EMA recommends the implementation of new measures to reduce valproate exposure during pregnancy

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Information on Valproate containing medicines

- Valproate containing medicines are approved throughout Europe to treat epilepsy, bipolar disorder and in some countries (but not in Malta) for prevention of migraine
- The active ingredient in these medicines may be valproic acid, magnesium valproate, sodium valproate, valproate semisodium or valpromide.

In Malta the following products are authorised through national licensing procedures

Active Ingredients	Product Name	Pharmaceutical Form	Classif-cation	Authorisation Number	MAH/license holder
Valproate sodium 400 mg	Epilim Intravenous	Powder and solvent for solution for infusion or injection	POM	MA082/04303	Sanofi Malta Limited
Valproate sodium 200 mg/5 ml	Epilim Liquid, 200mg/5ml, liquid	Oral solution	POM	MA082/04311	Sanofi Malta Limited
Valproate sodium 200 mg	Epilim Chrono 200 Controlled Release	Prolonged-release tablet	POM	MA082/04301	Sanofi Malta Limited
Valproate sodium 500 mg	Epilim Chrono 500 Controlled Release	Prolonged-release tablet	POM	MA082/04302	Sanofi Malta Limited
Valproate sodium 300 mg	Epilim Chrono 300 Controlled Release	Prolonged-release tablet	POM	MA082/04310	Sanofi Malta Limited
Valproate sodium 200 mg	Epilim 200 Gastro-resistant Tablets	Gastro-resistant tablet	POM	AA082/04313	Sanofi Malta Limited
Valproate sodium 500 mg	Epilim 500 Gastro-resistant Tablets	Gastro-resistant tablet	POM	AA082/04312	Sanofi Malta Limited

Active Ingredients	Product Name	Pharmaceutical Form	Classif-cation	Authorisation Number	MAH/license holder
Valproate sodium 100 mg	Epilim 100mg Crushable Tablets	Tablet	POM	AA565/25201	Central Procurement & Supplies Unit
Valproate sodium 100 mg/ml	Sodium Valproate (400mg/4ml) Solution for Inj/Inf 100mg/ml	Solution for infusion or injection	POM	MA154/10201	Wockhardt UK Limited
Valproate sodium 100 mg	Sodium Valproate (1000mg/10ml) Solution for Inj/Inf 100mg/ml	Solution for infusion or injection	POM	MA154/10202	Wockhardt UK Limited

Information from the EMA about the new restrictions and the pregnancy prevention programme to avoid valproate exposure in pregnant women

The Coordination Group for Mutual Recognition and Decentralised Procedures – Human (CMDh) at the European Medicines Agency (EMA) has endorsed new measures to avoid exposure of unborn babies to valproate containing medicines in the womb. Exposed babies are at high risk of malformations and developmental problems. The new measures endorsed by CMDh, strengthen previous restrictions on valproate use and requirements to inform women of the risk. The new measures are:

- Valproate-containing medicines must not be used in any woman or girl able to have children unless the conditions of a new pregnancy prevention programme are met
- The use of valproate-containing medicines approved to treat bipolar disorder will be banned during pregnancy
- Valproate-containing medicines are also banned on treating epilepsy during pregnancy unless there is no other effective treatment available
- A visual warning of the pregnancy risks must also be placed on the packaging of the medicines and warnings will be included on patient cards. Patient card will now be attached to the box and supplied with the medicine each time it is dispensed.
- Companies marketing these medicines are also required to carry out additional studies on the nature and extent of the risks and to monitor valproate use and the long-term effects from affected pregnancies.

Because the CMDh position was agreed by majority vote, the decision will now be sent to the European Commission, which will take a final legally binding decision valid across the EU in due course.

In Malta

Advice for patients and healthcare professionals

- Medicines containing valproate are known to cause malformations in the baby and developmental disorders after birth if taken in pregnancy.
- Although steps had been taken previously to better inform women about these risks and discourage use of valproate in girls and women unless there was no alternative, the evidence shows that this information is still not getting to patients.
- Valproate medicines are now therefore contraindicated, i.e. must not be used, in girls and women able to have children unless the terms of a special **pregnancy prevention programme** are followed. These include: −
    - an *assessment* of each patient's potential for becoming pregnant,
    - *pregnancy tests* before starting and during treatment as needed,
    - *counselling* about the risks of valproate treatment and the need for *effective contraception* throughout treatment,
    - a *review of ongoing treatment* by a specialist at least annually,
    - introduction of a new *risk acknowledgement form* that patients and prescribers will go through at each such annual review to confirm that appropriate advice has been given and understood.
- As before, valproate treatment should not be started unless alternative treatments are not suitable. This also applies to young girls below the age of puberty.
- In **pregnancy**, valproate is contraindicated and an alternative treatment should be decided on, with appropriate specialist consultation, for women planning pregnancy; however, there may be a small number of women with epilepsy for whom there is no suitable alternative treatment to valproate and who should be appropriately supported and counselled.
- There will be changes to the **product information** (package leaflet for patients and SmPC for healthcare professionals) to reflect these new conditions and to the packaging of the medicine, including a **visual warning** in the form of boxed text which may be accompanied by other elements such as a symbol.
- **Educational materials** in the form of guides for patients and doctors will also be updated to reflect the current situation and provide age-appropriate advice. In addition, there will be a **patient alert card** attached to the packaging so that pharmacists can go through it with the patient when the medicine is dispensed.
- It is important that patients discuss any concerns about their medication with an appropriate healthcare professional. **Women and girls who have been prescribed valproate should not stop taking their medicine without consulting their doctor as doing so could result in harm to themselves or to an unborn child.**

- Healthcare professionals will receive further information, including a DHPC letter in due course as the recommendations are implemented. Archived DHPCs can be found on the Medicines Authority website on http://www.medicinesauthority.gov.mt/dhpc

For more information, please refer to the European Medicines Agency's webpage on valproate and related substances.

Reporting Adverse Drug Reactions

Healthcare professionals and patients are encouraged to maintain vigilance on valproate containing medicines. Suspected Adverse Drug Reactions (side effects) may be reported using the Medicines Authority Form (available from http://www.medicinesauthority.gov.mt/adrportal) and sent by mail to Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000 or email to postlicensing.medicinesauthority@gov.mt or to the marketing authorisation holders or their local representatives.

Post-Licensing Directorate
Medicines Authority

Healthcare professionals and patients are encouraged to regularly check the Medicines Authority website for product safety updates as these are issued on an ongoing basis.

Feedback Form

The Medicines Authority thanks you for the time taken to read this safety circular. The dissemination of safety circulars is an important process whereby Regulatory Authorities can communicate important issues with respect to the safety of medicines, in order to protect and enhance public health

The Medicines Authority kindly invites your anonymous feedback about the regulatory action being communicated. This may be returned by folding this formt (address side up), stapling the ends and then posting (no stamp required)

Feedback:

We thank you for your interest and look forward to hearing your opinion.

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Pharmacovigilance Section

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