Annex II

Scientific conclusions

Scientific conclusions

Topiramate belongs to the pharmacotherapeutic group of antiepileptics (anatomical therapeutic chemical (ATC) classification system code: N03AX11). Topiramate is an antiepileptic drug (AED) that blocks voltage-gated sodium channels, reduces membrane depolarisation through-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA)/kainate subtypes of glutamate receptors, enhances gamma-aminobutyric acid (GABA)(A) receptor activity and is a weak inhibitor of carbonic anhydrase. The precise mechanism of action is unknown.

Topiramate was first approved in July 1995 in the United Kingdom. Medicinal products containing topiramate as a monocomponent are currently authorised in all European Union (EU) / European Economic Area (EEA) Member States. Topiramate monocomponent is indicated in the treatment of seizures and as prophylaxis of migraine. In June 2021, a fixed dose combination product containing topiramate/phentermine was authorised via a decentralised procedure (SE/H/1963/001-004/DC) in Denmark, Finland, Iceland, Norway, Poland and Sweden for the treatment of obesity and overweight under certain conditions.

It is well-established that topiramate is teratogenic in mice, rats, rabbits and humans. In humans, topiramate crosses the placenta and similar concentrations have been found in the umbilical cord and maternal blood. It is further known that clinical data from pregnancy registries indicate that infants exposed to topiramate monotherapy have a 3-fold increased risk of congenital malformations, including cleft lip and palate, hypospadias and microcephaly, which was already reflected in the product information. The product information for topiramate monocomponent products already contained information about these risks and a number of measures to reduce exposure of pregnant women are described. For the topiramate/phentermine combination product, in addition to the product information, there is an educational material for healthcare professionals as well as for patients, which includes the risk for serious adverse birth outcomes after in utero exposure to topiramate, and the measures for risk minimisation. Furthermore, a drug utilisation study to address the effectiveness of the risk minimisation measures to avoid use in pregnancy is in place.

In 2022, a pharmacoepidemiological study by Bjørk et al., 2022[1] was published in the literature on neurodevelopmental disorders (NDDs) associated with in utero exposure to several AED based on data from Nordic registries collected between 1996 and 2017. The study included 4.5 million mother-child pairs including nearly 25,000 children exposed in utero to at least one AED and followed-up until their eighth year of life on average. The study results suggested an increased risk of autism spectrum disorders (ASD) and intellectual disability (ID) in children whose mothers were taking topiramate during pregnancy.

Based on the results of the study by Bjørk et al., 2022, France (ANSM) initiated in June 2022 a signal procedure at the European level to evaluate the risk of NDDs due to in utero exposure to topiramate. Following initial evaluation at the PRAC, a thorough assessment of the potential risk of NDD was considered warranted. On 22 August 2022, France (ANSM) triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data and requested the PRAC to assess the impact of the above concerns taking into account the known risk of major congenital malformations (MCMs) on the benefit-risk balance of topiramate-containing products in pregnant women and women of childbearing potential (WCP) in all therapeutic indications and to issue a recommendation as to whether the marketing authorisations of these products should be maintained, varied, suspended or revoked.

[1] Bjørk MH, Zoega H, Leinonen MK, et al., 'Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability', JAMA Neurol. 2022, 79(7):672-681. Published online May 31, 2022. doi:10.1001/jamaneurol.2022.1269

The PRAC adopted a recommendation on 31 August 2023 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

The PRAC considered that the data reviewed in the context of this referral procedure do not bring into question the efficacy of topiramate-containing products as no new data were made available to change the already established benefit of the medicinal products in the respective approved indications.

With respect to risks, the PRAC reviewed the totality of the data submitted during this review in relation to NDDs, and further reviewed new relevant data on the known risk of MCMs. These data included the responses submitted in writing by the marketing authorisation holders (MAHs), additional available literature and the outcome of the consultation with the Scientific Advisory Group on Neurology (SAG-N).

Regarding NDDs, the Committee considered three pharmaco-epidemiological studies of major relevance for assessing this potential risk, because these studies were undertaken in useful data sources, had relevant designs and were well conducted.

The study by Bjørk et al., 2022 was undertaken in well-established national population-based healthcare registers from the five Nordic countries, which have similar healthcare contexts and health data structures. For topiramate, a higher prevalence of NDD outcomes was seen in children of mothers with epilepsy, who had been exposed to topiramate during pregnancy compared to children of unexposed mothers with epilepsy. Further review of the available data suggested that a substantial part of this increased occurrence of NDD outcomes is related to strong selection mechanisms behind the low proportion of pregnancy exposures to topiramate, although a causal role of topiramate for the development of NDDs is considered possible following prenatal exposure. However, it was not possible to determine the portion of the estimated relative risk that is actually due to topiramate or due to the underlying patient and/or disease characteristics, thus the evidence remains weak overall.

The study by Dreier et al., 2023[2] was undertaken in essentially the same dataset as the study by Bjørk et al., 2022 but focused on mothers with epilepsy only. In this study, an increased occurrence of attention deficit hyperactivity disorder (ADHD) was observed for children exposed in utero to topiramate compared with mothers/children unexposed to an AED. Further, increased point estimates for ASD and ID were also seen in this study, although they were not statistically significant. Taken together, the studies by Bjørk et al., 2022 and Dreier et al., 2023 suggest a 2- to-3-fold higher prevalence of ASD, ID or ADHD in almost 300 children of mothers with epilepsy exposed to topiramate in utero, compared with children of mothers with epilepsy not exposed to an AED. Similar to Bjørk et al., 2022, it remains also unclear for this study to what extent this higher risk of NDDs is caused by topiramate exposure or other risk factors more prevalent in mothers exposed to topiramate. Nevertheless, the PRAC considered that these data are sufficiently strong to be reflected in the product information.

The study by Hernandez-Diaz et al., 2022[3] was a cohort study in pregnant women and their children conducted in U.S. healthcare utilisation databases. Overall, 2,469 pregnancies exposed to topiramate were identified, and among those, 1,030 pregnancies were in mothers who had epilepsy. Data for both lamotrigine and valproate were also analysed in this study. Lamotrigine exposures are of particular relevance to address confounding by indication, since this substance is widely considered to be safe for

[2] Dreier JW, Bjørk M, Alvestad S, et al., 'Prenatal Exposure to Antiseizure Medication and Incidence of Childhood- and Adolescence-Onset Psychiatric Disorders', JAMA Neurol. Published online April 17, 2023. doi: 10.1001/jamaneurol.2023.0674. Online ahead of print. PMID: 37067807

[3] Hernandez-Diaz S, Straub L, Bateman B, et al., Topiramate During Pregnancy and the Risk of Neurodevelopmental Disorders in Children. (2022), In: ABSTRACTS of ICPE 2022, the 38th International Conference on Pharmacoepidemiology and Therapeutic Risk Management (ICPE), Copenhagen, Denmark, 26–28 August, 2022. Pharmacoepidemiol Drug Saf, 2022; 31 Suppl 2:3-678, abstract 47

the developing foetus. These analyses included 7,130 pregnancies exposed to lamotrigine, among which 3,134 were in mothers who had epilepsy. The increased risk of NDDs observed in children of pregnant mothers exposed to valproate may support analyses of assay sensitivity with its well-established increased risk for NDDs. For valproate, expected increases in hazard ratios (HRs) for NDD outcomes were seen. However, this study did not show increased HRs for neurodevelopmental outcomes in children of women with epilepsy exposed to topiramate or to lamotrigine in utero. This supports that other factors than topiramate exposure explain, at least partially, the increased occurrence of neurodevelopmental outcomes when comparing children exposed in utero to topiramate with non-exposed children from the general population. The PRAC considered that this study is of particular importance in this review given the large number of pregnancies exposed to topiramate, its appropriate design, the relevant length of children follow-up over 8 years, a notable proportion of relevant events and an appropriate attention to bias control.

Overall, while no firm conclusion could be drawn on the risk of NDDs in view of the inconsistent results of the currently available data, the PRAC concluded that NDDs should be considered as an important potential risk for topiramate use during pregnancy and that the data from these three observational studies should be reflected in the product information of all topiramate-containing products.

With regard to congenital malformations and foetal growth restrictions, these are well established identified risks after topiramate in utero exposure and are already reflected in the product information of all topiramate-containing products. Additional evidence from the studies by Cohen et al., 2023[4] and Hernandez-Diaz, 2017[5] further confirm the risks for serious adverse birth outcomes with topiramate and provide further clarity on the magnitude of these risks. Available data show that in women who took topiramate during pregnancy, 4 to 9 out of every 100 children had birth defects, compared with 1 to 3 out of every 100 children born to women who did not take such treatment. Further, around 18 children in every 100 were smaller and weighed less than expected at birth when mothers had taken topiramate during pregnancy, compared with 5 children in every 100 born to mothers without epilepsy and not taking antiepileptic medication. The PRAC was of the view that these results should be reflected in the product information of all topiramate-containing products.

Regarding risk minimisation measures in relation to these risks, the PRAC confirmed the measures already in place and recommended strengthening the contraindications further. The Committee also agreed on the implementation of further risk minimisation measures and tools in the form of a pregnancy prevention programme. A number of amendments of the exact wording of these measures was also made in the product information to provide further clarity.

Thus, the PRAC confirmed the contraindications in pregnancy when topiramate is used as migraine prophylaxis or for the treatment of obesity or overweight. Further, in all indications, advice on pregnancy testing before treatment of WCP and on the need for using a highly effective contraceptive method are already implemented. Statements about the necessity for women to be fully informed about the risks with use of topiramate during pregnancy are also available.

In addition, the Committee recommended the implementation of contraindications in the epilepsy indication. Although the SAG-N did not consider that there was sufficient available evidence to support a contraindication on the use of topiramate during pregnancy and in WCP for the treatment of epilepsy, the PRAC considered that a contraindication in pregnancy is warranted unless there is no suitable alternative treatment, as well as in WCP not using highly effective contraception. For the latter group, the PRAC agreed to introduce an exception for women for whom there is no suitable alternative but

[4] Cohen JM, Alvestad S, Cesta CE, et al., 'Comparative safety of antiseizure medication monotherapy for major malformations', Ann Neurol, 2023, 93:551-562
[5] Hernandez-Diaz S, McElrath TF, Pennell PB et al., 'Fetal growth and premature delivery in pregnant women on anti-epileptic drugs', North American Antiepileptic Drug Pregnancy Registry, Ann Neurol, 2017 Sept;82 (3):457-465. doi:10.1002/ana.25031. PMI:28856694

who plan a pregnancy and are fully informed about the risks of taking topiramate during pregnancy. This is in line with the SAG-N position.

In the epilepsy indication, the PRAC also confirmed the current advice to consider alternative therapeutic options in WCP, and the information about the risks of uncontrolled epilepsy to the pregnancy. The PRAC confirmed the current pieces of advice, namely the need for a preconception visit for women planning a pregnancy to reassess treatment with topiramate and consider other therapeutic options, as well as the need for patients to inform their doctor straight away in case of pregnancy and that patients should decide together with their doctor whether topiramate treatment should continue during pregnancy.

Moreover, the PRAC agreed that topiramate treatment of female children and WCP should be initiated and supervised by a physician experienced in the treatment of epilepsy or migraine. As highlighted by the SAG-N, topiramate is neither the first line medicine for epileptic disorders nor the only option for any particular syndrome. Therefore, alternative therapeutic options should be considered in female children and in WCP. For the topiramate/phentermine fixed dose combination product, the PRAC confirmed the current recommendation that treatment should be initiated and supervised by a clinician experienced in obesity treatment. In all indications, the need for treatment with topiramate should be reassessed at least annually to confirm that the pregnancy prevention programme is adhered to.

Based on the review of a potentially clinically relevant interaction between topiramate and systemic hormonal contraceptives, the PRAC recommended as a precautionary measure that women using systemic hormonal contraceptives should be advised to also use a barrier method to ensure highly effective contraception. Based on the need to cover at least one menstrual cycle and to ensure that topiramate has been adequately cleared from the body, the Committee also recommended to update the product information of all topiramate-containing products to reflect the need to continue contraception for at least 4 weeks after stopping treatment.

In the indications covering the use of topiramate in female children with epilepsy or as migraine prophylaxis, it is further emphasised that prescribers must ensure that parent(s)/caregiver(s) of female children understand the need to contact a specialist once the child experiences menarche. At that time, the patient and parent(s)/caregiver(s) should be provided with comprehensive information about the risks due to topiramate exposure in utero and about the need to use highly effective contraception as soon as relevant.

Moreover, the Committee considered it necessary to implement additional risk minimisation measures and tools as educational materials for healthcare professionals in the form of a healthcare professional guide, including a risk awareness form to be completed with the patient, and for patients in the form of a patient guide. These measures are put in place to increase awareness of healthcare professionals and patients on the risks of adverse outcomes after in utero exposure to topiramate, and to highlight the measures of the pregnancy prevention programme aiming at minimising pregnancy exposure during treatment with topiramate-containing products.

The Committee also recommended a patient card to be placed inside or affixed to one side of the outer packaging as well as a warning on the outer packaging to warn WCP on the risks to be pregnant while using topiramate. The PRAC noted that the use of a pictogram was discussed by the SAG-N but no consensus was reached on this possible measure. The PRAC considered that visual symbols can be interpreted differently across Member States. The PRAC further noted that, as part of their remit, the National Competent Authorities can decide to implement a pictogram at national level as relevant. It was also noted that the use of boxed warnings in the product information can be decided by the National Competent Authorities at national level as relevant.

Finally, the Committee considered that the MAHs of topiramate-monocomponent products should be requested to implement additional pharmacovigilance activities in the form of a drug utilisation study to evaluate the effectiveness of the implemented risk minimisation measures with a particular focus on preventing pregnancies and on further characterising the prescribing patterns for topiramate in the target populations for pregnancy prevention. Furthermore, the MAHs of topiramate-monocomponent products should carry out surveys amongst healthcare professionals and patients to assess their knowledge and behaviour as applicable with regard to the risks of topiramate use during pregnancy and the measures implemented to prevent pregnancy as well as receipt/use of educational materials as part of the pregnancy prevention programme. The protocols for the drug utilisation study and surveys should be submitted to the PRAC in accordance with Article 107n(1) of Directive 2001/83/EC according to agreed timelines.

A direct healthcare professional communication (DHPC) was also agreed, together with a communication plan, to inform relevant healthcare professionals of the new recommendations and risk minimisation measures agreed as described above.

In view of the above, the Committee considered that the benefit-risk balance of topiramate-containing products remains favourable subject to the agreed amendments to the product information, the agreed conditions to the marketing authorisations as applicable, and other risk minimisation measures.

Grounds for PRAC recommendation

Whereas,

- The PRAC considered the procedure under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data on topiramate-containing products.
- The PRAC reviewed the totality of the data submitted during this review in relation to the risk of NDDs, and further reviewed new relevant data on the known risk of MCMs. These data included the responses submitted in writing by the MAHs, additional available literature and the outcome of the consultation with the SAG-N.
- The PRAC confirmed the current knowledge that MCMs and foetal growth restrictions are identified risks.
- The PRAC considered an increased risk of NDDs including ASD, ID or ADHD in children of mothers with epilepsy exposed to topiramate in utero as possible, compared with children of mothers with epilepsy not exposed to an AED. However, no final conclusion could be drawn at this stage because available data from epidemiological studies on this matter show inconsistent results. Therefore, NDDs should be considered as an important potential risk for topiramate use during pregnancy.
- In view of the new potential risk of NDDs, taken together with the known risks of MCM and foetal growth restrictions, the PRAC concluded that there is a need to implement further risk minimisation measures in the form of a pregnancy prevention programme to reduce in utero exposure to topiramate.

  While the PRAC confirmed the contraindications in pregnancy and in WCP not using highly effective contraception in the indications of migraine and treatment of overweight, the Committee also recommended the implementation of contraindications in the epilepsy indication. In epilepsy, the PRAC also agreed that the contraindication in pregnancy is applicable unless there is no suitable alternative treatment, as well as in women of child-bearing potential not using highly effective contraception. However, for the latter group, an exception is included for women for whom there is no suitable alternative but who plan a pregnancy and who are fully informed about the risks of taking topiramate during pregnancy.

- The PRAC also recommended additional risk minimisation measures comprising of a patient card and educational materials for healthcare professionals including a risk awareness form and for patients. A warning was also added to the outer packaging.
- The PRAC requested the MAHs of topiramate monocomponent products to conduct post-authorisation studies to evaluate the effectiveness of the measures implemented, and to assess the level of knowledge of healthcare professionals and patients on the risks and minimisation measures implemented as an outcome of this review.

In view of the above, the Committee considered that the benefit-risk balance of topiramate-containing products remains favourable subject to the agreed conditions to the marketing authorisations, the agreed amendments to the product information and other risk minimisation measures as described above.

The Committee, as a consequence, recommended the variation to the terms of the marketing authorisations for topiramate-containing products.

The PRAC also agreed on the content of DHPC together with a communication plan for its distribution.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

For clarity purposes, the additional risk minimisation measures have been listed individually in the condition on the RMP requirement.

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of topiramate-containing medicinal products remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore, the CMDh recommends the variation to the terms of the marketing authorisations for topiramate-containing medicinal products.