

## **Decision in case 107/2020/EWM regarding risk minimisation measures, related to pregnancy, set out by the European Medicines Agency for a medicine for treating epilepsy and bipolar disorder**

Decision

**Case 107/2020/EWM - Opened on 16/04/2020 - Decision on 20/08/2020 - Institution concerned** European Medicines Agency ( No maladministration found ) |

The case concerned risk minimisation measures, related to pregnancy, that were set out by the European Medicines Agency (EMA) for valproate, a medicine used for treating epilepsy and bipolar disorder. These measures include a so-called 'pregnancy prevention programme', which aims to prevent the use of valproate during pregnancy, due to the risks for the foetus and children of those who become pregnant while taking valproate. The complainant considered the wording 'pregnancy prevention programme' and the terminology used in this programme to be offensive and inappropriate.

EMA adopted the updated risk minimisation measures in 2018, in response to growing concerns about the risks associated with valproate and the failure of measures enacted following a 2013/2014 review by the agency sufficiently to alert relevant healthcare professionals and their patients to the risks attached to taking the medicine in pregnancy,

The widely used medicine, which first came on the market in 1962, has been found to cause malformations in a significant number of foetuses and, in further cases, development problems for children in later life. Despite growing evidence of such risk from the very early days of its usage the medicine continued to be prescribed to women. Some became pregnant while taking valproate, with at times devastating consequences. In 2014, EMA recommended strengthened warnings on the use by women and girls of medicines containing valproate. However, evidence of the medicine being prescribed to women who became pregnant continued, leading EMA to adopt the new risk minimisation measures in 2018.

The Ombudsman acknowledges that, for those who wish to have children, it is a considerable source of distress that medicines they need may pose serious risks to a foetus. She is also mindful of trauma caused to women who became pregnant while taking valproate, and who did not feel sufficiently informed about the risks. The subsequent effects both on them and on their families cannot be underestimated. The Ombudsman considered, however, that EMA has clearly and appropriately explained why it considers the terminology used in the new risk minimisation measures to be proportionate. As such, the Ombudsman concluded that there was



no maladministration by EMA. She has however – in the context of EMA's work in reducing risk - suggested that EMA might further reflect on the serious concerns around the reported failures of General Practitioners in communicating the agency's multiple warnings about valproate to their patients, and counselling appropriately. This matter falls outside of the Ombudsman's mandate, but in this regard, the July 2020 UK Independent Medicines and Medical Devices Safety Review contains much that may be relevant. Trust in medical providers is critical in healthcare and the burden of making fully informed choices about medical treatment cannot be left to the patients alone.

## Background to the complaint

1. Medicines containing valproate are used to treat epilepsy and bipolar disorder, and in some EU Member States, migraine. These medicines first came on the market in 1962 and are widely used. However, over the years, there has been growing evidence of the risks posed by using valproate during pregnancy.

2. If a patient takes valproate during pregnancy, there is a risk that it will cause physical and mental malformations in the foetus and developmental problems as the child grows. [\[1\] \[Link\]](#)

3. In 2014, in response to mounting evidence of the risks associated with valproate, the European Medicines Agency (EMA) recommended strengthened warnings on the use by women and girls of medicines containing valproate. [\[2\] \[Link\]](#) In 2017, the French medicines regulator asked EMA to launch a formal review into how effective those recommendations had been, and to see if more could or should be done to prevent or minimise harm. [\[3\] \[Link\]](#)

4. As part of this review procedure, EMA's Pharmacovigilance Risk Assessment Committee (PRAC) carried out an expert consultation and sought input from stakeholders, which included the first-ever public hearing organised by the PRAC. The feedback was strongly in favour of much stricter risk minimisation measures than those that had previously been adopted.

5. EMA ultimately adopted the new risk minimisation measures in 2018. The measures aim to avoid valproate exposure during pregnancy, ensuring that patients are made fully aware of the risks of becoming pregnant whilst taking valproate. They include, in particular, the following restrictions and requirements:

Women able to have children and girls should not start treatment with valproate, unless alternative treatments are not suitable.

Valproate medicines must not be used by girls and women able to have children unless the conditions of a so-called 'pregnancy prevention programme' are followed. These include:

- an assessment of each patient's potential to become 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 once per year; and
- a new 'risk acknowledgement form', which patients and prescribers will go through at each such annual review to confirm that appropriate advice has been given and understood.

**6.** The complainant is a woman of childbearing age who takes valproate for epilepsy. Since the adoption of the new risk minimisation measures, patients like her have to sign up to the pregnancy prevention programme to obtain their medication.

**7.** She complained to EMA about the terminology used in the new risk minimisation measures. Dissatisfied with EMA's response, she turned to the Ombudsman.

## The inquiry

**8.** The Ombudsman opened an inquiry into the terminology used by EMA in the context of the new risk minimisation measures and how EMA dealt with the complaint.

**9.** In the course of the inquiry, the Ombudsman received additional comments from the complainant. She also received the written reply of EMA to the Ombudsman's request for additional observations. The complainant had the opportunity to comment on EMA's written reply.

## Arguments presented to the Ombudsman

**10.** The complainant considers that the term 'pregnancy prevention programme' implies that the programme aims at preventing women from becoming pregnant. According to the complainant, no regulatory body has the right to prevent pregnancy; this is a woman's choice. As such, the term is highly offensive and it is unacceptable for a regulatory body to use.

**11.** The complainant also criticised the provision that, unless they follow a pregnancy prevention programme, valproate must not be used by girls and women able to become pregnant. She argued that a regulatory body should not be able to oblige a patient to use a life-changing medicine only if they comply with this programme. The same applies to requirement to use contraception.

**12.** She further argued that the requirement to sign a risk awareness form on an annual basis is excessive. It should be sufficient for a patient to sign the form once, to record that the patient has understood the risks.

**13.** The complainant clarified that she has no issue with the fact that the risks of valproate for unborn children are being better communicated in the context of EMA's risk mitigation measures. However, she is concerned about the terminology used by EMA.



**14.** Finally, the complainant took issue with how EMA dealt with her complaint. She considered that EMA was dismissive and that its reply merely outlined how the new risk minimisation measures came about, whilst ignoring her request for the terminology to be changed.

**15.** In its reply to the Ombudsman, EMA stated that the new risk minimisation measures are both proportionate and scientifically justified. EMA considered that they were based on scientific evidence of the serious risks that valproate poses to the unborn child and on the need for more effective measures than the ones adopted in 2014. The new measures were based on extensive consultation, including a public hearing involving patient organisations and patient representatives. [\[4\]](#) [\[Link\]](#)

**16.** Concerning the effectiveness of the new risk minimisation measures, EMA noted that there are some independent studies suggesting a positive trend as regards the use of valproate by women of 'childbearing potential'. [\[5\]](#) [\[Link\]](#)

**17.** EMA noted that it has not received any other complaints about the terminology used in the new risk minimisation measures.

**18.** EMA also stated that it provided extensive and detailed responses to the substantive points raised by the complainant. Acknowledging that the matter must be a source of distress for the complainant, EMA considered that it provided its responses to those substantive points in a very short timeframe. In EMA's view, it used courteous, respectful and informative language in all its interactions with the complainant.

## The Ombudsman's assessment

**19.** The European Medicines Agency plays an important role in ensuring that the medicines we take are safe and effective. Part of this role involves identifying and evaluating risks posed by medicines, and ensuring that these risks are communicated effectively to healthcare professionals and patients.

**20.** To be effective, information for patients must be clear. This is particularly important where the risks associated with a medicine may have negative life-changing effects.

**21.** Given the ever-mounting evidence about the risks associated with the use of valproate by pregnant women, and the evidence that women were continuing to become pregnant while taking valproate, it is entirely understandable that EMA recommended strengthened measures in 2014 and again in 2018. Considerable trauma has been caused to the women – and to their families - who became pregnant while taking valproate and who subsequently gave birth to children injured through the effects of valproate while in the womb.

**22.** The Ombudsman does not question the scientific and medical judgement of EMA. If, after full consideration of the matter, EMA draws the scientific and medical conclusion that strengthened warnings and further risk minimisation measures are required, the Ombudsman



will not dispute such a conclusion. At the same time, any public administration should provide explanations for its actions.

**23.** In this case, the Ombudsman finds that EMA has explained to the complainant why it considers the revised terminology in the new risk minimisation measures to be proportionate.

**24.** EMA also explained that the new risk minimisation measures draw directly on the suggestions made by patients and families involved in the consultation. [\[6\]](#) [\[Link\]](#)

**25.** EMA explained to the complainant that “ *patients have a right to appropriate treatment, but what that treatment should be will depend on their circumstances and what is available. Children also have a right to be protected from the harms that might be caused by medication taken by their parents. Faced by conflicting demands, regulators must therefore try to make decisions for the greatest good of the greatest number .* ” This illustrates that EMA has recognised the conflicting interests at stake, and the difficult balancing exercise that it had to carry out.

**26.** The Ombudsman further appreciates the difficulty of communicating clearly to individuals in very different circumstances. Warnings about risks must be clear enough to take into account as far as possible the diverse needs **of all patients** , when it comes to information. This may mean that the information on packaging and on warnings may be more detailed than some patients expect. It is for each doctor to take into account the specific information needs of each patient when prescribing valproate and monitoring its use.

**27.** While the complainant in this case finds the wording used patronising and inappropriate, EMA has convincingly explained that many other individuals felt earlier warnings were inadequate and that it, as a result, saw the need to strengthen them. EMA noted that evidence had emerged indicating that the previous - less strongly-worded - risk minimisation measures for valproate had not been sufficiently effective. Many patients were still not being adequately informed of the risks, and children were exposed to valproate in the womb, sometimes with the most serious life-changing effects. EMA thus considered that stronger risk minimisation measures were needed.

**28.** The Ombudsman understands the great distress that can be caused to those who wish to have children by the fact that medicines they need may pose serious risks for a foetus. The conditions treated by valproate may be lifelong and the implications for women of child bearing age can be devastating. While these risks must be communicated clearly, the communication must be done in a way that is empathetic by recognising the potential gravity of the situation for the woman and the challenging choices she may have to make if, as in some cases, there may not be a suitable alternative to valproate.

**29.** The Ombudsman considers that EMA has shown itself to be sensitive to the potential distress that could be caused by such warnings. It organised a public hearing to listen to the concerns of parents and of those suffering from the side effects of valproate. Furthermore, in its correspondence with the complainant, EMA has communicated in a clear manner, whilst at the



same time being sensitive to her particular situation. It is nonetheless understandable that no communication – no matter how well intentioned – can ever encompass a full understanding of the feelings of those women having to make unthinkable difficult choices around their health and the possibility of having children. It is also understandable that regulatory language - necessarily and appropriately expressed strongly and unambiguously - may have seemed to the complainant as an intrusion on her personal autonomy. Language that is, as EMA describes it, ‘widely used’ and ‘understood by the scientific community’ may resonate differently with lay people. However, EMA has justified its use and clearly explained that – despite the warnings appropriately given - any decision regarding family planning continues to rest solely with the woman and not with a regulator. There was thus no maladministration by EMA.

**30.** While the medical judgement as to the precise level of risk of taking valproate while pregnant, and the precise nature of the warnings that are necessary to mitigate those risks, fall outside the Ombudsman’s mandate, the Ombudsman does note with concern that, according to a report [\[7\] \[Link\]](#) issued over two years after the adoption of the new risk minimisation measures, doctors (in the UK) still prescribe valproate to many women without informing them sufficiently about the significant risks and without offering an alternative treatment. It is of obvious concern that some doctors – the front line of defence against harm for their patients – are either not fully aware of the issues around valproate or have failed adequately to communicate them. This is particularly disturbing given the publicity around the harms caused by the drug over many decades and the regulatory alerts issued at various times about its dangers during pregnancy. The July 2020 UK review puts forward several possible reasons for these failures including ‘alert fatigue’, the difficulty for busy GPs to find time to keep updated on pharmacovigilance issues, and the possibility of conflicts of interest between health professionals and the pharmaceutical industry. This suggests that the actions of individual physicians, who are expected to be clearly better placed than any public body to determine with each individual patient how to assess and communicate the risks involved with valproate, need to be further examined. While these matters fall outside the Ombudsman’s mandate, she is confident that EMA will do whatever it can - within its mandate - to address such matters.

## Conclusion

Based on the inquiry, the Ombudsman closes this case with the following conclusion:

**There was no maladministration by the European Medicines Agency.**

The complainant and the European Medicines Agency will be informed of this decision .

Emily O'Reilly European Ombudsman

Strasbourg, 20/08/2020



[1] [Link] According to the European Medicines Agency in its response to the Ombudsman's request for reply, "[i]t has long been known that, if taken during pregnancy, they can cause malformations of the developing foetus. Over the years, the scientific evidence on the effects of valproate on the foetus have become more and more compelling, and the potential severity of the effects, including effects on the physical, mental and intellectual development of the child, have become better understood." EMA's response is available here:

<https://www.ombudsman.europa.eu/en/correspondence/en/130259> [Link].

[2] [Link]

<https://www.ema.europa.eu/en/documents/referral/valproate-related-substances-article-31-referral-cmdh-agrees-str>  
[Link]

[3] [Link] New evidence indicated that those measures had not been sufficiently effective, women were still not being adequately informed of the risks, and children were exposed in the womb with some suffering dire consequences:

[https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-notification\\_en.pdf](https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-notification_en.pdf)  
[Link]

[4] [Link] As detailed in EMA's response to the Ombudsman.

[5] [Link] See p. 14/15 of EMA's response.

[6] [Link] See the "Summary of the EMA public hearing on valproate in pregnancy –Public hearing held on

26 September 2017", in particular pages 4-5; available at:

[https://www.ema.europa.eu/en/documents/other/summary-ema-public-hearing-valproate-pregnancy\\_en.pdf](https://www.ema.europa.eu/en/documents/other/summary-ema-public-hearing-valproate-pregnancy_en.pdf)  
[Link].

[7] [Link] Please see in this respect the report publishes on 8 July 2020, *First Do No Harm – The report of the Independent Medicines and Medical Devices Safety Review* :

[https://www.immdsreview.org.uk/downloads/IMMDSReview\\_Web.pdf](https://www.immdsreview.org.uk/downloads/IMMDSReview_Web.pdf) [Link].