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GUIDE FOR HEALTHCARE PROFESSIONALS

Information on the risks of valproate (Valparin®ALKALETS 200/500, Valparin®CHRONO 200/300/500, Valparin®200, Depakote®, Depakote®XR) 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 minimization measure aimed at minimizing pregnancy exposure during treatment with valproate.

Information about valproate use can also be found on-line at www.sanofi.in

CONTENT

PURPOSE OF THIS GUIDE

This Guide for healthcare professionals (HCPs) is an educational tool part of the **valproate Pregnancy Prevention Program**, which targets both healthcare professionals and patients.

Its objective is to provide information about the teratogenic risks associated with the use of valproate during pregnancy, the actions necessary to minimize 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 **neuro-developmental 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 minimization measures described in this Guide apply to the use of valproate regardless of the indication.

HCPs targeted by this Guide include, but are not limited to: Specialist involved in the treatment of epilepsy or bipolar disorder, General Practitioners, Gynecologists / Obstetricians

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

- The Patient Guide
- The Annual Risk Acknowledgement Form, and
- The Patient Card.

Use this booklet together with the Patient Guide.

You should give a copy of the **Patient Guide** to all your female patients treated with valproate - girls and women of child bearing potential (or their parents / legal guardian or caregiver for patients who are minors or without the capacity to make an informed decision).

You should 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 the specialist, and in the case of any pregnancy that might occur whilst on treatment.

You should give the **Patient Card** to your female patients each time valproate is prescribed.

For patients who are minors or without the capacity to make an informed decision, provide the information and advice on effective methods of contraception and on the use of valproate during pregnancy to their parents / legal guardian / caregiver and make sure they clearly understand the content.

Please read the most up-to-date version of the Prescribing Information before prescribing valproate.

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 AND GENERAL PRACTIONNERS*:

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

- Initiate valproate only if there is no suitable alternative treatment,
- Explain to your patient the risks related to valproate when used in pregnancy,
- Explain to your patient that the use of effective contraception without interruption during the entire duration of treatment with valproate is mandatory,
- 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

- Reassess at each visit whether treatment with valproate is still appropriate for your patient,
- Remind the patient at each visit of the risks related to valproate when used in pregnancy,
- Remind your patient at each visit that effective contraception without interruption during the entire duration of treatment with valproate is mandatory,
- 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

- Remind your patient of the risks related to valproate when used in pregnancy,
- Discontinue valproate treatment and switch to another alternative treatment if suitable for your patient (see section 5 in this Guide),
- Remind your patient that switching takes time,
- Explain to your patient that contraception should only be stopped after complete cessation of valproate.

Women with unplanned pregnancy

- Arrange an urgent consultation with your patient,
- Explain why she should continue with her treatment until the date of the appointment,
- Make sure your patient and her partner have understood the risks related to valproate and refer them to a specialist for further counselling,
- Discontinue valproate treatment and switch to another alternative treatment if suitable for your patient (see section 5 in this Guide).

GYNECOLOGISTS / OBSTETRICIANS

- Provide counselling on contraception methods and pregnancy planning,
- Provide information about the risks of using valproate during pregnancy,
- When a patient consults for pregnancy refer the patient and her partner to a Specialist for evaluation and counselling regarding the exposed pregnancy.

1 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.

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 2-3%). 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, cranio-stenosis, 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.

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 THE ROLE OF THE DIFFERENT HCPs*

SPECIALIST:

- Diagnosis
- Treatment initiation after negative pregnancy test (i.e. plasma pregnancy test) result
- Explain the risks of congenital malformations and neurodevelopmental disorders when using valproate during pregnancy and ensure patient understanding
- Provide the Patient Guide and remind that online information about the use of valproate in women of child-bearing potential and risks of valproate use during pregnancy can also be found online at www.Sanofi.in
- Provide counselling on effective contraception and pregnancy prevention
- Annual treatment review, and ad-hoc treatment review as required
- Switching and discontinuation
- Complete the Annual Risk Acknowledgment Form with your patient, at:
    - o treatment initiation,
    - o every annual visit,
    - o when a patient consults for planned or unplanned pregnancy
- In case of exposed pregnancy, refer to a specialist for pregnancy monitoring and for evaluation and counselling regarding the exposed pregnancy

GENERAL PRACTITIONER:

- Refer patient to the relevant specialist to confirm the diagnosis of epilepsy or bipolar disorder, and to initiate treatment
- Ensure appropriate treatment continuation
- Remind the patient of their annual visit to the specialist
- Provide full information about the risks of using valproate during pregnancy and ensure patient understanding
- Provide counselling on effective contraception and pregnancy prevention
- Refer the patient to their specialist when a patient consults for pregnancy
- Refer patient to their specialist for switching and discontinuation or if their condition worsens
- Provide the Patient Guide and remind that online information about the use of valproate in women of child-bearing potential and risks of valproate use during pregnancy can also be found online at www.Sanofi.in

GYNECOLOGIST / OBSTETRICIAN:

Provide counselling on effective contraception and pregnancy prevention counselling

- Provide full information about the risks of using valproate during pregnancy and ensure patient understanding
- Refer the patient to their specialist when a patient consults for pregnancy
- When a patient consults for pregnancy refer patient and her partner to a specialist for evaluation and counselling regarding the exposed pregnancy

3 CONDITIONS OF VALPROATE PRESCRIPTION: PREGNANCY PREVENTION PROGRAM

Valproate is an effective treatment for epilepsy and bipolar disorder.

In female children and women of childbearing potential valproate must be initiated and supervised by a specialist experienced in the management of epilepsy or bipolar disorder.

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:

- 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 minimize 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 is capable of complying 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 specialist experienced in the management of epilepsy or bipolar disorders.
- 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 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 amenorrhea she must follow all the advice on effective contraception.*

4 TREATMENT OF FEMALE PATIENTS WITH VALPROATE

FEMALE PATIENT- FIRST PRESCRIPTION

This is what you should do if - after medical evaluation - you are considering prescribing valproate to your patient for the first time.

You should:

- **Confirm that treatment with valproate is appropriate for your patient**
  - You must have confirmed that other treatments are ineffective or not tolerated
- **Explain and make sure your patient or her parents / legal guardian / caregiver have perfectly understood the following:**
  - 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
  - The risks to pregnancy associated with the underlying condition
  - The specific risks related to valproate when used in a pregnancy
  - The need to comply with 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
- **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
  - Reassess the need for valproate therapy at least annually and consider alternative treatment options in female children who have experienced menarche
  - Assess all options to switch female children to alternative treatment before they reach adulthood
- **Give a copy of the Patient Guide to your patient or her parents / legal guardian / caregiver**
- **For the specialist:**
  - Complete the Annual Risk Acknowledgment Form with your patient or her parents / legal guardian / caregiver
  - This form is to ensure your patient has fully understood the risks and recommendations associated with the use of valproate during pregnancy
  - Keep a copy of the Annual Risk Acknowledgment Form in the patient's medical records (if possible an electronic copy) and give a copy to the patient or her parents / legal guardian / caregiver
- **Plan to review the need for treatment when your patient plans to become pregnant or when she is able to become pregnant.**

WOMEN OF CHILDBEARING POTENTIAL WHO ARE NOT PLANNING PREGNANCY

This is what you should do if - after medical evaluation - you are considering renewing a valproate prescription to your patient. You should:

- **Confirm that treatment with valproate is appropriate for your patient**
  - You must have confirmed that other treatments are ineffective or not tolerated
  - Ensure regular (at least annual) review of treatment
- **Explain and make sure your patient understands**
  - The risks to pregnancy that are associated with the underlying condition
  - The risks related to valproate when used in pregnancy
  - The need to comply with effective method of contraception without interruption during the entire duration of treatment with valproate to avoid an unplanned pregnancy, and consider a pregnancy test (plasma pregnancy test), if needed
  - The need to urgently consult her physician in case of pregnancy
  - The need for regular (at least annually) review of treatment
- **Discuss contraception methods and direct as needed to preconception counselling.**
- **Give a copy of the Patient Guide to your patient or her parents / legal guardian / caregiver**
- **For the specialist:**
  - Complete the Annual Risk Acknowledgment Form with your patient or her parents / legal guardian / caregiver
  - This form is to inform and ensure your patient has fully understood the risks and recommendations associated with the use of valproate during pregnancy
  - Keep a copy of the Annual Risk Acknowledgment Form in the patient's medical records (if possible an electronic copy) and give a copy to the patient or her parents / legal guardian / caregive
- **Plan to review the need for treatment with valproate when your patient plans a pregnancy.**

WOMAN OF CHILDBEARING POTENTIAL WHO ARE PLANNING PREGNANCY

- **Remind and make sure your patient understands the risks of birth defects and neurodevelopmental disorders.**
  - Inform your patient that these can be seriously debilitating when taking valproate 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]
  - But also inform your patient them about the risks of untreated seizures or bipolar disorder
- **Switch and discontinue valproate to other therapeutic alternative if suitable:**
  - Read section 5 in this Guide on switching or discontinuing valproate
  - 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

- **Refer your patient to specialist for preconception counselling.**
- **Instruct your patient to consult their family doctor 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 for evaluation and counselling regarding the exposed pregnancy
- **Give a copy of the Patient Guide to your patient or her parents / legal guardian / caregiver.**
- **For the specialist:**
  - Complete the Annual Risk Acknowledgment Form with your patient or her parents / legal guardian / caregiver
  - This form is to inform and to ensure your patient has fully understood the risks and recommendations associated with the use of valproate during pregnancy
  - Keep a copy of the Annual Risk Acknowledgment Form in the patient's medical records (if possible and electronic copy) and give a copy to the patient or her parents / legal guardian / caregiver

WOMAN WITH AN UNPLANNED PREGNANCY

- **Arrange an urgent consultation with your patient to reassess her treatment as soon as possible.**
- **Explain 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
- **Switch and discontinue to other therapeutic alternatives if suitable.**
  - Read section 5 in this Guide on switching or discontinuing valproate
- **Make sure that your patient:**
  - Has fully understood the risks related to valproate and,
  - Consider further counselling
- **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
  - Patient and her partner should be referred to a specialist for evaluation and counselling regarding the exposed pregnancy
- **General Practitioners should refer their patient to the specialist for switching and discontinuation.**
- **Give a copy of the Patient Guide to your patient or her parents / legal guardian / caregiver.**
- **For the specialist:**
  - Complete the Annual Risk Acknowledgment Form with your patient or her parents / legal guardian / caregiver
  - This form is to inform and to ensure your patient has fully understood the risks and recommendations associated with the use of valproate during pregnancy
  - Keep a copy of the Annual Risk Acknowledgment Form in the patient's medical records (if possible an electronic copy) and give a copy to the patient or her parents / legal guardian / caregiver

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."[11]

"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."[12]

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 for evaluation and counselling regarding the exposed pregnancy

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. *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.*
12. *Minutes and answers from the SAG Psychiatry meeting on Valproate- EMA/679681/2017*