<Date>

Valproate - containing medicines: new measures regarding the potential risk of neurodevelopmental disorders in children of fathers treated with valproate in the 3 months prior to conception

Dear healthcare professional,

This letter is sent in agreement with the European Medicines Agency (EMA) and the <National Competent Authority > to inform you of the following:

Summary

- **A retrospective observational study in 3 Nordic countries suggests an increased risk of neurodevelopmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate as monotherapy in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam as monotherapy. Due to study limitation, this risk is possible but is not confirmed.**

New measures for valproate use in male patients

- **It is recommended that in male patients valproate is initiated and supervised by a specialist experienced in treatment of epilepsy, bipolar disorder <or migraine>.**
- **Prescribers should inform male patients about the potential risk and discuss with them the need to consider effective contraception, including for a female partner, while using valproate and for 3 months after stopping the treatment.**
- **Treatment with valproate in male patients should be regularly reviewed by prescribers to evaluate whether valproate remains the most suitable treatment for the patient.**
- **For male patients planning to conceive a child, suitable alternative treatment options should be considered and discussed with the patient. Individual circumstances should be evaluated for each patient. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar> <migraine> should be sought as appropriate.**
- **The male patients should be advised to not donate sperm during treatment and for at least 3 months after treatment discontinuation.**
- **A patient guide should be provided to male patients.**

Background on the safety concern

EMA's Pharmacovigilance Risk Assessment Committee (PRAC) has evaluated data from a study (EUPAS34201[1]) conducted by pharmaceutical companies of valproate containing products as an obligation following a previous EU-wide review of valproate use during pregnancy. The primary objective was to investigate the risk of NDDs in offspring paternally exposed to valproate as monotherapy, compared to lamotrigine or levetiracetam as monotherapy treatment, in the 3 months period prior to conception. This retrospective observational study was conducted using data from multiple registry databases in Denmark, Sweden and Norway. The primary outcome of interest was NDDs (composite endpoint including autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders, movement disorders) in offspring up to 11 years of

1 https://catalogues.ema.europa.eu/node/3611/administrative-details

age. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group.

- The meta-analysis of data from the 3 countries resulted in a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07) for NDDs in children from fathers treated with valproate monotherapy in the 3 months prior to conception compared to the composite lamotrigine/levetiracetam monotherapy group.
- The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group monotherapy versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy group.

The study was not large enough to investigate associations with specific NDD subtypes. Due to study limitations, including potential confounding by indication and differences in follow-up time between exposure groups, the risk of NDDs in children of fathers that used valproate in the 3 months prior to conception is considered a potential risk and a causal association with valproate is not confirmed.

The study did not evaluate the risk of NDD to children born to men who had discontinued valproate treatment for more than 3 months before conception (i.e., allowing a new spermatogenesis without valproate exposure).

The observed potential risk of NDDs after paternal exposure in the 3 months before conception is of lower magnitude than the known risk for NDDs after maternal exposure during pregnancy. When valproate is administered as monotherapy to women, studies in pre-school children exposed in utero to valproate show that up to 30-40% experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Based on the available data, new measures for valproate use in men have been adopted as specified in the "summary" above. The product information of all valproate-containing medicines is being updated to inform healthcare professionals and patients of the potential risk of NDD in children of men treated with valproate and to provide guidance regarding use of valproate in men. In addition, educational materials will be available for healthcare professionals and male patients. These include:

- An updated guide for healthcare professionals with a dedicated section on the use of valproate in male patients;
- A new patient guide for males, which should be provided to male patients using valproate;
- An update of the existing patient card with the information for male patients, included in or attached to the outer packaging, so that it will be provided in the pharmacy to the patient each time the medicine is dispensed.

Call for reporting

Any suspected adverse events should be reported to {Insert details of the national spontaneous reporting system e.g. name, postal address, fax number, website}

This medicinal product is subject to additional monitoring.

{Insert details (e.g. name, postal address, fax number, website address) on how to access to the national spontaneous reporting system}

Company contact point

<Contact point details for access to further information, including relevant website address(es), telephone numbers and a postal address>

DHPC communication plan

DHPC COMMUNICATION PLAN	
Medicinal product(s)/active substance(s)	Valproate <invented name>
Marketing authorisation holders	For a full list of marketing authorisation holders, please refer to Appendix I. It is expected that a single consistent message is sent to healthcare professionals in each EU Member State, including in those where the DHPC concerns several marketing authorisation holders. All concerned marketing authorisation holders in each Member State are strongly encouraged to collaborate, so that a single DHPC is prepared and circulated in each Member State. The letter circulated in each Member State should cover all active substance-containing products authorised in that Member State. It is encouraged that the originator marketing authorisation holder (where available) in each Member State acts as the contact point for the national competent authority, on behalf of the other concerned marketing authorisation holders in the same Member State. If no originator product is marketed in the Member State, it is encouraged that one of the concerned generic companies acts as contact point for the competent authority.
Safety concern and purpose of the communication	Potential risk to children of fathers treated with valproate: New information and measures regarding the potential risk of neurodevelopmental disorders in children of fathers treated with valproate as monotherapy in the 3 months prior to conception in comparison to those treated with lamotrigine / levetiracetam as monotherapy
DHPC recipients	HCPs who prescribe the treatment with valproate and related substances (neurologists, psychiatrists, pediatricians, general practitioners) pharmacists and other HCPs involved in the management of patients suffering from epilepsy and bipolar disorder <or migraine>. The target group should be further defined at the national level, in agreement with the respective national competent authority.
Member States where the DHPC will be distributed	All EU and EEA Member States

Timetable	Date
DHPC and communication plan (in English) agreed by PRAC	11 January 2024
DHPC and communication plan (in English) agreed by CMDh	25 January 2024
Submission of translated DHPCs to the national competent authorities for review	01 February 2024
Agreement of translations by national competent authorities	08 February 2024
Dissemination of DHPC	19 February 2024