Direct Healthcare Professional Communication

Oral valproate-containing medicines:

Restriction of indication for male and female patients aged under 55 years;

use revised educational materials

This letter is for **healthcare professionals** involved in the management of patients treated with valproate-containing medicines including general practitioners who provide primary care to these patients

Valproate-containing medicines are sodium valproate [Epilim▼, Convulex▼, Episenta▼, Epival▼]; sodium valproate, valproic acid [Epilim Chrono/Chronosphere▼, Dyzantil▼]; valproate semisodium [Depakote▼, Syonell▼, Belvo▼]

January 2024

Dear Healthcare Professional,

Sanofi, on behalf of the Marketing Authorisation Holders of the valproate-containing medicines named above, in agreement with the Medicines and Healthcare products Regulatory Agency (MHRA), would like to inform you of the following updates to the requirements for oral valproate-containing medicines.

Further to the National Patient Safety Alert issued on 28 November 2023, the purpose of this letter is to notify you of an **important restriction of indication for new male patients and all female patients aged under 55 years, along with updated contraindications, warnings, and measures to prevent valproate exposure during pregnancy, as well as the availability of revised educational materials to support discussions with patients.**

Summary of actions required from healthcare professionals prescribing valproate:

1. Review and implement in your prescribing the **important updates to the indication for new male patients and all female patients aged under 55 years,** along with updated contraindications, warnings, and measures to prevent valproate exposure during pregnancy.
2. At initiation of all patients aged under 55 years and at the next annual review for existing female patients, **use the updated educational materials provided, dated December 2023, to inform patients of the risks and precautions with use** – this must include completion of the:
    - updated Annual Risk Acknowledgement Form for female patients.
    - new Risk Acknowledgement Form for male patients starting valproate.
3. Copies of previous valproate educational materials, dated November 2021 or earlier, should be discarded to prevent inadvertent use.
4. The existing conditions of **prevent - the valproate Pregnancy Prevention Programme must be fulfilled** when prescribing valproate in female patients of childbearing potential.
5. See the **MHRA website** (https://www.gov.uk/government/collections/valproate-safety-measures) for further guidance about the implementation of these measures.

Summary of Updates

Female patients aged under 55 years:

- No new female patients aged under 55 years should be prescribed valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment, and for women of childbearing potential the conditions of **prevent - the valproate Pregnancy Prevention Programme** are fulfilled, by completing the updated Annual Risk Acknowledgement Form for female patients.
- For female patients aged under 55 years currently receiving valproate, at their next annual review two specialists should independently consider and document that there is no other effective or tolerated treatment, and for women of childbearing potential the conditions of **prevent - the valproate Pregnancy Prevention Programme** are fulfilled, by completing the updated Annual Risk Acknowledgement Form for female patients.

New male patients aged under 55 years:

- No new male patients aged under 55 years should be initiated on valproate unless two specialists independently consider and document that there is no other effective or tolerated treatment or the risk of infertility or potential risk of testicular toxicity are not applicable by completing the new Risk Acknowledgement Form for male patients starting valproate.

Updated Contraindications:

In epilepsy:

- valproate is contraindicated in pregnancy **unless two specialists independently consider and document that there is no other effective or tolerated treatment.**
- valproate is contraindicated in women of childbearing potential aged under 55 years, **unless two specialists independently consider and document that there is no other effective or tolerated treatment** and the conditions of **prevent - the valproate Pregnancy Prevention Programme** described in the documents enclosed, are fulfilled.

In bipolar disorder:

- valproate is contraindicated in pregnancy *[Note: there is no change to this contraindication as part of this license update].*
- valproate is contraindicated in women of childbearing potential aged under 55 years, **unless two specialists independently consider and document that there is no other effective or tolerated treatment** and the conditions of **prevent - the valproate Pregnancy Prevention Programme** described in the documents enclosed, are fulfilled.

Background on the Safety Concerns

Valproate Exposure During Pregnancy

As reported by the MHRA in December 2022, data on the use of valproate in England demonstrates continued prescribing of valproate in pregnancy. Children exposed to valproate *in utero* are at high risk for major congenital malformations **(11%)** and neuro-developmental disorders **(up to 30-40%) which may lead to permanent disability.**

Other Important Updates

- The risk of major congenital malformations in children after *in utero* exposure to anti-epileptic drug polytherapy including valproate is higher than that of anti-epileptic drug polytherapy not including valproate.
- When valproate is administered in polytherapy with other anti-epileptic drugs during pregnancy, the risks of neuro-developmental disorders in the offspring were also significantly increased as compared with those in children from the general population or born to untreated women with epilepsy.

- The list of major congenital malformations after *in utero* exposure to valproate has been expanded to include eye malformations, which may affect vision.

For more information, please refer to the Summary of Product Characteristics (SmPC).

Risk of Testicular Toxicity and Infertility in Males

Toxicity studies in animals exposed to valproate have shown testicular degeneration/atrophy, spermatogenesis abnormalities and decrease in testes weight in adult rats. Testicular atrophy and decrease in testes weight have been observed in juvenile animal populations.

The relevance of the toxicological testicular findings in juvenile animals to human testicular development, particularly in the paediatric population, is unknown.

Male infertility has been listed as a possible side effect for many years. However, Section 4.6: Fertility, pregnancy and lactation has been updated to indicate that for some patients the infertility may be reversible when valproate is stopped or the dose of valproate is reduced. However, in some cases, the reversibility of the male infertility is unknown.

Updated Educational Materials

In order to assist Healthcare Professionals and patients to comply with the restriction of indication for new male patients and all female patients aged under 55 years, and with the requirements of **prevent - the valproate Pregnancy Prevention Programme,** revised educational materials have been produced.

Included with this letter are the following materials:

- 1 copy of the **updated** *Guide for Healthcare Professionals* including specialists, general practitioners, pharmacists, and other Healthcare Professionals involved in the care of patients using valproate-containing medicines. **This contains details of the restriction of indication for new male patients and all female patients aged under 55 years, along with the new warnings concerning risk of infertility in males and testicular toxicity data in animals, and prevent - the valproate Pregnancy Prevention Programme.** The updated Guide for Healthcare Professionals should be read carefully.
- 1 copy of the **updated** *valproate Annual Risk Acknowledgement Form for female patients* for the specialist to document that the patient has acknowledged the risks at their annual visit. **This should be signed by two specialists independently as well as by the patient at initiation of treatment and during the next annual treatment review for existing patients. A copy of the form should be saved in their Patient Medical Record.** A copy should be given to the patient and one copy sent to their GP.
- 1 copy of the **NEW** *Risk Acknowledgement Form* ***for male patients*** aged under 55 years *starting valproate* for the specialist to document that the patient has acknowledged the risks when treatment was initiated. **This form should be signed by two specialists independently as well as by the patient. A copy of the form should be saved in their Patient Medical Record.** A copy should be given to the patient and one copy sent to their GP.
- 3 copies of the **updated** *Patient Guide* for Healthcare Professionals to provide a copy to:
  - Male patients aged under 55 years initiating treatment with valproate-containing medicines.
  - Female patients aged under 55 years who are initiating or continuing treatment with valproate-containing medicines.

A *Patient Card* is also available and should be provided to female patients by the pharmacist when dispensing.

Additional hard copies of these materials can be ordered by contacting Sanofi Medical Information on 0800 035 2525 or by emailing uk-medicalinformation@sanofi.com.

Electronic copies are also available from the eMC website (http://www.medicines.org.uk/emc/) linked with entries for valproate-containing medicines.

Patient materials (e.g., Patient Information Leaflet, Patient Guide, Patient Card, Annual Risk Acknowledgement Form for female patients, Risk Acknowledgement Form for male patients starting valproate) can also be found by scanning the QR Code printed on the Patient Information Leaflet.

Please highlight this QR code to your patients.

Copies of previous valproate educational materials, dated November 2021 or earlier, are now obsolete and should be discarded to prevent inadvertent use.

Call for Reporting

Please continue to report suspected adverse drug reactions (ADRs) to the MHRA through the Yellow Card Scheme.

Please report:

- all suspected ADRs that are serious or result in harm. Serious reactions are those that are fatal, life-threatening, disabling or incapacitating, those that cause a congenital abnormality or result in hospitalisation, and those that are considered medically significant for any other reason
- all suspected ADRs associated with new drugs and vaccines identified by the black triangle▼

You can report via:

- the Yellow Card website (https://yellowcard.mhra.gov.uk)
- the free Yellow Card app available from the Apple App Store or Google Play Store
- some clinical IT systems (EMIS/SystmOne/Vision/MiDatabank) for healthcare professionals

Alternatively, you can report a suspected side effect to the Yellow Card scheme by calling 0800 731 6789 for free, Monday to Friday between 9am and 5pm.

When reporting please provide as much information as possible, including information about medical history, any concomitant medication, onset, treatment dates, and product brand name.

- Valproate▼ is subject to additional monitoring. This will allow quick identification of new safety information.
- Please report ANY suspected adverse drug reactions (ADRs) to new drugs and vaccines identified by the black triangle▼ to the MHRA through the Yellow Card Scheme.

Yours faithfully

Deborah Woods

Sanofi UK and Ireland Head of Medical, General Medicines

This letter is sent on behalf of the Marketing Authorisation Holders of the valproate-containing medicines named above.