Annex I

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisation(s)

Scientific conclusions

Taking into account the PRAC Assessment Report for the non-interventional imposed PASS final report for the medicinal product(s) containing the active substance valproate and concerned by the PASS final report, the scientific conclusions are as follows.

Having considered the results of the post-authorisation safety study (PASS) final report, imposed to the MAHs of medicinal product(s) containing valproate in the European Union (EU), in the framework of the Article 31 referral completed in 2018, together with non-clinical, literature data to date, the input of external stakeholders (including representative of patients and HCP organisations) and clinical experts who attended at the scientific advisory group (SAG) neurology, as agreed during the plenary meeting held on 8-11 January 2024, the PRAC agreed that:

The results of the population-based, retrospective cohort study using databases from Denmark (DK), Sweden (SE) and Norway (NO), conducted to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders (NDD), including autism spectrum disorders (ASD), as well as congenital malformations (CM) in the offspring, suggested an increased risk of NDD, including ASD, but no difference in the risk of CM in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine or levetiracetam. A trend for an increased risk of NDD (including ASD), although not significant in the three individual countries, was apparent in the data from NO, SE and DK, and the combined data from these three countries showed a borderline statistically significant increased risk. However, taking into consideration the study limitations, including potential confounding by indication and differences in follow-up time between exposure groups, together with (limited) information from other sources, and the input of external stakeholders and clinical experts, the risk was considered by PRAC as potential (i.e. causality has not been established).

Considering the seriousness of the NDDs (including ASD) and their life-long impact on children and families, the PRAC also concluded that the study findings, including their uncertainties, should be communicated to patients and healthcare professionals (HCP) and confirmed that current available data were sufficient to justify applying precautionary, risk proportionate, measures, also in light of the confirmed and higher risk for children following *in utero* exposure to valproate. The input obtained from clinical experts and stakeholders also supported the PRAC's conclusion on the request to the MAHs to address the uncertainty of this potential risk, via (new) additional analyses (including subgroup analyses and stratification), as part of a new category 1 PASS with appropriate milestones.

In light of all the above, with regard to male patients, the PRAC recommended to **update the product information** of medicinal products containing valproate to include that / with:

- It is recommended that valproate is initiated and supervised by a specialist experienced in the management of epilepsy <or> bipolar disorder <or migraine>. Specialists are generally best aware of prescribing conditions and they are best placed to (re-)evaluate the need for initiating or continuing treatment with valproate or the need to switch to other medication, in case of a wish for fathering a child.

- The need for a regular review by a specialist, to evaluate whether valproate is (still) the most suitable treatment and to remind the male patient about the potential risk for NDD (including ASD) with valproate when used during conception and talk about whether the male patient wishes to conceive a child. The need and frequency of such review can be decided by the patient and HCP, considering the patient's need and individual circumstances.

- Information on the potential risk of NDD in the offspring born to fathers using valproate around the conception period, including the recommendation for prescribers to inform patients on the potential

risk, discuss the need to consider effective contraception in male patients using valproate (and their female partner), advice male patients to consult their specialist when they are planning to conceive a child and before discontinuing contraception, and to consider the possibility of treatment alternatives in case the male patients using valproate is planning to conceive a child. Male patients should also be advised to not donate sperm while on valproate treatment, and for at least 3 months after treatment discontinuation.

- Educational materials are made available for healthcare professionals (HCP) and patients. A patient guide should be provided to male patients using valproate.

The PRAC also recommended the following **additional risk minimisation measures**:

- To update the existing HCP guide with a dedicated section on male patients, to inform HCPs about the potential risk of NDD (including ASD) following paternal exposure to valproate and the advices to provide to male patients and their female partners. An updated English 'core version of the HCP guide' with a dedicated section on use of valproate in male patients is agreed by the committee, to complement the current version, focussed on pregnancy prevention program for girls and women of childbearing potential.
- To update the valproate patient card with information on the potential risk of NDD after paternal exposure to valproate. This card, attached to the outer packaging, ensures distribution of information to all patients each time valproate is dispensed. In addition, it facilitates pharmacists to remind patients about risks associated with the product without the need to distribute materials themselves.
- A new, dedicated guide for male patients to inform and facilitate a discussion of the risks. As only limited information could be included in the existing patient card, the PRAC considered critical that patients are well informed about the potential risk to the offspring when valproate is used around the time of conception and advised on how to minimize this risk. The patient guide should explain the available evidence, uncertainties about the risk, and detail considerations for valproate use in male patients. As the key messages to be addressed in this patient educational material for males differ from the key messages addressed in the material for females, a separate guide for male patients was deemed necessary by the PRAC.

The PRAC recommended distribution of a **DHPC** to inform HCPs about the potential risk of valproate in male patients, the need to inform current male valproate users about the potential risk and the need to consider a treatment review in these male patients, and the proposed recommendations, and PI updates.

All MAHs should submit an updated RMP, within 3 months after completion of procedure EMEA-H-N-PSR-J-0043, to reflect that the paternal PASS was completed, the results of this study and all routine and additional RMM agreed by the PRAC in the current procedure are reflected accordingly. The new category 1 PASS, as recommended above, should also be included in the document.

Further actions for the MAHs:

- The MAHs are strongly encouraged to publish the results of this PASS in a scientific journal: sharing the study results would be helpful and relevant for future research.
- With regard to the additional analyses, a study protocol should be provided for PRAC review and approval within 6 months after finalisation of the current procedure. The additional analyses should be performed as part of a new category 1 PASS, addressing the questions listed in the PRAC AR.

Further actions for National Competent Authorities (NCA):

To enhance awareness in clinical practice, NCA might consider additional tools (including relevant journals) and tailored initiatives at national level to foster dissemination of information on the potential risk of NDD in children of fathers treated with valproate and the advice for HCP and patients.

The CMDh agrees with the scientific conclusions made by the PRAC.

Grounds for the variation to the terms of the Marketing Authorisation(s)

On the basis of the scientific conclusions for the results of the study for the medicinal product(s) containing the active substance valproate and concerned by the PASS final report, the CMDh is of the opinion that the benefit-risk balance of the medicinal product(s) mentioned above is unchanged subject to the proposed changes above detailed.

The CMDh reaches the position that the marketing authorisation(s) of the products concerned by this PASS final report should be varied.

Annex II

Amendments to the product information of the nationally authorised medicinal product(s)

Amendments to be included in the relevant sections of the Summary of Product Characteristics (new text **underlined and in bold,** deleted text ~~strike through~~)

The following changes to the product information of medicinal products containing the active substance valproate are recommended, in SmPC sections 4.2, 4.4 and 4.6, and PIL section 2 and 3 (new text **underlined and in bold**, deleted text in ~~strikethrough~~):

Summary of Product characteristics

[…]

4.2 Posology and method of administration

Posology
[…]

Female children and women of childbearing potential
<Invented name> must be initiated and supervised by a specialist experienced in the management of epilepsy <or> bipolar disorder or <migraine>. Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.
Valproate is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme (sections 4.3 and 4.4).
The benefit and risk should be carefully reconsidered at regular treatment reviews.
Valproate should preferably be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation. The daily dose should be divided into at least two single doses (see section 4.6).
Males
It is recommended that <Invented name> is initiated and supervised by a specialist experienced in the management of epilepsy <or> bipolar disorder <or migraine> (see sections 4.4 and 4.6).

Patients with renal insufficiency
[…]

Method of administration
[…]

4.4 Special warnings and precautions for use

Pregnancy Prevention Programme
Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations and neurodevelopmental disorders (see section 4.6).

<Invented name> is contraindicated in the following situations:

Treatment of epilepsy
- in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.6).
- in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.6).

Treatment of bipolar disorder <and prophylaxis of migraine attacks>
- in pregnancy (see sections 4.3 and 4.6).
- in women of childbearing potential, unless the conditions of the Pregnancy Prevention Programme are fulfilled (see sections 4.3 and 4.6).

Conditions of Pregnancy Prevention Programme:
The prescriber must ensure that

- Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
- the potential for pregnancy is assessed for all female patients.
- the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
- the patient is counselled regarding contraception, and that the patient is capable of complying with the need to use effective contraception (for further details please refer to subsection contraception of this boxed warning), without interruption during the entire duration of treatment with valproate.
- the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy, or bipolar disorders <or migraine>.
- the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- the patient understands the need to urgently consult her physician in case of pregnancy.
- the patient has received the patient guide.
- the patient has acknowledged that she has understood the hazards and necessary precautions associated with valproate use (Annual Risk Acknowledgement Form).

These conditions also concern women who are not currently sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

<u>Female children</u>
- The prescribers must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- The prescriber must ensure that parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neurodevelopmental disorders including the magnitude of these risks for children exposed to valproate *in utero*.
- In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch the female children to alternative treatment before they reach adulthood.

<u>Pregnancy test</u>
Pregnancy must be excluded before start of treatment with valproate. Treatment with valproate must not be initiated in women of childbearing potential without a negative pregnancy test (plasma pregnancy test) result, confirmed by a health care provider, to rule out unintended use in pregnancy.

<u>Contraception</u>
Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with valproate. These patients must be provided with comprehensive information on pregnancy prevention and should be referred for contraceptive advice if they are not using effective contraception. At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used. Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures. Even if she has amenorrhea she must follow all the advice on effective contraception.

<u>Estrogen-containing products</u>
Concomitant use with estrogen-containing products, including estrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy (see section 4.5). Prescribers should monitor clinical response (seizure control or mood control) when initiating or discontinuing estrogen-containing products.
On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

<u>Annual treatment reviews by a specialist</u>

The specialist should at least annually review whether valproate is the most suitable treatment for the patient. The specialist should discuss the annual risk acknowledgement form, at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning.
For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning.

For the indication bipolar disorder <and> <migraine> if a woman is planning to become pregnant a specialist experienced in the management of bipolar disorder <and> <migraine> must be consulted and treatment with valproate should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

In case of pregnancy
If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative options. The patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in <teratology> {to be adapted depending on health care system} for evaluation and counselling regarding the exposed pregnancy (see section 4.6).

Pharmacist must ensure that
- the patient card is provided with every valproate dispensing and that the patients understand its content.
- the patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.

Educational materials
In order to assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings and provide guidance regarding use of valproate in women of childbearing potential and the details of the pregnancy prevention programme. A patient guide and patient card should be provided to all women of childbearing potential using valproate.

An annual risk acknowledgement form needs to be used at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Use in male patients

A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to conception compared to those born to men treated with lamotrigine or levetiracetam (see section 4.6).

As a precautionary measure, prescribers should inform male patients about this potential risk (see section 4.6) and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <or> <migraine> should be sought as appropriate.

Educational materials are available for healthcare professionals and male patients. A patient guide should be provided to male patients using valproate.

[…]

4.6 Fertility, pregnancy and lactation

Pregnancy **and women of childbearing potential**

[…]

Teratogenicity and developmental effects **from in utero exposure**

Pregnancy Exposure Risk related to valproate
In females, ~~B~~**b**oth valproate monotherapy and valproate polytherapy including other antiepileptics are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate.
Valproate was shown to cross the placental barrier both in animal species and in humans (see section 5.2).
In animals: teratogenic effects have been demonstrated in mice, rats and rabbits (see section 5.3).

Congenital malformations ***from in utero exposure***
[…]

Neurodevelopmental disorders ***from in utero exposure***
[…]

If a woman plans a pregnancy
[…]

Pregnant women
[…]

Risk in the neonate
[…]

Males and potential risk of neuro-developmental disorders in children of fathers treated with valproate in the 3 months prior to conception

A retrospective observational study in 3 Nordic countries suggests an increased risk of neuro-developmental 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, with a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07). The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam group. The study was not large enough to investigate associations with specific NDD subtypes and study limitations included potential confounding by indication and differences in follow-up time between exposure groups. 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. Overall an increased risk of NDDs in children of fathers treated with valproate in the 3 months prior to conception is possible however the causal role of valproate is not confirmed. In addition, the study did not evaluate the risk of NDDs to children born to men stopping valproate for more than 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure).

As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation (see section 4.4). Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.

Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate is the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of <epilepsy> <bipolar disorder> <migraine> should be sought as appropriate.

Breast-feeding
[…]

Fertility
[…]

Package Leaflet

[…]

2. What you need to know before you <take> <use> X

[…]

Pregnancy, breast-feeding and fertility

Important advice for women
Bipolar disorder <and> <migraine>
- For bipolar disorder <and> <migraine>, you must not use <Invented name> if you are pregnant.

For bipolar disorder <and> <migraine>, if you are a woman able to have a baby, you must not take <Invented name>, unless you use effective method of birth control (contraception) during your entire treatment with <Invented name>. Do not stop taking <Invented name> or your contraception, until you have discussed this with your doctor. Your doctor will advise you further.

Epilepsy
- For epilepsy, you must not use <Invented name> if you are pregnant, unless nothing else works for you.
- For epilepsy, if you are a woman able to have a baby, you must not take <Invented name> unless you use effective method of birth control (contraception) during your entire treatment with <Invented name>. Do not stop taking <Invented name> or your contraception, until you have discussed this with your doctor. Your doctor will advise you further.

The risks of valproate when taken during pregnancy (irrespective of the disease for which valproate is used)
- Talk to your doctor immediately if you are planning to have a baby or are pregnant.
- Valproate carries a risk if taken during pregnancy. The higher the dose, the higher the risks but all doses carry a risk, including when valproate is used in combination with other medicines to treat epilepsy.
- It can cause serious birth defects and can affect the physical and mental development of the child as it grows after birth.
- The most frequently reported birth defects include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; limb defects and multiple associated malformations affecting several organs and parts of the body. Birth defects may result in disabilities which may be severe.
- Hearing problems or deafness have been reported in children exposed to valproate during pregnancy.
- Eye malformations have been reported in children exposed to valproate during pregnancy in association with other congenital malformations. These eye malformations may affect vision.
- If you take valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because valproate has been used for many years we know that in women who take valproate around 11 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born to women who don’t have epilepsy
- It is estimated that up to 30-40% of preschool children whose mothers took valproate during pregnancy may have problems with early childhood development. Children affected can be slow

to walk and talk, intellectually less able than other children, and have difficulty with language and memory.
- Autistic spectrum disorders are more often diagnosed in children exposed to valproate during pregnancy and there is some evidence that children exposed to valproate during pregnancy are at increased risk of developing Attention Deficit Hyperactivity Disorder (ADHD).
- Before prescribing this medicine to you, your doctor will have explained what might happen to your baby if you become pregnant whilst taking valproate. If you decide later you want to have a baby you must not stop taking your medicine or your method of contraception until you have discussed this with your doctor.
- Some birth control pills (oestrogen-containing birth control pills) may lower valproate levels in your blood. Make sure you talk to your doctor about the method of birth control (contraception) that is the most appropriate for you.
- If you are a parent or a caregiver of a female child treated with valproate, you should contact the doctor once your child using valproate experiences menarche.
- Ask your doctor about taking folic acid when trying for a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Please choose and read the situations which apply to you from the situations described below:
- **I AM STARTING TREATMENT WITH <INVENTED NAME>**
- **I AM TAKING <INVENTED NAME> AND NOT PLANNING TO HAVE A BABY**
- **I AM TAKING <INVENTED NAME> AND PLANNING TO HAVE A BABY**
- **I AM PREGNANT AND I AM TAKING <INVENTED NAME>**

I AM STARTING TREATMENT WITH <invented name>
If this is the first time you have been prescribed <Invented name> your doctor will have explained the risks to an unborn child if you become pregnant. Once you are able to have a baby, you will need to make sure you use an effective method of contraception without interruption throughout your treatment with <Invented name>. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:
- Pregnancy must be excluded before start of treatment with <Invented name> with the result of a pregnancy test, confirmed by your doctor.
- You must use an effective method of birth control (contraception) during your entire treatment with <Invented name>.
- You must discuss the appropriate methods of birth control (contraception) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control.
- You must get regular (at least annual) appointments with a specialist experienced in the management of bipolar disorder or epilepsy <or> <migraine>. During this visit your doctor will make sure you are well aware and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.
- Tell your doctor immediately if you are pregnant or think you might be pregnant.

I AM TAKING <invented name> AND NOT PLANNING TO HAVE A BABY
If you are continuing treatment with <Invented name> but you are not planning to have a baby make sure you are using an effective method of contraception without interruption during your entire treatment with <Invented name>. Talk to your doctor or family planning clinic if you need advice on contraception.

Key messages:
- You must use an effective method of birth control (contraception) during your entire treatment with <Invented name>.
- You must discuss contraception (birth control) with your doctor. Your doctor will give you information on preventing pregnancy, and may refer you to a specialist for advice on birth control.
- You must get regular (at least annual) appointments with a specialist experienced in the management of bipolar disorder or epilepsy <or> <migraine>. During this visit your doctor will make sure you are well aware and have understood all the risks and advice related to the use of valproate during pregnancy.
- Tell your doctor if you want to have a baby.

- Tell your doctor immediately if you are pregnant or think you might be pregnant.

I AM TAKING <invented name> AND PLANNING TO HAVE A BABY
If you are planning to have a baby, first schedule an appointment with your doctor.

Do not stop taking <Invented name> or your contraception, until you have discussed this with your doctor. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating. Your doctor will refer you to a specialist experienced in the management of bipolar disorder <migraine> or epilepsy, so that alternative treatment options can be evaluated early on. Your specialist can put several actions in place so that your pregnancy goes as smoothly as possible and any risks to you and your unborn child are reduced as much as possible.

Your specialist may decide to change the dose of <Invented name> or switch you to another medicine, or stop treatment with <Invented name>, a long time before you become pregnant – this is to make sure your illness is stable.

Ask your doctor about taking folic acid when planning to have a baby. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
- Do not stop taking <Invented name> unless your doctor tells you to.
- Do not stop using your methods of birth control (contraception) before you have talked to your doctor and worked together on a plan to ensure your condition is controlled and the risks to your baby are reduced.
- First schedule an appointment with your doctor. During this visit your doctor will make sure you are well aware and have understood all the risks and advice related to the use of valproate during pregnancy.
- Your doctor will try to switch you to another medicine, or stop treatment with <Invented name> a long time before you become pregnant.
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.

I AM PREGNANT AND I AM USING <INVENTED NAME>
Do not stop taking <Invented name>, unless your doctor tells you to as your condition may become worse. Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant. Your doctor will advise you further.

Babies born to mothers who have been on valproate are at serious risk of birth defects and problems with development which can be seriously debilitating.

You will be referred to a specialist experienced in the management of bipolar disorder, or epilepsy, so that alternative treatment options can be evaluated.

In the exceptional circumstances when <Invented name> is the only available treatment option during pregnancy, you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing. You and your partner could receive counselling and support regarding the valproate exposed pregnancy.

Ask your doctor about taking folic acid. Folic acid can lower the general risk of spina bifida and early miscarriage that exists with all pregnancies. However, it is unlikely that it will reduce the risk of birth defects associated with valproate use.

Key messages:
- Schedule an urgent appointment with your doctor if you are pregnant or think you might be pregnant.
- Do not stop taking <Invented name> unless your doctor tells you to.
- Make sure you are referred to a specialist experienced in the treatment of epilepsy or bipolar disorder <or > migraine> to evaluate the need for alternative treatment options.
- You must get thorough counselling on the risks of <Invented name> during pregnancy, including teratogenicity (birth defects) and physical and mental development disorders in children.

- Make sure you are referred to a specialist for prenatal monitoring in order to detect possible occurrences of malformations.

[This sentence below should be adapted to National requirements]
Make sure you read the patient guide that you will receive from your doctor. Your doctor will discuss the Annual Risk Acknowledgement Form and will ask you to sign it and keep it. You will also receive a Patient Card from your pharmacist to remind you of valproate risks in pregnancy.

<If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your <doctor> <or> <pharmacist> for advice before taking this medicine.>

Important advice for male patients

Potential risks related to taking valproate in the 3 months before conception of a child

A study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to fathers treated with valproate in the 3 months before conception. In this study, around 5 children in 100 had such disorders when born to fathers treated with valproate as compared to around 3 children in 100 when born to fathers treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease). The risk for children born to fathers who stopped valproate treatment 3 months (the time needed to form new sperm) or longer before conception is not known. The study has limitations and therefore it is not clear if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate. The study was not large enough to show which particular type of movement and mental developmental disorder children may be at risk of developing.

As a precautionary measure, your doctor will discuss with you:
- **The potential risk in children born to fathers treated with valproate**
- **The need to consider effective contraception (birth control) for you and your female partner during treatment and for 3 months after stopping treatment**
- **The need to consult your doctor when you are planning to conceive a child and before stopping contraception (birth control)**
- **The possibility of other treatments that can be used to treat your disease, depending on your individual situation**

Do not donate sperm when taking valproate and for 3 months after stopping valproate.

Talk to your doctor if you are thinking about having a baby.

If your female partner becomes pregnant while you used valproate in the 3 months period before conception and you have questions, contact your doctor. Do not stop your treatment without talking to your doctor. If you stop your treatment, your symptoms may become worse.

You should get regular appointments with your prescriber. During this visit your doctor will discuss with you the precautions associated with valproate use and the possibility of other treatments that can be used to treat your disease, depending on your individual situation.

Make sure you read the patient guide that you will receive from your doctor. You will also receive a Patient Card from your pharmacist to remind you of the potential risks of valproate.

3. How to take <invented name>

[…]

Female children and women of childbearing potential

<Invented name> treatment must be started and supervised by a doctor specialised in the treatment of <epilepsy> <or> <bipolar disorder> <or> <migraine>.

Male patients

It is recommended that <Invented name> is initiated and supervised by a specialist experienced in the management of epilepsy <or> bipolar disorder <or migraine>- see section 2 Important advice for male patients.

Annex III

Conditions to the Marketing Authorisation(s)

Conditions to the marketing authorisation(s) of medicinal product(s) containing valproate and related substances.

The marketing authorisation holder(s) (MAHs) shall complete the following condition(s) within the stated timeframe:

The MAHs of medicinal products with substances related to valproate shall conduct a new non-interventional post-authorisation safety study to provide the results of the additional analyses requested in the framework of the assessment of the results of study EUPAS34201, in order to further investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders (including autism) in the offspring. Protocol to be submitted to the PRAC in accordance with Article 107n (1) of Directive 2001/83/EC: The final study report shall be submitted to the PRAC:	 Within **6 months** of the CMDh position / commission decision. Within **1 year** of the endorsement of the study protocol.
The MAHs of medicinal products with substances related to valproate shall develop and submit educational materials according to the agreed core elements. These materials should ensure that prescribers are informed and the patients understand the potential risk associated with paternal exposure to valproate. These should be submitted to the National Competent Authorities:	 Within **3 months** of the CMDh position / Commission decision.
All MAHs should update their RMP and submit it to the relevant national Competent Authorities through an appropriate procedure. The RMP should reflect: - Neurodevelopmental disorders in children born to fathers treated with valproate before conception as an important potential risk - That the category 1 paternal PASS is completed - The new category 1 study in order to further investigate the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders (including autism) in the offspring. - The additional risk minimization measures related to valproate use in male patients: o Patient guide for male patients o Updated core version of HCP guide o Updated core version of patient card	Within **3 months** of CMDh position / Commission decision.

Annex IV

Timetable for the implementation of this position

Timetable for the implementation of the position

Adoption of CMDh position:	January 2024 CMDh meeting
Transmission to National Competent Authorities of the translations of the annexes to the position:	11 March 2024
Implementation of the position by the Member States (submission of the variation by the Marketing Authorisation Holder):	09 May 2024