Registratiehouders
(t.a.v. registratieafdeling)

You letter Your reference Utrecht,
-- -- ...

Case number Our reference
../..

Case manager Telephone number

Subject
Request for change in the product information following the PhVWP/CMDh decision

Topiramate – Updated information on risk of congenital malformations

Following assessment of the available data relating to the risk of congenital malformations in association with the use of topiramate in pregnancy and discussion at the Pharmacovigilance Working Party and the Coordination Group for Mutual Recognition and Decentralised Products – human (CMDh), all Marketing Authorisation (MA) holders for topiramate-containing products are being requested to submit type 1B variations (variation number C.1.3.a) (or equivalent national procedures – see below) for their relevant products to implement the final SmPC wording agreed by the PhVWP. The Package Leaflet (PL) has not been revised as the PL already contains information on increased risk for birth defects with us in pregnancy.

Link to the website with the published decision: http://www.hma.eu/222.html

You are requested to change the SmPC of

<product> <RVG>

The agreed text, together with the translation in Dutch, is attached to this letter.

The text should be included literally in the SmPC. However, you are requested to check the SmPC carefully to make sure that there is no overlap with the current text. If there is such overlap, you should replace the current text with wording from the agreed text.

For products registered via a MRP or DCP procedure, the RMS takes responsibility on behalf of CMS to request the variation from the MA holder and initiate the procedure.

The applications do not require supporting information or expert statements and will be accepted by Member States Competent Authorities without further assessment or amendment.

For nationally approved products there is no need to submit a Variation Application Form.

Applying for the type IB variation

The MEB has already assigned a case number for this variation. You should send your application via e-mail to case@cbg-meb.nl, stating case number <XXXXXX> in the subject field. Please attach the adapted SmPC (both clean and track-changes version in Word format).
If the product was registered via MRP with NL = RMS, you are also asked to include a variation application form and dispatch list with the submission dates in the CMSs. Please be informed that you have to submit both the English text and the national translation.

Please mention the following information in the ‘Subject’ field:

- Case number
- Procedure number (if applicable)
- Type IB on request of the MEB
- Name of the medicinal product
- RVG number of the lowest strength

And in the message:

- Implementation of PhVWP/CMDh decision
- The RVG number(s)
- The MRP number (if applicable)
- Name, phone number and e-mail address of the representative
- Your reference (if applicable)
- When submitting the amended texts, please confirm that it concerns only the implementation of agreed PhVWP/CMDh decision
- Please mention other variations concerning SmPC changes that are currently under consideration by the MEB (if applicable)

**Timetable for implementation**

You should submit variations no later than the 1st of May 2012.

On behalf of the Medicines Evaluation Board in the Netherlands,

*This notification has been produced centrally in an automated process and consequently does not bear a signature.*

Attachment:

Annex 1: agreed text (English and Dutch version)
ANNEX 1

Topiramate – and risk of congenital malformations

PhVWP core SmPC wording section 4.6 – Fertility, pregnancy and lactation

Data from the U.K. pregnancy register and the North American Antiepileptic Drug (NAAED) pregnancy registry indicate that infants exposed to topiramate monotherapy in the first trimester have an increased risk of congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems). The NAAED pregnancy registry data for topiramate monotherapy showed an approximate 3-fold higher incidence of major congenital malformations, compared with a reference group not taking antiepileptic drugs. Furthermore, there was a higher prevalence of low birth weight (<2500 grams) following topiramate treatment than in the reference group.

Dutch translation:

Gegevens uit het U.K. zwangerschapsregister en het North American Antiepileptic Drug (NAAED) zwangerschapsregister geven aan dat zuigelingen die in het eerste trimester van de zwangerschap zijn blootgesteld aan topiramaat-monotherapie, een verhoogd risico hebben op aangeboren afwijkingen (bijv. craniofaciale defecten, zoals een gespleten lip/gehemelte, hypospadie en afwijkingen bij diverse lichaamssystemen). De gegevens voor topiramaat-monotherapie uit het NAAED zwangerschapsregister lieten een ongeveer driemaal hogere incidentie van ernstige congenitale afwijkingen zien in vergelijking met een referentiegroep die geen anti-epileptica innam. Daarnaast was er een hogere prevalentie van een laag geboortegewicht (< 2500 gram) na behandeling met topiramaat dan in de referentiegroep.