Summary of risk management plan for ABSENOR; (Sodium valproate) Orion Corporation

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This is a summary of the risk management plan (RMP) for Absenor. The RMP details important risks of Absenor, how these risks can be minimized, and how more information will be obtained about Absenor's risks and uncertainties (missing information).

Absenor's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how Absenor should be used.

Important new concerns or changes to the current ones will be included in updates of Absenor's RMP.

I. The medicine and what it is used for

Absenor is authorized for the following indications (according to the national registrations):

• Treatment of epilepsy.

• Treatment of manic episodes in bipolar disorder. The continuation of treatment after manic episode could be considered in patients who have responded to valproate for acute mania.

It contains valproate as the active substance and it is given by oral and rectal routes of administration.

See SmPC for the full information.

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

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

Measures to minimise the risks identified for Absenor are:

- Specific information, such as warnings, precautions, and advice on correct use, in the SmPC and PL addressed to healthcare professionals (HCP) and patients;
- Visual text warning and pictogram on the outer packaging and depending on the countries a pictogram may be added on the primary packaging;
- The medicine’s legal status — the way a medicine is supplied to the patient (treatment initiation and reassessment by a specialist).

Together, these measures constitute routine risk minimisation measures.

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

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Absenor are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. 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 Absenor. 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);

Summary of safety concerns	
Important identified risks	• Teratogenicity
Important potential risks	• Risks to unborn children via third generation and paternal exposure
Missing information	None

II.B Summary of important risks

The safety information in the proposed product information is aligned to the originator/reference medicinal product.

Important identified risk: Teratogenicity	
Evidence for linking the risk to the medicine	Preclinical data, pharmacovigilance database (clinical and postmarketing data), and worldwide scientific literature.
Risk factors and risk groups	<u>Risk factors:</u> Multiple-drug therapy that includes valproate (especially in high dose) induces a higher risk of teratogenicity than therapy with valproate alone. This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established. <u>Population at risk:</u> Women of childbearing potential and pregnant women.
Risk minimisation measures	<u>Routine risk minimisation measures:</u> Information in SmPC sections 4.2, 4.3, 4.4, 4.6 and 4.8. A visual reminder on the outer and primary package including a text warning and a symbol/pictogram. Prescription only medicine. <u>Additional risk minimisation measures:</u>

Important identified risk: Teratogenicity	
	A Pregnancy Prevention Programme (PPP) is put in place. It combines the use of educational tools with interventions to minimize pregnancy exposure during treatment with valproate. The educational materials: • Direct Healthcare Professional Communication (DHPC) • Guide for Healthcare professionals • Guide for Patients • Annual Risk Acknowledgement Form • Patient Card
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Drug Utilization Study (VALNAC09343, an extension of drug utilization study VALNAC07557) to assess the effectiveness of the new risk minimization measures and to further characterize the prescribing patterns for valproate Survey among HCP (VALNAC09348) to assess knowledge of HCP and behavior with regard to PPP as well as receipt/use of DHPC and educational materials Survey among Patients (VALNAC09348) to assess knowledge of patients with regards to PPP as well as receipt/use of educational materials PASS preferably based on existing registries to further characterize the fetal anticonvulsant syndrome in children with valproate in utero exposure as compared to other anti-epileptic drugs

Important potential risk: Risks to unborn children via third generation and paternal exposure	
Evidence for linking the risk to the medicine	Pharmacovigilance database (clinical and postmarketing data), and worldwide scientific literature.
Risk factors and risk groups	Unknown
Risk minimisation measures	<u>Routine risk minimisation measures:</u> Prescription only medicine <u>Additional risk minimisation measures:</u> None
Additional pharmacovigilance activities	<u>Additional pharmacovigilance activities:</u> Retrospective observational study (VALNAC09345): To investigate the association between paternal exposure to

Important potential risk: Risks to unborn children via third generation and paternal exposure	
	valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring

II.C Post-authorisation development plan

The following studies are conditions of the marketing authorization:

Drug utilization study (VALNAC09343, an extension of drug utilization study VALNAC07557)
Purpose of the study To assess the effectiveness of the risk minimizations measures and to further characterize the prescribing patterns for valproate.
Observational study to evaluate and identify the best practices for switching of valproate in clinical practice (VALNAC09344)
Purpose of the study To provide guidance to clinicians on the switch and discontinuation of valproate.
Survey among heathcare professionals (VALNAC09348)
Purpose of the study To assess knowledge of heathcare professionals and behavior with regard to Pregnancy Prevention Programme (PPP) as well as receipt/use of Direct Healthcare Professional Communication (DHPC) and educational materials.
Survey among patients (VALNAC09348)
Purpose of the study To assess knowledge of patients with regards to PPP as well as receipt/use of educational materials.
Post-authorisation safety study (PASS) preferably based on existing registries
Purpose of the study To further characterize the fetal anticonvulsant syndrome in children exposed to valproate in utero as compared to other anti-epileptic drugs.
Retrospective observational study (VALNAC09345)
Purpose of the study To investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring.