Subject

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

Antiepileptics – Risk of bone disorders

Following assessment of the available data relating to the risk of bone disorders in association with long-term use of antiepileptics 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 products with active substance Carbamazepine, Phenobarbital, Phenytoin, Primidone, Oxcarbazepine, Lamotrigine and Sodium Valproate 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 and PL wording agreed by the PhVWP.

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

You are requested to change the SmPC and Package Leaflet (PL) of <product> <RVG>

The agreed texts, together with the translation in Dutch, are attached to this letter.

These texts should be included literally in the SmPC and PL. However, you are requested to check the SmPC and PL carefully to make sure that there is no overlap with the current texts. If there is such overlap, you should replace the current text with wording from the agreed texts. With regard to PL wording, further user testing by individual MA holders will not be expected on this occasion.

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.
Active substances with a known risk of Steven-Johnson syndrome and toxic epidermal necrolysis.

Please be informed that recently the PhVWP recommended key elements of warnings for the product information of the antiepileptics carbamazepine, lamotrigine, phenobarbital and phenytoin, regarding their rare risk of life-threatening Steven-Johnson syndrome and toxic epidermal necrolysis for early detection of these adverse reactions and subsequent permanent discontinuation of the medicine to improve their outcomes.

You are requested to determine whether or not the currently approved SmPC and PL do reflect these key elements. If this is not the case it would be highly appreciated if this opportunity would be taken to submit both the class wording for antiepileptics as the key elements of warnings for the above mentioned antiepileptics as a grouped variation.

Applying for the type IB variation

The MEB has already assigned you a case number for this variation. You should send your application via e-mail to case@cbg-meb.nl, stating case number <XXXXX> in the subject field. Please attach the adapted SmPC and PL (both clean and track-changes versions 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 texts and the national translations.

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(s)
- The RVG numbers
- 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 and/or PL changes that are currently under consideration by the MEB (if applicable)

Timetable for implementation

You should submit variations no later than the 16th of April 2012.

You are obliged to start incorporating updated PLs into new production batches within a 6 month timeframe after approval

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.

Attachments:
Annex 1: Agreed wording Antiepileptics and risk of bone disorders (English and Dutch versions)
Annex 2: Adopted key elements for SmPC/PL regarding Steven-Johnson Syndrome/Toxic Epidermal Necrolysis for “high risk” drugs.
ANNEX 1

Antiepileptics and possible risk of bone disorders

The PhVWP agreed the following harmonised wording to be included in the product information for all products containing carbamazepine, phenobarbital, phenytoin, primidone, oxcarbazepine, lamotrigine and sodium valproate.

PhVWP core SmPC wording section 4.8 – Undesirable effects

There have been reports of decreased bone mineral density, osteopenia, osteoporosis and fractures in patients on long-term therapy with <drug name>. The mechanism by which <product name> affects bone metabolism has not been identified.

PhVWP core PIL wording (to be included in section 4 – Possible side effects)

There have been reports of bone disorders including osteopenia and osteoporosis (thinning of the bone) and fractures. Check with your doctor or pharmacist if you are on long-term antiepileptic medication, have a history of osteoporosis, or take steroids.

Dutch translation:

PhVWP core SmPC wording section 4.8 – Undesirable effects

Er zijn meldingen van verminderde minerale botdichtheid, osteopenie, osteoporose en botbreuken in patiënten die een langdurige behandeling onderragen met <stofnaam>. Het mechanisme van de beïnvloeding van het bot metabolisme is niet bekend.

PhVWP core PIL wording (to be included in section 4 – Possible side effects)

Er zijn meldingen van botafwijkingen waaronder dunner worden van het bot (osteopenie, osteoporose) en botbreuken. Indien u langdurig met een middel tegen epilepsie (anti-epilepticum) wordt behandeld, u eerder osteoporose heeft gehad of indien u steroïden gebruikt dient u met uw arts te overleggen.
ANNEX 2

*Adopted key elements for SmPC/PL regarding Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis for “high risk” drugs (for systemic use): allopurinol, carbamazepine, lamotrigine, phenobarbital, phenytoin, sulfamethoxazol, sulfasalazine, sulfadiazine, sulfafurazole, sulfadoxine, meloxicam, piroxicam, tenoxicam (and nevirapine; centrally authorized product)*

Summary of product Characteristics

**Section 4.4 – Special warnings and precautions for use**

- Life-threatening cutaneous reactions Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with the use of <product name>.

- Patients should be advised of the signs and symptoms and monitored closely for skin reactions. The highest risk for occurrence of SJS or TEN is within the first weeks of treatment. *(Adoption to individual drug if such data are available)*

- If symptoms or signs of SJS or TEN (e.g. progressive skin rash often with blisters or mucosal lesions) are present, <product name> treatment should be discontinued.

- The best results in managing SJS and TEN come from early diagnosis and immediate discontinuation of any suspect drug. Early withdrawal is associated with a better prognosis.

- If the patient has developed SJS or TEN with the use of <product name>, <product name> must not be re-started in this patient at any time.

**Section 4.8 – Undesirable effects**

Severe cutaneous adverse reactions (SCARs): Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported (see section 4.4). Frequency: very rare *(If robust frequency data are available for a particular drug, the frequency may be assigned based on these data)*.

Package leaflet

**Section 2 – What you need to know before you take <product name>**

- Potentially life-threatening skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported with the use of <product name>, appearing initially as reddish target-like spots or circular patches often with central blisters on the trunk.

- Additional signs to look for include ulcers in the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes).

- These potentially life-threatening skin rashes are often accompanied by flu-like symptoms. The rash may progress to widespread blistering or peeling of the skin.

- The highest risk for occurrence of serious skin reactions is within the first weeks of treatment. *(Adoption to individual drug if such data are available)*

- If you have developed Stevens-Johnson syndrome or toxic epidermal necrolysis with the use of <product name>, you must not be re-started on <product name> at any time.
Choose between these two alternatives depending on the existing information:

- If you develop a rash or these skin symptoms, stop taking <product name>, seek urgent advice from a doctor and tell him that you are taking this medicine.
  [For antiepileptics this sentence can be completed with a warning on danger of epileptic seizure due to drug withdrawal.]

or

- If you develop a rash or these skin symptoms, seek immediate advice from a doctor and tell him that you are taking this medicine.

Section 4 – Possible side effects

Potentially life-threatening skin rashes (Stevens-Johnson syndrome, toxic epidermal necrolysis) have been reported (see section 2).
Frequency: very rare
(If robust frequency data are available for a particular drug, the frequency may be assigned based on these data).