Valproate: New restrictions on use; pregnancy prevention programme to be put in place.

Direct healthcare professional communication
June 2021

Dear Healthcare professional,

This letter is sent in agreement with European Medicines Agency (EMA) and the local competent authority to inform you of **important new contraindications, strengthened warnings and measures to prevent valproate exposure during pregnancy.**

Summary

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

• Children exposed in utero to valproate are at a high risk of serious developmental disorders (in up to 30-40% of cases) and of congenital malformations (in approximately 10% of cases).

• In pregnancy and in women of childbearing potential new contraindications apply:

In 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 (described below) are fulfilled

• For women of childbearing potential currently using valproate the treatment may need to be re-evaluated to decide if the conditions of the pregnancy prevention programme (described below) are fulfilled.

Key elements of the Pregnancy Prevention Programme:

The prescriber must ensure that:
• Individual circumstances should be evaluated in each case, involving the patient in the discussion, to guarantee her engagement, discuss therapeutic options and ensure her understanding of the risks and the measures needed to minimise the risks.
• the potential for pregnancy is assessed for all female patients.
• the patient has understood and acknowledged the risks of congenital malformations and neurodevelopmental disorders, including the magnitude of these risks for children exposed to valproate in utero.
• the patient understands the need to undergo pregnancy testing prior to initiation of treatment and during treatment, as needed.
• the patient is counselled regarding contraception, and that the patient can comply with the need to use effective contraception, without interruption during the entire duration of treatment with valproate.
• the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy.
• the patient understands the need to consult her physician as soon as she is planning a pregnancy to ensure timely discussion and switching to alternative treatment 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 valproate use (Annual Risk Acknowledgement Form).
These conditions also concern women who are not sexually active unless the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy.

More detailed instructions related to the following topics are provided in the Annex of this letter:
• the use of valproate in female children,
• the need to rule out pregnancy before valproate initiation,
• the use of effective contraception,
• the annual treatment review by a specialist
• the use of the annual risk acknowledgement form (at treatment initiation and during treatment review, at least annually),
• what to do with valproate treatment at the time of pregnancy planning and during pregnancy
• specific actions to be taken by the pharmacist such as provision of the patient card

The product information of all valproate-containing products will be updated accordingly.
It is recommended that pregnant women taking valproate are enrolled in registries of antiepileptic drugs and pregnancy or such data collection at a national level.

Educational materials

To assist healthcare professionals and patients in avoiding exposure to valproate during pregnancy, a Patient Card (on the outer package), a Patient Guide, an annual risk acknowledgment form, and a Guide for prescribers, pharmacists and other healthcare providers involved in the care of women of childbearing potential using valproate will be available to inform healthcare professionals and patients/caregivers on the risks of valproate and the conditions for use.
A patient guide and patient card should be provided to all women of childbearing potential using valproate. An annual risk acknowledgement form needs to be used by the specialists at time of treatment initiation and during each annual review of valproate treatment by the specialist.

Background information

In 2014 the warnings and restrictions on the use of valproate medicines in women and girls were strengthened, to minimise the risk of malformations and developmental problems in babies exposed to valproate in the womb. EMA's safety experts, the Pharmacovigilance Risk Assessment Committee (PRAC) has now reviewed the impact of these measures following concerns that the measures were not sufficiently effective in increasing awareness and reducing valproate use appropriately during pregnancy.
The PRAC found these concerns to be well founded and has therefore introduced new measures.

Risk of abnormal pregnancy outcomes

Valproate is associated with a dose-dependent risk of abnormal pregnancy outcomes, whether taken alone or in combination with other medicines. Data suggest that when valproate is taken for epilepsy with other medicines, the risk of abnormal pregnancy outcomes is greater than when valproate is taken alone.
• The risk of congenital malformations is approximately 10%, while studies in preschool children exposed in utero to valproate show that in up to 30-40%, early development such as talking, and walking is delayed and they have low intellectual abilities, poor language skills and memory problems.[1,2,3,4,5]
• Intelligence quotient (IQ) measured in a study of 6-year-old children with a history of valproate exposure in utero was on average 7-10 points lower than children exposed to other antiepileptics.[6]
• 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.[7]
• Limited data suggest that children exposed to valproate in utero may be more likely to develop symptoms of attention deficit/hyperactivity disorder (ADHD).[8]

Call for reporting
Any suspected adverse events should be reported to the national pharmacovigilance point of contact.
This medicinal product is subject to additional monitoring.

Company contact point
Any suspected adverse events should be reported to drugs.camwi@sanofi.com
If in need of further information please contact us through infomed.pac@sanofi.com

Annex

Further details on the pregnancy prevention programme

The following information should be read in conjunction with the conditions of the pregnancy prevention programme which are described in the letter above.

Female children

- Valproate should not be prescribed to female children or women of childbearing potential, unless there is no suitable alternative treatment.
- The prescribers must ensure that parents/caregivers of female children understand the need to contact the specialist once the female child using valproate experiences menarche.
- The prescriber must ensure that 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 valproate *in utero*.
- In patients who experienced menarche, the prescribing specialist must reassess the need for valproate therapy annually and consider alternative treatment options. If valproate is the only suitable treatment, the need for using effective contraception and all other conditions of pregnancy prevention programme should be discussed. Efforts should be made by the specialist to switch the female children to alternative treatment before they reach adulthood.

Pregnancy test

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

Contraception

Women of childbearing potential who are prescribed valproate must use effective contraception, without interruption during the entire duration of treatment with 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 a specialist

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

For the indication epilepsy, 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 switching is not possible, the woman should receive further counselling regarding the valproate risks for unborn child to support her informed decision making regarding family planning.

For the indications bipolar disorder and migraine if a woman is planning to become pregnant a specialist experienced in the management of bipolar disorder and migraine must be consulted and treatment with valproate should be discontinued and if needed switched to an alternative treatment prior to conception, and before contraception is discontinued.

In case of pregnancy

Valproate as treatment for bipolar disorder and prophylaxis of migraine attacks is contraindicated for use during pregnancy. Valproate as treatment for epilepsy is contraindicated in pregnancy unless there is no suitable alternative treatment.

If a woman using valproate becomes pregnant, she must be immediately referred to a specialist to re-evaluate treatment with valproate and consider alternative treatment options. During pregnancy, maternal tonic clonic seizures and status epilepticus with hypoxia may carry a particular risk of death for mother and the unborn child.

If, despite the known risks of valproate in pregnancy and after careful consideration of alternative treatment, in exceptional circumstances a pregnant woman must receive valproate for epilepsy, it is recommended to:

- 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 to avoid high peak plasma concentrations.

All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in teratology for evaluation and counselling regarding the exposed pregnancy. Specialized 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 valproate exposure.

<u>Pharmacists must ensure that</u>

- the patient card is provided with every valproate dispensing and that the patients understand its content.
- Reinforce the safety messages including the need for effective contraception.
- the patients are advised not to stop valproate medication and to immediately contact a specialist in case of planned or suspected pregnancy.
- Dispense valproate in the original package with an outer warning. In some countries where valproate might be unpacked in pharmacies; unpacking should be avoided. In the situations where this cannot be avoided, always provide a copy of the package leaflet, patient card and the outer box if available.

REFERENCES

1 Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child.
Cochrane Database of Systematic Reviews 2016, Issue 11. Art. No.: CD010224.
2 Bromley RL, et al. Early cognitive development in children born to women with epilepsy: a prospective report. *Epilepsia* 2010 October;
51(10):2058–65.
3 Cummings C 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 SV et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. *Epilepsy and Behaviour* 2008
(13):229–236.
6 Meador KJ, et al. NEAD Study Group. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective
observational study. *Lancet Neurol* 2013;12(3):244-52.
7 Christensen J et al. Prenatal valproate exposure and risk of autism spectrum disorders and childhood autism. *JAMA* 2013;309(16):1696–
1703.
8 Cohen MJ et al. Fetal antiepileptic drug exposure: motor, adaptive and emotional/behavioural functioning at age 3 years. *Epilepsy Behav*.
2011; 22(2):240–246.

Information on the risks of valproate (Valpakine®) 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 part of the valproate Pregnancy Prevention Program aimed at minimizing pregnancy exposure during treatment with valproate.
Information about valproate use can also be found on-line at https://www.sanofi-pacifico-caribe.com/
It is recommended that pregnant women taking valproate are enrolled in a registry capturing the use of antiepileptic drugs during pregnancy or any similar data collection exercise at a national level.

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 neurodevelopmental disorders in children exposed to valproate during pregnancy.

The nature of the risks for children exposed to valproate during pregnancy are the same irrespective of the indication for which valproate has been prescribed. Therefore, the risk 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, Gynaecologists / Obstetricians, Midwives, Nurses and Pharmacists.

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 childbearing 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 dispensed.
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 Summary of Product Characteristics 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 developmental 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.

<u>Female patients - first prescription</u>
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.

<u>Women of childbearing potential - not planning a pregnancy</u>
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.

<u>Women with unplanned pregnancy</u>
1. Arrange an urgent consultation with your patient,
2. Explain why she should continue with her treatment until the date of the appointment,
5
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).

GYNECOLOGISTS / OBSTETRICIANS, MIDWIVES, NURSES*:

1. Provide counselling on contraception methods and pregnancy planning,
2. Provide information about the risks of using valproate during pregnancy,
3. When a patient consults for pregnancy refer the patient and her partner to a specialist experienced in <teratology> {to be adapted depending on healthcare system} for evaluation and counselling regarding the exposed pregnancy.

PHARMACISTS*:

1. Ensure that the patient card is provided every time valproate is dispensed and that the patient understands its content,
2. Remind the patient of the safety messages including the need for effective contraception,
3. Advise the patient not to stop valproate and to contact their doctor urgently when planning a pregnancy or in case of a suspected pregnancy.

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

1. INFORMATION ON CONGENITAL MALFORMATIONS AND ON DEVELOPMENTAL 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 developmental disorders. These risks are briefly described below.

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%)[2] of children of epileptic women exposed to valproate monotherapy during pregnancy suffer from congenital malformations). 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 systems. In utero exposure to valproate may also result in unilateral or bilateral hearing impairment or deafness, that may not be reversible[3].

2. 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 regardless of when during the pregnancy exposure

occurs cannot be excluded.
Studies[4-7] 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[8]. 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[9].
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[10].

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 https://www.sanofi-pacifico-caribe.com/

· Provide counselling on effective contraception and pregnancy prevention

· Annual treatment review, and ad-hoc treatment review as required

· Switching and discontinuation

· Complete and sign the Annual Risk Acknowledgment Form with your patient, at:

- treatment initiation,
- every annual visit,
- when a patient consults for planned or unplanned pregnancy

· In case of exposed pregnancy, refer to a specialist for pregnancy monitoring and to a specialist experienced in teratology 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 https://www.sanofi-pacifico-caribe.com/

GYNECOLOGIST / OBSTETRICIAN; MIDWIFE; NURSE:

· 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 experienced in teratology for evaluation and counselling regarding the exposed pregnancy.

PHARMACIST:

· Ensure that the patient card is provided every time valproate is dispensed and that the patient understands its content

· Remind the patient of the safety messages including the need for effective contraception

· Ensure the patient has received 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 https://www.sanofi-pacifico-caribe.com/

· Advise the patient not to stop valproate medication and to urgently contact their doctor when planning or in the case of suspected pregnancy

· Dispense Valproate in the original package with an outer warning. For countries where valproate may be unpacked in pharmacies; unpacking should be avoided. In the situations where this cannot be avoided, always provide a copy of the package leaflet, patient card and the outer box if available.

*see also recommendations in section 4 in this Guide.

3- CONDITIONS OF VALPROATE PRESCRIPTION:

PREGNANCY PREVENTION PROGRAM- CONDITIONS

Valproate is an effective treatment for epilepsy.
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 childbearing 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 can comply with the need to use effective contraception*, without interruption during the entire duration of treatment with valproate.

· The patient understands the need for regular (at least annual) review of treatment by a 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 intrauterine 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

A. 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:

Firstly

1. Confirm that treatment with valproate is appropriate for your patient
1. You must have confirmed that other treatments are ineffective or not tolerated.
2. 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.

3. 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.

Secondly you should give your patient additional information:

4. Prescribers: give a copy of the Patient Guide to your patient or her parents / legal guardian / caregiver
5. Pharmacists:

· Ensure that the patient card is provided every time valproate is dispensed and that the patient understands its content

· Tell the patient to keep the Patient Card

· Reinforce the safety messages including the need for effective contraception

· Ensure the patient has received 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 https://www.sanofi-pacifico-caribe.com/

· Advise patients not to stop the treatment with valproate and to immediately contact their doctor when planning a pregnancy or in case of a suspected pregnancy

· Dispense Valproate in the original package with an outer warning. For countries where valproate may be unpacked in pharmacies; unpacking should be avoided. In the situations where this cannot be avoided, always provide a copy of the package leaflet, patient card and the outer box if available.

Finally

6. For the specialist:

· Complete and sign 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 signed 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.

7. Plan to review the need for treatment when your patient plans to become pregnant or when she can become pregnant.

B. 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:

Firstly

1. 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.

2. Explain and make sure your patient understands

· The risks to pregnancy that are associated with the underlying condition

2. The risks related to valproate when used in pregnancy

3. 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.

3. Discuss contraception methods and direct as needed to preconception counselling.

Secondly you should give your patient additional information:

4. Prescribers: give a copy of the Patient Guide to your patient or her parents / legal guardian / caregiver
5. Pharmacists:

· Ensure that the patient card is provided every time valproate is dispensed and that the patient understands its content

· Tell the patient to keep the Patient Card

· Reinforce the safety messages including the need for effective contraception

· Ensure the patient has received 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 https://www.sanofi-pacifico-caribe.com/

· Advise patients not to stop valproate medication and to urgently contact their specialist in case of suspected pregnancy

· Dispense Valproate in the original package with an outer warning. For countries where valproate may be unpacked in pharmacies; unpacking should be avoided. In the situations where this cannot be avoided, always provide a copy of the package leaflet, patient card and the outer box if available.

Finally

6. For the specialist:

· Complete and sign 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 signed 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.

7. Plan to review the need for treatment with valproate when your patient plans a pregnancy.

C. WOMAN OF CHILDBEARING POTENTIAL WHO ARE PLANNING PREGNANCY

Firstly

1. Remind and make sure your patient understands the risks of birth defects and developmental 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 [11]

· But also inform your patient them about the risks of untreated seizures or bipolar disorder.

2. 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.

3. Refer your patient to specialist for preconception counselling.

4. 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 experienced in teratology for evaluation and counselling regarding the exposed pregnancy.

<u>Secondly you should give your patient additional information</u>:

5. Prescribers: give a copy of the Patient Guide to your patient or her parents / legal guardian / caregiver.

6. Pharmacists:

· Ensure that the patient card is provided every time valproate is dispensed and that the patient understands its content

· Tell the patient to keep the Patient Card

· Reinforce the safety messages including the need for effective contraception

· Ensure the patient has received 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 https://www.sanofi-pacifico-caribe.com/

· Advise patients not to stop valproate medication and to immediately contact their specialist when planning or in case of suspected pregnancy

· Dispense Valproate in the original package with an outer warning. For countries where valproate may be unpacked in pharmacies; unpacking should be avoided. In the situations where this cannot be avoided, always provide a copy of the package leaflet, patient card and the outer box if available.

Finally

7. For the specialist:

· Complete and sign 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 signed 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.

D. WOMAN WITH AN UNPLANNED PREGNANCY

Firstly

1. Arrange an urgent consultation with your patient to reassess her treatment as soon as possible
2. Explain why she should continue her treatment until you have seen her

・Unless you can give other advice based on your assessment of the situation.

3. Switch and discontinue to other therapeutic alternatives if suitable

・Read section 5 in this Guide on switching or discontinuing valproate.

4. Make sure that your patient:

・Has fully understood 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

・Patient and her partner should be referred to a specialist experienced in teratology for evaluation and counselling regarding the exposed pregnancy.

6. General Practitioners should refer their patient to the specialist for switching and discontinuation

Secondly you should give your patient additional information:

7. Prescribers: give a copy of the Patient Guide to your patient or her parents / legal guardian / caregiver
8. Pharmacists:

・Ensure that the patient card is provided every time valproate is dispensed and that the patient understands its content

・Tell the patient to keep the Patient Card

・Reinforce the safety messages

・Ensure the patient has received 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 https://www.sanofi-pacifico-caribe.com/

・Advise patients not to stop valproate medication and to immediately contact their specialist

・Dispense Valproate in the original package with an outer warning. For countries where valproate may be unpacked in pharmacies; unpacking should be avoided. In the situations where this cannot be avoided, always provide a copy of the package leaflet, patient card and the outer box if available.

Finally

9. For the specialist

・Complete and sign 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 signed 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 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 to avoid high peak plasma concentrations

· All patients with a valproate exposed pregnancy and their partners should be referred to a specialist experienced in teratology for evaluation and counselling regarding the exposed pregnancy.

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. 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
3. 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.
4. 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.
5. Cummings et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child 2011;96: 643-647
6. Meador K et al. Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. NEJM 2009; 360 (16): 1597- 1605
7. Thomas S.V et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy and Behaviour 2008 (13):229-236
8. 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
9. Christensen J et al. Prenatal Valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. JAMA 2013; 309(16):1696-1703
10.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
11 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.
12 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.
13 Minutes and answers from the SAG Psychiatry meeting on Valproate- EMA/679681/2017

Patient Guide
Valproate* (Valpakine®) Contraception and pregnancy: what you should know

This booklet is for you if you are a girl or a woman taking any medicine containing valproate, or your caregiver/legal representative.
It is a risk minimization measure part of the valproate Pregnancy Prevention Program aiming to minimize pregnancy exposure during treatment with valproate.
It contains key information about the risk of valproate use during pregnancy.
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 https://www.sanofi-pacifico-caribe.com/

This booklet is for girls and women of childbearing age taking any medicine which contains valproate*, or their caregiver/legal representative.
 It contains key information about the risks of taking valproate during pregnancy.
 It is important to read this if your doctor has recommended valproate as the best treatment for you.
 The type of risks of using valproate during pregnancy is the same for all girls and women using valproate. Read this booklet along with the leaflet inside the medicine box.
 It is important that you read the leaflet even if you have been taking valproate for a while.
 This is because it contains the most up to date information on your medicine. You might find it helpful to talk about this booklet with your partner, friends, and family.
 Ask your doctor, midwife, or pharmacist if you have any questions. Keep this booklet. You may need to read it again.

CONTENTS

1- KEY INFORMATION TO REMEMBER
 Valproate* is an effective medicine for epilepsy and bipolar disorder.
 Valproate should only be taken by women or girls unless nothing else works. This is because valproate can seriously harm an unborn child when taken during pregnancy. Whatever your illness, never stop taking valproate unless your doctor tells you to do so.
 Always use effective contraception when taking valproate
- Use contraception for the whole time you are taking valproate
- Do not stop using the contraception at any time
Your doctor will recommend effective contraception for you.
This is to stop you having an unplanned pregnancy.
 Schedule an urgent appointment with your doctor if you think you are pregnant.
 Consult your doctor promptly if you are thinking about having a baby and do not stop using contraception until you have done so.
 Never stop taking valproate unless your doctor tells you because your illness may become worse.
 Remember to visit your specialist regularly- at least annually.
 During this visit both yourself and your doctor will discuss and sign a Risk Acknowledgement Form to ensure you are aware of and understand the risks of valproate use during pregnancy.

*Valproate also known as Valpakine®

2. CONTRACEPTION FOR FEMALE ADOLESCENTS AND WOMEN WHO ARE ABLE TO BECOME PREGNANT

Why do I need to use contraception?
Always use effective contraception when taking valproate:
- Use contraception for the whole time you are taking valproate
- Do not stop using the contraception at any time

Your doctor will recommend effective contraception for you.
This is to stop you having an unplanned pregnancy.
What type of contraception should I use?
Please discuss with your doctor the best method of contraception for you.
Please refer to your doctor, gynaecologist/obstetrician, or midwife for complete counselling.

3. WHAT ARE THE RISKS OF TAKING VALPROATE* DURING PREGNANCY?

Risks to your unborn child
If you take valproate when you are pregnant it can seriously harm your unborn child.
- The risks are higher with valproate than with other medicines for epilepsy or bipolar disorder.
- The risks are present even with smaller doses of valproate - the higher the dose the higher the risk.

How could my child be harmed?
Taking valproate whilst pregnant can harm your child in two ways:
- Birth defects when the child is born
- Problems with development and learning as the child grows up.

4. BIRTH DEFECTS

Taking valproate during pregnancy can cause serious birth defects.
In women in the general population:
- 2 to 3 babies in every 100 will have a birth defect.

In women who take valproate while pregnant:
- Around 10 babies in every 100 will have a birth defect.

What type of birth defects can happen?
- Spina bifida - where the bones of the spine do not develop properly.
- Face and skull malformations - including ‘cleft lip’ and ‘cleft palate’. This is where the upper lip or and bones in the face are split.
- Malformations of the limbs, heart, kidney, urinary tract and sexual organs.
- Hearing problems or deafness.

5. DEVELOPMENT AND LEARNING PROBLEMS

Taking valproate* while pregnant could affect your child’s development as they grow up.
In women who take valproate while pregnant:
- Up to 30 to 40 children in every 100 may have problems with development.

The long-term effects are not known.
The following effects on development could be observed:
- Being late in learning to walk and talk.
- Lower intelligence than other children of the same age.
- Poor speech and language skills.
- Memory problems.

Children of mothers who take valproate in pregnancy are more likely to have autism or autistic spectrum problems and are at increasing risk of developing Attention Deficit and/or Hyperactivity Disorder.

6. WHAT DOES THIS MEAN FOR ME?

Please choose and read the situations which apply to you from the situations described below:
- I am starting treatment with valproate*.
- I am taking valproate* and not planning a family.
- I am taking valproate* and planning a family.
- I am taking valproate* and I have become pregnant.

*Valproate also known as Valpakine®

I am starting treatment with valproate*

Your doctor will explain you why they feel valproate is the right medicine for you and tell you about all the known risks:

 If you are too young to become pregnant:

- Your doctor should only treat you with valproate if nothing else works.
- It is important that you and your parents/caregiver know about these risks of valproate when used during pregnancy. This is so you know what to do when you are old enough to have children.
- You or your parents/caregivers should contact the specialist once you experience menarche during valproate use.

 If you are already old enough to become pregnant:

- Your doctor should only treat you with valproate if you are not pregnant and you are using contraception.
- Your doctor will ask you to perform a pregnancy test before starting valproate, or thereafter if needed. This is to make sure you are not pregnant.
- Always use effective contraception when taking valproate:

 Use contraception for the whole time you are taking valproate

 Do not stop using the contraception at any time.

Your doctor will recommend effective contraception for you.

This is to make sure you do not become pregnant.

- You will need to review your treatment with your doctor regularly, (at least each year).
- At this initial visit your doctor will ask you to read and sign an Annual Risk Acknowledgement Form: this is to make sure you are well aware and have understood all the risks related to the use of valproate during pregnancy and recommendations to avoid you may become pregnant while taking valproate.

 If you decide you want to start a family, talk to your doctor about this as soon as possible

- Do not stop valproate or using contraception - until you have been able to discuss this with your doctor.
- You need to talk to your doctor about the risks for your baby's health while keeping your illness under control.
- You and your doctor should agree on what to do with your treatment before you start trying for a baby.

I am taking valproate* and not planning a family

Always use effective contraception if you are taking valproate and do not plan to have a baby.

 Use contraception for the whole time you are taking valproate

 Do not stop using the contraception at any time.

Talk to your doctor or gynaecologist/obstetrician or midwife/professional at the family planning clinic if you need advice on the method of contraception.

Consult your doctor at once if you think you are pregnant.

Never stop taking valproate until you have discussed this with your doctor even in case you have become pregnant as it can be dangerous for you and your baby.

You will need to review your treatment with your doctor regularly, (at least each year).

During the annual visit your doctor will ask you to read and sign a Risk Acknowledgement Form: this is to make sure you are aware and have understood all the risks related to the use of valproate during pregnancy and recommendations to avoid you may become pregnant while taking valproate.

I am taking valproate* and planning a family

If you are planning a baby, first talk to your doctor but:

 Keep taking valproate

 Keep using contraception until you have talked with your doctor. It is important that you do not become pregnant until you and your doctor have talked.

 Your doctor may need to change your medicine a long time before you become pregnant – this is to make sure your illness is stable.

 You need to talk about what can be done to reduce the risks for your baby's health while keeping your illness under control.

 Ask your doctor about taking folic acid when planning to have 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.

You will need to review your treatment with your doctor regularly, (at least each year).

During this visit your doctor will ask you to read and sign a Risk Acknowledgement Form: this is to make sure you are well aware and have understood all the risks and recommendations related to the use of valproate during pregnancy.

*Valproate also known as Valpakine®

I am taking valproate* and I have become pregnant

If you think you may be pregnant:

Do not stop taking valproate - this is because your epilepsy or bipolar disorder may become worse.

Talk promptly to your doctor. This is so that you can talk about your options. Your doctor may tell that you may need to switch to another treatment and will explain how to make the transition from valproate to this new treatment.

The babies of mothers who take valproate during pregnancy are at a higher risk of:

- birth defects and
- developing and learning problems.

These can both seriously affect your child's life.

In some circumstances, it may not always be possible to switch to another treatment. Please refer to your doctor for additional information.

During this visit your doctor will ask you to read and sign a Risk Acknowledgement Form: this is to make sure you are aware and have understood all the risks and recommendations related to the use of valproate during pregnancy.

You will be monitored very closely:

- This is to make sure your illness is controlled.
- It is also to check how your baby is developing.

*Valproate also known as Valpakine®

Patient Card

Patient Card for Valproate (Valpakine®): Contraception and Pregnancy

What you must know *

- **Valproate is an effective medicine for epilepsy.**
- **Valproate can seriously harm an unborn child when taken during pregnancy.**
- **Always use effective contraception without interruption during the entire duration of treatment with valproate.**
- **Remember to visit your specialist at least each year.**

What you must do *

- **Read the package leaflet carefully before use.**
- **Never stop taking valproate unless your doctor tells you to as your condition may become worse.**
- **If you are thinking about having a baby, do not stop using valproate and contraception before you talked to your doctor.**
- **If you think you are pregnant: Schedule an urgent appointment with your doctor.**
- **Ask your doctor to give you the patient guide.**

More information about valproate use can be found at https://www.sanofi-pacifico-caribe.com/ *or reaching out to infomed.pac@sanofi.com*

** This applies to all girls and women using valproate and who could become pregnant*

Keep this card safe so you always know what to do.