

### **Annex III**

#### **Amendments to relevant sections of the summary of product characteristics and package leaflets**

*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.

## SUMMARY OF PRODUCT CHARACTERISTICS

*[This statement below should be inserted at the top of the SmPC for all products referred to in Annex I]*

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

*[...]*

*[For all products in Annex I, the existing product information shall be amended (insertion, replacement or deletion of the text, as appropriate) to reflect the agreed wording as provided below]*

*[...]*

### Section 4.2 Posology and method of administration

*[...]*

Female children, female adolescents, women of childbearing potential and pregnant women

<Invented name> should be initiated and supervised by a specialist experienced in the management of <epilepsy> <or> <bipolar disorder>. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.4 and 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably <invented name> should be prescribed as monotherapy and at the lowest effective dose, if possible as a prolonged release formulation to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses.

*[...]*

*[The paragraph below should be included in this section where the marketing authorisation currently includes the indication prophylaxis of migraine attacks]*

<Invented name> should only be initiated and supervised by a specialist experienced in the management of migraine. Treatment should only be initiated if other treatments are ineffective or not tolerated (see section 4.3, 4.4 and 4.6) and the benefit and risk should be carefully reconsidered at regular treatment reviews.

*[...]*

### Section 4.3 Contraindications

*[The text below is only to be implemented where the marketing authorisation currently includes the indication prophylaxis of migraine attacks]*

*[...]*

<Invented name> is contraindicated in the following situations:

*[...]*

- Prophylaxis of migraine attacks in pregnancy and women of childbearing potential who are not using effective methods of contraception during treatment with valproate (see sections 4.4 and 4.6). Pregnancy must be excluded before start of treatment with valproate.

*[...]*

#### Section 4.4 Special warnings and precautions for use

[...]

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

##### **Female children/Female adolescents/Women of childbearing potential/Pregnancy:**

<Invented name> should not be used in female children, in female adolescents, in women of childbearing potential and pregnant women unless alternative treatments are ineffective or not tolerated because of its high teratogenic potential and risk of developmental disorders in infants exposed in utero to valproate. The benefit and risk should be carefully reconsidered at regular treatment reviews, at puberty and urgently when a woman of childbearing potential treated with <invented name> plans a pregnancy or if she becomes pregnant.

Women of childbearing potential must use effective contraception during treatment and be informed of the risks associated with the use of <invented name> during pregnancy (see section 4.6).

*[The following sentence should be inserted only where the marketing authorisation currently includes the indication prophylaxis of migraine attacks]*

<Invented name> is contraindicated as migraine prophylaxis in pregnant women and in women of childbearing potential, who do not use effective methods of contraception, as sufficient therapeutic alternatives are present (see section 4.3).

The prescriber must ensure that the patient is provided with comprehensive information on the risks alongside relevant materials, such as a patient information booklet, to support her understanding of the risks.

In particular the prescriber must ensure the patient understands:

- The nature and the magnitude of the risks of exposure during pregnancy, in particular the teratogenic risks and the risks of developmental disorders.
- The need to use effective contraception.
- The need for regular review of treatment.
- The need to rapidly consult her physician if she is thinking of becoming pregnant or there is a possibility of pregnancy.

In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible (see section 4.6).

*[The following sentence should be inserted only where the marketing authorisation currently includes the indication prophylaxis of migraine attacks]*

In women planning to become pregnant or who are pregnant valproate therapies should be stopped.

*[The sentence below should be inserted only where the marketing authorisation currently includes the indications epilepsy and/or bipolar disorders].*

Valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of

<epilepsy> <or> <bipolar disorder>.

[...]

#### **Section 4.6 Fertility, pregnancy and lactation**

[...]

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

<Invented name> should not be used in female children, in female adolescents, in women of childbearing potential and in pregnant women unless other treatments are ineffective or not tolerated. Women of childbearing potential have to use effective contraception during treatment. In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

##### *Pregnancy Exposure Risk related to valproate*

Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that antiepileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy.

##### *Congenital malformations*

Data derived from a meta-analysis (including registries and cohort studies) has shown that 10.73% of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations (95% CI: 8.16 -13.29). This is a greater risk of major malformations than for the general population, for whom the risk is about 2-3%. The risk is dose dependent but a threshold dose below which no risk exists cannot be established.

Available data show an increased incidence of minor and major malformations. The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body systems.

##### *Developmental disorders*

Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists, cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

Studies in preschool 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.

Intelligence quotient (IQ) measured in school aged children (age 6) with a history of valproate exposure in utero was on average 7-10 points lower than those children exposed to other antiepileptics. Although the role of confounding factors cannot be excluded, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ.

There are limited data on the long term outcomes.

Available data show that children exposed to valproate in utero are at increased risk of autistic spectrum disorder (approximately three-fold) and childhood autism (approximately five-fold) compared with the general study population.

Limited data suggests that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

*Female children, female adolescents and woman of childbearing potential (see above and section 4.4)*

*If a Woman wants to plan a Pregnancy*

*[The sentence below should be inserted only where the marketing authorisation currently includes the epilepsy indication]*

- During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

*[The sentence below should be inserted only where the marketing authorisation currently includes the epilepsy and/or bipolar indications]*

- In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed

*[The sentence below should be inserted where the marketing authorisation currently includes the indication prophylaxis of migraine attacks]*

- If a woman plans a pregnancy or becomes pregnant, valproate therapy should be stopped.

*[The sentence below should be inserted only where the marketing authorisation currently includes the epilepsy and/or bipolar disorders indications]*

- In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.

*[All text below should be inserted only where the marketing authorisation currently includes the indications epilepsy and/or bipolar disorders]*

Valproate therapy should not be discontinued without a reassessment of the benefits and risks of the treatment with valproate for the patient by a physician experienced in the management of <epilepsy> <or> <bipolar disorder>. If based on a careful evaluation of the risks and the benefits valproate treatment is continued during the pregnancy, it is recommended to:

- Use the lowest effective dose and divide the daily dose 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.
- Folate supplementation before the pregnancy may decrease the risk of neural tube defects common to all pregnancies. However the available evidence does not suggest it prevents the birth defects or malformations due to valproate exposure.
- To institute specialized prenatal monitoring in order to detect the possible occurrence of neural tube defects or other malformations.

*[The following paragraph should be inserted only where the marketing authorisation currently includes the indication prophylaxis of migraine attacks]*

<Invented name> is contraindicated for prophylaxis of migraine attacks in pregnancy and women of childbearing potential who are not using effective methods of contraception during treatment with valproate (see sections 4.4 and 4.6 above). Pregnancy must be excluded before start of treatment with valproate.

*[For all products referred to in Annex I]*

#### Risk in the neonate

- Cases of hemorrhagic syndrome have been reported very rarely in neonates whose mothers have taken valproate during pregnancy. This hemorrhagic syndrome is related to thrombocytopenia, hypofibrinogenemia and/or to a decrease in other coagulation factors. Afibrinogenemia has also been reported and may be fatal. However, this syndrome must be distinguished from the decrease of the vitamin-K factors induced by phenobarbital and enzymatic inducers. Therefore, platelet count, fibrinogen plasma level, coagulation tests and coagulation factors should be investigated in neonates.
- Cases of hypoglycaemia have been reported in neonates whose mothers have taken valproate during the third trimester of their pregnancy.
- Cases of hypothyroidism have been reported in neonates whose mothers have taken valproate during pregnancy.
- Withdrawal syndrome (such as, in particular, agitation, irritability, hyper-excitability, jitteriness, hyperkinesia, tonic disorders, tremor, convulsions and feeding disorders) may occur in neonates whose mothers have taken valproate during the last trimester of their pregnancy.

#### Breastfeeding

Valproate is excreted in human milk with a concentration ranging from 1% to 10% of maternal serum levels. Hematological disorders have been shown in breastfed newborns/infants of treated women (see section 4.8).

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from <invented name> therapy taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman.

#### Fertility

Amenorrhoea, polycystic ovaries and increased testosterone levels have been reported in women using valproate (see section 4.8). Valproate administration may also impair fertility in men (see section 4.8). Case reports indicate that fertility dysfunctions are reversible after treatment discontinuation.

*[...]*

### **Section 4.8 Undesirable effects**

*[...]*

Congenital malformations and developmental disorders (see section 4.4 and section 4.6).

[...]

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V\*.

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

[...]

## PACKAGE LEAFLET

*[This statement below should be inserted at the top of the package leaflet for all products referred to in Annex I]*

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

*[...]*

### WARNING

Valproate can cause birth defects and problems with early development of the child if it is taken during pregnancy. If you are a female of childbearing age you should use an effective method of contraception throughout your treatment.

Your doctor will discuss this with you but you should also follow the advice in section 2 of this leaflet. Tell your doctor at once if you become pregnant or think you might be pregnant.

**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>**

*[...]*

### **Pregnancy, breast feeding and fertility**

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

*[...]*

### **Important advice for women**

- Valproate can be harmful to unborn children when taken by a woman during pregnancy.

*[The paragraph below should be inserted only where the marketing authorisation currently includes the indication "prophylaxis of migraine attacks"].*

- Do not take valproate if you are pregnant or if you are a woman of childbearing potential and you are not using effective contraception.

*[The following text should be inserted in all products referred to in Annex I]*



- 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 2-3 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).
- If you are a woman capable of becoming pregnant your doctor should only prescribe valproate for you if nothing else works for you.
- 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 child you should not stop taking your medicine until you have discussed this with your doctor and agreed a plan for switching you onto another product if this is possible.
- 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.

## FIRST PRESCRIPTION

If this is the first time you have been prescribed valproate your doctor will have explained the risks to an unborn child if you become pregnant. Once you are of childbearing age, you will need to make sure you use an effective method of contraception throughout your treatment. Talk to your doctor or family planning clinic if you need advice on contraception.

### Key messages:

- Make sure you are using an effective method of contraception.
- Tell your doctor at once if you are pregnant or think you might be pregnant.

*[The paragraph below should be inserted only where the marketing authorisation currently includes the indication "prophylaxis of migraine attacks"].*

- Pregnancy must be excluded before start of treatment with valproate.

## CONTINUING TREATMENT AND NOT TRYING FOR A BABY

If you are continuing treatment with valproate but you don't plan to have a baby make sure you are using an effective method of contraception. Talk to your doctor or family planning clinic if you need advice on contraception.

**Key messages:**

- Make sure you are using an effective method of contraception
- Tell your doctor at once if you are pregnant or think you might be pregnant.

**CONTINUING TREATMENT AND CONSIDERING TRYING FOR A BABY**

*[The paragraph below should be inserted only where the marketing authorisation currently includes the indication "prophylaxis of migraine attacks"].*

If you are trying for a baby you should not use valproate. Do not stop taking your contraception, until you have discussed this with your doctor. Your doctor will stop your treatment and advise you further.

*[All text below should be inserted only where the marketing authorisation currently includes the indications for epilepsy and/or bipolar disorder].*

If you are continuing treatment with valproate and you are now thinking of trying for a baby you must not stop taking either your valproate or your contraceptive medicine until you have discussed this with your prescriber. You should talk to your doctor well before you become pregnant so that you 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 doctor may decide to change the dose of valproate or switch you to another medicine before you start trying for a baby.

If you do become pregnant you will be monitored very closely both for the management of your underlying condition and to check how your unborn child is developing.

*[The text below should be inserted in all indications].*

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.

**Key messages:**

- Do not stop using your contraception before you have talked to your doctor and worked together on a plan to ensure your epilepsy/bipolar disorder is controlled and the risks to your baby are reduced.

*[The text below should be inserted only where the marketing authorisation currently includes indications for the epilepsy and/or bipolar disorder].*

- Tell your doctor at once when you know or think you might be pregnant.

*[The paragraph below should be inserted only where the marketing authorisation currently includes the indication "prophylaxis of migraine attacks"].*

- Stop taking your valproate and schedule an urgent appointment if you are pregnant or think you might be pregnant.

## UNPLANNED PREGNANCY WHILST CONTINUING TREATMENT

*[The paragraph below should be inserted only where the marketing authorisation currently includes the indication "prophylaxis of migraine attacks"].*

Stop taking valproate and schedule an urgent appointment with your doctor. 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.

*[All text below should be inserted only where the marketing authorisation currently includes the indications for the epilepsy and/or bipolar disorder].*

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. If you are taking valproate and you think you are pregnant or might be pregnant contact your doctor at once. Do not stop taking your medicine until your doctor tells you to.

*[The text below should be inserted in all indications].*

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:

- Tell your doctor at once if you know you are pregnant or think you might be pregnant.

*[The sentence below should be inserted only where the marketing authorisation currently includes indications for the epilepsy and/or bipolar disorder].*

- Do not stop taking valproate unless your doctor tells you to.

*[The sentence below should be inserted only where the marketing authorisation currently includes the indication "prophylaxis of migraine attacks"].*

- Stop taking your valproate and schedule an urgent appointment if you are pregnant or think you might be pregnant.

*[This sentence below should be adapted to National requirements]*

**Make sure you read the patient booklet and sign the Acknowledgement of Risk form which should be given to you and discussed with you by your doctor or pharmacist.**

[...]

### 3. How to take <invented name>

[...]

*[The text below should be inserted only where the marketing authorisation currently includes indications for the epilepsy and/or bipolar disorder].*

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

*[The paragraph below should be inserted only where the marketing authorisation currently includes the indication "prophylaxis of migraine attacks"].*

<Invented name> treatment must be started and supervised by a doctor specialised in the treatment of 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.]*