Female children, women of childbearing potential aged under 55 years and pregnant women:

Pregnancy Prevention Programme

Valproate has a high teratogenic potential and children exposed *in utero* to valproate have a high risk for congenital malformations (11%) and neuro-developmental disorders (up to 30-40%) which may lead to permanent disability.

Valproate must only be initiated by two specialists who independently consider and document that there is no other effective or tolerated treatment.

Valproate is contraindicated in the following situations:

• In pregnancy unless two specialists independently consider and document that there is no other effective or tolerated treatment.

• In women of childbearing potential aged under 55 years, unless two specialists independently consider and document that there is no other effective or tolerated treatment and the conditions of the pregnancy prevention programme are fulfilled.

Conditions of Pregnancy Prevention Programme:

The specialist must ensure that:

• Individual circumstances should be evaluated in each case. Involving the patient in the discussion to support 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 neuro-developmental disorders which may lead to permanent disability, 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.

• The patient understands the need to consult her general practitioner (GP) for referral to a specialist as soon as she is planning a pregnancy to ensure timely discussion and switching to another treatment prior to conception and before contraception is discontinued.

• The patient understands the need to urgently consult her GP for urgent referral to a specialist 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 apply to women who are not currently sexually active unless the specialist considers that there are compelling reasons to indicate that there is no risk of pregnancy.

Female children

The specialist must ensure that:

• The parents/caregivers of female children understand the need to contact their GP once the female child using valproate experiences menarche. Their GP will refer the patient back to the specialist.

• The parents/caregivers of female children who have experienced menarche are provided with comprehensive information about the risks of congenital malformations and neuro-developmental disorders which may lead to permanent disability including the magnitude of these risks for children exposed to valproate *in utero.*

In patients who have experienced menarche, the prescribing specialist must annually reassess the need for valproate therapy and consider other treatment options. If valproate is the only effective and tolerated treatment, the need for using effective contraception and all other conditions of the pregnancy prevention programme should be discussed. Every effort should be made by the specialist to switch female children to another treatment before they reach menarche.

Pregnancy test

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 healthcare 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 support her engagement and compliance with the chosen measures. Even if she has amenorrhea, she must follow all the advice on effective contraception.

Oestrogen-containing products

Concomitant use with oestrogen-containing products, including oestrogen-containing hormonal contraceptives, may potentially result in decreased valproate efficacy. Prescribers should monitor

clinical response (seizure control) when initiating or discontinuing oestrogen-containing products. On the opposite, valproate does not reduce efficacy of hormonal contraceptives.

Annual treatment reviews by a specialist

The specialist should review at least annually whether valproate is the most suitable treatment for the patient. The specialist should discuss and complete the Annual Risk Acknowledgement Form with the patient and/or carer at initiation and during each annual review and ensure that the patient has understood its content.

Pregnancy planning

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

In case of pregnancy

If a woman using valproate becomes pregnant, she must immediately contact her GP to be referred to a specialist to re-evaluate treatment with valproate and consider switching to other treatment options. The patients with valproate-exposed pregnancy and their partners should be referred by their GP to a specialist experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy.

Pharmacists must ensure that:

• The Patient Card is provided with every valproate pack dispensation and that patients understand its content.

• Patients are advised not to stop valproate medication and to immediately contact their GP to be referred to 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, provide guidance regarding use of valproate in women of childbearing potential and provide 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 discussed and completed with the patient and/or carer at time of treatment initiation and during each annual review of valproate treatment by the specialist.

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