PART VI. SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for Pro-Epanutin (fosphenytoin)

This is a summary of the RMP for Pro-Epanutin. The RMP details important risks of Pro-Epanutin, how these risks can be minimised, and how more information will be obtained about Pro-Epanutin's risks and uncertainties (missing information).

Pro-Epanutin's SmPC and its package leaflet provide essential information to HCPs and patients on how Pro-Epanutin should be used.

I. The Medicine and What It Is Used For

Pro-Epanutin (fosphenytoin) is authorised for the control of SE of the tonic-clonic (grand mal) type, prevention and treatment of seizures occurring in connection with neurosurgery and/or head trauma and as substitute for oral phenytoin if oral administration is not possible and/or contraindicated. It contains fosphenytoin as the active substance and it is given either by IV or IM route of administration.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of fosphenytoin, together with measures to minimise such risks and the proposed studies for learning more about fosphenytoin's risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

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

In the case of Pro-Epanutin, these measures are supplemented with *additional risk minimisation* measures mentioned under relevant important risks, below.

Additional risk minimisation measures to minimise the risks identified for Pro-Epanutin include:

Dosing Aids (adult and pediatric) (leaflet/wall-chart)

- Ensure that HCPs are aware of the issue of medication errors with fosphenytoin as well as updates to the SmPC to address this issue.
- Provide a simplified guide for the calculation of fosphenytoin dosing and determination of rate of administration
- To improve understanding of the approved age range (5 years and older) for use of fosphenytoin in children.

II.A List of Important Risks and Missing Information

Important risks of fosphenytoin 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 fosphenytoin. 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 long-term use of the medicine);

Table 14. List of important risks and missing information

Important identified risks	Medication Errors Off-label use in children less than 5 years of age
Important potential risks	None
Missing information	None

II.B Summary of Important Risks

Table 15. Important Identified Risk - Medication Errors

Evidence for linking the risk to the medicine	• Postmarketing safety database. • The relationship between fosphenytoin administration and hemodynamically unstable cardiac arrhythmias[54] has been reported in the postmarketing setting following IV administration at high doses and high rates of administration. Continuous monitoring of electrocardiogram, blood pressure and respiratory function for the duration of the infusion is essential.[55]

Table 15. Important Identified Risk - Medication Errors

Risk factors and risk groups	• Risk factors include complex dosing and administration instructions, complex/unclear vial and package labelling, unclear prescribing information, and the use of fosphenytoin in emergency settings. • Risk groups include children, who may be more vulnerable to medication errors leading to overdose because fewer vials are needed for significant overdoses (and the smaller number of vials may be less likely to prompt a re-check of the dose).
Risk minimisation measures	Routine risk communication: EU-SmPC Section 4.1, Therapeutic indications EU-SmPC Section 4.2, Posology and method of administration EU-SmPC Section 4.4 Special warnings and precautions for use EU-SmPC Section 4.9 Overdose Sections of the Patient Information Leaflet Sections of the Vial Label and Carton. Routine risk minimisation activities recommending specific clinical measures to address the risk: Important information to help prevent medication errors of fosphenytoin are included in SmPC Section 4.1. Posology and method of administration for medication errors of fosphenytoin is included in SmPC Section 4.2. Special warnings and precautions for medication errors of fosphenytoin is included in SmPC Section 4.4. Overdose for medication errors of fosphenytoin is included in SmPC Section 4.9. The sections of the Vial Label and Carton for medication errors of fosphenytoin were updated. Additional risk minimisation measures: **Direct Healthcare Professional Communication** A DHPC was distributed to HCPs and regulatory agencies in the EEA to ensure awareness of the risk of medication errors with fosphenytoin. **Dosing Aid (leaflet/wall-chart)** A Dosing Aid has been developed and distributed to HCPs, regulatory agencies, and implemented in product packaging (carton) in the EEA with the intention to reduce medication error risk and to optimize its ability to provide useful information to HCPs involved in the administration of fosphenytoin.
Additional pharmacovigilance activities	Not applicable

EEA = European Economic Area; DHPC = Direct Healthcare Professional Communication; EU = European Union; HCP = Healthcare Professional; SmPC = Summary of Product Characteristics.

Table 16. Important Identified Risk - Off-Label Use in Children Less than 5 Years of Age

Evidence for linking the risk to the medicine	Postmarketing safety database.
Risk factors and risk groups	Risk factors: Lack of effective medication alternatives for the treatment of epilepsy and status epilepticus in children less than 5 years of age. Lack of HCP awareness that fosphenytoin is not approved for use in children less than 5 years of age. Risk Groups: Paediatric patients less than 5 years of age.
Risk minimisation measures	Routine risk communication: EU-SmPC Section 4.1, Therapeutic indications EU-SmPC Section 4.2, Posology and method of administration EU-SmPC Section 4.4 Special warnings and precautions for use Sections of the Patient Information Leaflet Routine risk minimisation activities recommending specific clinical measures to address the risk: Important information to help prevent off-label use in children less than 5 years of age of fosphenytoin are included in SmPC Section 4.1. Posology and method of administration for off-label use in children less than 5 years of age of fosphenytoin is included in SmPC Section 4.2. Special warnings and precautions for off-label use in children less than 5 years of age of fosphenytoin is included in SmPC Section 4.4. Additional risk minimisation measures: **Direct Healthcare Professional Communication** A DHPC was distributed to HCPs and regulatory agencies in the EEA to ensure awareness of the risk of medication errors with fosphenytoin. **Dosing Aid (leaflet/wall-chart)** A Dosing Aid has been developed and distributed to HCPs, regulatory agencies, and implemented in product packaging (carton) in the EEA with the intention to reduce medication error risk and to optimize its ability to provide useful information to HCPs involved in the administration of fosphenytoin.
Additional pharmacovigilance activities	Not applicable

DHPC = Direct Healthcare Professional Communication; EU = European Union; HCP = Healthcare Professional; SmPC = Summary of Product Characteristics.

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 obligations for Pro-Epanutin.

II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies required for Pro-Epanutin.