Part VI: Summary of the risk management plan

Summary of risk management plan for Orfiril and Orfiril chrono

This is a summary of the risk management plan (RMP) for the following sodium valproate and valproic acid containing medical products of Desitin Arzneimittel GmbH:

- **Orfiril** (containing 50/200/300/600 mg sodium valproate)
- **Orfiril retard** (containing 300 mg sodium valproate)
- **Orfiril long** (containing 150/300/500/1000 mg sodium valproate)
- **Orfiril Syrup** (containing 60 mg/ml sodium valproate)
- **Orfiril solution for injection** (containing 100 mg/ml sodium valproate)
- **Orfiril chrono** (containing 199,8/333 mg sodium valproate and 87/145 mg valproic acid)

For a better readability of this summary, the above mentioned medicinal products are summarised as 'Orfiril and Orfiril chrono' in the following course of this summary.

The RMP details important risks of Orfiril and Orfiril chrono, how these risks can be minimised, and how more information will be obtained about Orfiril's's and Orfiril chrono's risks and uncertainties (missing information).

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

I. The medicine and what it is used for

Orfiril and Orfiril chrono is authorised for:

Treatment of epilepsy as anticonvulsant agent in case of generalised seizures like absences, myoclonic seizures and tonic-clonic seizures, focal and secondarily generalised seizures and combination therapy in case of complex symptomatology

Treatment of manic episodes in bipolar disorder, as alternative to lithium. (only applicable for certain pharmaceutical forms in certain countries)

Prophylaxis of migraine in adults and children over 12 years of age. (only applicable for Orfiril long in CZ)

It contains sodium valproate, and, for Orfiril chrono, supplementary valproic acid, as the active substance and it is given by oral administration or per injection.

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

Important risks of Orfiri and Orfiril chrono, together with measures to minimise such risks and the proposed studies for learning more about Orfiril's and Orfiril chrono'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 (section 2 and 3) and SmPC (section 4.2 to 4.8) 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 Orfiril and Orfiril chrono, 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 analysed regularly, including periodic overall 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 Orfiril or Orfiril chrono is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Orfiril and Orfiril chrono are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be taken safely. Important risks are either 'identified' or 'potential'. Identified risks are concerns for which there is sufficient proof of an association with the use of Orfiril or Orfiril chrono. Potential risks are concerns for which an association is possible, based on available data, but this association has not been clearly 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).

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

Important identified risk: Teratogenicity[a]	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.3, 4.4, 4.6 and 4.8* *PL section introduction (warning), 2, 3 and 4* *Advice relating to pregnancy in SmPC sections 4.4, 4.6 and PL section 2* *Restricted medical prescription* Additional risk minimisation measures: • *Pregnancy Prevention Programme (PPP)* • *Direct Health Care Communication Letter* • *Educational materials:* 1. *Guide for Healthcare professionals* 2. *Female Patient Guide* 3. *Male Patient Guide* 4. *Annual Risk Acknowledgement Form* 5. *Patient Card*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: – *(Extension) Drug Utilization Study (DUS) to assess the effectiveness of the new risk minimisation measures and to further characterize the prescribing patterns for valproate.* – *Characterization of neurodevelopmental disorders in children exposed or unexposed in utero to valproate and/or other antiepileptic drugs with long-term follow-up: retrospective study of multiple European data sources* – *Health Care Professionals and Patients' perceptions, behaviors, perspectives, and barriers on the im-plementation of the new (2018) Risk Minimization Measures (RMMs) of valproate in Europe: A Quali-tative Non-Interventional Post-Authorization Safety Study (PASS)*
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.	

Important identified risk: Neurodevelopmental disorders including autism spectrum disorder after in utero exposure	
Risk minimisation measures	Routine risk minimisation measures:

	SmPC sections 4.2, 4.3, 4.4, 4.6 and 4.8 *PL section introduction (warning), 2, 3 and 4* *Advice relating to pregnancy in SmPC sections 4.4, 4.6 and PL section 2* *Restricted medical prescription* Additional risk minimisation measures: • *Pregnancy Prevention Programme (PPP)* • *Direct Health Care Communication Letter* • *Educational materials:* 1. *Guide for Healthcare professionals* 2. *Female Patient Guide* 3. *Male Patient Guide* 4. *Annual Risk Acknowledgement Form* 5. *Patient Card*
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Important potential risk: Risks to unborn children via paternal exposure	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.4, and 4.6* *PL sections 2 and 3* *Advice relating to pregnancy in SmPC sections 4.2, 4.4, 4.6 and PL sections 2 and 3* *Restricted medical prescription* Additional risk minimisation measures: 1. *Guide for Healthcare professionals* 2. *Male Patient Guide* 3. *Annual Risk Acknowledgement Form* 4. *Patient Card*

Important potential risk: Risks to unborn children via paternal exposure	
Additional pharmacovigilance activities	Additional pharmacovigilance activities: – *Analysis to further investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders (including autism) in the offspring*

Important potential risk: Risks to unborn children up to third generation	
Risk minimisation measures	Routine risk minimisation measures: *SmPC sections 4.2, 4.4, and 4.6* *PL sections 2 and 3* *Advice relating to pregnancy in SmPC sections 4.2, 4.4, 4.6 and PL sections 2 and 3* *Restricted medical prescription* Additional risk minimisation measures: 1. *Guide for Healthcare professionals* 2. *Male Patient Guide* 3. *Annual Risk Acknowledgement Form* 4. *Patient Card*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: – *Analysis to further investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders (including autism) in the offspring*

II.C Post-authorisation development plan

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

Joint Drug Utilisation Study (DUS) of valproate and related substances, in Europe, using databases (extension study)
Purpose of the study: Drug Utilisation Study to assess the effectiveness of the new risk minimisation measures and further characterise the prescribing pattern for valproate (extension of ongoing DUS).

Characterization of neurodevelopmental disorders in children exposed or unexposed in utero to valproate and/or other antiepileptic drugs
Purpose of the study: retrospective study of multiple European data sources to investigate the risk and the course of neurodevelopmental disorders (NDD) (including autism spectrum disorders (ASD) and attention deficit hyperactivity disorder (ADHD)), in infants, children and adolescents exposed in utero to valproate (VPA) and other antiepileptic drugs (AEDs), with a long-term follow-up from birth (until maximum 17 years of age)

Analysis to further investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders (including autism) in the offspring
Purpose of the study: provide results of additional analyses requested by PRAC to further investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders (including autism) in the offspring.

Study among Health Care Professionals and Patients on the implementation of the new (2018) Risk Minimization Measures (RMMs) of valproate in Europe
Purpose of the study: a PASS to identify, qualify and describe the barriers and reasons for insufficient compliance to the valproate RMMs by HCPs who prescribe or dispense valproate in Europe and by WOCBP / pregnant women / female adolescents treated with valproate in Europe

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

There are no other studies planned for Orfiril or Orfiril chrono.