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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 17 TAHUN 2016: DIREKTIF BAGI SEMUA PRODUK YANG MENGANDUNGI SODIUM VALPROATE BAGI MEMPERKUKUHKAN AMARAN BERKAITAN RISIKO *ABNORMAL PREGNANCY OUTCOMES*

Adalah saya merujuk kepada Arahan Bilangan 17 Tahun 2016 oleh Pengarah Kanan Perkhidmatan Farmasi.

2. Dimaklumkan bahawa Pengarah Kanan Perkhidmatan Farmasi, Kementerian Kesihatan Malaysia dalam Arahan Bilangan 17 Tahun 2016 telah bersetuju untuk menambah kenyataan amaran berkaitan risiko kesan advers *abnormal pregnancy outcomes* bagi semua produk yang mengandungi sodium valproate seperti pada surat arahan Bil. (3) BPFK/PPP/07/25 Jld. 1.

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

Sekian, terima kasih.

"BERKHIDMAT UNTUK NEGARA"

Saya yang menurut perintah,

(DR. SALMAH BT. BAHRI)
Pengarah Regulatori Farmasi
Agensi Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia
ra/nb/ppp/NPRA/071016

BPFK/PPP/07/25 (3) Jld 1

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

BILANGAN 17 TAHUN 2016

DIREKTIF BAGI SEMUA PRODUK YANG MENGANDUNGI SODIUM VALPROATE BAGI MEMPERKUKUHKAN AMARAN BERKAITAN RISIKO *ABNORMAL PREGNANCY OUTCOMES*

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 produk yang mengandungi sodium valproate bagi memperkukuhkan amaran berkaitan risiko *abnormal pregnancy outcomes.*

LATAR BELAKANG

2.1 Pihak Berkuasa Kawalan Dadah (PBKD) dalam mesyuarat kali ke **304** pada **27 September 2016** telah membuat keputusan bagi semua produk yang mengandungi sodium valproate bagi memperkukuhkan amaran berkaitan risiko *abnormal pregnancy outcomes.*

PELAKSANAAN

3.1 Oleh itu kenyataan amaran berkaitan risiko kesan advers *abnormal pregnancy outcomes* perlu dikemaskini pada sisip bungkusan untuk semua produk yang mengandungi sodium valproate dengan memperkukuhkan maklumat pada bahagian *Posology and Method of administration, Special Warnings and Precautions for Use dan Fertility, pregnancy and lactation* seperti berikut:-

3.1.1 Pada bahagian *Posology and Method of administration* :

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

[Product Name] should be initiated and supervised by a specialist experienced in the management of epilepsy. Treatment should only be initiated if other treatments are ineffective or not tolerated and the benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably [Product 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.

3.1.2 Pada bahagian *Special warnings and precautions for use* :

Female children/Female adolescents/ Women of childbearing potential/Pregnancy

[Product 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 [Product 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 [Product Name] during pregnancy (see Fertility, Pregnancy and Lactation).

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:

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.

3.1.3 Pada bahagian *Fertility, pregnancy and lactation*:

[Product 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.

<u>Pregnancy Exposure Risk related to valproate</u>
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.

<u>Congenital malformations</u>
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 Special Warnings and Precautions for use)

If a Woman wants to plan a Pregnancy

- *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.*
- *In women planning to become pregnant or who are pregnant, valproate therapy should be reassessed*
- *In women planning to become pregnant all efforts should be made to switch to appropriate alternative treatment prior to conception, if possible.*

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. 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.*

4. Guide for Healthcare Professionals perlu disediakan dan diedarkan kepada ahli profesional kesihatan, dengan maklumat minimum seperti di **Lampiran A.**

5. Guide for Female Patients/ Caregivers perlu disediakan dan diberikan kepada semua pesakit perempuan, dengan maklumat minimum seperti di **Lampiran B**.

6. Tarikh pelaksanaan keperluan mengemaskini maklumat dan penyediaan garis panduan berkenaan bagi semua produk yang mengandungi sodium valproate bagi:

(a) Permohonan baru dan produk yang sedang dalam proses penilaian : **1 November 2016**

(b) Produk berdaftar : **1 Mei 2017**

7. Permohonan pindaan pada sisip bungkusan bagi produk berdaftar perlu dikemukakan sebagai permohonan variasi.

8. Tarikh kuat kuasa arahan ini ialah mulai **1 November 2016.**

"BERKHIDMAT UNTUK NEGARA"

(DR. SALMAH BT. BAHRI)
Pengarah Regulatori Farmasi
b.p Pengarah Kanan Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia
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s.k. 1. Pengarah Regulatori Farmasi
Agensi Regulatori Farmasi Negara
Kementerian Kesihatan Malaysia.

2. Pengarah Penguatkuasa Farmasi
Bahagian Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia.

3. Pengarah Amalan dan Perkembangan Farmasi
Bahagian Perkhidmatan Farmasi
Kementerian Kesihatan Malaysia.

LAMPIRAN A

GUIDE FOR HEALTHCARE PROFESSIONALS
MEDICINES RELATED TO VALPROATE:
UPDATES ON THE RISK OF ABNORMAL PREGNANCY OUTCOMES

Note: *It is known that valproate is associated with the risk of abnormal pregnancy outcomes. This guide is to inform you of important new information and strengthened warnings related to this risk.*

BACKGROUND INFORMATION: SAFETY DATA

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), which 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 the risk is dose dependent. The risk is greatest at higher doses (above 1 g daily). A threshold dose below which no risk exists cannot be established based on available data.

Developmental Disorders

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[2-5].

RECOMMENDATIONS

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

- Sodium valproate **should not be used in female children, female adolescents, 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.
- Treatment should only be initiated if other treatments are ineffective or not tolerated.
- 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, 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.
- **Women of childbearing potential must use effective contraception during treatment** and be informed of the risks associated with the use of sodium valproate during pregnancy.
- Advise patients to contact their healthcare professional immediately if they become pregnant or think they might be pregnant.

References:

1. Meador K, Reynolds MW, Crean S, Fahrbach K, Probst C. Pregnancy outcomes in women with epilepsy: a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res. 2008;81(1):1-13.
2. 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 October;51(10):2058-65.
3. Cummings et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child 2011;96:643-647
4. Meador K et al. Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. NEJM 2009;360 (16): 1597- 1605
5. Thomas S.V et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy and Behaviour 2008 (13):229-236

LAMPIRAN B

GUIDE FOR FEMALE PATIENTS/ CAREGIVERS:
VALPROATE: UPDATES ON THE RISKS TO THE UNBORN CHILD

The information in this leaflet is for **women and girls who are being prescribed valproate** and are able to get pregnant (of **child-bearing age**). Please read this leaflet and talk to your doctor or pharmacist if you have any questions.

KEY POINTS:

- Valproate is an effective medicine used to treat epilepsy and bipolar disorder.
- 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.

What you must do if you are being prescribed valproate:

- For women who are able to get pregnant (of child-bearing age):
  When taking valproate, always **use reliable contraception** so you do not have an unplanned pregnancy.
- If you are thinking about having a baby, speak to your doctor and do not stop using contraception until you have done so.
  - 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.
- Tell your doctor at once if you think you may be pregnant or know you are pregnant.
- **Never stop** taking valproate **unless your doctor tells you** to as your condition may become worse.

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 (Public → Reporting → ConSERF).**

INFORMATION ON THE RISKS TO THE UNBORN CHILD

- Valproate can be harmful to unborn children when taken by a woman during pregnancy.
- 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 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 in the general population.
- 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. 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 valproate.

PANDUAN UNTUK PESAKIT PEREMPUAN/ PENJAGA:
VALPROATE: MAKLUMAT TERKINI BERKAITAN RISIKO KEPADA ANAK DI DALAM KANDUNGAN

Maklumat di dalam risalah ini adalah untuk **wanita dan kanak-kanak perempuan yang dipreskrib dengan valproate** dan berpotensi untuk hamil (***child-bearing age***). Sila baca risalah ini dan bincang dengan doktor atau ahli farmasi anda sekiranya anda mempunyai sebarang pertanyaan.

MAKLUMAT PENTING:

- Valproate adalah ubat yang berkesan untuk merawat penyakit epilepsi dan kecelaruan bipolar *(bipolar disorder)*.
- Valproate boleh memudaratkan anak di dalam kandungan apabila diambil semasa hamil, dan tidak boleh diambil oleh wanita dan kanak-kanak perempuan melainkan jika rawatan dengan ubat-ubatan lain tidak berkesan.

Apakah yang anda perlu lakukan jika anda dipreskrib dengan valproate:

- Bagi wanita yang berpotensi untuk hamil (*child-bearing age*):
  Semasa mengambil valproate, sila gunakan **kaedah pencegahan kehamilan** yang berkesan supaya anda tidak mendapat kehamilan yang tidak dirancang.
- Jika anda merancang untuk hamil, rujuk kepada doktor anda dan jangan berhenti menggunakan kaedah pencegahan kehamilan tanpa nasihat doktor.
  - Sila berbincang dengan doktor anda berkaitan pengambilan suplemen asid folik semasa anda cuba untuk hamil. Asid folik boleh mengurangkan risiko am mengalami *spina bifida* (dimana tulang belakang tidak terbina dengan sempurna) dan keguguran awal kandungan yang wujud dengan semua kehamilan. Namun, ia tidak dapat mengurangkan risiko kecacatan kelahiran yang dikaitkan dengan penggunaan valproate.
- Maklumkan kepada doktor anda dengan segera sekiranya anda hamil atau mungkin hamil.
- **Jangan berhenti mengambil valproate kecuali dinasihatkan oleh doktor anda.** Ini mungkin akan menerukkan penyakit anda jika ubat dihentikan secara tiba-tiba.

Anda boleh membantu dengan melaporkan sebarang kesan sampingan ubat yang dialami. Laporkan secara terus kepada Agensi Regulatori Farmasi Negara (NPRA) melalui laman sesawang **http://npra.moh.gov.my (*Public* → *Reporting* → *ConSERF*).**

MAKLUMAT BERKAITAN RISIKO KEPADA ANAK DI DALAM KANDUNGAN

- Valproate boleh memudaratkan anak di dalam kandungan apabila diambil oleh wanita yang hamil.
- Valproate boleh menyebabkan anak di dalam kandungan mengalami kecacatan (*birth defects*) yang serius dan boleh mempengaruhi perkembangan anak semasa membesar. Contoh kecacatan yang boleh dialami termasuk *spina bifida*; kecacatan bentuk muka dan tengkorak; kecacatan jantung, buah pinggang, salur kencing dan organ seks; serta kecacatan anggota.
- Memandangkan valproate sudah lama digunakan, adalah diketahui bahawa dalam kalangan wanita yang mengambil valproate, lebih kurang 10 bayi daripada setiap 100 akan mengalami kecacatan. Ini berbanding 2-3 bayi daripada setiap 100 yang dilahirkan dalam populasi umum.
- Kajian terhadap kanak-kanak pra-sekolah yang terdedah kepada valproate semasa di dalam kandungan menganggarkan sebanyak 30-40% mengalami perkembangan yang tidak normal *(developmental disorders)* termasuk lambat bercakap atau berjalan, intelektual yang rendah, kemahiran bahasa yang lemah, dan masalah memori. Tambahan pula, penyakit yang boleh memberi kesan kepada cara seseorang berkomunikasi dan berinteraksi dengan orang lain, contohnya penyakit autisme, lebih kerap didiagnos dalam kalangan kanak-kanak yang terdedah kepada valproate.