**PHARMACY AND POISONS BOARD**
**HONG KONG**
**香港藥劑業及毒藥管理局**

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**貴處檔號**

***Our Ref.*** **:** DH DO PRIE/1-55/1
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23rd October 2025

To: Certificate holders of registered pharmaceutical products

Dear Sir/Madam,

## New Warnings for Valproate Medicines

The Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances) Committee (the Committee) under the Pharmacy and Poisons Board has recently reviewed and considered the latest warnings regarding the risk of neurodevelopmental disorders in children of fathers treated with valproate, the risk of impaired fertility in males, and the risk of lower weight at birth for the gestational age from in utero exposure issued by the drug regulatory authorities of Australia, the European Union, Singapore and the United Kingdom, as well as the related safety labelling information as approved by the drug regulatory authorities of Canada and the United States, and decided that the sales pack labels and / or package inserts of registered pharmaceutical products containing valproate medicines (including **valproic acid, sodium valproate, valproate pivoxil, valproate semisodium, valpromide, etc.**) shall include the following new safety information (or equivalent [Note 1]) as appropriate:

*"**Special warnings and precautions for use***

***Use in male patients***
*A retrospective observational study suggests an increased risk of neuro-developmental disorders (NDDs) in children born to men treated with valproate in the 3 months prior to*

Note 1 Related safety information with other wording in accordance with reputable references and/or approved package inserts from drug regulatory authorities of reference countries may also be accepted on a case-by-case basis.

*conception compared to those born to men treated with lamotrigine or levetiracetam.*
*As a precautionary measure, prescribers should inform male patients about this potential risk and discuss the need to consider effective contraception, including for a female partner, while using valproate and for at least 3 months after treatment discontinuation. Male patients should not donate sperm during treatment and for at least 3 months after treatment discontinuation.*
*Male patients treated with valproate should be regularly reviewed by their prescriber to evaluate whether valproate remains the most suitable treatment for the patient. For male patients planning to conceive a child, suitable treatment alternatives should be considered and discussed with the male patients. Individual circumstances should be evaluated in each case. It is recommended that advice from a specialist experienced in the management of epilepsy or bipolar disorder should be sought as appropriate.*

***Fertility, pregnancy and lactation***

***Fertility***
*Valproate administration may also impair fertility in men. Fertility dysfunctions are in some cases reversible at least 3 months after treatment discontinuation. Limited numbers of case reports suggest a dose reduction may improve fertility function. However, in some cases, the reversibility of male infertility was unknown.*

***Lower weight at birth for the gestational age from in utero exposure***
*In utero exposure to valproate can lead to a lower weight at birth for the gestational age.*
*In preclinical studies a dose-related fetal weight decrease was demonstrated in animals exposed to valproate in utero compared to unexposed animals.*
*Epidemiological studies have reported a decrease in mean birth weight, and higher risk of being born with a low birth weight (<2500 grams) or small for gestational age (defined as birth weight below the 10th percentile corrected for their gestational age, stratified by gender) for children exposed to valproate in utero in comparison to unexposed or lamotrigine-exposed children.*
*Available data in humans do not allow for a conclusion on a potential dose-related effect.*

***Undesirable effects***

*'Male infertility' is listed as an adverse reaction under 'Reproductive system and breast disorders'."*

You are therefore required to ensure the sales pack labels and / or package inserts of the concerned products registered by your company contain the above safety information to comply with the new requirements.

In addition, the safety information for valproate medicines previously endorsed by the Committee has been reviewed and updated. Please review and ensure the sale pack labels and / or package inserts of registered pharmaceutical products containing valproate medicines contain the updated safety information provided in the Annex (or equivalent [see Note 1 above]).

Please submit application for the change of the registered particular(s) to the Drug Office via the online Pharmaceutical Registration System 2.0 (PRS 2.0) at www.drugoffice.gov.hk/prs2-ext/client_authentication.jsp for approval within 2 months from the date of this letter. Failing to comply with the above requirements may result in de-registration of the products or registration not being renewed by the Committee upon certificate expiry.

For further enquiries on the registration matters of pharmaceutical products, please contact the Drug Office at 3974 4175.

Yours faithfully,

(Y. F. YEUNG)
Secretary,
Pharmacy and Poisons (Registration of Pharmaceutical Products and Substances) Committee

c.c. 7-15/3, Product Files

**Annex**

**Updated safety information endorsed by the Pharmacy and Poisons (Registration of Pharmaceutical Substances) Committee**

(a) For anti-epileptic drugs containing, divalproex, ethosuximide, ethotoin, felbamate, fosphenytoin, gabapentin, lamotrigine, lacosamide, levetiracetam, mephenytoin, methosuximide, oxcarbazepine, phenobarbitone, phenytoin, pregabalin, primidone, rufinamide, stiripentol, tiagabine, topiramate, trimethadione, vigabatrin, valproic acid/ valproate, zonisamide:

(i) The safety information related to the suicidal behavior and ideation (suicidality). Example of wording as follows:

"***Special warnings and precautions for use***

***Suicidal Behavior and Ideation (suicidality)***

*Antiepileptic drugs, including <Product or generic name>, increase the risk of suicidal thoughts or behavior in patients taking these drugs for any indication. Patients treated with any antiepileptic drugs for any indication should be monitored for the emergence or worsening of depression, suicidal thoughts or behavior, and/or any unusual changes in mood or behavior.*"

(b) For all pharmaceutical products containing valproate medicines:

(i) **"*Contraindications***

***Treatment of epilepsy***

- *In pregnancy unless there is no suitable alternative treatment.*
- *In women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled.*

***Treatment of bipolar disorder and prophylaxis of migraine***

- *In pregnancy*
- *In women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled.*"

(ii) "***Posology and method of administration***

***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 is prescribed and dispensed according to the Valproate Pregnancy Prevention Programme.*

***Special warning and precautions for use***

***Pregnancy Prevention Programme***

- *Valproate has a high teratogenic potential and children exposed in utero to valproate have a high risk for congenital malformations and neurodevelopmental disorders.*
- *Conditions of 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 is capable of complying with the need to use effective contraception, without interruption during the entire duration of treatment with valproate.*
- *the patient understands the need for regular (at least annual) review of treatment by a specialist experienced in the management of epilepsy, or bipolar disorders.*
- *the patient understands the need to consult her physician as soon as she is planning pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception, and before contraception is discontinued.*
- *the patient understands the need to urgently consult her physician in case of pregnancy.*
- *the patient has received the patient guide.*

*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.*"

(iii) The safety information related to the increased risks of malformations and impaired cognitive development in children exposed to valproate during pregnancy. Example of wording as follows:
"***Special warning and precautions for use***

***Teratogenicity and Developmental Effects from in utero exposure***
*Pregnancy Exposure Risk related to valproate : In females, both valproate monotherapy and valproate polytherapy including other antiepileptics, are frequently associated with abnormal pregnancy outcomes. Available data show an increased risk of major congenital malformations and neurodevelopmental disorders in both valproate monotherapy and polytherapy compared to the population not exposed to valproate. Valproate was shown to cross the placental barrier both in animal species and in humans.*"

(iv) **Risk minimisation measures on use for valproate medicines in relation to the high teratogenic potential and developmental disorders in women of childbearing potential**
Registered pharmaceutical products containing valproate medicines are required to implement the following risk minimisation measures:

(a) A patient information leaflet in both Chinese and English should be provided, highlighting the teratogenic potential and children exposed in utero to valproate have a high risk for congenital malformations and neurodevelopmental disorders;

(b) A letter to be sent to all doctors to whom the product is supplied, to advise them of the high teratogenic potential and developmental disorders in pregnancy of the product and the precautions associated with the use of the product, and that the product should only be supplied to patients along with the above-mentioned patient information leaflet; and

(c) To provide education materials to healthcare professionals and patients to reinforce the warnings and provide guidance regarding use of valproate in women of childbearing potential and details of the risk minimisation measures in relation to the high teratogenic potential and developmental disorders in pregnancy. A patient guide and patient card should be provided to all women of childbearing potential using valproate.