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 **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) • *NPRA website*

1. ORAL RETINOIDS 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

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

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.

Studies[3-6] 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 population[6].

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.
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. Bromley RL, Mawer G, Love J, Kelly J, Purdy L, McEwan L et al. Early cognitive development in children born to women with epilepsy: a prospective report. Epilepsia 2010 October; 51(10):2058-65.
4. Cummings et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child 2011;96: 643-647
5. Meador K et al. Cognitive Function at 3 years of age after fetal exposure to antiepileptic drugs. NEJM 2009; 360 (16): 1597- 1605
6. Thomas S.V et al. Motor and mental development of infants exposed to antiepileptic drugs in utero. Epilepsy and Behaviour 2008 (13):229-236
7. Christensen J et al. Prenatal Sodium valproate Exposure and Risk of Autism Spectrum Disorders and Childhood Autism. JAMA 2013; 309(16):1696-1703
8. Cohen M.J et al. Fetal Antiepileptic Drug Exposure: Motor, Adaptive and Emotional/Behavioural Functioning at age 3 years.Epilepsy Behav. 2011; 22(2):240-246

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 of 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.