosphenytoin, are complex and when used in an emergency setting (e.g. status epilepticus), differences in rate of availability of phenytoin could be critical. Studies have, therefore, empirically determined an infusion rate for fosphenytoin that gives a rate and extent of phenytoin systemic availability similar to that of a 50 mg/min phenytoin sodium infusion. Because fosphenytoin is completely absorbed and converted to phenytoin following IM administration, systemic phenytoin concentrations are generated that are similar enough to oral phenytoin to allow essentially interchangeable use and to allow reliable IM loading dose administration.

The conversion half-life of fosphenytoin to phenytoin is approximately 15 minutes. Phenytoin hepatic metabolism is saturable and, following administration of single IV fosphenytoin doses of 400 to 1200 mg PE, total and unbound phenytoin AUC values increase disproportionately with dose. Mean total phenytoin half-life values (12.0 to 28.9 hr) following fosphenytoin administration at these doses are similar to those after equal doses of parenteral phenytoin and tend to be longer at higher plasma phenytoin concentrations.

Biowaiver
The application is based on a Biopharmaceutical Classification System (BCS) based biowaiver and no bioequivalence study has been submitted.

No bioequivalence study has been submitted. The applicant claims that a bioequivalence study is not necessary according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1) since the product is a parenteral solution.

The applicant states that the product is administered intravenously or intramuscularly as an aqueous solution. The test product is of the same type of solution and contains the same concentration of the same active substance and the same excipients in similar amounts as the medicinal product currently approved and therefore bioequivalence studies are not required.

Discussion and overall conclusion

The applied product is an aqueous solution that can be administered either intravenously or intramuscularly. It contains the same active substance in the same concentration as the currently authorised product. The applied product contains the same excipients (with the exception that the applied product may also contain NaOH for pH adjustment) in similar amounts as the reference product. For this type of product, no bioequivalence studies are required according to the Guideline on the investigation of Bioequivalence (CHMP/QWP/EWP/1401/98 Rev. 1). Thus, the waiver of bioequivalence studies is acceptable.

Pharmacodynamics/Clinical efficacy/Clinical safety

No new studies on pharmacodynamics, clinical efficacy or clinical safety have been submitted which is acceptable.

Risk Management Plan

The MAH has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to fosphenytoin in procedure SE/H/2123/01/DC.

Safety specification

The MAH has submitted the version 1.0 RMP dated 2022-07-19 for procedure SE/H/2123/01/DC and proposed the following summary safety concerns:

Summary of safety concerns	
Important identified risks	Medication errors
	Off label use in children less than 5 years of age
Important potential risks	None
Missing information	None

The proposed Summary of safety concerns is in line with the reference product (Pro-Epanutin) and is acceptable.

Pharmacovigilance Plan

Routine pharmacovigilance is suggested and no additional pharmacovigilance activities are proposed by the applicant, which is endorsed.

Risk minimisation measures

The MAH updated their Risk minimisation measures and propose the following:

Safety concern	Risk minimisation measures	Pharmacovi-gilance activities
Medication errors	Routine risk minimisation measures: SmPC section 4.1, 4.2, 4.4, 4.9 Section 2 of the PIL Sections of the Vial Label and Carton For the carton: - Total vial content (500 mg PE in 10 mL) has been made more prominent and is now more prominent than the concentration of fosphenytoin - Reference to 750 mg of fosphenytoin has been minimized to avoid confusion - Wording has been added to instruct HCP's to refer to the package insert for important dosing and infusion rate instructions - Instructions regarding the need to dilute the solution prior to infusion are more prominent For the vial label: - Total vial content (500 mg PE in 10 mL) has been made more prominent - Reference to 750 mg of fosphenytoin has been removed - Instructions regarding the need to dilute the solution prior to infusion are more prominent Additional risk minimisation measures Educational material for healthcare professional: Dosing aid for adults Dosing aid for children 5 years and over Details are already covered in Annex 6 under key messages.	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection**: None **Additional pharmacovigilance activities:** None
Off label use in children less than 5 years of age	Routine risk minimisation measures SmPC section 4.1, 4.2, 4.4 Sections of the PIL Additional risk minimisation measures Educational material for healthcare professional: Dosing aid for adults Dosing aid for children 5 years and over -Direct Healthcare Professional Communication to ensure awareness of the approved age range (5 years and older) for fosphenytoin in children	**Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection:** None **Additional pharmacovigilance activities:** None

Assessor´s comment: The risk minimisation measures are in line with the risk minimisation measures of the originator, which is acceptable.

Summary of the RMP

The submitted Risk Management Plan, version 1.0 signed 2022-07-19 for procedure SE/H/2123/01/DC is considered acceptable.

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 RMS;
- 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 dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time, but via different procedures.

V. USER CONSULTATION

The user test has been assessed and accepted.
The package leaflet for Fosphenytoin Eugia has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PL was English.
In conclusion, the user test is considered acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

The quality of the generic product, Fosphenytoin Eugia, is found adequate. There are no objections to approval of Fosphenytoin Eugia, from a non-clinical and clinical point of view. The product information is acceptable. The application is therefore recommended for approval.

List of recommendations not falling under Article 21a/22a/22 of Directive 2001/83/EC in case of a positive benefit risk assessment

N/A

List of conditions pursuant to Article 21a/22a or 22 of Directive 2001/83/EC

N/A

VII. APPROVAL

The decentralised procedure for Fosphenytoin Eugia, 75 mg/ml (50 mg PE/ml), Concentrate for solution for injection/infusion was positively finalised on 2022-09-20.

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Public Assessment Report – Update

Procedure number*	Scope	Product Information affected (Yes/No)	Date of end of procedure	Approval/ non approval	Summary/ Justification for refuse

*Only procedure qualifier, chronological number and grouping qualifier (when applicable)

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