Convulex®

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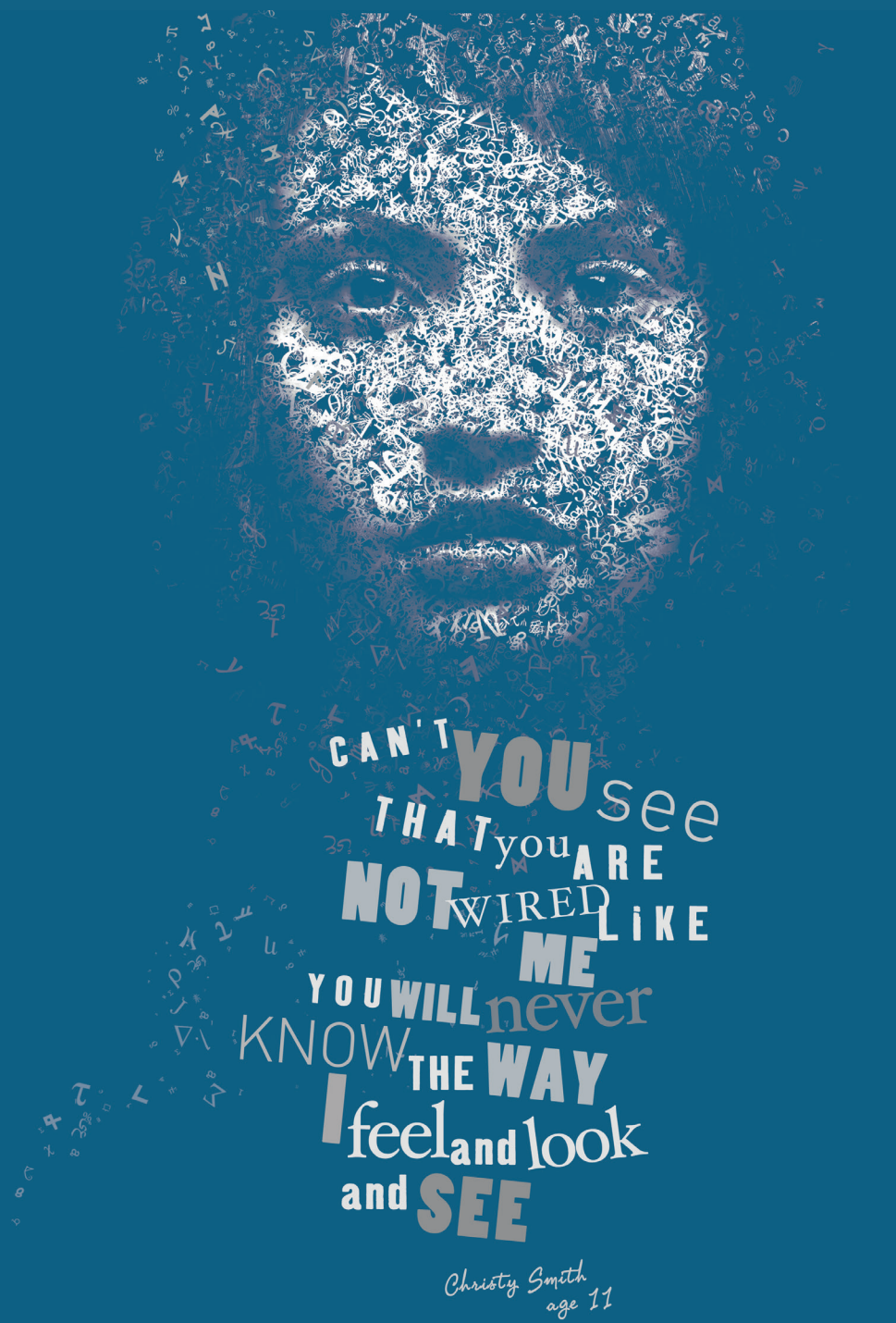

Valproate Guide

FOR HEALTHCARE PROFESSIONALS

AP805

CHECK LIST

- ✓ Information on the risks of valproate (CONVULEX®) use in female patients and pregnant women.
- ✓ Contraception and pregnancy prevention
- ✓ Read this booklet carefully before any prescription of valproate to female patients.

This booklet is a risk minimisation measure part of the valproate Pregnancy Prevention Programme aimed at minimising pregnancy exposure during treatment with valproate.

Please read the most up-to-date version of the Professional Information before prescribing valproate containing medicine.

CONTENTS

1. PURPOSE OF THIS GUIDE

This guide for healthcare professionals (HCPs) is an educational tool part of the valproate pregnancy prevention programme, which targets both HCPs and patients. Its objective is to provide information about the teratogenic risks associated with the use of valproate during pregnancy, the actions necessary to minimise the risks to your patients, and to ensure your patient has an adequate level of understanding of the risk.

It provides up-to-date information about the risks of congenital malformations and neurodevelopmental disorders in children exposed to valproate during pregnancy.

The nature of the risks for children exposed to valproate during pregnancy are the same irrespective of the indication for which valproate has been prescribed. Therefore, the risk minimisation measures described in this guide apply to the use of valproate regardless of the indication.

HCP for which this guide is of particluar importance include; specialists in the management of epilepsy, acute mania in bipolar affective disorders and migraines, and pharmacists.

The valproate educational tools developed specifically for female adolescents and women of childbearing potential treated with valproate comprise of:

- The annual risk acknowledgement form,
- The patient guide,
- The patient card.

Use this booklet together with the patient guide.

It is suggested that you provide a copy of the patient guide to all your female patients treated with valproate - female adolescents and women of childbearing potential or their parents or caregiver.

HCPs are advised to use the annual risk acknowledgement form, and properly document such use:

- At initiation of treatment with valproate,
- During each annual review of valproate treatment by a healthcare practitioner experienced in the management of epilepsy or bipolar,
- In the case of any pregnancy that might occur whilst on treatment.

HCPs should consider giving the patient card to your female patients each time valproate is dispensed.

HCPs are further encouraged to ensure that parents/caregivers of female adolescents 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 infants exposed to Convulex® in utero.

2. INFORMATION ON CONGENITAL MALFORMATIONS AND ON NEURODEVELOPMENTAL DISORDERS

Valproate contains valproic acid, an active ingredient with known teratogenic effects, which may result in congenital malformations. Available data also show that in utero exposure to valproate can be associated with an increased risk of neurodevelopmental disorders. These risks are briefly described below.

2.1 CONGENITAL MALFORMATIONS

A meta-analysis (including registries and cohort studies) showed that about 10,73% of children of epileptic women exposed to valproate monotherapy during pregnancy had major congenital malformations. This is greater than the risk of major malformations in the general population (about 2-3%). Both valproate monotherapy and valproate polytherapy are associated with abnormal pregnancy outcomes. Available data suggest that anti-epileptic polytherapy including valproate is associated with a greater risk of congenital malformations than valproate monotherapy. This risk is dose-dependent in valproate monotherapy, and available data suggest it is dose-dependent in valproate polytherapy. However, a threshold dose below which no risk exists cannot be established.

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. Data have shown that exposure to valproate in utero can have adverse effects on mental and physical development of the exposed children.

2.2 NEURODEVELOPMENTAL 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 of neurodevelopmental disorders seems to be dose-dependent when valproate is used in monotherapy but a threshold dose below which no risk exists, cannot be established based on available data. 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 risk throughout the entire pregnancy cannot be excluded.

When valproate is administered in monotherapy, studies in preschool children exposed in utero 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 years old) with a history of valproate exposure in utero was on average 7-10 points lower than those of children exposed to other antiepileptics. Although the role of confounding factors cannot be ruled out, there is evidence in children exposed to valproate that the risk of intellectual impairment may be independent from maternal IQ. There is limited data on the long-term outcomes. Available data from a population-based study 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 to the general study.

Available data from another population-based study show that children exposed to valproate in utero are at increased risk of developing attention-deficit hyperactivity disorder (ADHD) compared to the unexposed population in the study .

IT IS RECOMMENDED THAT HCPs:

- Provide the Patient Guide.
- Provide counselling on effective contraception and pregnancy prevention.
- Perform an annual as well as ad-hoc treatment reviews, as required.
- Consider switching and discontinuation.
- Complete and sign the Annual Risk Acknowledgement Form with your patient at:
  - Treatment initiation,
  - Every annual visit,
  - When a patient consults for planned or unplanned pregnancy.
- In case of exposed pregnancy, refer to a specialist for pregnancy monitoring and to a healthcare practitioner experienced in teratology (where appropriate) or pre-natal medicine for evaluation and counselling regarding the exposed pregnancy.

References:
Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L, *et al.* Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia.* 2010;**51**(10):2058-2065.
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Christensen J, Pedersen L, Sun Y, Dreier JW, Brikell I, Dalsgaard S. Association of prenatal exposure to valproate and other antiepileptic drugs with risk for attention deficit/hyperactivity disorder in offspring. *JAMA Netw Open.* 2019;**2**(1):e186606.
Cummings C, Stewart M, Stevenson M, Morrow J, Nelson J. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child.* 2011;**96**:643-647.
Meador KJ, Baker GA, Browning N, Clayton-Smith J, Combs-Cantrell DT, Cohen M, *et al.* Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. *NEJM.* 2009;**360**(16):1597-1605.
Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, *et al.* Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol.* 2013;**12**(3):244-252.
Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, *et al.* Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochr Database Syst Rev.* 2016;**11**:CD010224.

3. EXECUTIVE MANAGEMENT

Valproate contains valproic acid which, when administered during pregnancy, is associated with an:

- Increased risk of congenital malformations
- Increased risk of neurodevelopmental disorders.

3.1 HEALTHCARE PRACTITIONER EXPERIENCED IN THE MANAGEMENT OF EPILEPSY OR BIPOLAR DISORDER

Valproate may be initiated in female adolescents as treatment only if other treatments are ineffective or not tolerated.

Pregnancy must be excluded before initiation of treatment with valproate.

Treatment with valproate must not be initiated in women of childbearing potential without a negative pregnancy test (i.e. plasma pregnancy test) result confirmed by a health care provider, to rule out unintended use in pregnancy.

If you decide to treat any female adolescents or women of childbearing potential with valproate, the treatment should be reviewed regularly, at least annually.

In case of exposed pregnancy, refer to a specialist for pregnancy monitoring and to a healthcare practitioner experienced in teratology (where appropriate) or pre-natal medicine for evaluation and counselling regarding the exposed pregnancy.

3.1.1 Female patients - first prescription recommendations

1. Diagnosis of a condition requiring valproate treatment

2. Prior to the first prescription a pregnancy must be excluded through a negative pregnancy test result (i.e. a plasma pregnancy test), and thereafter if needed.

3. Initiate valproate only if there is no suitable alternative treatment due to if other treatments are ineffective or not tolerated.

4. Explain to your patient the risks related to valproate when used in pregnancy.

5. Complete and sign the Annual Risk Acknowledgement Form with your patient, at:
   - Treatment initiation,
   - Every annual visit,
   - When a patient consults for planned or unplanned pregnancy.

6. Provide the Patient Guide

7. Explain to your patient that the use of effective contraception without interruption during the entire duration of treatment with valproate is mandatory.

8. Tell your patient to contact you immediately if she thinks she might be pregnant or becomes pregnant.

9. Ensure appropriate treatment continuation.

3.1.2 Females of childbearing potential - not planning a pregnancy recommendations

1. Reassess at each visit whether treatment with valproate is still appropriate for your patient.
2. Complete and sign the Annual Risk Acknowledgement Form with your patient, at:
   - Treatment initiation,
   - Every annual visit,
   - When a patient consults for planned or unplanned pregnancy.
3. Provide the Patient Guide
4. Remind the patient at each visit of the risks related to valproate when used in pregnancy.
5. Remind your patient at each visit that effective contraception without interruption during the entire duration of treatment with valproate is mandatory.
6. Remind your patient at each visit to contact you immediately if she thinks she might be pregnant or becomes pregnant.

3.1.3 Females of childbearing potential - planning pregnancy recommendations

1. Remind your patient of the risks related to valproate when used in pregnancy.
2. Complete and sign the Annual Risk Acknowledgement Form with your patient:
   - When a patient consults for planned or unplanned pregnancy.
3. Provide the Patient Guide
4. Make sure the patient understands the need to consult you as soon as she is planning pregnancy, and the need to switch to alternative treatment prior to conception.
5. Discontinue valproate treatment and switch to another alternative treatment if suitable for your patient.
6. Remind your patient that switching takes time.
7. Explain to your patient that contraception should only be stopped after complete cessation of valproate.

3.1.4 Females with unplanned pregnancy recommendations

1. Arrange an urgent consultation with your patient.
2. Patients are advised not to stop their valproate medication.
3. Complete and sign the Annual Risk Acknowledgement Form with your patient:
   - When a patient consults for planned or unplanned pregnancy.
4. Provide the Patient Guide
5. Make sure your patient and her partner have understood the risks related to valproate and refer them to a healthcare practitioner experienced in teratology or in pre-natal medicine for further counselling (where appropriate).
6. Discontinue valproate treatment and switch to another alternative treatment if suitable for your patient.

3.2 DOCTORS/HCPs SPECIALISED IN MANAGING PREGNANCY

1. Provide counselling on contraception methods and pregnancy planning.

2. Provide information about the risks of using valproate during pregnancy.

3. When a patient consults for pregnancy, refer the patient and her partner to a healthcare practitioner experienced in teratology or in pre-natal medicine for evaluation and counselling regarding the exposed pregnancy, where appropriate.

3.3 PHARMACISTS

1. Ensure that the Patient Card is provided every time valproate is dispensed and that the patient understands its content.

2. Remind the patient of the safety messages including the need for effective contraception.

3. Advise the patient not to stop valproate and to contact their doctor/HCP urgently when planning a pregnancy or in case of a suspected pregnancy.

4. CONDITIONS OF VALPROATE PRESCRIPTION: PREGNANCY PREVENTION PROGRAMME

Valproate may be initiated in girls and women of childbearing potential only if the conditions of the valproate Pregnancy Prevention Programme are fulfilled.

4.1 CONDITIONS OF THE 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 can comply with the need to use effective contraception, 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 healthcare practitioner experienced in the management of epilepsy or bipolar disorders.
- The patient understands the need to consult a healthcare practitioner experienced in the management of epilepsy or bipolar disorder 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 a healthcare practitioner experienced in the management of epilepsy or bipolar disorder 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 the use of valproate (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.
- 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 amenorrhoea, she must follow all the advice on effective contraception.

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ALCOHOL FREE SYRUP

Capsules: Valproic acid

Syrup: Sodium valproate

References: 1. Peterson GM, Naunton M. Valproate: a simple chemical with so much to offer. *J Clin Pharm Therap.* 2005;**30**:417-421. **2.** Pelzl G, Mamoli B. Single Daily Dose of Valproic Acid: A Pharmacodynamic and Clinical Study. *Wien Klin Wochenshc.* 1992;**104**(10):286-289. **3.** Vajda FJE. Valproate and neuroprotection. *J Clin Neurosci.* 2002;**9**(5):508-514. **4.** Roberts D, Easter D, O'Bryan-Tear G. Epilim® Chrono: a multidose, crossover comparison of two formulations of valproate in healthy volunteers. *Biopharm Drug Disposit.* 1996;**17**:175-182.

For full prescribing information refer to the professional information approved by the Regulatory Authority.

S3 **Convulex®** 150/300/500 (Tablets) COMPOSITION: Each tablet contains 150/300/500 mg valproic acid respectively. Registration numbers: R/2.5/218; R/2.5/219; W/2.5/20

S3 **Convulex® Syrup**: COMPOSITION: One ml contains 50 mg sodium valproate. Registration number:

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