

Annex III

Amendments to relevant sections of the Product Information

Note:

These amendments to the relevant sections of the Summary of Product Characteristics and package leaflet are the outcome of the referral procedure.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the Reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

MAHs of all valproate and related substances containing products authorised in the EU should amend the product information (insertion, replacement or deletion of the text, as appropriate) to reflect the wording as provided below, and in conjunction to the Scientific conclusions:

Summary of product characteristics

[...]

Section 4.2 Posology and method of administration

[...]

Female children and women of childbearing potential

Valproate must be initiated and supervised by a specialist experienced in the management of epilepsy, 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).

[...]

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).

[...]

Section 4.3 Contraindications

[...]

<Invented name> is contraindicated in the following situations:

[...]

Treatment of epilepsy

- in pregnancy unless there is no suitable alternative treatment (see section 4.4 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.4 and 4.6).

Treatment of bipolar disorder <and prophylaxis of migraine attacks>

- in pregnancy (see section 4.4 and 4.6).
- in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see section 4.4 and 4.6).

[...]

Section 4.4 Special warnings and precautions for use

[...]

[This section should be amended to include the following box]

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.

Female children

- 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.

Pregnancy test

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

Contraception

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.

Annual treatment reviews by a specialist

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(s) <bipolar disorder> <and> <migraine> if a woman is planning to become pregnant a specialist experienced in the management of <bipolar disorder> <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.

[...]

[...]

Section 4.6 Fertility, pregnancy and lactation

[...]

[This section should be amended to include the following wording]

Valproate is contraindicated as treatment for bipolar disorder <and migraine> during pregnancy. Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Valproate is contraindicated for use in women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.4).

Teratogenicity and Developmental Effects

[...]

If a woman plans a pregnancy

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 4.4). 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(s) <bipolar disorder> <and> <migraine> if a woman is planning to become pregnant a specialist experienced in the management of <bipolar disorder> <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.

Pregnant women

Valproate as treatment for bipolar disorder <and prophylaxis of migraine attacks> is contraindicated for use during pregnancy. Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment (see sections 4.3 and 4.4).

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:

- Use the lowest effective dose and divide the daily dose of valproate into several small doses to be taken throughout the day. The use of a prolonged release formulation may be preferable to other treatment formulations in order to avoid high peak plasma concentrations (see section 4.2).

All 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. Specialized prenatal monitoring should take place to detect the possible occurrence of neural tube defects or other malformations. Folate supplementation before the pregnancy may decrease the risk of neural tube defects which may occur in all pregnancies.

However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.

[...]

PACKAGE LEAFLET

[Quick Response (QR) code: A QR code should be included in the packaging material and/or the package leaflet, and its location should take into account the overall readability.]

WARNING

<Invented name> , <INN> can seriously harm an unborn child when taken during pregnancy. If you are a female able to have a baby you must use effective method of birth control (contraception) without interruptions during your entire treatment with <Invented name>. Your doctor will discuss this with you but you must also follow the advice in section 2 of this leaflet.

Schedule an urgent appointment with your doctor if you want to become pregnant or if you think you are pregnant.

Do not stop taking <Invented name> unless your doctor tells you to as your condition may become worse.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their symptoms seem the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

[...]

2. What you need to know before you take <invented name>

[...]

Do not take <invented name>

[This section should be amended to include the below wording]

[...]

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 (see below under "Pregnancy, breast-feeding and fertility – Important advice for women").

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 (see below under "Pregnancy, breast-feeding and fertility – Important advice for women").

[...]

Pregnancy, breast feeding and fertility

[This section should be amended to include the below wording]

[...]

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.
- It can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects which have been reported 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.
- 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 10 babies in every 100 will have birth defects. This compares to 2 to 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 and there is some evidence children may be more likely to develop symptoms of 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.
- 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 advices 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 advices 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 <or> <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 advices 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, <migraine> 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, 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 and developmental effects 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.

[...]

3. How to take <invented name>

[...]

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

[...]

4. Possible side effects

[This section should be amended to include the below wording in all indications]

[...]

Reporting of side effects

If you get any side effects, talk to your <doctor> <or> <,> <pharmacist> <or nurse>. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V*. By reporting side effects you can help provide more information on the safety of this medicine.

*[*For the printed material, please refer to the guidance of the annotated QRD template.]*