Part VI: Summary of the risk management plan

Summary of risk management plan for Topiramat Aristo, (topiramate)

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

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

I. The medicine and what it is used for

Topiramat Aristo is authorised for monotherapy in adults, adolescents and children over 6 years of age with partial seizures with or without secondary generalised seizures, and primary generalised tonic-clonic seizures; adjunctive therapy in children aged 2 years and above, adolescents and adults with partial onset seizures with or without secondary generalization or primary generalized tonic-clonic seizures and for the treatment of seizures associated with Lennox-Gastaut syndrome; and for the prophylaxis of migraine headache after careful evaluation of possible alternative treatment options in adults (see SmPC for the full indication). It contains topiramate as the active substance and it is given by oral route.

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

Important risks of Topiramat Aristo, together with measures to minimise such risks and the proposed studies for learning more about Topiramat Aristo'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 and SmPC 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 Topiramat Aristo, 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 Topiramat Aristo 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 Topiramat Aristo. 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	Major congenital malformations Foetal growth restrictions
Important potential risks	Neurodevelopmental disorders
Missing information	None

**Safety concerns are based on the documentation published in the EMA website from the topiramate referral (https://www.ema.europa.eu/en/medicines/human/referrals/topiramate).*

II.B Summary of important risks

Important identified risk 1: Major congenital malformations	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.4, 4.6 and 4.8.* *As stated in sections 4.3, 4.4 and 4.6, topiramate is contraindicated during pregnancy (unless no suitable alternative for epilepsy treatments are available) or in women of childbearing potential not using highly effective contraception (with the exception of woman for whom there is no suitable alternative but who plans a pregnancy and who is fully informed about the risks of taking topiramate during pregnancy). Topiramate is contraindicated in pregnancy and in women of childbearing potential not using highly effective contraception for the indication of prophylaxis of migraine.* *Section 4.4 describes the PPP that includes the pregnancy test that must be performed before initiating treatment with product, the use of contraceptive methods, the annual assessment of treatment, the re-evaluation of treatment in patients that plan to become pregnant, the prompt contact with a specialist if a patient becomes pregnant or thinks that she might be, and educational materials to inform about risks of use of topiramate during pregnancy available for healthcare professionals and patients (or parents/caregivers).* *Careful prenatal monitoring and counselling if topiramate is used during pregnancy in SmPC section 4.6.* *PL section 2 states for each indication, in which scenarios a pregnant women or a WOCBP can or cannot use topiramate and what measures should be taken.* *Warning (and a pictogram, if considered appropriate by each national competent authority) placed on the outer packaging.* Additional risk minimisation measures:

Important identified risk 1: Major congenital malformations	

	PPP including:
	• *Educational materials:*
	  ○ *Healthcare professional guide (including risk awareness form)*
	  ○ *Patient guide*
	  ○ *Patient card*
	DHPC

Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Post-Authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: Drug Utilization Study.* *Post-Authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: HCP and Patient Knowledge and Behavior Survey.* See section II.C of this summary for an overview of the post-authorisation development plan.

Important identified risk 2: Foetal growth restrictions	
Risk minimisation measures	Routine risk minimisation measures:> *SmPC section 4.4, 4.6 and 4.8.* *As stated in sections 4.3, 4.4 and 4.6, topiramate is contraindicated during pregnancy (unless no suitable alternative for epilepsy treatments are available) or in women of childbearing potential not using highly effective contraception (with the exception of woman for whom there is no suitable alternative but who plans a pregnancy and who is fully informed about the risks of taking topiramate during pregnancy). Topiramate is contraindicated in pregnancy and in women of childbearing potential not using highly effective contraception for the indication of prophylaxis of migraine.* *Section 4.4 describes the PPP that includes the pregnancy test that must be performed before initiating treatment with product, the use of contraceptive methods, the annual assessment of treatment, the re-evaluation of treatment in patients that plan to become pregnant, the prompt contact with a specialist if a patient becomes pregnant or thinks that she might be, and educational materials to inform about risks of use of topiramate during pregnancy available for healthcare professionals and patients (or parents/caregivers).* *Careful prenatal monitoring and counselling if topiramate is used during pregnancy in SmPC section 4.6.*

Important identified risk 2: Foetal growth restrictions	
	PL section 2 states for each indication, in which scenarios a pregnant women or a WOCBP can or cannot use topiramate and what measures should be taken. *Warning (and a pictogram, if considered appropriate by each national competent authority) placed on the outer packaging.* Additional risk minimisation measures: *PPP including:* • *Educational materials:* o *Healthcare professional guide (including risk awareness form)* o *Patient guide* o *Patient card* *DHPC*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Post-Authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: Drug Utilization Study.* *Post-Authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: HCP and Patient Knowledge and Behavior Survey.* See section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk 1: Neurodevelopmental disorders	
Risk minimisation measures	Routine risk minimisation measures:> *SmPC section 4.4 and 4.8.* *As stated in sections 4.3, 4.4 and 4.6, topiramate is contraindicated during pregnancy (unless no suitable alternative for epilepsy treatments are available) or in women of childbearing potential not using highly effective contraception (with the exception of woman for whom there is no suitable alternative but who plans a pregnancy and who is fully informed about the risks of taking topiramate during pregnancy). Topiramate is contraindicated in pregnancy and in women of childbearing potential not using highly effective contraception for the indication of prophylaxis of migraine.* *Section 4.4 describes the PPP that includes the pregnancy test that must be performed before initiating treatment with product, the use of contraceptive methods, the annual assessment of treatment, the re-evaluation of treatment in patients that plan to become pregnant, the prompt contact with a specialist if a patient becomes pregnant or thinks that she might be, and educational materials to inform about risks of use*

Important potential risk 1: Neurodevelopmental disorders	
	of topiramate during pregnancy available for healthcare professionals and patients (or parents/caregivers). *Careful prenatal monitoring and counselling if topiramate is used during pregnancy in SmPC section 4.6.* *PL section 2 states for each indication, in which scenarios a pregnant women or a WOCBP can or cannot use topiramate and what measures should be taken.* *Warning (and a pictogram, if considered appropriate by each national competent authority) placed on the outer packaging.* Additional risk minimisation measures: *PPP including:* • *Educational materials:* o *Healthcare professional guide (including risk awareness form)* o *Patient guide* o *Patient card* *DHPC*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Post-Authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: Drug Utilization Study.* *Post-Authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: HCP and Patient Knowledge and Behavior Survey.* See section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

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

The following studies are conditions of the marketing authorisation:

Post-Authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: Drug Utilization Study

In the European Union (EU) and the United Kingdom (UK), topiramate mono-component products are used to treat epilepsy and prevent migraine. In 2022, a study of population-based registries in five Nordic countries reported increased risk of neurodevelopmental disorders (NDDs) in children born to mothers with epilepsy exposed to topiramate in pregnancy compared to children whose mothers were unexposed (Bjørk et al. 2022). Given the potential increased risk of NDDs highlighted by this study and the known risk of congenital malformations, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in 2023 recommended updates to summaries of product characteristics (SmPCs) and the implementation of additional risk minimization measures in the form of educational materials (health care professional guide and patient guide) under a Pregnancy Prevention

Program (PPP). All these actions are henceforth collectively referred to as "newly implemented risk minimization measures (RMMs)."

Before PRAC requested these newly implemented RMMs, topiramate was already contraindicated for migraine prevention in pregnancy and in women of childbearing potential (WOCBP) who are not using highly effective contraception. New contraindications now apply for the treatment of epilepsy. Specifically, topiramate is contraindicated (1) in pregnancy unless no suitable alternative treatment is available, and (2) in WOCBP not using highly effective contraception, with the only exception being a woman for whom there is no suitable anti-epileptic drug alternative but who plans a pregnancy and who is fully informed about the risks of taking topiramate during pregnancy.

The PRAC requested the MAHs of medicinal products containing topiramate as a mono-component to conduct a drug utilization study to evaluate the effectiveness of the newly implemented RMMs.

The overarching goal of this drug utilization study is to compare the use of topiramate among WOCBP with epilepsy or migraine diagnosis during the pre- and post-implementation periods of the newly implemented RMMs.

Objectives

The primary objectives are to:

1. Compare the prevalence and incidence of topiramate use during the pre- and post-implementation periods of the newly implemented RMMs among WOCBP with epilepsy or migraine.
2. Describe pregnancy exposure to topiramate during the pre- and post- implementation periods of the newly implemented RMMs among incident users of topiramate in the WOCBP with epilepsy or migraine.

The secondary objectives are to:

1. Compare the prevalence and incidence of topiramate use during the pre- and post-implementation periods of the newly implemented RMMs among WOCBP.
2. Describe pregnancy exposure to topiramate during the pre- and post- implementation periods of the newly implemented RMMs among incident users of topiramate in the WOCBP.
3. Characterize the incident (new) users of topiramate during the pre- and post- implementation periods of the newly implemented RMMs, separately, among the overall WOCBP (any indication) and among WOCBP with epilepsy or migraine.

This study will also aim to investigate the following exploratory objectives when feasible:

Compare the incidence of topiramate use as first-line treatment during the pre- and post- implementation periods of the newly implemented RMMs among WOCBP with epilepsy or migraine.

Post-Authorization Safety Study to Assess the Effectiveness of the Newly Implemented Risk Minimization Measures for Topiramate: HCP and Patient Knowledge and Behavior Survey.

In the European Union (EU) and the United Kingdom (UK), topiramate mono-component products are used to treat seizures, epilepsy, and prevent migraine. In 2022, a study of population-based registries in five Nordic countries reported increased risk of neurodevelopmental disorders in children born to mothers with epilepsy exposed to topiramate in pregnancy compared to children whose mothers were unexposed (Bjørk et al. 2022). Given the potential increased risk of neurodevelopmental disorders highlighted by this study and the known risk of congenital malformations, the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA) in 2023 recommended updates

to summaries of product characteristics (SmPC) and the implementation of additional risk minimization measures in the form of educational materials (health care professional guide and patient guide) under a Pregnancy Prevention Program (PPP). All these actions are henceforth collectively referred to as "newly implemented risk minimization measures (RMMs)."

Before PRAC requested these newly implemented RMMs, topiramate was already contraindicated for migraine prevention in pregnancy and in women of childbearing potential (WOCBP) who are not using highly effective contraception. New contraindications now apply for the treatment of epilepsy. Specifically, topiramate is contraindicated (1) in pregnancy unless no suitable alternative treatment is available, and (2) in WOCBP not using highly effective contraception, with the only exception being a woman for whom there is no suitable anti-epileptic drug alternative but who plans a pregnancy and who is fully informed about the risks of taking topiramate during pregnancy.

To evaluate the impact of these RMMs, the PRAC requested an HCP and patient survey to be conducted to assess the effectiveness of the newly implemented RMMs (i.e., updated label warnings and contraindications, HCP guide including risk awareness form, patient guide, patient card, outer package warnings) in raising the awareness and understanding of this target population with respect to the safe use of topiramate.

The objectives are:

To assess the awareness of:

- Women of childbearing potential treated with topiramate mono-component products with respect to the receipt of the Educational Materials (EMs).
- HCPs with respect to the receipt of Direct Healthcare Professional Communication (DHPC) and HCP guide for topiramate mono-component products.

To assess the knowledge of:

- Women of childbearing potential treated with topiramate mono-components products with respect to risks associated with use of topiramate during pregnancy and measures to prevent exposed pregnancies.
- HCPs with respect to risks associated with use of topiramate during pregnancy and measures to prevent pregnancies among women of childbearing potential exposed to topiramate mono-component products.

To assess the self-reported behavior of:

- Women of childbearing potential treated with topiramate mono-component products with respect to measures to prevent exposed pregnancies.
- HCPs with respect to measures to prevent pregnancies among women of childbearing potential exposed to topiramate mono-component products.

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

There are no studies required for Topiramate Aristo.