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NOTE

From:	General Secretariat of the Council
To:	Council
Subject:	**Employment, Social Policy, Health and Consumer Affairs Council** meeting on 8 December 2017 Valproate and teratogenic medicinal products – *Information from the Belgian delegation* (Any Other Business item)

Delegations will find in Annex an information note from the Belgian delegation on the above-mentioned subject to be raised under "Any Other Business" at the session of the Council (EPSCO) on 8 December 2017.

ANNEX

Valproate and teratogenic medicinal products

1. Procedures – European Medicines Agency (EMA)

1.1. October 2013 – October 2014:

Article 31 referral reviewing the risk-benefit balance of valproate-containing medicines. These medicines are approved nationally in the European Union (EU) to treat epilepsy, bipolar disorder and in some countries, migraine.

Outcome:

– The EU product information for valproate has been updated (to strengthen warnings and restrictions on valproate use in women and girls, due to the risk of malformations and developmental problems in babies who are exposed to valproate in the womb).

– Educational materials should be provided to all healthcare professionals in the EU and to women prescribed valproate to inform them of these risks. It consists of:
  - a guide for healthcare professionals,
  - a patient booklet and an acknowledgment of risk information form (including a checklist) for prescribers,
  - a checklist for patient or carer.

European patients' organisations have also been involved by the EMA Pharmacovigilance Risk Assessment Committee, and their views on options for improving risk communication were asked. Most of the participants recommended that a **dedicated symbol** is placed on the packaging and package leaflet of the product to warn about the risk during pregnancy (*e.g.* a pregnant woman figure in a red triangle). The **EMA Pharmacovigilance Risk Assessment Committee** advised the participants that there is currently **no officially recognised logo at EU level for this risk** and that many logos are often **misinterpreted** by medicines users.

As such this demand was **not retained by the EMA Pharmacovigilance Risk Assessment Committee**, pictograms being considered of limited value and possibly leading to misinterpretation of the intended message.

The 2014 review also recommended studies at EU level to measure how effective the proposed measures were.

1.2. July 2016:

Member State Request for advice from the EMA Pharmacovigilance Risk Assessment Committee on valproate-containing medicines: need for **boxed warning** and **patient alert card** in addition to risk minimisation measures agreed during the October 2014 Article 31 referral.

Context:

– **France** informed the Member States about **approval of visual warning and inclusion of a pictogram** on the outer labelling.

– **UK** informed all Member States about additional measures at the national (UK) level: a **patient alert card** and inclusion of a **warning on the outer labelling**.

– The marketing authorisation holder **Sanofi** informed that they will submit the proposal to include this outer package labelling warning and pictogram on its Depakine® medicine **globally**.

Recommendation from the EMA Pharmacovigilance Risk Assessment Committee: In addition to the measures agreed in 2014, **national authorities** in individual EU Member States **may take additional measures** to ensure that the risks of valproate use during pregnancy are appropriately communicated and managed, taking usage patterns and characteristics of the healthcare system in individual countries into consideration.

1.3. March 2017:

New Article 31 referral reviewing the use of valproate-containing medicines in the treatment of women and girls who are pregnant or of childbearing age.

Since the 2014 Article 31 referral, some EU Member States have carried out additional assessments of the impact of the measures at national level and concerns have been raised about **how effective the measures are**. Therefore, the French medicines regulator (ANSM) asked the EMA to review the measures and consider whether further EU-wide action should be recommended to minimise the risks in women who are pregnant or of childbearing age.

As part of this referral procedure, the EMA held a **public hearing** on 26 September 2017.

During this first EMA public hearing, it has been noted that **a strong support for a visible reminder of the risks on the outer packaging** of valproate medicines is amongst the proposals and ideas from participants. Although the previous EMA Pharmacovigilance Risk Assessment Committee discussions about a special symbol had identified some questions, this should be revisited in the light of the representations at the hearing. Following this public hearing, the EMA Pharmacovigilance Risk Assessment Committee will reflect on the experiences and suggestions shared by the speakers and consider their input in assessing the safety of valproate. The EMA Pharmacovigilance Risk Assessment Committee will now convene follow-up meetings and is expected to issue its recommendation in the upcoming months.

2. Situation in Belgium on warnings/pictograms

For valproate specifically:

- dd. **14 March 2016:** Sanofi submitted a variation in Belgium, to add a **boxed textual warning** for its Depakine®
- dd. **21 November 2016:** Sanofi submitted another variation in Belgium, to introduce a **pictogram** on its Depakine® outer packaging:

- The Belgian Federal Agency for Medicines and Health Products (FAMHP) **approved both the boxed textual warning and the addition of the pictogram** for Depakine® in June 2016 and March 2017 respectively.
- **Generic marketing authorisation holders** with valproate containing medicines have been requested to also implement the boxed textual warning and pictogram. All marketing authorisations holders did introduce a notification to the Belgian Federal Agency for Medicines and Health Products to add the warning/pictogram on the packaging. **By end of March 2018 at the latest, all packages being manufactured will have been modified.**

Teratogenic medicines in general:

In 2016 a legislative proposal to **impose a visual warning on the packaging of all medicinal products with teratogenic/developmental toxicity potential** was submitted to the **Belgian House of Representatives**, aiming to better inform all stakeholders and mainly patients and healthcare professionals on the risks of teratogenic medicines for the unborn child (**DOC 54 1593/001**).

The **Belgian Commission for medicines for human use**, established within the Belgian Federal Agency for Medicines and Health Products, was consulted on this matter and issued the following advice:

- Package warning

  A package warning should be applied on products with demonstrated teratogenic/developmental toxicity potential to warn about this risk.

  The medicinal products qualifying for a package warning were considered to be:

  i) Medicinal products for which additional risk minimisation measures have been imposed regarding the teratogenicity/developmental toxicity risks (educational material, Pregnancy Prevention Plan,…).

  ii) Medicinal products for which the summary of product characteristics explicitly documents that a risk of developmental toxicity or teratogenicity has been identified based on the analysis of human data.

- Information Campaign

  The implementation of the package warning should be accompanied by a national communication plan towards healthcare professionals and patients.

Belgium is **currently still deliberating** on the possibility to implement a warning on the packaging of (all) teratogenic/developmental toxicity medicines, following the recommendations from the Belgian Commission for medicines for human use.

Main pro arguments for a warning/pictogram: as the summary of product characteristics and the leaflet are not always (re-)read by patients who have the habit of using certain medicines, the packaging is an important communication channel, reminding them of the teratogenicity/developmental toxicity and the need to obtain more information. It also reminds healthcare professionals on the need to inform patients on the teratogenicity/developmental toxicity and promotes dialogue on e.g. the need to use effective contraceptives. The current experience with retinoids or valproate shows that educational materials or boxed text warnings alone are not sufficient. A pictogram accompanying a text warning may attract the patient's eye (even illiterate patients), and may prompt a search for additional information or dialogue with the healthcare professionals on the risk of teratogenicity/developmental toxicity associated with the drug.

Main contra arguments for a warning/pictogram: consulted experts warn that a teratogenicity label - in the absence of additional information - may cause patients to perceive these medicinal products as unsafe and to discontinue treatment. Also, medications left with no warning sign may induce a false sense of security, while drugs should always be used with caution during pregnancy.

Another important discussion point is the **identification of the drugs that qualify for the teratogenicity/developmental toxicity label**. A ready-to-use reference list does not exist: the "absence" of teratogenic potential has been indisputably demonstrated in only a very limited number of drugs, while teratogenicity/developmental toxicity remains a possibility (even minor) for most drugs and may depend on many factors. For this reason, the **summary of product characteristics** has been put forward as the primary source for identifying medicinal products with a recognised risk for developmental toxicity. It is a regulatory reviewed and approved source in which all available knowledge (both published and proprietary data) is taken into account, including clinical data, pharmacological activity, results from non-clinical studies, and knowledge.

➔ There are pro and cons for putting a pictogram on the package of medicinal products containing substances with teratogenicity/developmental toxicity. In any event, **a national approach is not suitable because it would create discrepancies between Member States**. Indeed, member states do not have the same point of view concerning the best way to minimize the risk and the list of products which are concerned by the risk. Such discrepancies are not easy to understand for the patient especially for the patients moving or travelling across the EU. The patient has the right to be informed on the same way for a risk which is obviously the same in all countries. In view of the free movement of persons and goods in the EU and the need for equal access to information between European citizens, a concertized and harmonised action at a EU level should therefore be considered.

Belgian campaign

In the next months, the Belgian Federal Agency for Medicines and Health Products will launch a public campaign dedicated to women of childbearing age:
"*Medicines and pregnancy or breastfeeding: talk to your doctor or pharmacist*".
The purpose of this campaign is to inform patients about the correct use and risks of medicines used during pregnancy or breastfeeding.

The key messages would be:

- Are you pregnant or are you breastfeeding? Before taking any medicine, talk to your doctor or pharmacist first. Some medicines may be dangerous to the unborn child or the child that is breastfed.
- In some conditions (epilepsy, diabetes, hypertension, etc.) it is necessary that certain medicines are continued in order to protect the mother's and child's health. Do not hesitate to talk with your doctor.
- Do you already take a medicine and are you planning a pregnancy? Talk to your doctor or pharmacist beforehand.
- Useful information about the use of a medication during pregnancy or breastfeeding is provided in the leaflet. Some medicines should not be taken during a certain period of the pregnancy, other medicines should be avoided throughout the whole pregnancy.
- Some medicines contain additional information that complements the information in the leaflet. Your doctor or pharmacist will provide you with these "educational materials".
- If you experience any unexpected side effects with a drug, it is useful that you report this to the Belgian Federal Agency for Medicines and Health Products. This can be done by your doctor or pharmacist or you can also report yourself. Your report will help the competent authorities to better identify the safety profile of the medicine.

3. Situation in other Member States on warnings/pictograms

3.1. In **September 2016**, the Belgian Federal Agency for Medicines and Health Products launched a Non Urgent Information among the other EU Member States, which were interrogated on **existing or planned actions for a teratogenicity visual warning/pictogram on the outer box of valproate-containing products or other teratogenic products**.

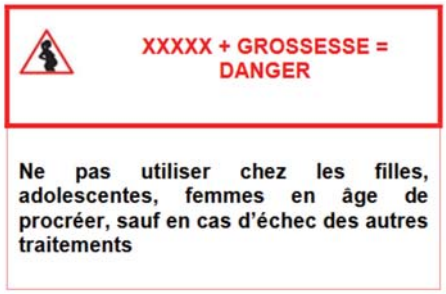
- Of the 17 Member States that responded, 6 already approved a proposal from the Brand leader marketing authorisation holder for valproate to add a written warning on the outer packaging of valproate-containing products, and France also requested a pictogram for valproate-containing medications.
- In Germany, a discussion with experts of teratogenicity/drug use during pregnancy is planned regarding risk minimisation measures (including pictograms) for teratogenic medication.
- Finland also possesses package warnings on teratogenicity/developmental toxicity, but at the present time restricted to medication which are contraindicated during pregnancy only.
- Other Member States were **not in favour of a pictogram** on the packaging of potentially teratogenic medications, as they considered it open to **misinterpretation**. They argued that little is known on the impact of such a measure in the real-life setting. A major downside could be that patients would quit medications without any discussion with an healthcare professional exposing them to higher health risks than the use of the medication itself.

3.2. In **December 2016,** another Non Urgent Information was issued by EMA, requesting for information on the **implementation at national level of the outcome of the 2014 Article 31 referral**.

Of the 28 Member States that responded and have valproate-containing products on their market, 10 were considering/had already implemented a visual boxed warning/pictogram relating to the teratogenicity/foetoxicity of valproate-containing products:

- In the Netherlands and the Czech Republic, a warning regarding the risks associated with valproate use during pregnancy on the outer package was agreed.

– In Spain, the warning has already been implemented.
– In 6 other Member States, the procedure was ongoing or still the subject of discussion.
– In France, since March 2016; a red text in a red box was printed on the outer packaging of valproate containing products : “Tradename (or valproate for generic products) + Pregnancy = Risk”. France changed this labelling in 2017 to “Tradename (or valproate for generic products) + Pregnancy = Danger” and add a pictogram (see below).



3.3. As announced in the **notification 2016/629/F from the European Commission**, **France** has further decided to implement at a national level **3 types of pictograms** relating to teratogenicity/developmental toxicity on the packaging of medications.

3.4. **In August 2017**, the French medicines regulator (ANSM) has published a **FAQ** on its website to the attention of the marketing authorisation holders concerning the **“pregnant women” pictogram**:
http://ansm.sante.fr/var/ansm_site/storage/original/application/bc475f36387bdece14d72aea014c4a9b.pdf

3.5. **On October 13, 2017**, **Press release French Health Directorate**:
“A pictogram "pregnant women" arrives, as of October 17, 2017, on the boxes of drugs presenting risks for women during their pregnancy. It is put on the boxes by the laboratories of the medicines concerned and allows a better visibility of the information relative to these risks, as already indicated in the leaflet.”.