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

Following assessment of the available data assessed by the PhVWP on

- Risk of bone fractures (SSRI’s and TCA’s)
- Risk of Persistent Pulmonary Hypertension in Neonates/PPHN (SSRI’s and SNRI’s)

All Marketing Authorisation (MA) holders for products with <active substance> as active ingredient are being requested to submit type IB variations (variation number C1.3.a) (or equivalent national procedures – see below) for their relevant products to implement the PhVWP/CMD(h) decision. As this variation concerns 2 different changes to the SmPC and PL, it should be submitted as a grouped IB variation.

Links to published information on bone fractures, PPHN and congenital malformations:
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.

The applications do not require supporting information or expert statements and will be accepted by Member States Competent Authorities without further assessment or amendment.
If there is no reason to update your product information via a type IB variation, you are requested to reply to this letter with a statement that the product information does not need to be changed.

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

**Applying for the type IB variation in a different way**

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 despatch 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
- 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 texts, please confirm that it concerns only the implementation of agreed PhVWP/CMDh decision
- Please, mention other variations concerning SmPC and/or PL that are currently under consideration of the MEB

**Timetable for implementation**

You should submit variations no later than datum xxx.

**Special note for parallel registered products and related authorisation**

With this letter we just would like to inform you concerning a change of the SmPC and/or PL of the original product in the Netherlands. However, you are kindly requested not to submit these documents for your product until the Board has approved the SmPC/PL of the original product. Please consult our website (GIB, Medicines Information Databank) regularly to be informed if the variation for the original product has been implemented. This means that the submission date, <date>, does not apply to your product.

In order to ensure rapid implementation, you are kindly requested to submit the texts with only the required adaptations. This means that you should use the currently, MEB approved texts. Please confirm this upon delivery. The implementation of any other variation and/or adaptation to the current QRD template should be dealt with in a separate case.
On behalf of the Medicines Evaluation Board in the Netherlands,

Ms. Drs. K.H. Doorduyn-van der Stoep.
Deputy-secretary

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

Attachments: agreed texts (UK and Dutch versions)
Annex 1: Risk of bone fractures (SSRI’s and TCA’s)
Annex 2: Risk of Persistent Pulmonary Hypertension in Neonates/PPHN (SSRI’s and SNRI’s)
Risk of bone fractures

PhVWP core SPC wording section 4.8 for all SSRIs and TCAs:

Class effects
Epidemiological studies, mainly conducted in patients 50 years of age and older, show an increased risk of bone fractures in patients receiving SSRIs and TCAs. The mechanism leading to this risk is unknown.

PhVWP core PIL wording for all SSRIs and TCAs (to be included in section 4 – section possible side effects):

An increased risk of bone fractures has been observed in patients taking this type of medicines.

Dutch translation:

PhVWP core SPC wording section 4.8 for all SSRIs and TCAs:

Klasse-effecten
Epidemiologische studies, voornamelijk bij patiënten van 50 jaar en ouder, laten bij patiënten die SSRIs en TCAs krijgen een hoger risico op botfracturen zien. Het mechanisme dat dit hogere risico veroorzaakt is onbekend.

PhVWP core PIL wording for all SSRIs and TCAs (to be included in section 4 – section possible side effects):

Bij patiënten die dit soort geneesmiddelen gebruiken, is een hogere kans op botbreuken gezien.
ANNEX 2

Risk of Persistent Pulmonary Hypertension in Neonates/PPHN

PhVWP core SPC wording section 4.6 for all SSRIs;

Epidemiological data have suggested that the use of SSRIs in pregnancy, particular in late pregnancy, may increase the risk of persistent pulmonary hypertension in the newborn (PPHN). The observed risk was approximately 5 cases per 1000 pregnancies. In the general population 1 to 2 cases of PPHN per 1000 pregnancies occur.

PhVWP core PIL wording for all SSRIs (to be included in section 2 – subsection pregnancy and breastfeeding):

Make sure your midwife and/or doctor know you are on <TRADENAME>. When taken during pregnancy, particularly in the last 3 months of pregnancy, medicines like <TRADENAME> may increase the risk of a serious condition in babies, called persistent pulmonary hypertension of the newborn (PPHN), making the baby breathe faster and appear bluish. These symptoms usually begin during the first 24 hours after the baby is born. If this happens to your baby you should contact your midwife and/or doctor immediately.

Dutch translation:

PhVWP core SPC wording (Section 4.6) for all SSRIs:

Epidemiologische gegevens wijzen erop dat het gebruik van SSRI’s tijdens de zwangerschap, vooral laat in de zwangerschap, het risico op persisterende pulmonale hypertensie bij de neonaat (PPHN) kan verhogen. Het waargenomen risico was ongeveer 5 gevallen per 1000 zwangerschappen. In de algemene populatie komen 1 tot 2 gevallen van PPHN per 1000 zwangerschappen voor.

PhVWP core PIL wording for all SSRIs (to be included in section 2 – subsection pregnancy and breastfeeding):

Zorg dat uw verloskundige en/of arts weet dat u <HANDELSNAAM> gebruikt. Bij gebruik tijdens de zwangerschap, vooral in de laatste drie maanden van de zwangerschap, kunnen geneesmiddelen als <HANDELSNAAM> het risico op een bepaalde ernstige aandoening bij baby’s verhogen. Deze aandoening wordt ‘persisterende pulmonale hypertensie van de pasgeborene’ (PPHN) genoemd en veroorzaakt een versnelde ademhaling en blauwachtige verkleuring van de huid van de baby. Deze verschijnselen beginnen meestal in de eerste 24 uur nadat de baby is geboren. Als dit met uw baby gebeurt, moet u onmiddellijk contact opnemen met uw verloskundige en/of arts.