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Tarikh : 08 JAN 2020

SEMUA PEMEGANG PENDAFTARAN

SEMUA PERSATUAN BERKENAAN
(SEPERTI DI SENARAI EDARAN)

Tuan/ Puan,

PERATURAN-PERATURAN KAWALAN DADAH DAN KOSMETIK 1984
ARAHAN PENGARAH KANAN PERKHIDMATAN FARMASI BILANGAN 21 TAHUN 2019: DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI SODIUM VALPROATE: PENGUKUHAN MAKLUMAT KESELAMATAN PADA LABEL, SISIP BUNGKUSAN DAN RISALAH MAKLUMAT UBAT UNTUK PENGGUNA (RiMUP) BERKAITAN RISIKO KECACATAN KONGENITAL DAN MASALAH PERKEMBANGAN DALAM KALANGAN BAYI DAN KANAK-KANAK YANG TERDEDAH KEPADA PENGGUNAAN SODIUM VALPROATE SEMASA DALAM KANDUNGAN SERTA PENYEDIAAN BAHAN-BAHAN PENGAJARAN (*EDUCATIONAL MATERIALS*) BAGI PRODUK YANG MENGANDUNGI SODIUM VALPROATE

Adalah saya merujuk kepada Arahan Bilangan 21 Tahun 2019 oleh Pengarah Kanan Perkhidmatan Farmasi.

2. Dimaklumkan bahawa Pengarah Kanan Perkhidmatan Farmasi, Kementerian Kesihatan Malaysia dalam Arahan Bilangan 21 Tahun 2019 telah bersetuju untuk memperkukuhkan maklumat keselamatan berkaitan risiko kecacatan kongenital dan masalah perkembangan dalam kalangan bayi dan kanak-kanak yang terdedah kepada penggunaan sodium valproate semasa dalam kandungan serta penyediaan bahan-bahan pengajaran (*educational materials*) bagi produk yang mengandungi sodium valproate seperti pada surat arahan Bil.(21) BPFK/PPP/07/25 Jld.3.

3. Pihak pemegang pendaftaran adalah diarahkan untuk mematuhi keperluan tersebut.

Sekian, terima kasih.

"**BERKHIDMAT UNTUK NEGARA**"

Saya yang menjalankan amanah,

(DATIN DR. FARIDAH ARYANI BINTI MD. YUSOF) **RPh 1197**
Pengarah
Bahagian Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia

AAG/nb/ppp/NPRA/061219

ARAHAN DI BAWAH PERATURAN 29 PERATURAN – PERATURAN KAWALAN DADAH DAN KOSMETIK 1984

BILANGAN 21 TAHUN 2019

i. **DIREKTIF UNTUK SEMUA PRODUK YANG MENGANDUNGI SODIUM VALPROATE: PENGUKUHAN MAKLUMAT KESELAMATAN PADA LABEL, SISIP BUNGKUSAN DAN RISALAH MAKLUMAT UBAT UNTUK PENGGUNA (RiMUP) BERKAITAN RISIKO KECACATAN KONGENITAL DAN MASALAH PERKEMBANGAN DALAM KALANGAN BAYI DAN KANAK-KANAK YANG TERDEDAH KEPADA PENGGUNAAN SODIUM VALPROATE SEMASA DALAM KANDUNGAN**

ii. **PENYEDIAAN BAHAN-BAHAN PENGAJARAN (*EDUCATIONAL MATERIALS*) BAGI PRODUK YANG MENGANDUNGI SODIUM VALPROATE:**
- **KAD PESAKIT**
- **BORANG SENARAI SEMAK UNTUK KEGUNAAN PRESKRIBER (*ANNUAL RISK ACKNOWLEDGEMENT FORM)***
- **RISALAH PANDUAN BAGI PROFESIONAL KESIHATAN**
- **RISALAH PANDUAN BAGI PESAKIT**

TUJUAN

1.1 Arahan ini dikeluarkan oleh Pengarah Kanan Perkhidmatan Farmasi di bawah Peraturan 29 (1) Peraturan-peraturan Kawalan Dadah dan Kosmetik 1984.

1.2 Arahan ini ditujukan kepada semua pemegang pendaftaran produk yang mengandungi bagi semua produk yang mengandungi sodium valproate bagi :

(i) Memperkukuhkan maklumat keselamatan berkaitan risiko kecacatan kongenital dan masalah perkembangan dalam kalangan bayi dan kanak-kanak yang terdedah kepada penggunaan sodium valproate semasa dalam kandungan

(ii) Menyediakan bahan-bahan pengajaran (*educational materials*) bagi produk yang mengandungi sodium valproate:
- Kad pesakit
- Borang senarai semak untuk kegunaan preskriber (*annual risk acknowledgement form)*
- Risalah panduan bagi profesional kesihatan
- Risalah panduan bagi pesakit

LATAR BELAKANG

2.1 Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke **341** pada **5 Disember 2019** telah membuat keputusan bagi semua produk yang mengandungi sodium valproate bagi :

(i) Memperkukuhkan maklumat keselamatan berkaitan risiko kecacatan kongenital dan masalah perkembangan dalam kalangan bayi dan kanak-kanak yang terdedah kepada penggunaan sodium valproate semasa dalam kandungan

(ii) Menyediakan bahan-bahan pengajaran (*educational materials*) bagi produk yang mengandungi sodium valproate:
- Kad pesakit
- Borang senarai semak untuk kegunaan preskriber (*annual risk acknowledgement form)*
- Risalah panduan bagi profesional kesihatan
- Risalah panduan bagi pesakit

PELAKSANAAN

3.1 Oleh itu arahan – arahan berikut perlu dipatuhi untuk semua produk yang mengandungi sodium valproate bagi seperti berikut:-

3.1.1 Pengemaskinian ke atas label, sisip bungkusan dan Risalah Maklumat Ubat untuk Pengguna (RiMUP) bagi semua produk yang mengandungi sodium valproate seperti berikut [menggantikan bahagian *Posology and Method of administration, Warnings and Precautions dan Fertility, pregnancy and lactation* dalam Direktif Bil.(3) dlm. BPFK/PPP/07/25 Jld. 1 bertarikh 11 Oktober 2016]:

3.1.1.1 LABEL (KOTAK LUAR)

A boxed warning should be added to the outer packaging as follows:

> ***WARNING FOR WOMEN AND GIRLS***
>
> *This medicine can seriously harm an unborn baby*
>
> *Always use effective contraception during treatment with sodium valproate*
>
> *If you are thinking about becoming pregnant, or if you are pregnant, contact your doctor urgently.*
>
> *You must CONTINUE taking sodium valproate unless your doctor tells you to stop*

3.1.1.2 SISIP BUNGKUSAN

3.1.1.2.1 Pada bahagian *Posology and Method of administration:*

Female children and women of childbearing potential
Sodium valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated (see Contraindications, Warnings and precautions and Fertility, pregnancy and lactation sections). The benefit and risk should be carefully reconsidered at regular treatment reviews. Sodium 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.

3.1.1.2.2 Pada bahagian *Contraindications:*

Sodium valproate is contraindicated in the following situations:

- *In epilepsy*
  - *sodium valproate is contraindicated in pregnancy unless there is no suitable alternative treatment*
  - *sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Warnings and precautions and Fertility, pregnancy and lactation sections)*
- *In bipolar disorder*
  - *sodium valproate is contraindicated in pregnancy*
  - *sodium valproate is contraindicated in women of childbearing potential, unless the conditions of Pregnancy Prevention Programme are fulfilled (see Female children, Women of childbearing potential, pregnant women section)*

3.1.1.2.3 Pada bahagian *Warnings and Precautions:*

Female children, Women of childbearing potential, and pregnant women:
Sodium valproate has a high teratogenic potential and children exposed in utero to sodium valproate have a high risk for congenital malformations and neurodevelopmental disorders.

Sodium valproate is contraindicated in the following situations:

- *In pregnancy unless there is no suitable alternative treatment for epilepsy indication.*
- *In pregnancy for bipolar disorder indication.*
- *In women of childbearing potential unless below conditions are fulfilled.*

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 sodium valproate in utero.*
- *The patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.*

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

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

- *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 sodium valproate.*
- *The patient understands the need for regular (at least annual) review of treatment by a prescriber experienced in the management of epilepsy.*
- *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 sodium 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 prescriber must ensure that:

- *The parents/caregivers of female children understand the need to contact the doctor once the female child using sodium valproate experiences menarche.*
- *The 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 sodium valproate in utero.*

In patients who have experienced menarche, the prescriber must annually reassess the need for sodium valproate therapy and consider alternative treatment options. If sodium valproate is the only suitable 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 prescriber to switch female children to alternative treatment before they reach adulthood.

Pregnancy test

Pregnancy must be excluded before start of treatment with sodium valproate. Treatment with sodium 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 sodium valproate must use effective contraception without interruption during the entire duration of treatment with sodium 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 the prescriber

The prescriber should review at least annually whether sodium valproate is the most suitable treatment for the patient. The prescriber 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

If a woman is planning to become pregnant, a prescriber experienced in the management of epilepsy must reassess sodium 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. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning.

In case of pregnancy

If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to re-evaluate treatment with sodium valproate and consider alternative treatment options. The patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy.

Pharmacists must ensure that:

- *The Patient Card is provided with every sodium valproate dispensation and that patients understand its content.*
- *Patients are advised not to stop sodium valproate medication and to immediately contact the prescriber in case of planned or suspected pregnancy.*

Educational materials

In order to assist healthcare professionals and patients in avoiding exposure to sodium valproate during pregnancy, the Marketing Authorisation Holder has provided educational materials to reinforce the warnings, provide guidance regarding use of sodium 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 sodium valproate.

An Annual Risk Acknowledgement Form needs to be used at time of treatment initiation and during each annual review of sodium valproate treatment by the prescriber. at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant

Sodium valproate therapy should only be continued after a reassessment of the benefits and risks of the treatment with sodium valproate for the patient by a doctor experienced in the

management of epilepsy.

3.1.1.2.4 Pada bahagian *Fertility, Pregnancy and Lactation:*

- *Sodium valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy.*
- *Sodium valproate is contraindicated as treatment for bipolar disorder during pregnancy.*
- *Sodium valproate is contraindicated for use in women of childbearing potential unless the above-mentioned conditions of Pregnancy Prevention Programme are fulfilled (see Contraindications and Warnings and precautions sections)*

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

Teratogenicity and developmental effects
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 sodium 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 sodium 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 sodium 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 sodium 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 sodium 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 sodium 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 sodium valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).

Female children and woman of childbearing potential (see Contraindications and Warnings and precautions sections)

If a Woman plans a Pregnancy
If a woman is planning to become pregnant, a doctor experienced in the management of epilepsy must reassess sodium 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. If switching is not possible, the woman should receive further counselling regarding the risks of sodium valproate for the unborn child to support her informed decision-making regarding family planning.

Pregnant women
Sodium valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment. If a woman using sodium valproate becomes pregnant, she must be immediately referred to a doctor to consider alternative treatment options.

During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for the mother and the unborn child. If in exceptional circumstances, despite the known risks of sodium valproate in pregnancy and after careful consideration of alternative treatment, a pregnant woman must receive sodium valproate for epilepsy.

It is recommended to:
- *Use the lowest effective dose and divide the daily dose sodium 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 to avoid high peak plasma concentrations.*

All patients with sodium valproate-exposed pregnancy and their partners should be referred to a doctor experienced in prenatal medicine for evaluation and counselling regarding the exposed pregnancy. Specialised 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 sodium valproate exposure.

3.1.1.3 RISALAH MAKLUMAT UBAT UNTUK PENGGUNA (RIMUP)

3.1.1.3.1 Pada bahagian *Before you use [product name]*:

WARNING FOR WOMEN AND GIRLS

Before you start to use it:
This medicine can seriously harm an unborn baby

Always use effective contraception during treatment with sodium valproate

If you are thinking about becoming pregnant, or if you are pregnant, contact your doctor urgently.

You must CONTINUE taking sodium valproate unless your doctor tells you to stop

Before you start to use it:

- *Tell your healthcare professionals if you are pregnant.*
- *If you are a woman able to have a baby you must not take sodium valproate unless you use an effective method of birth control (contraception) at all times during your treatment with sodium valproate.*

3.1.1.3.2 Pada bahagian *While you are using it:*

Things you must do:

- *Schedule an urgent appointment with your doctor if you want to become pregnant or if you think you are pregnant.*
- *If you are a parent or a caregiver of a female child treated with sodium valproate, you should contact their doctor once your child experiences their first period (menarche).*

Things you must not do:

- *Continue taking sodium valproate or using your birth control (contraception) until you have discussed your pregnancy or your plan to get pregnant with your doctor.*

Things to be careful of:

- *Sodium valproate can seriously harm an unborn baby when 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 sodium valproate during pregnancy you have a higher risk than other women of having a child with birth defects that require medical treatment. Because sodium valproate has been used for many years it is known that in women who take sodium 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 sodium 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 sodium valproate and there is some evidence children may be more likely to develop symptoms of Attention Deficit Hyperactivity Disorder (ADHD)*

3.2 Penyediaan bahan-bahan pengajaran *(educational materials)* seperti kad pesakit, borang senarai semak untuk kegunaan preskriber (*annual risk acknowledgement form*), risalah panduan bagi profesional kesihatan serta risalah panduan bagi pesakit dengan **maklumat minimum** seperti berikut:

3.2.1 Kad pesakit

3.2.1.1 Kad pesakit perlu dicetak dan dibekalkan oleh syarikat pemegang pendaftaran produk untuk edaran ke fasiliti-fasiliti yang dibekalkan dengan sodium valproate.

3.2.1.2 Kad pesakit boleh diedarkan oleh profesional kesihatan seperti pegawai perubatan atau pegawai farmasi semasa pesakit kali pertama menerima rawatan sodium valproate.

3.2.1.3 Pesakit perlu dimaklumkan dengan risiko berkaitan sodium valproate dan diingatkan agar menyimpan kad pesakit ini dengan cermat.

3.2.1.4 Kad pesakit ini perlu dicetak sekurang-kurangnya dalam dua (2) bahasa, iaitu Bahasa Melayu dan Bahasa Inggeris untuk kegunaan pesakit.

Muka Hadapan Kad

Patient Card for Sodium valproate [Product Name]: Contraception and Pregnancy
What You Must Know

- *Sodium valproate is an effective medicine to treat epilepsy or bipolar disorder*
- *Sodium valproate can cause serious harm to your baby when taken during pregnancy*
- *Always use effective contraception throughout the entire duration of treatment*

Note:
- This also applies to all girls and women taking sodium valproate who could become pregnant
- Keep this card safe so you always know what to do

Muka Belakang Kad

Patient Card for Sodium valproate [Product Name]: Contraception and Pregnancy
What You Must Do

- *Read the package leaflet carefully before use*
- *Never stop taking sodium valproate unless your doctor tells you as your condition may become worse*
- *If you are thinking of getting pregnant, CONTINUE taking your sodium valproate and contraception until you talk to your doctor*
- *If you think you are pregnant, CONTINUE taking sodium valproate. Make an urgent appointment with your doctor.*

Note:
- This also applies to all girls and women taking sodium valproate who could become pregnant
- Keep this card safe so you always know what to do

3.2.2 Borang senarai semak untuk kegunaan preskriber (*annual risk acknowledgement form)*

3.2.2.1 Borang ini perlu disediakan oleh syarikat pemegang pendaftaran produk untuk edaran ke fasiliti-fasiliti yang dibekalkan dengan sodium valproate untuk kegunaan pegawai perubatan yang memberikan rawatan kepada pesakit.

3.2.2.2 Borang ini bertujuan untuk memastikan pesakit atau penjaganya telah berbincang dengan preskriber berkaitan rawatan yang diterima dan memahami risiko berkaitan sodium valproate.

3.2.2.3 Bahagian A dan B pada borang perlu dilengkapkan dan ditandatangani oleh preskriber. Bahagian B pada borang perlu ditandatangani oleh preskriber dan pesakit. Bahagian B diberikan kepada pesakit. Preskriber perlu menyimpan bahagian A dan salinan bahagian B sebagai rujukan.

3.2.2.4 Borang ini digunapakai semasa:

i. pesakit kali pertama dipreskrib sodium sodium valproate
ii. penilaian pada setiap tahun rawatan
iii. pesakit merancang kehamilan atau telah hamil.

3.2.3.5 Borang ini perlu dicetak sekurang-kurangnya dalam dua (2) bahasa, iaitu Bahasa Melayu dan Bahasa Inggeris untuk kegunaan pesakit.

ANNUAL RISK ACKNOWLEDGEMENT FORM
PART A. TO BE COMPLETED AND SIGNED BY THE PRESCRIBER

Patient name : _____
MRN / ICNo. : _____
Address : _____

For girls and women of childbearing age treated with sodium valproate <Product Name>
Read, complete and sign this form during a visit with the prescriber: at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant.

Name of patient or care-giver: _____
I confirm that the above-named patient needs sodium valproate because:

☐ *this patient does not respond adequately to other treatments or*

☐ *this patient does not tolerate other treatments*

☐ *that this patient is already stable on ..... dose and she is reluctant to change to other medication.*

☐ *Other reason.....(to specify)*

I have discussed the following information with the above-named patient or care-giver:

☐ *The overall risk to fetus and children whose mothers are exposed to sodium valproate during pregnancy are:*
- *an approximately 10% chance of birth defects and*
- *up to 30 to 40% chance of a wide range of early developmental problems that can lead to learning difficulties.*

☐ *Sodium valproate should not be used during pregnancy (except in rare situations for epileptic patients that are resistant or intolerant to other treatments)*

☐ *The need for regular (at least annually) review and the need to continue sodium valproate treatment by the prescriber.*

☐ *The need for negative pregnancy test at treatment initiation and as required thereafter (if child bearing age).*

☐ *The need for an effective contraception without interruption during the entire duration of treatment with sodium valproate (if childbearing age).*

☐ *The need to arrange an appointment with her doctor 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 need to contact her doctor immediately for an urgent review of the treatment in case of suspected or inadvertent pregnancy.*

☐ *In case of pregnancy, I confirm that this pregnant patient:*
• received the lowest possible effective dose of sodium valproate to minimise the possible harmful effect on the unborn
• is informed about the possibilities of pregnancy support or counselling and appropriate monitoring of her baby if she is pregnant.

Name of Prescriber: _____ *Signature:* _____ *Date:* _____

Part A and B shall be completed: all boxes shall be ticked, and the form signed by the prescriber. This is to make sure all the risks and information related to the use of sodium valproate during pregnancy have been understood.

Part A – to be kept by the prescriber

ANNUAL RISK ACKNOWLEDGEMENT FORM
PART B. TO BE COMPLETED BY PRESCRIBER AND SIGNED BY THE PATIENT OR CAREGIVER

Patient name : _____
MRN / ICNo. : _____
Address : _____

For girls and women of childbearing age treated with sodium valproate <Product Name>
Read, complete and sign this form during a visit with the prescriber: at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant.

I have discussed the following with my doctor and understand:

- ☐ *Why I need sodium sodium valproate rather than other medicine*
- ☐ *I have decided to continue with the treatment after being advised on the risk*
- ☐ *That I should visit the prescriber regularly (at least annually) to review whether sodium valproate treatment remains the best option for me*
- ☐ *The overall risk to fetus and children whose mothers took sodium sodium valproate during pregnancy are:*
  - *an approximately 10% chance of birth defects and*
  - *up to 30 to 40% chance of a wide range of early developmental problems that can lead to significant learning difficulties*
- ☐ *Why I need a negative pregnancy test at treatment initiation and if needed thereafter (if child bearing age)*
- ☐ *That I must use an effective contraception without interruption during the entire duration of my treatment with sodium valproate (if childbearing age).*
- ☐ *We discussed the possibilities of effective contraception or we planned a consultation with a professional who is experienced in advising on effective contraception.*
- ☐ *The need for regular (at least annually) review and the need to continue sodium valproate treatment by the prescriber.*
- ☐ *The need to consult my doctor as soon as I am planning to become pregnant to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.*
- ☐ *That I should request an **urgent** appointment if I think I am pregnant*
- ☐ *In case of a pregnancy, I have discussed the following with my doctor and understand:*
  - *The possibilities of pregnancy support or counselling*
  - *The need to appropriate monitoring of my baby if I am pregnant*

Name of Patient/Caregiver: _____ *Signature:* _____ *Date:* _____

Name of Prescriber: _____ *Signature:* _____ *Date:* _____

Part B shall be completed: all boxes shall be ticked, and the form signed by prescriber and the patient. This is to make sure all the risks and information related to the use of sodium valproate during pregnancy have been understood.
Part B - to be given to patient
- a copy to be kept by the prescriber

3.2.3 Risalah panduan bagi profesional kesihatan dan pesakit:

3.2.3.1 Risalah panduan bagi professional kesihatan dan pesakit ini perlu dicetak dan dibekalkan oleh syarikat pemegang pendaftaran produk untuk edaran ke fasiliti-fasiliti yang dibekalkan dengan sodium valproate.

3.2.3.2 Risalah panduan ini bertujuan untuk memberi maklumat kepada profesional kesihatan sebagai panduan perawatan dan kepada pesakit bagi memberikan maklumat berkaitan langkah-langkah yang perlu diambil bagi mengurangkan risiko susulan penggunaan sodium valproate.

3.2.3.3 Risalah panduan bagi pesakit boleh diedarkan oleh profesional kesihatan seperti pegawai perubatan dan pegawai farmasi semasa pesakit menerima rawatan sodium valproate, contohnya semasa temujanji rawatan atau semasa pendispensan ubat.

3.2.3.4 Risalah panduan bagi pesakit perlu dicetak sekurang-kurangnya dalam dua (2) bahasa, iaitu Bahasa Melayu dan Bahasa Inggeris untuk kegunaan pesakit.

GUIDE FOR HEALTHCARE PROFESSIONALS
RISK OF CONGENITAL MALFORMATIONS AND NEURODEVELOPMENTAL DISORDERS FOLLOWING USE OF SODIUM VALPROATE

Note: This guide is to inform you of important information and strengthened warnings related to this risk

BACKGROUND INFORMATION: SAFETY DATA

1. Congenital Malformations

Data derived from two meta-analysis (including registries and cohort studies) have shown that 10.73% (95% Confidence Interval: 8.16-13.29%)[1] to 10.93% (95% Confidence Interval: 8.91-13.13%) of children of epileptic women exposed to sodium valproate monotherapy during pregnancy suffer from congenital malformations)[2]. This represents a greater risk of major malformations than for the general population, for whom the risk is equal to about 2-3%[1]. Available data show that the risk is dose dependent.The risk is greatest at higher doses (above 1g daily). A threshold dose below which no risk exists cannot be established based on available data.

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 system.

2. Developmental Disorders

Exposure to sodium 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 regardless of when during the pregnancy exposure occurs cannot be excluded.

Studies[3-6] in preschool children show that up to 30-40% of children with a history of sodium valproate exposure in utero experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Available data show that children with a history of sodium valproate exposure in utero are at increased risk of autistic spectrum disorder (an approximately three-fold) and childhood autism (an approximately fivefold) compared with the general study population[6].

Limited data suggests that children with a history of sodium valproate exposure in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD)[7].

RECOMMENDATIONS

1. The use of sodium valproate had been restricted in pregnancy as such:
   - In epilepsy
     - sodium valproate is contraindicated unless there is no suitable alternative treatment.
   - In bipolar disorder
     - sodium valproate is contraindicated in pregnancy.
2. The use of sodium valproate in women of childbearing potential is contraindicated unless patient had been assessed and counselled appropriately on the risks associated with sodium valproate.
3. Treatment should only be initiated if other treatments ineffective or not tolerated.

4. Treatment should only be initiated after pregnancy has been excluded (negative pregnancy test).
5. The benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably, sodium valproate should be prescribed as monotherapy and at the lowest effective dose. A prolonged release formulation is preferred to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses
6. Carry out annual review and ad-hoc treatment review when required. The benefit and risk should be carefully reconsidered during every treatment review.
7. In the case where sodium valproate must be used during pregnancy, prenatal monitoring is recommended to detect any malformations.

COUNSELLING POINT

- advise patient/ caretaker on the risk of congenital malformations and neurodevelopmental disorders associated with sodium valproate. Inform patient also about the risks of untreated seizure or bipolar disorder.

- advise patient to use effective contraception without interruption throughout the entire duration of sodium valproate treatment

- advise patient not to stop treatment abruptly and to urgently contact the doctor when planning for pregnancy or in the case of suspected pregnancy.

- ensure that patient has received educational materials such as patient card and patient guide that has been provided by the supplier of sodium valproate.

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GUIDE FOR FEMALE PATIENTS/ CAREGIVERS
RISK OF BIRTH DEFECT & DEVELOPMENTAL PROBLEM FOLLOWING USE OF SODIUM VALPROATE

This information in this leaflet is for women and girls who are prescribed with sodium valproate and are able to get pregnant (child-bearing age). Please read this leaflet carefully and talk to your doctor of pharmacist if you have any question

KEY POINTS:

- Sodium valproate is an effective medicine used to treat seizure (epilepsy) and bipolar disorder.
- Sodium valproate can seriously harm an unborn child when taken during pregnancy and should not be taken by women and girls unless no other medicine works.
- Never stop taking sodium valproate unless your doctor tells you to stop.
- Always use contraception and do not stop using as long as you are taking sodium valproate.
- See your doctor at once if you are planning pregnancy or if you suspect that you are pregnant. Do not stop taking sodium valproate.
- Please make sure that you receive the patient educational materials such as patient card and patient guide from your healthcare provider.

What you must do if you are being prescribed sodium valproate:

- For women who are able to get pregnant (of child-bearing age):
  - When taking sodium valproate, always use **reliable contraception** and never stop using it so you do not have unplanned pregnancy as long as you are taking sodium valproate
  - Tell your doctor at once if you think you may be pregnant or know you are pregnant.
  - Never stop taking sodium valproate unless your doctor tells you to as your condition may become worse
- If you are thinking to get pregnant:
  - Arrange urgent appointment with your doctor if you plan to get pregnant or if you suspect that you are pregnant. Do not stop taking sodium valproate and contraception until you have seen your doctor.

You can help by reporting any side effects that you may get directly to the National Pharmaceutical Regulatory Agency (NPRA) through the website http://npra.moh.gov.my (Consumer→Consumer Reporting of Side effects To Medicines Or Vaccines→ConSERF).

INFORMATION ON THE RISKS TO THE UNBORN CHILD

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

- Sodium valproate can cause serious birth defects and can affect the way in which the child develops as it grows. 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; and limb defects.
- Because sodium valproate has been used for many years, we know that in women who take sodium valproate, around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born in the general population.

- It is estimated that up to 30-40% of preschool children whose mothers took sodium 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. In addition, disorders which affect the way a child communicates and interacts with others, for example autism, are more often diagnosed in children exposed to sodium valproate.

4. Tarikh pelaksanaan keperluan mengemaskini maklumat berkenaan pada semua produk yang mengandungi sodium valproate bagi:

(a) Permohonan baru dan produk yang sedang dalam proses penilaian : **15 Januari 2020.**

(b) Produk berdaftar : **15 Julai 2020.**

5. Permohonan pindaan pada label, sisip bungkusan dan RiMUP bagi produk berdaftar perlu dikemukakan sebagai permohonan variasi.

6. Tarikh kuat kuasa arahan ini ialah mulai **15 Januari 2020.**

"BERKHIDMAT UNTUK NEGARA"

(DR. RAMLI BIN ZAINAL) RPh. 1045
Pengarah Kanan Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia

AAG/nb/ppp/NPRA/061219

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Kementerian Kesihatan Malaysia

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Bahagian Amalan dan Perkembangan Farmasi
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3. Pengarah
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