Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR(s) for topiramate, the scientific conclusions are as follows:

Topiramate is known to be teratogenic and foetotoxic. During the PSUR reporting period a signal "small for gestational age (SGA)" was confirmed on the basis of literature data. The PRAC agreed that this information paired with an increased exposure of topiramate during the reporting period involving women of childbearing potential warrants the need for additional wording in section 4.4 of the product information to strengthen the precautionary warnings for teratogenicity.
In relation to the teratogenic risk, data published before and during the covered PSUR period also suggest that topiramate crosses the human placenta. Furthermore, the data also indicate a possible dose-effect relationship regarding malformative risk and that there is a trend toward a higher risk for recurrent malformations in pregnancies exposed to topiramate. In view of this the PRAC agreed that recommendations for the management of the exposure during pregnancy be added to section 4.6 of the summary of product characteristics. The information regarding lactation has also been updated to reflect the reported cases of drug exposure during lactation and the publication by Westergren et al., 2014.
Lastly, the PRAC agreed that a note should be added under the adverse reactions table in section 4.8 to reflecting the observed adverse drug reactions of congenital malformations and foetal growth restriction.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for topiramate the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) containing topiramate is unchanged subject to the proposed changes to the product information.

The CMDh reaches the position that the marketing authorisation(s) of products in the scope of this single PSUR assessment should be varied. To the extent that additional medicinal products containing topiramate are currently authorised in the EU or are subject to future authorisation procedures in the EU, the CMDh recommends that such marketing authorisations are varied accordingly.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Product Information (new text **underlined and in bold**, deleted text ~~strike through~~)

Summary of Product Characteristics

- Section 4.4

A warning should be added as follows:

[…]

Women of childbearing potential

Topiramate may cause fetal harm and fetal growth restriction (small for gestational age and low birth weight) when administered to a pregnant woman. The North American Antiepileptic Drug pregnancy registry data for topiramate monotherapy showed an approximate 3-fold higher prevalence of major congenital malformations (4.3%), compared with a reference group not taking AEDs (1.4%). In addition, data from other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of AEDs in combination therapy.

Before the initiation of treatment with topiramate in a woman of childbearing potential, pregnancy testing should be performed and a highly effective contraceptive method advised (see section 4.5). The patient should be fully informed of the risks related to the use of topiramate during pregnancy (see sections 4.3 and 4.6).

- Section 4.6

[…]

Risk related to topiramate

Topiramate was teratogenic in mice, rats and rabbits (see section 5.3). In rats, topiramate crosses the placental barrier.

In humans, topiramate crosses the placenta and similar concentrations have been reported in the umbilical cord and maternal blood.

Clinical data from pregnancy registries indicate that infants exposed to topiramate monotherapy have:

- An increased risk of congenital malformations (particularly cleft lip/palate, hypospadias, and anomalies involving various body systems) following exposure during the first trimester. The North American Antiepileptic Drug pregnancy registry data for topiramate monotherapy showed an approximate 3-fold higher ~~incidence~~ **prevalence** of major congenital malformations **(4.3%)**, compared with a reference group not taking AEDs **(1.4%)**. In addition, data from other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of AEDs in combination therapy. **The risk has been reported to be dose dependent; effects were observed in all doses. In women treated with topiramate who have had a child with a congenital malformation, there appears to be an increased risk of malformations in subsequent pregnancies when exposed to topiramate.**
- A higher prevalence of low birth weight (<2500 grams) compared with a reference group.
- An increased prevalence of being small for gestational age (SGA; defined as birth weight below the 10^{th} percentile corrected for their gestational age, stratified by sex). The long term consequences of the SGA findings could not be determined.

~~It is recommended that women of child bearing potential use highly effective contraception (see section 4.5) and consider alternative therapeutic options.~~

[…]

Breast feeding

Animal studies have shown excretion of topiramate in milk. The excretion of topiramate in human milk has not been evaluated in controlled studies. Limited observations in patients suggest an extensive excretion of topiramate into breast milk. **Effects that have been observed in breastfed newborns/infants of treated mothers include diarrhea, drowsiness, irritability and inadequate weight gain.** ~~Since many medicinal products are excreted into human milk~~ **Therefore**, a decision must be made whether to suspend breast feeding or to discontinue/ abstain from topiramate therapy taking into account the importance of the medicinal product to the mother (see section 4.4).

- Section 4.8 (under table)

[…]

Congenital malformations and fetal growth restrictions (see section 4.4 and section 4.6).

Package Leaflet

Text should be amended as follows:

2. What you need to know before you take X

Do not take X
- if you are allergic to topiramate or any of the other ingredients of this medicine (listed in section 6).
- for migraine prevention*:* if you are pregnant or **if you** are ~~able to become pregnant~~**a woman of childbearing potential unless you are** ~~you are not~~ using effective contraception (see section 'Pregnancy and breastfeeding' for further information). **You should talk to your doctor about the best kind of contraception to use while you are taking X.**

Warnings and precautions
Talk to your doctor or pharmacist before taking X if you:
- …
- are **taking X to treat epilepsy and you are** pregnant or **a woman of childbearing potential** ~~could a become pregnant~~ (see section 'Pregnancy and breastfeeding' for further information)

Other medicines and X
…
Especially, tell your doctor or pharmacist if you are taking:
- …
- birth control pills. X may make your birth control pills less effective. **You should talk to your doctor about the best kind of contraception to use while you are taking X.**

Pregnancy and breast-feeding
~~If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.~~

Migraine prevention:
X can harm an unborn baby. You must not use X if you are pregnant. You must not use X for migraine prevention if you are a woman of childbearing potential unless you are using effective contraception. Talk to your doctor about the best kind of contraception and whether X is suitable for you. Before the start of treatment with X a pregnancy test should be performed.

Treatment of epilepsy:
If you are a woman of childbearing potential you should talk to your doctor about other possible treatments instead of X. If the decision is made to use X, you should use effective contraception. Talk to your doctor about the best kind of contraception to use while you are taking X. Before the start of treatment with X a pregnancy test should be performed. ~~Your doctor will discuss use of contraceptives with you, as well as discussing whether X is suitable for you.~~
Talk to your doctor if you wish to become pregnant.
As with other anti-epileptic medicines, there is a risk of harm to the unborn child if X is used during pregnancy. Make sure you are very clear about the risks and the benefits of using X for epilepsy during pregnancy.

- **If you take X during pregnancy, your baby has a higher risk for birth defects, particularly, cleft lip (split in the top lip) and cleft palate (split in the roof of the mouth). Newborn boys may also have a malformation of the penis (hypospadia). These defects can develop early in pregnancy, even before you know you are pregnant.**
- **If you take X during pregnancy, your baby may be smaller than expected at birth. Talk to your doctor if you have questions about this risk during pregnancy.**
- **There may be other medicines to treat your condition that have a lower risk of birth defects.**
- **Tell your doctor straight away if you become pregnant while taking X. You and your doctor should decide if you will continue to take X while you are pregnant.**

~~You should not take X for migraine prevention if you are pregnant or you are able to become pregnant and you are not using effective contraception.~~

Breast-feeding
The active substance in X (topiramate) passes into breast milk. Effects have been seen in breastfed babies of treated mothers, including diarrhea, feeling sleepy, feeling irritable, and poor weight gain. Therefore, your doctor will discuss with you whether you abstain from breast-feeding or whether to abstain from treatment with X. Your doctor will take into account the importance of the medicine to the mother and the risk for the baby.
Mothers who breast-feed while taking X must tell the doctor as soon as possible if the baby experiences anything unusual.

Annex III

Timetable for the implementation of this position

Timetable for the implementation of this position

Adoption of CMDh position:	September 2017 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	29 October 2017
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	28 December 2017