GUIDE FOR HEALTHCARE PROFESSIONALS

Information on the risks of valproate (Depalept Chrono) use in female patients and pregnant women.

Contraception and pregnancy prevention

This guide is a mandatory part of the Depalept Chrono Marketing Authorization as an additional measure to minimize the risk of congenital malformations and neuro-developmental disorders and improve the benefit/risk ratio of Depalept Chrono. The purpose of this guide is therefore to ensure that healthcare professionals who prescribe Depalept Chrono and patients who use Depalept Chrono are aware of and understand the specific safety requirements concerning the use of Depalept Chrono.

The objective of this guide is to prevent Depalept Chrono exposure during pregnancy. The types of risks in children exposed to Depalept Chrono during pregnancy are the same regardless of the indication in which Depalept Chrono was prescribed. The risk minimization measures described in this guide therefore apply to the use of Depalept Chrono in any indication.

Read this guide carefully before prescribing Depalept Chrono to female patients. This guide is part of the Depalept Chrono Pregnancy Prevention Program and should be used along with the Patient Guide, the Patient Card and Physician Checklist.
Keep a copy of the checklist once it has been completed.

It is recommended that you keep an electronic version in the patient's file.
Give the Patient Guide to every patient treated with Depalept Chrono. It can be found at MOH (Ministry of Health) site. For further information about Depalept Chrono, read the prescribing information completely before prescribing Depalept Chrono.

CONTENT

EXECUTIVE SUMMARY

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

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

SPECIALISTS *:

Valproate may be initiated in female children 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 healthcare provider, to rule out unintended use in pregnancy.

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

Female patients - first prescription

1. Initiate valproate only if there is no suitable alternative treatment,

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

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

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

Women of childbearing potential - not planning a pregnancy

1. Reassess at each visit whether treatment with valproate is still appropriate for your patient,

2. Remind the patient at each visit of the risks related to valproate when used in pregnancy,

3. Remind your patient at each visit that effective contraception without interruption during the entire duration of treatment with valproate is mandatory,

4. Remind your patient at each visit to contact you immediately if she thinks she might be pregnant or becomes pregnant.

Women of childbearing potential - planning pregnancy

1. Remind your patient of the risks related to valproate when used in pregnancy,

2. Discontinue valproate treatment and switch to another alternative treatment if suitable for your patient (see section 5 in this Guide),

3. Remind your patient that switching takes time,

4. Explain to your patient that contraception should only be stopped after complete cessation of valproate.

Women with unplanned pregnancy

1. Arrange an urgent consultation with your patient,

2. Explain why she should continue with her treatment until the date of the appointment,

3. Make sure your patient and her partner have understood the risks related to valproate and refer them to a specialist for further counselling,

4. Discontinue valproate treatment and switch to another alternative treatment if suitable for your patient (see section 5 in this Guide).

*More details can be found in section 2 in this Guide.

1. INFORMATION ON CONGENITAL MALFORMATIONS AND ON NEURODEVELOPMENTAL DISORDERS

Depalept Chrono contains valproic acid (valproate), 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 neurodevelopment disorders (e.g. autistic disorders, ADHD and lower intelligence quotient [IQ]). These risks are briefly described in the next few pages.

1. CONGENITAL MALFORMATIONS

A meta-analysis (including registries and cohort studies) showed that about 11%[1] of children of epileptic women exposed to valproate monotherapy during pregnancy had major congenital malformation. This is greater than the risk of major malformations in the general population (about 3% at birth). The risk of major congenital malformations in children after in utero exposure to anti-epileptic polytherapy including valproate is higher than that of anti-epileptic drugs polytherapy not including valproate. 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.

In utero exposure to valproate may also result in:

- unilateral or bilateral hearing impairment or deafness, that may not be reversible[2],
- eye malformations (including colobomas, microphthalmos) that have been reported in conjunction with other congenital malformations. These eye malformations may affect vision.

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 (including that of autism) 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. When valproate is administered in polytherapy with other anti-epileptic drugs during pregnancy, the risks of neurodevelopment disorders in the offspring were also significantly increased as compared with those in children from general population or born to untreated epileptic mothers.

The exact gestational period of risk for these effects is uncertain and the possibility of a risk throughout the entire pregnancy cannot be excluded.

When valproate is administered in monotherapy, Studies[3-6]in preschool children show that up to 30-40% of children with a history of 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.

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 children exposed to other antiepileptic drugs[7]. 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 are limited data on the long term outcomes.

Available data from a population-based study show that children with a history of valproate exposure in utero are at increased risk of autistic spectrum disorder (an approximately 3-fold) and childhood autism (an approximately 5-fold) compared to the unexposed population in the study[8].
Available data from another population-based study show that children with a history of valproate exposure in utero are at increasing risk of developing attention deficit/hyperactivity disorder (ADHD) (approximately 1.5-fold) compared to the unexposed population in the study[9].

2. WHAT TO CONSIDER WHEN PRESCRIBING VALPROATE (PHYSICIANS):

Epilepsy is one of the most prevalent neurologic conditions and an important cause of disability and mortality[11]. During pregnancy, generalized tonic-clonic seizures are associated with risks to the foetus as well as to the pregnant woman[12].

Valproate is an effective drug to treat epilepsy but when administered during pregnancy, is associated with an:

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

SPECIALIST:

- Assess the need to treat your patient with valproate – is this medicinal product really indicated for this condition – Is there really no alternative treatment for my patient?
- Inform the patient about the teratogenic risks of valproate and advise her about effective methods of contraception and pregnancy prevention or ensure that your patient has been sufficiently advised by a gynecologist – Is my patient aware of the risks?
- Comply with the conditions of the Pregnancy Prevention Program (see section 3) – Are all measures being taken to prevent pregnancy during valproate use?
- Complete Physician Checklist with your patient:
  - at treatment initiation,
  - at the annual visit,
  - if a patient asks for advice because she is planning pregnancy or unplanned pregnancy
- Assess your patient's valproate treatment on an annual basis or as needed – Does my patient still need to be treated with valproate?
- Give your patient the Patient Guide and indicate that additional information is available at MOH Site.
- If pregnancy occurs during treatment with valproate, refer your patient to a specialist to monitor the pregnancy as well as a specialist with experience in embryo-toxicology or prenatal medicine.

3. CONDITIONS OF PREGNANCY PREVENTION PROGRAM

Valproate should not be used in female children and women of childbearing potential unless other treatments are ineffective or not tolerated.

Valproate may be initiated in girls and women of child bearing potential only if the conditions of Valproate Pregnancy Prevention Program (outlined below) are fulfilled.

Conditions of the Pregnancy Prevention Program

The prescriber must ensure that:

- You have assessed the patient's potential for pregnancy
- You have taken the individual circumstances of the patient into account and made sure of her cooperation.
- You explained to the patient the risks of congenital malformations and neuro-developmental disorders including the magnitude of these risks for children exposed to valproate in utero.
- Pregnancy was ruled out at the beginning of treatment.
- The patient has been advised on contraception, and she is capable of complying with the need to use effective contraception* without interruption during the entire duration of treatment with valproate.
- You explained to the patient the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy or bipolar disorder.
- You explained to the patient the need to consult her physician as soon as she is planning a pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.
- You explained to the patient the need to contact her doctor immediately in case of pregnancy.
- The patient has received the Patient Guide.
- You explained to the patient the risks and necessary precautions associated with the use of valproate (Physician Checklist completed annually).

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.

* Use of 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. 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.

4. TREATMENT OF FEMALE PATIENTS WITH VALPROATE

A. FEMALE PATIENT- FIRST PRESCRIPTION

1. Confirm that treatment with valproate is appropriate for your patient

(i.e. treatment should only be initiated if other treatments are ineffective or not tolerated).

2. Discuss the following topics with your patient and her parents/caregivers :

- The risks to pregnancy associated with the underlying condition
- The specific risks related to valproate when used in a pregnancy
- The need for an effective contraception, without interruption, during the entire duration of treatment with valproate to avoid an unplanned pregnancy
- The need for regular (at least annual) review of the patient's treatment by a specialist
- The need to urgently consult her physician in case of pregnancy.

3. Ensure that your patient or her parents/legal guardian have received an explanation about the potential consequences of a pregnancy and can adequately evaluate the risks.

4. Recommendations when valproate is prescribed to female children:

- Assess the most appropriate time to give advice on contraception and prevention of pregnancy (Refer your patient to a specialist for counselling if needed)
- Explain the risk of congenital malformations and neurodevelopmental disorders to the parents / legal guardian / caregiver (and to the child depending on her age)
- Explain to the parents / legal guardian / caregiver (and to the child depending on her age) the importance of contacting a specialist as soon as the female child treated with valproate experiences menarche
- Review the need for valproate therapy at least annually and consider alternative treatment options in female children who have experienced menarche
- Review all options to switch female children to alternative treatment before they reach adulthood.

5. Make additional information available to your patient and complete the Physician Checklis

- Give your patient or the parents / legal guardian a copy of the Patient Guide
- Complete the Physician Checklist together with your patient:
  - Keep a copy of the checklist in the patient's file and give a copy to the patient or her legal guardian.

6. Schedule a treatment review if your patient is planning to become pregnant or if she reaches childbearing age.

B. WOMEN OF CHILDBEARING POTENTIAL WHO ARE NOT PLANNING PREGNANCY

1. **Confirm that treatment with valproate is appropriate for your patient**

   (i.e. treatment should only be initiated if other treatments are ineffective or not tolerated).

2. **Make sure that treatment is evaluated at least once annually.**

3. **Discuss the following topics with your patient and make sure that she has understood the risks and can adequately evaluate them:**

   - The risks to pregnancy that are associated with the underlying condition
   - The risks related to valproate when used in a pregnancy
   - The need for an effective method of contraception throughout the entire duration of treatment with valproate to prevent an unplanned pregnancy.
   - The need to urgently consult her physician in case of pregnancy.
   - The need for regular (at least annually) review of the treatment

4. **Discuss contraception methods and direct as needed to a gynecologist**

5. **Make additional information available to your patient and complete the Physician Checklist**
   - Give your patient or the parents / legal guardian a copy of the Patient Guide
   - Complete the Physician Checklist together with your patient:
     - o Keep a copy of the checklist in the patient's file and give a copy to the patient or her legal guardian.

6. **Schedule a treatment review if your patient is planning to become pregnant or if she reaches childbearing age**

C. WOMAN OF CHILDBEARING POTENTIAL WHO ARE PLANNING PREGNANCY

1. **Switch and discontinue valproate to other therapeutic alternative if suitable:**
   - Information about switching or discontinuing treatment with valproate can be found in section 5 of this guide.
   - Tell your patient to not stop contraception until the switch is achieved
   - General Practitioners should refer their patient to the specialist for switching and discontinuation.

   Below subsections relate only to epileptic patients planning for pregnancy when there is no suitable alternative treatment:

2. **Confirm that treatment with valproate is appropriate for your patient**
   (i.e. treatment should only be initiated if other treatments are ineffective or not tolerated)
3. **Make sure that treatment is evaluated at least once annually.**
4. **Ensure that your patient has understood the risks of congenital malformations and neurodevelopmental disorders and can adequately evaluate these risks.**
   - Inform your patient that these risks can lead to severe disabilities if valproate is taken during pregnancy
   - 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 valproate exposure[10]
   - You should also inform your patient of the risks to the unborn child and the patient herself of untreated epilepsy.

5. **Refer your patient to specialist for preconception counselling.**
6. **Instruct your patient to consult their gynecologist and specialist as soon as she suspects or confirms she is pregnant.**
   - This is to start appropriate pregnancy monitoring
   - This includes prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations
   - When a patient consults for pregnancy refer the patient and her partner to a specialist with experience in embryo-toxicology or prenatal medicine who will assess and explain in detail the effects of valproate exposure during pregnancy.

7. **Make additional information available to your patient and complete the Physician Checklist**

- Give your patient or the parents / legal guardian a copy of the Patient Guide
- Complete the Physician Checklist together with your patient:
  - Keep a copy of the checklist in the patient's file and give a copy to the patient or her legal guardian.

D. WOMAN WITH AN UNPLANNED PREGNANCY

1. **Schedule an urgent consultation with your patient to reassess her treatment as soon as possible**
2. **Explain to her why she should continue her treatment until you have seen her**
   - Unless you are able to give other advice based on your assessment of the situation.
3. **Switch to an alternative treatment and discontinue treatment with valproate if this is possible for your patient**
   - Information about switching or discontinuing treatment with valproate can be found in section 5 of this guide

General Practitioners must refer the patient to the specialist for switching and discontinuing.

4. **Make sure that your patient:**
   - Has received an explanation about the risks related to valproate and,
   - Consider further counselling
5. **Start specialized prenatal monitoring.**
   - This is to start appropriate pregnancy monitoring
   - This includes prenatal monitoring to detect the possible occurrence of neural tube defects or other malformations
   - Refer the patient and her partner to a specialist with experience in embryo-toxicology or prenatal medicine who will assess and explain in detail the effects of valproate exposure during pregnancy.
6. **Make additional information available to your patient and complete the Physician Checklist**
   - Give your patient or the parents / legal guardian a copy of the Patient Guide
   - Complete the Physician Checklist together with your patient:
     - Keep a copy of the checklist in the patient's file and give a copy to the patient or her legal guardian.

5. SWITCHING OR DISCONTINUING VALPROATE

Patients with bipolar disorder

Valproate is contraindicated in pregnancy.

Valproate is contraindicated in women of childbearing potential unless the conditions of the pregnancy prevention program are fulfilled (see section 3 in this Guide).

If a woman is planning to become pregnant, the prescriber must switch the patient to another treatment. Switching should be achieved prior to conception and before contraception is discontinued.

If a woman becomes pregnant, treatment with valproate must be switched and discontinued to another treatment.

General considerations for bipolar disorder patients:

"If mood stabilizers are to be withdrawn, it is recommended that the dose be tapered down slowly as this reduces the risk of relapse."[13]

"Therefore valproate is to be discontinued gradually over few weeks to reduce early recurrence. In the case of an acute manic episode in a pregnant woman taking valproate, a much faster cross tapering while installing the alternative is recommended."[14]

Patients with epilepsy

Valproate is contraindicated in pregnancy unless there is no suitable alternative treatment.

Valproate is contraindicated in women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see section 3 in this Guide).

If a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess 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 a woman becomes pregnant on valproate, she must be immediately referred to a specialist to consider alternative treatment options.

General considerations for epileptic patients:

Issued by Task Force of Commission of European Affairs of International League Against Epilepsy (CEA-ILAE) and European Academy of Neurology (EAN):

- "Drug withdrawal is usually undertaken gradually over weeks to months, which allows an opportunity to identify the likely minimum required dose should a seizure occur during drug withdrawal".

- “The switch of valproate to an alternative treatment will commonly occur over at least 2–3 months. The new medication is usually first gradually introduced as add on to valproate. This can take up to 6 weeks to reach a potentially effective dose of the new treatment; thereafter an attempt can be made to gradually withdraw valproate”.

If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman (or a woman planning to become pregnant) must receive valproate for epilepsy:

- There is no dose threshold considered to be without any risk. However, the risk of birth defects and developmental disorders is higher at greater doses
- Use the lowest effective dose and divide the daily dose of 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

- All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in embryo-toxicology or prenatal medicine who will assess and explain in detail the effects of valproate exposure during pregnancy.

Healthcare professionals are asked to report any suspected adverse reactions to the ministry of health by means of the online form for reporting adverse reactions located at: https://sideeffects.health.gov.il
Additionally may be reported to Sanofi Israel Pharmacovigilance: PV.Israel@sanofi.com

The Ministry of Health has approved the format and the content of Health Care Professional guide in August 2022.

References

1. Weston J, Bromley R, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, Hounsome J, McKay AJ, Tudur Smith C, Marson AG. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD010224
2. Foch C, Araujo M, Weckel A, Damase-Michel C, Montastruc JL, Benevent J, et al. In utero drug exposure and hearing impairment in 2-year-old children A case-control study using the EFEMERIS database. Int J Pediatr Otorhinolaryngol. 2018 Oct;113: 192-7.
3. 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.
4. Cummings et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child 2011;96: 643-647
5. Meador K et al. Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. NEJM 2009; 360 (16): 1597- 1605
6. Thomas S.V et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy and Behaviour 2008 (13):229-236
7. Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J,Kalayjian LA, Kanner A, Liporace JD, Pennell PB, Privitera M, Loring DW; NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. Lancet Neurol. 2013 Mar; 12(3):244-52
8. Christensen J et al. Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. JAMA 2013; 309(16):1696-1703
9. 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 New Open. 2019;2(1): e186606
10. Jentink J, Bakker MK, Nijenhuis CM, Wilffert B, de Jong-van den Berg LT. Does folic acid use decrease the risk for spina bifida after in utero exposure to valproic acid? Pharmacoepidemiol Drug Saf. 2010 Aug;19(8):803-7.
11. Fiest KM et al. Prevalence and incidence of epilepsy: A systematic review and meta-analysis of international studies. Neurology. 2017 Jan 17;88 (3):296-303.
12. Tomson T et al., Management of epilepsy in pregnancy: a report from the International League Against Epilepsy Task Force on Women and Pregnancy. Epileptic Disord 2019; 21 (6): 497-517
13. Malhi GS, Bassett D, Boyce P, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. Australian and New Zealand J. Psychiatry 2015, Vol. 49(12) 1-185.
14. Minutes and answers from the SAG Psychiatry meeting on Valproate- EMA/679681/2017