PART VI: SUMMARY OF THE RISKMANAGEMENT PLAN

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[2]"). The RMP details important risks of all tradenames of valproate related products where Sanofi is the marketing authorization holder (MAH)[2] how these risks can be minimized, and how more information will be obtained about all tradenames of valproate's[2] risks and uncertainties (missing information).

The SmPC and PL give essential information to HCPs and patients on how all tradenames of valproate related products[2] should be used.

I. THE MEDICINE AND WHAT IT IS USED FOR

All tradenames of valproate related products[2] are authorized for the following indications (according to the national registrations):

- Treatment of epilepsy.
- Treatment of manic episodes in BPD when lithium is contraindicated or not tolerated. The continuation of treatment after manic episode could be considered in patients who have responded to valproate for acute mania. (*Further to Referral Article 31, EC Decision dated 26 August 2010, procedure EMEA/H/A-31/1163*).

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

[2] 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

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

Important risks of all tradenames of valproate[2], 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 a pictogram may be added on the primary packaging (depending on the countries);
- 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[2], 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 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
- 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.

II.A List of important risks and missing information

Important risks of all tradenames of valproate[2] 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[2]. 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 15 - 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

II.B Summary of important risks

Table 16 - Important identified risk: Teratogenicity with corresponding risk minimization activities and additional pharmacovigilance activities

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 3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established. **Population at risk**: Girls, WOCBP 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 and Sections 2; 4 of PL. • Visual warning corresponding to warning text and associated pictogram on the outer packaging (details to be agreed at national level). • Pictogram on the primary packaging (details to be agreed at national level). • Prescription only medicine (first prescription done by a specialist experienced in the management of epilepsy or BPD). **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: • Direct Healthcare Professional Communication. • Guide for HCPs. • Guide for Patients. • Annual Risk Acknowledgement Form. • Patient Card.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Drug Utilization Study extension (VALNAC09343) to assess the effectiveness of the new risk minimization measures and to further characterize the prescribing patterns for valproate.

Teratogenicity	
	• Survey among HCPs (VALNAC09348) to assess knowledge of HCP and behavior with regards 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 (VALNAC09346/AVALON).

BPD: Bipolar Disorder; DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professional; PASS: Post-Authorization Safety Study; PL: Package Leaflet; PPP: Pregnancy Prevention Plan; SmPC: Summary of Product Characteristics; WOCBP: Women of Childbearing Potential.

Table 17 - Important potential risk: Risks to unborn children via third generation and paternal exposure with corresponding risk minimization activities and additional pharmacovigilance activities

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 (first prescription done by a specialist experienced in the management of epilepsy or BPD). **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. • Non-clinical epigenetic study: To study the potential impact of valproate on the epigenome of male and female germ cells.

BPD: Bipolar Disorder.

II.C Post-authorization development plan

II.C.1 Studies which are conditions of the marketing authorization

The following studies are conditions of the marketing authorization:

Table 18 - Studies which are conditions of the marketing authorization

Drug utilization study extension (VALNAC09343)) (extension of the completed Drug utilization study [VALNAC07557]) (Cat. 1)
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) (Cat. 1)
Purpose of the study: To provide guidance to clinicians on the switch and discontinuation of valproate.
Survey among HCPs (VALNAC09348) (Cat. 1)
Purpose of the study: To assess knowledge of HCPs and behavior with regards to PPP as well as receipt/use of DHPC and educational materials.
Survey among Patients (VALNAC09348) (Cat. 1)
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 (VALNAC09346/AVALON) (Cat. 1)
Purpose of the study: To further characterize the FACS in children exposed to valproate in utero as compared to other anti-epileptic drugs. This study aims to investigate the risk and the course of NDD, ASD and ADHD, in children and adolescents exposed in utero to valproate and other AEDs, with a follow up of at least 10 years from birth. Further aim is to investigate incidence and characteristics of minor CMs related to FACS in children exposed in utero to valproate.
Retrospective observational study (VALNAC09345) (Cat. 1)
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.
Non-clinical epigenetic study (Cat. 1) **As committed with EMA, following an EMA Scientific Advice, supported by a Panel of Experts in epigenetics and in animal behaviors, Sanofi will be setting up Study(ies) to investigate the topics suggested by the PRAC.**
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 (EMA Scientific Advice received 28-Mar-2019).

ADHD: Attention Deficit Hyperactive Disorder; AED: Anti-Epileptic Drug; ASD: Autism Spectrum Disorder; CM: Congenital Malformation; DHPC: Direct Healthcare Professional Communication; EMA: European Medicines Agency; FACS: Fetal Anticonvulsant Disorder; HCP: Healthcare Professional; NDD: Neurodevelopmental Disorder; PASS: Post-Authorization Safety Study; PPP: Pregnancy Prevention Programme; PRAC: Pharmacovigilance Risk Assessment Committee.

II.C.2 Other studies in post-authorization development plan

There are no studies required for all tradenames of valproate[2].