RISK MANAGEMENT PLAN – PART VI: SUMMARY OF THE RISK MANAGEMENT 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 risk management plan (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 (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 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[2] should be used.

Important new concerns or changes to the current ones will be included in updates of all tradenames of valproate's[2] RMP.

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 bipolar disorder (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.

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 (RMMs).

In the case of all tradenames of valproate[2], these measures are supplemented with additional risk minimization measures (aRMMs) 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 to minimize the risks of "Teratogenicity" and "Neurodevelopmental disorders including autism spectrum disorder after *in utero* exposure". The PPP combines the use of educational tools with interventions to control appropriately access to the valproate to female patients.

Additionally, educational materials addressing the potential risk of Neurodevelopmental disorders (NDDs) after paternal exposure to valproate have also been developed.

The educational tools include:

- Direct Healthcare Professional Communication for female patients
- Direct Healthcare Professional Communication for male patients
- Guide for HCPs (common to female and male patients)
- Guide for female patients,
- Guide for male patients
- Annual Risk Acknowledgement Form for female patients
- Patient Card (common to female and male patients)

In addition to these measures, information about adverse reactions will be collected continuously and regularly analyzed, including 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 17 - List of important risks and missing information

Important identified risks	Teratogenicity[a]
	Neurodevelopmental disorders including autism spectrum disorder after *in utero* exposure
Important potential risks	Risks to unborn children *via* paternal exposure
	Risks to unborn children up to third generation
Missing information	None

a Including hearing impairment/loss due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function resulting from *in utero* exposure to valproate.

II.B Summary of important risks

Table 18 - Important identified risk: Teratogenicity with corresponding risk minimization activities and additional pharmacovigilance activities

Teratogenicity[a]	
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** The risk is dose dependent for malformations. 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, 3 and 4 of PL. • Prescription only medicine (in addition, for female children, WOCBP, initiation and supervision by a specialist experienced in the management of epilepsy or BPD). • 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). **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.

Teratogenicity[a]	
	Educational materials: • DHPC for female patients. • Guide for HCPs (common to female and male patients). • Guide for female patients. • Patient Card (common to female and male patients). • Annual Risk Acknowledgement Form for female patients.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Drug Utilization Study extension (VALNAC09343) to assess the effectiveness of the new RMMs and to further characterize the prescribing patterns for valproate. • 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 AEDs (VALNAC09346/AVALON).

a Including hearing impairment/loss due to ear and/or nose malformations (secondary effect) and/or to direct toxicity on the hearing function resulting from *in utero* exposure to valproate.

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

Table 19 - Important identified risk: Neurodevelopmental disorders including autism spectrum disorder after *in utero* exposure with corresponding risk minimization activities and additional pharmacovigilance activities

Neurodevelopmental disorders including autism spectrum disorder after *in utero* exposure	
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:** The risk seems to be dose-dependent for NDDs including autism and ADHD. 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, 3 and 4 of PL. • Prescription only medicine (in addition, for female children, WOCBP, initiation and supervision done by a specialist experienced in the management of epilepsy or BPD). • 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). **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. Educational materials: • DHPC for female patients. • Guide for HCPs (common to female and male patients).

Neurodevelopmental disorders including autism spectrum disorder after *in utero* exposure	
	• Guide for female patients. • Patient Card (common to female and male patients). • Annual Risk Acknowledgement Form for female patients.
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • Drug Utilization Study extension (VALNAC09343) to assess the effectiveness of the new RMMs and to further characterize the prescribing patterns for valproate. • 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 AEDs (VALNAC09346/AVALON).

ADHD: Attention Deficit Hyperactivity Disorder; AED: Anti-Epileptic Drug; BPD: Bipolar Disorder; DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professional; NDD: Neurodevelopmental Disorder; PASS: Post-Authorization Safety Study; PL: Package Leaflet; PPP: Pregnancy Prevention Plan; RMM: Risk Minimization Measure; SmPC: Summary of Product Characteristics; WOCBP: Women of Childbearing Potential.

Table 20 - Important potential risk: Risks to unborn children via paternal exposure with corresponding risk minimization activities and additional pharmacovigilance activities

Risks to unborn children via paternal exposure	
Evidence for linking the risk to the medicine	Pharmacovigilance database (clinical and postmarketing data), PASS paternal data and worldwide scientific literature.
Risk factors and risk groups	Unknown
Risk minimization measures	**Routine risk minimization measures:** SmPC: Labeled in Sections 4.2, 4.4 and 4.6. PL: Labeled in Section 2 and 3. Prescription only medicine. It is recommended that valproate is initiated and supervised by a specialist experienced in the management of epilepsy <or bipolar disorder>. **Additional risk minimization measures:** Educational materials: • DHPC for male patients • Guide for HCPs (common to female and male patients) • Guide for male patients • Patient Card (common to female and male patients)
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** • PASS Paternal Exposure 2 (TANGO) • Non-clinical epigenetic programme to study the potential impact of valproate on the epigenome of male germ cells.

DHPC: Direct Healthcare Professional Communication; HCP: Healthcare Professional; PASS: Post-Authorization Safety Study; PL: Package Leaflet; SmPC: Summary of Product Characteristics.

Table 21 - Important potential risk: Risks to unborn children up to third generation with corresponding risk minimization activities and additional pharmacovigilance activities

Risks to unborn children up to third generation	
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:** • 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 22 - 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 RMMs 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 AEDs. 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.
PASS Paternal Exposure 2 (TANGO) - Retrospective observational study (Cat. 1)
Purpose of the study: To further investigate the association between paternal exposure to AEDs including valproate and adverse outcomes 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; RMM: Risk Minimization Measure.

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

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