

APPENDIX 22

EDUCATIONAL MATERIALS

NO. PRODUCTS

1. ORAL RETINOIDS INDICATED FOR TREATMENT OF SKIN DISEASES

- 1.1 [Patient Reminder Card](#)
- 1.2 [Prescriber Checklist/ Acknowledgement Form](#)
- 1.3 [Pharmacist Checklist](#)

Reference: Directive No. 16, 2019, [BPFK/PPP/07/25\(16\) Jld.3](#). Direktif Untuk Semua Produk Yang Mengandungi Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit (Termasuk Topikal): Pengemaskinian Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Bagi Memperkukuhkan Maklumat Keselamatan Berkaitan Kesan Teratogenik Serta Penyediaan Bahan-bahan Pengajaran (Educational Materials) Bagi Produk Yang Mengandungi Oral Retinoid Yang Diindikasikan Untuk Rawatan Penyakit Kulit (27 September 2019)

2. SODIUM VALPROATE

- 2.1 [Patient Card](#)
- 2.2 [Annual Risk Acknowledgement Form](#)
- 2.3 [Guide for Healthcare Professionals](#)
- 2.4 [Guide for Female Patients/ Caregivers](#)
- 2.5 [Guide for Male Patients](#)

References:

- **Directive No. 21, 2019, [BPFK/PPP/07/25\(21\) Jld.3](#):** Direktif Untuk Semua Produk Yang Mengandungi Sodium Valproate: Pengukuhan Maklumat Keselamatan Pada Label, Sisip Bungkusan dan Risalah Maklumat Ubat Untuk Pengguna (RiMUP) Berkaitan Risiko Kecacatan Kongenital dan Masalah Perkembangan Dalam Kalangan Bayi dan Kanak-kanak Yang Terdedah Kepada Penggunaan Sodium Valproate Semasa Dalam Kandungan Serta Penyediaan Bahan-bahan Pengajaran (Educational Materials) Bagi Produk Yang Mengandungi Sodium Valproate (8 January 2020)
 - **Directive No. 15, 2025, [NPRA.600-1/9/13 \(62\)Jld.1](#):** Direktif Untuk Semua Produk Yang Mengandungi Valproate Termasuk Terbitannya (Sodium Valproate, Valproic Acid) (18 August 2025)
 - [NPRA website](#)
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1. ORAL RETINIDS INDICATED FOR TREATMENT OF SKIN DISEASES

1.1 Patient Reminder Card

Important information to know:

- [Product name] must not be taken during pregnancy. [Product name] can seriously harm an unborn baby if a pregnant woman takes it.
- If you become pregnant or think you might be pregnant, stop taking [product name] immediately and contact your doctor.
- If you have any questions or concerns about taking [product name], talk to your doctor or pharmacist.

What you must do:

- You must use effective contraception before, during and for 1 month* [*for acitretin: 3 years] after stopping treatment with [product name].
- You must not become pregnant while taking [product name], or for 1 month* [*for acitretin: 3 years] after stopping treatment.
- You must attend regular follow-up visits and have regular pregnancy testing.

Reminder for Men and Women

Do not share this medication with anybody and return any unused capsules back to the pharmacy. You should not donate blood during treatment with this medicine and for 1 month* [*for acitretin: 3 years] after stopping treatment.

1.2 Prescriber Checklist/ Acknowledgement Form

PRESCRIBER CHECKLIST/ ACKNOWLEDGEMENT FORM FOR PRESCRIBING [PRODUCT NAME] TO FEMALE PATIENTS

The potential for pregnancy must be assessed for all female patients prescribed [product name].

A woman has a potential for pregnancy if one of the following applies:

Is a sexually mature woman who:

1. has not had a hysterectomy or bilateral oophorectomy
2. is not in a natural postmenopause for a minimum of 24 consecutive months (i.e., menstruated at a certain point in the last 24 consecutive months).

Before initiating [product name] in a female patient, the following checklist is to be completed by the prescriber and kept with the patient notes to document compliance with the [product name] Pregnancy Prevention Programme. After completion, a copy of this document should be given to the patient.

[Product name] belongs to the retinoid class of drugs that cause severe birth defects. Foetal exposure to [product name], even for short periods, presents a high risk of congenital malformations. [Product name] is therefore strictly contraindicated in women of childbearing potential, unless all conditions in the [product name] Pregnancy Prevention Programme are fulfilled.

As the prescriber, you must make sure that the risk of serious harm from drug exposed pregnancy is fully understood by all female patients before treating them with [product name].

This checklist should also be used in all follow-up visits with women of childbearing potential.

Please use the patient reminder card to support your discussion with the patient.

Is the patient a woman of childbearing potential? If No, go to Section 4.

Women of childbearing potential: **Review the below statements**, explain them to the patient and record confirmation of this and acknowledgment from the patient in this form. If the answer to any of these questions is NO, [product name] must not be prescribed.

	Prescriber confirm: I have explained this to my patient		Patient confirm: I have understood this	
Is the patient suffering from a severe form of acne, which is resistant to standard therapies? [for acitretin: Is the patient suffering from a severe form of psoriasis or severe disorder of keratinization ?]	Yes ☐	No ☐	Yes ☐	No ☐
1. Teratogenicity				
The patient understands that [product name] belongs to a class of drugs (retinoids) known to cause severe birth defects and that they must not get pregnant whilst taking it. [Product name] also increases the risk of miscarriage when taken during pregnancy.	Yes ☐	No ☐	Yes ☐	No ☐
2. Contraception				
The patient understands that she must consistently and correctly use at least 1 highly effective method of contraception (i.e. a user-independent form such as an intra-uterine device or implant) or 2 complementary methods of birth control (i.e. user-dependent forms such as oral contraceptive and barrier method) before and during treatment.	Yes ☐	No ☐	Yes ☐	No ☐
The patient understands that the risk persists even after the medication is stopped and that she must not get pregnant within 1 month* [*for acitretin: 3 years] after stopping treatment.	Yes ☐	No ☐	Yes ☐	No ☐
The patient has received advice on contraception which is appropriate for her and has committed to using it throughout the risk period.	Yes ☐	No ☐	Yes ☐	No ☐
The patient is aware of the risk of contraceptive failure.	Yes ☐	No ☐	Yes ☐	No ☐

	Prescriber confirm: I have explained this to my patient		Patient confirm: I have understood this	
3. Pregnancy Testing & Ideally Monthly Prescriptions				
The first prescription for [product name] can only be given after the patient has had one negative medically supervised pregnancy test. This is to make sure she is not already pregnant before starting treatment.	Yes ☐	No ☐	Yes ☐	No ☐
Patient understands that in order to support regular follow up, including pregnancy testing and monitoring, ideally the prescription be limited to 30 days.	Yes ☐	No ☐	Yes ☐	No ☐
Patient understands the need for and agrees to pregnancy testing before, during and after treatment.	Yes ☐	No ☐	Yes ☐	No ☐
Patient understands the need to do a pregnancy test 1 month* after stopping treatment [*for acitretin: 1-3 monthly intervals throughout treatment and also for a period of 3 years after stopping treatment] because the drug stays in the body for 1 month* [*for acitretin: 3 years] after the last dose and can damage an unborn baby if pregnancy occurs.	Yes ☐	No ☐	Yes ☐	No ☐
The contraceptive methods and pregnancy test results were recorded in the patient's medical records.	Yes ☐	No ☐	Yes ☐	No ☐
The patient knows to contact their doctor if they have unprotected sex, miss their period, become pregnant, or suspect that they have become pregnant during the risk period.	Yes ☐	No ☐	Yes ☐	No ☐
If pregnancy occurs, treatment must be stopped and the patient should be referred to an expert physician specialised or experienced in teratology for advice.	Yes ☐	No ☐	Yes ☐	No ☐
The patient has received a reminder card and copy of this form.	Yes ☐	No ☐	Yes ☐	No ☐

	Prescriber confirm: I have explained this to my patient		Patient confirm: I have understood this	
4. Other Precautions				
Patient understands that [product name] has been prescribed to her only and must not be shared with others.	Yes ☐	No ☐	Yes ☐	No ☐
Patient understands that she must not donate blood during treatment with [product name] and for one month* [*for acitretin: 3 years] after discontinuation due to the potential risk to the foetus of a pregnant transfusion recipient.	Yes ☐	No ☐	Yes ☐	No ☐

1.3 PHARMACIST CHECKLIST - GUIDANCE FOR DISPENSING [PRODUCT NAME]

[Product name] belongs to the retinoid class of drugs that cause severe birth defects. Foetal exposure to [product name], even for short periods of time, presents a high risk of congenital malformations and miscarriage.

[Product name] is therefore strictly contraindicated during pregnancy and in women of childbearing potential, unless all conditions in the Pregnancy Prevention Programme are fulfilled.

Female patient must use effective contraception before, during and for 1 month* [*for acitretin: 3 years] after stopping treatment with [product name].

If you are aware that a female patient has become pregnant within 1 month* [*for acitretin: 3 years] of stopping [product name], she should be referred to her prescribing doctor.

As the pharmacist, you should only dispense [product name] after checking the following information:

For women of child-bearing potential:	
In order to support regular follow up, including pregnancy testing and monitoring, the prescription for [product name] ideally be limited to a 30-day supply.	
All patients should be instructed:	
Never to give the [product name] to another person.	
To return any unused capsules to their pharmacist at the end of treatment.	
Not to donate blood during [product name] therapy and for 1 month* [*for acitretin: 3 years] after discontinuation due to the potential risk to the foetus of a pregnant transfusion recipient.	

2. SODIUM VALPROATE

2.1 Patient Card

PATIENT CARD

Muka Hadapan Kad

Patient Card for Sodium valproate [Product Name]: Contraception and Pregnancy

What You Must Know

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

Note:

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

Muka Belakang Kad

Patient Card for Sodium valproate [Product Name]: Contraception and Pregnancy

What You Must Do

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

Note:

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

Males (of reproductive potential) using valproate:

- There is a possible risk of movement and mental developmental disorders in children when valproate is taken by male patients in the 3 months before conception.
- Discuss this possible risk and the need for effective contraception with your doctor.
- Valproate is an effective medicine for epilepsy and bipolar disorder.
- Never stop taking valproate unless your doctor tells you to as your condition may become worse.
- If you are planning for a child, do not stop using valproate and contraception before you speak to your doctor.
- Ask your doctor for the patient guide.

2.2 Annual Risk Acknowledgement Form

ANNUAL RISK ACKNOWLEDGEMENT FORM

PART A. TO BE COMPLETED AND SIGNED BY THE PRESCRIBER

Patient Name : _____

MRN / IC No. : _____

Address : _____

For girls and women of childbearing age treated with sodium valproate <Product Name>

Read, complete and sign this form during a visit with the prescriber: at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant.

Name of patient or care-giver: _____

I confirm that the above-named patient needs sodium valproate because:

- ☐ this patient does not respond adequately to other treatments or
- ☐ this patient does not tolerate other treatments
- ☐ that this patient is already stable on dose and she is reluctant to change to other medication.
- ☐ Other reason (to specify)

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

- ☐ The overall risk to fetus and children whose mothers are exposed to sodium valproate during pregnancy are:
- an approximately 10% chance of birth defects and
 - up to 30 to 40% chance of a wide range of early developmental problems that can lead to learning difficulties.
- ☐ Sodium valproate should not be used during pregnancy (except in rare situations for epileptic patients that are resistant or intolerant to other treatments)
- ☐ The need for regular (at least annually) review and the need to continue sodium valproate treatment by the prescriber.
- ☐ The need for negative pregnancy test at treatment initiation and as required thereafter (if child bearing age).
- ☐ The need for an effective contraception without interruption during the entire duration of treatment with sodium valproate (if childbearing age).
- ☐ The need to arrange an appointment with her doctor as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.
- ☐ The need to contact her doctor immediately for an urgent review of the treatment in case of suspected or inadvertent pregnancy.
- ☐ In case of pregnancy, I confirm that this pregnant patient:
- received the lowest possible effective dose of sodium valproate to minimise the possible harmful effect on the unborn
 - is informed about the possibilities of pregnancy support or counselling and appropriate monitoring of her baby if she is pregnant.

Name of Prescriber: _____ Signature: _____ Date: _____

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

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

Patient name : _____

MRN / ICNo. : _____

Address : _____

For girls and women of childbearing age treated with sodium valproate <Product Name>

Read, complete and sign this form during a visit with the prescriber: at treatment initiation, at the annual visit, and when a woman plans a pregnancy or is pregnant.

I have discussed the following with my doctor and understand:

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

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

Name of Prescriber : _____ Signature: _____ Date: _____

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

Part B - to be given to patient

- a copy to be kept by the prescriber

Annual Risk Acknowledgment Form for male patients of reproductive potential treated with valproate (*Product Name*)

Read, complete and sign this form during a visit with the specialist: at treatment initiation and at the annual visit. This is to make sure that after discussion with their specialist, male patients or their caregiver acknowledged the potential risk and understood the precautions associated with valproate use.

Part A. To be completed and signed by the Specialist

Name of patient or caregiver: _____

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

The potential risk of neurodevelopmental disorders (NDDs) in children born to males treated with valproate in the 3 months prior to conception:	☐
- A retrospective observational study on electronic medical records in 3 European Nordic countries indicates an increased risk of neuro-developmental disorders (NDDs) in children (from 0 to 11 years old) born to men treated with valproate in the 3 months prior to conception, compared to those treated with lamotrigine or levetiracetam. - The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy group. The pooled adjusted hazard ratio (HR) for NDDs overall obtained from the meta-analysis of the datasets was 1.50 (95% CI: 1.09-2.07). - Due to study limitations, it is not possible to determine which of the studied NDDs subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs. - The risk to children born to men stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known.	
The need for regular (at least annual) review of the treatment and consideration of alternative therapeutic options.	☐
The need for effective contraception, including for the female partner, while using valproate and for 3 months after stopping the treatment.	☐
That the patient should not donate sperm during treatment and for 3 months after stopping the treatment.	☐
The need for patient to consult his doctor to discuss alternative treatment options as soon as he is planning to father a child, and before discontinuing contraception.	☐
The need for patient and his female partner to contact their doctor for counselling in case a child was conceived while he used valproate within 3 months prior to conception.	☐
That the patient should not stop taking valproate without talking to their doctor, as the epilepsy or bipolar disorder could become worse.	☐
I have given the patient or caregiver a copy of the patient guide.	☐

Name of Specialist

Signature

Date

Annual Risk Acknowledgment Form for male patients of reproductive potential treated with valproate (*Product Name*)

Read, complete and sign this form during a visit with your specialist: at treatment initiation and at the annual visit. This is to make sure that after discussion with your specialist, you or your caregiver acknowledged the potential risk and understood the precautions associated with valproate use.

Part B. To be completed and signed by the Patient or caregiver.

That I should visit a specialist regularly (at least annually) to review whether valproate treatment remains the best option for me	☐
The potential risk of taking valproate in male patients when planning to have a child: - A study suggests that if I take valproate in the 3 months prior to conception, my child may have a higher risk for impaired mental and/or motor development compared to children born to males who used lamotrigine or levetiracetam, other medicines that can be used to treat my disease. - In this study, around 5 children in 100 had such disorders when born from male patients treated with valproate, and around 3 children in 100 from male treated with the other medicines. - There are no data on this potential risk to children of male patients conceived more than 3 months after stopping valproate treatment (the time needed for new sperm to be formed).	☐
That I and my female partner should use effective contraception (birth control) while I am treated with valproate and for 3 months after stopping treatment.	☐
That I need to consult my doctor to discuss alternative treatment options, as soon as I plan for a child, and before discontinuing contraception (birth control).	☐
That I should not donate sperm during treatment with valproate and for 3 months after stopping treatment.	☐
The need for both me and my female partner to contact the doctor for counselling in case we conceived a child while I was using valproate in the 3 months prior to conception.	☐
That I should not stop my treatment without talking to my doctor. If I stop my treatment, my symptoms may become worse.	☐
I have received a copy of the patient guide	☐

Name of patient or caregiver

Signature

Date

2.3 Guide for Healthcare Professionals

GUIDE FOR HEALTHCARE PROFESSIONALS

RISK OF CONGENITAL MALFORMATIONS AND NEURODEVELOPMENTAL DISORDERS FOLLOWING USE OF SODIUM VALPROATE

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

BACKGROUND INFORMATION: SAFETY DATA

1. Congenital Malformations

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

The most common types of malformations include neural tube defects, facial dysmorphism, cleft lip and palate, craniostenosis, cardiac, renal and urogenital defects, limb defects (including bilateral aplasia of the radius), and multiple anomalies involving various body system.

2. Developmental Disorders

Exposure to sodium valproate in utero can have adverse effects on mental and physical development of the exposed children. The risk seems to be dose-dependent but a threshold dose below which no risk exists cannot be established based on available data. The exact gestational period of risk for these effects is uncertain and the possibility of a risk regardless of when during the pregnancy exposure occurs cannot be excluded.

Studies³⁻⁶ in preschool children show that up to 30-40% of children with a history of sodium valproate exposure in utero experience delays in their early development such as talking and walking later, lower intellectual abilities, poor language skills (speaking and understanding) and memory problems.

Available data show that children with a history of sodium valproate exposure in utero are at increased risk of autistic spectrum disorder (an approximately three-fold) and childhood autism (an approximately fivefold) compared with the general study population⁶.

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

RECOMMENDATIONS

1. The use of sodium valproate had been restricted in pregnancy as such:
 - In epilepsy
 - sodium valproate is contraindicated unless there is no suitable alternative treatment.
 - In bipolar disorder
 - sodium valproate is contraindicated in pregnancy.
2. The use of sodium valproate in women of childbearing potential is contraindicated unless patient had been assessed and counselled appropriately on the risks associated with sodium valproate.
3. Treatment should only be initiated if other treatments ineffective or not tolerated.
4. Treatment should only be initiated after pregnancy has been excluded (negative pregnancy test).
5. The benefit and risk should be carefully reconsidered at regular treatment reviews. Preferably, sodium valproate should be prescribed as monotherapy and at the lowest effective dose. A prolonged release formulation is preferred to avoid high peak plasma concentrations. The daily dose should be divided into at least two single doses
6. Carry out annual review and ad-hoc treatment review when required. The benefit and risk should be carefully reconsidered during every treatment review.
7. In the case where sodium valproate must be used during pregnancy, prenatal monitoring is recommended to detect any malformations.

COUNSELLING POINT

- advise patient/ caretaker on the risk of congenital malformations and neurodevelopmental disorders associated with sodium valproate. Inform patient also about the risks of untreated seizure or bipolar disorder.
- advise patient to use effective contraception without interruption throughout the entire duration of sodium valproate treatment
- advise patient not to stop treatment abruptly and to urgently contact the doctor when planning for pregnancy or in the case of suspected pregnancy.
- ensure that patient has received educational materials such as patient card and patient guide that has been provided by the supplier of sodium valproate.

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.
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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
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7. Christensen J et al. Prenatal Sodium valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. *JAMA* 2013; 309(16):1696-1703
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GUIDE FOR HEALTHCARE PROFESSIONALS
RISK OF NEURODEVELOPMENTAL DISORDERS (NDDs) FOLLOWING USE OF SODIUM VALPROATE IN MALE PATIENTS OF REPRODUCTIVE POTENTIAL

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

BACKGROUND INFORMATION: SAFETY DATA

A retrospective observational study was conducted using data from multiple registry databases in Denmark, Sweden and Norway to investigate the risk of NDDs in offspring paternally exposed to valproate as monotherapy, compared to lamotrigine or levetiracetam as monotherapy treatment, in the 3 months period prior to conception. The main outcome of interest was NDDs (composite endpoint including autism spectrum disorders, intellectual disability, communication disorders, attention deficit/hyperactivity disorders, movement disorders) in offspring up to 11 years of age. The mean follow-up time of children in the valproate group ranged between 5.0 and 9.2 years compared to 4.8 and 6.6 years for children in the lamotrigine/levetiracetam group.

1. Risk of Neurodevelopmental Disorders (NDDs)

- The meta-analysis of data from the 3 countries resulted in a pooled adjusted hazard ratio (HR) of 1.50 (95% CI: 1.09-2.07) for NDDs in children from males treated with valproate monotherapy in the 3 months prior to conception compared to the composite lamotrigine/levetiracetam monotherapy group.
- The adjusted cumulative risk of NDDs ranged between 4.0% to 5.6% in the valproate group monotherapy versus between 2.3% to 3.2% in the composite lamotrigine/levetiracetam monotherapy group.
- Due to study limitations, it is not possible to determine which of the studied NDD subtypes (autism spectrum disorder, intellectual disability, communication disorder, attention deficit/hyperactivity disorder, movement disorders) contributes to the overall increased risk of NDDs.
- The risk to children born to male patients stopping valproate at least 3 months prior to conception (i.e., allowing a new spermatogenesis without valproate exposure) is not known

Recommendations for valproate use in male patients of reproductive potential

- The use of sodium valproate in male patients is initiated and supervised by a specialist experienced in treatment of epilepsy or bipolar disorder.
- Male patients should be informed about the potential risk of Neurodevelopmental Disorders (NDDs) and the need to consider effective contraception, including for a female partner, while using valproate and for 3 months after stopping the treatment;
- Treatment with valproate in male patients should be regularly reviewed by prescribers to evaluate whether valproate remains the most suitable treatment for the patient.
- For male patients planning to have a child, suitable alternative treatment options should be considered and discussed with the patient. Individual circumstances should be evaluated for each patient. It is recommended that advice from a specialist experienced in the management of epilepsy or bipolar should be sought as appropriate.
- The male patients should be advised to not donate sperm during treatment and for at least 3 months after treatment discontinuation.

COUNSELLING POINT

- advise patient/ caregiver on the risk of neurodevelopmental disorders associated with children from men taking sodium valproate three (3) months prior to conception.
- advise patient and his female partner to use effective contraception without interruption throughout the entire duration of sodium valproate treatment and three (3) months after stopping the drug.
- Inform patient not to donate sperm during treatment and for three (3) months after stopping the treatment
- inform patient also about the risks of untreated seizure or bipolar disorder and advise patient not to stop treatment abruptly.
- ensure that patient/ caregiver acknowledges the potential risk and understands the precautions associated with sodium valproate using the annual risk acknowledgement form for males and receives the patient card and patient guide provided by the product registration holder of sodium valproate.

References

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2. Minutes and answers from the SAG Psychiatry meeting on Valproate- EMA/679681/2017.
3. Cummings *et al.* Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. *Arch Dis Child* 2011;96:643-647.
4. Meador K *et al.* Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. *NEJM* 2009; 360 (16):1597-1605.
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2.4 Guide for Female Patients/ Caregivers

GUIDE FOR FEMALE PATIENTS/ CAREGIVERS

RISK OF BIRTH DEFECT & DEVELOPMENTAL PROBLEM FOLLOWING USE OF SODIUM VALPROATE

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

KEY POINTS:

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

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

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

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

INFORMATION ON THE RISKS TO THE UNBORN CHILD

- Sodium valproate can be harmful to unborn children when taken by a woman during pregnancy.
- Sodium valproate can cause serious birth defects and can affect the way in which the child develops as it grows. Birth defects include spina bifida (where the bones of the spine are not properly developed); facial and skull malformations; heart, kidney, urinary tract and sexual organ malformations; and limb defects.
- Because sodium valproate has been used for many years, we know that in women who take sodium valproate, around 10 babies in every 100 will have birth defects. This compares to 2-3 babies in every 100 born in the general population.
- It is estimated that up to 30-40% of preschool children whose mothers took sodium valproate during pregnancy may have problems with **early childhood development**. Children affected can be slow to walk and talk, intellectually less able than other children, and have difficulty with language and memory. In addition, disorders which affect the way a child communicates and interacts with others, for example autism, are more often diagnosed in children exposed to sodium valproate.

2.5 Guide for Male Patients

GUIDE FOR MALE PATIENTS RISK OF NEURODEVELOPMENTAL DISORDERS (NDDs) FOLLOWING USE OF SODIUM VALPROATE IN MALE PATIENTS OF REPRODUCTIVE POTENTIAL

This guide contains key information about the potential risk of sodium valproate when used by male patients of reproductive potential in the three (3) months before conception of a child.

Ask your doctor or pharmacist if you have any questions.

INFORMATION ABOUT THE RISK:

A study suggests a possible risk of movement and mental developmental disorders (problems with early childhood development) in children born to males treated with valproate in the 3 months before conception. In this study, around 5 children in every 100 had such disorders when born to males treated with valproate, as compared to around 3 children in every 100 when born to males treated with lamotrigine or levetiracetam (other medicines that can be used to treat your disease).

However, the study has limitations and therefore it is not entirely clear if the increased risk for movement and mental developmental disorders suggested by this study is caused by valproate. A wide range of movement and mental developmental disorders were investigated in the study. However, the study was not large enough to show which particular type of disorder children may be at risk of developing. For example, problems with your child's movement and mental development as they grow up may include :

- Movement problems
- Lower intelligence than other children of the same age
- Poor speech and language skills
- Autism or autistic spectrum problems
- Attention Deficit and/or Hyperactivity Disorder

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

- Use **effective contraception** (birth control) for you and your female partner during valproate use and for three (3) months after stopping valproate (the time needed for new sperm to be formed).
- Consult your doctor when you **are planning to conceive a child** and before stopping contraception.
- Ask your doctor of the possibility of **other treatments** that can be used to treat your disease, depending on your individual situation.
- **Do not donate sperm** when taking valproate and for three (3) months after stopping valproate treatment.
- **Talk to your doctor** if you are planning a child.
- If your **female partner becomes pregnant** while you used valproate in the three (3) months before conception and you have questions, **contact your doctor**.
- **Do not stop your treatment** without talking to your doctor. If you stop your treatment, your symptoms may become worse.
- Follow your **regular appointments** with your prescriber.
- Discuss with your doctor if you have any concerns and report any side effects.