RISK MANAGEMENT PLAN - PART VI

SUMMARY OF THE RISK MANAGEMENT PLAN

Active substance(s) (INN or common name)	**Valproate and related substances**
Product's concerned (Brand name(s))	**DEPAKINE®, DEPAKINE CHRONO®, DEPAKINE CHRONOSPHERE®, DEPAKIN®, DEPAKIN CHRONO®, MICROPAKINE L.P. ®, EPILIM®, EPILIM CHRONO®, EPILIM CHRONOSPHERE®, ERGENYL®, ERGENYL CHRONO®, ERGENYL RETARD®, DEPRAKINE® DEPRAKINE RETARD®, DEPAKOTE®, DEPAMIDE®, VALPROATE DE SODIUM ZENTIVA®, SODIO VALPROATO SANOFI®**
Name of Marketing Authorization Holder or Applicant	**Sanofi**
Data lock point (DLP) for this module	**23-Jan-2018**
Version number of Risk Management Plan (RMP) when this module was last updated	**Version 5.1**

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ABBREVIATIONS

DHPC:	Direct Healthcare Professional Communication
DLP:	Data Lock Point
EMA:	European Medicines Agency
HCP:	Healthcare Professional
PASS:	Post-Authorization Safety Study
PBRER:	Periodic Benefit Risk Evaluation Report
PL:	Package Leaflet
PPP:	Pregnancy Prevention Programme
PSUR:	Periodic Safety Update Report
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics

Summary of risk management plan for DEPAKINE, DEPAKINE CHRONO, DEPAKINE CHRONOSPHERE, DEPAKIN, DEPAKIN CHRONO, MICROPAKINE L.P., EPILIM, EPILIM CHRONO, EPILIM CHRONOSPHERE, ERGENYL, ERGENYL CHRONO, ERGENYL RETARD, DEPRAKINE, DEPRAKINE RETARD, DEPAKOTE, DEPAMIDE, VALPROATE DE SODIUM ZENTIVA, SODIO VALPROATO SANOFI (Valproate)

This is a summary of the RMP for DEPAKINE, DEPAKINE CHRONO, DEPAKINE CHRONOSPHERE, DEPAKIN, DEPAKIN CHRONO, MICROPAKINE L.P., EPILIM, EPILIM CHRONO, EPILIM CHRONOSPHERE, ERGENYL, ERGENYL CHRONO, ERGENYL RETARD, DEPRAKINE, DEPRAKINE RETARD, DEPAKOTE, DEPAMIDE, VALPROATE DE SODIUM ZENTIVA, SODIO VALPROATO SANOFI (in future referred to as "all tradenames of valproate[1]"). The RMP details important risks of all tradenames of valproate related products where Sanofi is the Marketing Authorization Holder, [1]how these risks can be minimized, and how more information will be obtained about all tradenames of valproate's[1] risks and uncertainties (missing information).

The Summary of Product Characteristics (SmPC) and package leaflet (PL) give essential information to healthcare professionals (HCPs) and patients on how all tradenames of valproate related products[1] should be used.

VI.1. THE MEDICINE AND WHAT IT IS USED FOR

All tradenames of valproate related products[1] are 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 parenteral routes of administration.

[1] DEPAKINE, DEPAKINE CHRONO, DEPAKINE CHRONOSPHERE, DEPAKIN, DEPAKIN CHRONO, MICROPAKINE L.P., EPILIM, EPILIM CHRONO, EPILIM CHRONOSPHERE, ERGENYL, ERGENYL CHRONO, ERGENYL RETARD, DEPRAKINE, DEPRAKINE RETARD, DEPAKOTE, DEPAMIDE, VALPROATE DE SODIUM ZENTIVA, SODIO VALPROATO SANOFI

VI.2. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

Important risks of all tradenames of valproate[1], together with measures and other pharmacovigilance activities to minimize such risks or further characterize them, are outlined below.

Measures to minimize the risks identified for valproate are:

- Specific information, such as warnings, precautions, and advice on correct use, in the SmPC and PL addressed to HCPs 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 minimization measures.

In the case of all tradenames of valproate[1], these measures are supplemented with additional risk minimization measures mentioned under relevant important risks, outlined in the next sections. The additional measures consist of a Pregnancy Prevention programme (PPP) aimed at minimizing pregnancy exposure during treatment with valproate. The PPP combines the use of educational tools with interventions to control appropriately access to the valproate to female patients.

The educational tools include:

- Direct Healthcare Professional Communication (DHPC)
- Guide for HCPs
- Guide for Patients
- Annual Risk Acknowledgement Form
- Patient Card

In addition to these measures, information about adverse reactions will be collected continuously and regularly analyzed, including Periodic Safety Update Report (PSUR)/Periodic Benefit-Risk Evaluation Report (PBRER) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of all tradenames of valproate[1] is not yet available, it is listed under 'missing information' outlined in the next section.

VI.2.1. List of important risks and missing information

Important risks of all tradenames of valproate[1] are risks that need special risk management activities to further investigate or minimize 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 all tradenames of valproate[1]. 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.

Table 1 - List of important risks and missing information

Important identified risk	Teratogenicity
Important potential risk	Risks to unborn children via third generation and paternal exposure
Missing information	None

VI.2.2. Summary of important risks

Table 2 - Important risk: Teratogenicity with corresponding risk minimization activities and additional pharmacovigilance activities if any

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	**Risk factors**: 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. **Population at risk**: Women of childbearing potential and pregnant women.
Risk minimization measures	**Routine risk minimization measures**: Labeled in sections 4.2; 4.3; 4.4; 4.6 and 4.8 of the SmPC. A visual reminder on the outer and primary package including a text warning and a symbol/pictogram. Prescription only medicine. **Additional risk minimization measures**: A 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: o DHPC o Guide for HCPs o Guide for Patients o Annual Risk Acknowledgement Form o Patient Card

Teratogenicity	
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Drug Utilization Study (on-going- VALNAC07557) to assess the effectiveness of the new risk minimization measures and to further characterize the prescribing patterns for valproate Drug Utilization Study extension (VALNAC09343) 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

DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professional; PASS: Post-Authorization Safety Study; PPP: Pregnancy Prevention Plan; SmPC: Summary of Product Characteristics.

Table 3 - Potential risk: Risks to unborn children via third generation and paternal exposure with corresponding risk minimization activities and additional pharmacovigilance activities if any

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 minimization measures	**Routine risk minimization measures:** Prescription only medicine **Additional risk minimization measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** Retrospective observational study (VALNAC09345): To investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring. Nonclinical genotoxic studies: o Bacterial reverse mutation assay (Ames test) (HIS2350). o Gene mutations assay in L5178Y tk ± mouse lymphoma cells (mouse lymphoma assay). (LYM0372) Non-clinical epigenetic study: o To study the potential impact of valproate on the epigenome of male and female germ cells.

VI.2.3. Post-authorization development plan

VI.2.3.1. Studies which are conditions of the marketing authorization

The following studies are conditions of the marketing authorization:

Table 4 - Studies which are conditions of the marketing authorization

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.
Drug utilization study extension (VALNAC09343)
Purpose of the study: To assess the effectiveness of the new risk minimization 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 HCPs (VALNAC09348)
Purpose of the study: 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)
Purpose of the study: To assess knowledge of patients with regards to PPP as well as receipt/use of educational materials.
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.
Bacterial reverse mutation assay (Ames test) (HIS2350)
Purpose of the study: To evaluate mutagenic activity in vitro in order to better characterize the genotoxic potential of valproate.

Gene mutations assay in L5178Y tk ± mouse lymphoma cells (mouse lymphoma assay) (LYM0372)
Purpose of the study: To evaluate mutagenic and clastogenic activity in vitro in order to better characterize the genotoxic potential of valproate.
Nonclinical epigenetic study
Purpose of the study To study the potential impact of valproate on the epigenome of male and female germ cells, based on recommendations of a panel of experts after seeking EMA scientific advice.

DHPC: Direct Healthcare Professional Communication; EMA: European Medicines Agency; HCP: Healthcare Professional; PASS: Post-Authorization Safety Study; PPP: Pregnancy Prevention Programme.

VI.2.3.2. Other studies in post-authorization development plan

None.