EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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30 June 2020
EMA/323331/2020

Subject: European Medicines Agency's response in relation to the complaint related to the referral procedure on medicinal products containing valproate and other related substances (EMA/2017/09/PE)

Dear Ms O'Reilly,

We are writing in response to your letter of 16 April 2020, by which you notified us of the complaint of 15 January 2020 from [redacted] (EMEA/H/A-31/1454) against the European Medicines Agency ("*EMA*" or "*Agency*", hereinafter).

The complaint concerns a number of measures that were adopted by the European Commission by virtue of "*Commission Implementing Decision of 31 May 2018 concerning, in the framework of Article 31 of Directive 2001/83/EC of the European Parliament and of the Council, the marketing authorisations of medicinal products for human use containing substances related to "Valproate" (sodium valproate, valproic acid, valproate semisodium, valpromide, valproate magnesium)*" ("*respective Commission Implementing Decision*", hereinafter), which concluded the 2017-18 referral procedure for valproate-containing medicinal products.[1]

In that respect, you asked EMA to provide observations related to the following points:

[1] This referral procedure dealt with medicinal products containing valproate or related substances. For ease of reference, the present document refers to them collectively as "*valproate-containing medicinal products*". Detailed information on the 2017-18 referral procedure is available on the website of EMA at: https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances-0.

- the complainant's allegation that the "Pregnancy Prevention Programme" for valproate-containing medicinal products prevents women from becoming pregnant and the complainant's criticism of the terminology used to describe said programme;

- the complainant's criticism of the statement that "*valproate must not be used in girls and women able to become pregnant unless the terms of a pregnancy prevention programme are followed*";

- the complainant's allegation that "[signing] *an Annual Risk Awareness Form is exaggerated and unnecessary. Signing a Risk Awareness Form once should be enough for records to show that the patient has understood the risks*"; and

- the complainant's criticism of the statement on the need for effective contraception whilst taking valproate.

In addition, you ask for the Agency's position on whether the new methodology and risk-minimisation measures (as they emerged from the 2017-18 referral procedure) have been more effective than the measures previously implemented. Further, you ask whether other persons have expressed concerns in respect of the terminology and procedures used.

In the present response, we would like to set out the position of the Agency regarding the above-mentioned questions. Prior to setting out that position, we would like to provide some background information in relation to the 2017-18 referral procedure.

Last, we will conclude our response with considerations pertinent to the complainant's allegation that EMA did not handle her complaint appropriately.

I. Background to the referral procedure

Valproate and related substances have been licensed as nationally authorised medicines by most EU Member States since the 1960s for the treatment of epilepsy, manic episodes in bipolar disorder, and in some EU Member States, for the prophylaxis of migraine. It 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 has become more and more compelling, and the potential severity of the effects, including effects on the physical, mental and intellectual development of the child, has become better understood. In particular, children exposed to valproate in the womb have a more than 10% risk of malformations and birth defects such as neural tube defects at birth, a 30-40% chance of neuro-developmental issues such as delayed walking and talking, memory problems, difficulty with speech and language and lower intellectual ability, and 3 to 5 times the incidence of autism disorders seen in the general population.

In view of the emerging new data on the effects of valproate on the foetus, the Member States have twice instituted a Union referral procedure before EMA, under Article 31 of Directive 2001/83/EC, on this issue.

Specifically, in October 2013, the UK initiated a referral on valproate-containing medicinal products giving, *inter alia*, the following justification:

> "*In recent years, results of further studies have emerged which have improved our understanding and allow us to better characterise the risk of the longer term potential neurodevelopmental effects following* in utero *exposure to valproate. These studies have highlighted that in some children the effects appears* [sic] *to persist and manifest as a range of neurodevelopmental abnormalities and autism spectrum disorder. These emerging data suggest that the risk of neurodevelopmental delay and autism spectrum disorder may be independent of maternal confounders*".[2]

Following the assessment and the recommendations by the EMA's Pharmacovigilance Risk Assessment Committee ("*PRAC*", hereinafter) that referral procedure was concluded by the "Co-ordination group for Mutual recognition and Decentralised procedures – human" ("*CMDh*", hereinafter) adopting, by consensus, a position advising doctors in the EU

> "*not to prescribe valproate for epilepsy or bipolar disorder in pregnant women, in women who can become pregnant or in girls unless other treatments are ineffective or not tolerated. Those for whom valproate is the only option for epilepsy or bipolar disorder should be advised on the use of effective contraception and treatment should be started and supervised by a doctor experienced in treating these conditions. Women and girls who have been prescribed valproate should not stop taking their medicines without consulting their doctor as doing so could result in harm to themselves or to an unborn child*".[3]

In addition, other risk minimisation measures were recommended to inform patients and healthcare professionals of the new risk, including an acknowledgement form to be given to the patient.

However, after the implementation of the risk minimisation measures recommended in the 2013-14 referral, new evidence emerged indicating that those measures had not been sufficiently effective,

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[2] Notification by the UK of 7 October 2013 of a referral under Article 31 of Directive 2001/83/EC for valproate-containing medicinal products; available at: https://www.ema.europa.eu/en/documents/referral/valproate-related-substances-article-31-referral-notification_en.pdf.

[3] In this respect, see: Notice on the website of EMA titled "CMDh agrees to strengthen warnings on the use of valproate medicines in women and girls Women to be better informed of risks of valproate use in pregnancy and need for contraception"; available at: https://www.ema.europa.eu/en/documents/referral/valproate-related-substances-article-31-referral-cmdh-agrees-strengthen-warnings-use-valproate_en.pdf.
Detailed information on the 2013-14 referral procedure is available on the website of EMA at: https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances.

women were still not being adequately informed of the risks, and children were exposed in the womb and suffering the dire consequences.[4]

Accordingly, the 2017-18 referral procedure was initiated to assess specifically the effectiveness of these risk minimisation measures. For the purpose of this review and in addition to the diverse expert consultations, PRAC held its first-ever **public hearing**, consulting a significant number of stakeholders. EMA chose to carry out this public hearing for valproate-containing medicinal products in order to ensure that all relevant information from patients and women's health representatives, children affected by exposure while in the womb, healthcare professionals involved in prescribing the medicines, experts in family planning (gynaecologists, midwives) as well as representatives of the pharmaceutical industry, would be duly assessed. As detailed in the respective scientific assessment:

> "*A wide consultation was done on the request of PRAC to gather all the latest information in terms of scientific and clinical knowledge with the consultation of two scientific groups (neurology and psychiatry), and to collect information from* ***healthcare professionals****,* ***female patients themselves as well their families****, from* ***patient organisations*** *(public hearing, stakeholders meeting) who* ***are advocating to better characterise and increase the awareness on the risk of harm to the foetus when using valproate during pregnancy****.* ***From these consultations it was evident that*** *the specialists are aware of the risks discussed, but* ***the information is not adequately reaching the patients timely and effectively****. In addition to the measures to increase awareness about risks of valproate, the different expert consultations provided* ***clear recommendations to restrict the use of valproate****.*
>
> *They also provided experience from clinical practice on the management of women* [with epilepsy] *who wish to become pregnant or are pregnant. In particular,* ***experience from HCPs regarding the discontinuation of valproate or switch to other treatment was provided***" (emphasis added).[5]

The feedback in the report submitted to EMA by all stakeholders mentioned above (mostly female patients) favoured strongly the imposition of (much) stricter risk minimisation measures than those that had been adopted in the context of the 2013-14 referral, in view of the seriousness of the risk of harm to the foetus, the limited information provided to patients despite the measures put in place after the previous (2013-2014) referral, and the strong wish of the patients and patient organisations to put in place measures that would ensure the provision of all information to the patients at different times in their life.[6]

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[4] See data on the Studies of use of valproate that led to the triggering by France of the referral procedure of Article 31 of Directive 2001/83/EC, see the respective notification 8 March 2017, as published on the website of EMA: https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-notification_en.pdf.

[5] In this respect, see: Annex II to the respective Commission Implementing Decision, page 44; available at: https://ec.europa.eu/health/documents/community-register/2018/20180531140837/anx_140837_en.pdf. A recording of the public hearing is available at: https://www.youtube.com/watch?v=CzeJSzkrygM.

[6] In this respect, see: "Summary of the EMA public hearing on valproate in pregnancy –Public hearing held on 26 September 2017", in particular pages 4-5; available at:

On 8 February 2018, PRAC adopted a recommendation, setting out a number of stricter risk minimisation measures, intended to better create awareness at the level of the healthcare professionals (HCPs) and patients about the risks and what measures might further reduce the risk of exposure of the unborn child to valproate-containing medicinal products. Further to the receipt of the PRAC recommendation, the CMDh adopted, on 21 March 2018, its position in respect of this referral procedure. Last, on 31 May 2018, the respective Commission Implementing Decision was adopted, concluding the 2017-18 referral.

II. Preliminary remarks

Before setting out its considerations in respect of the questions asked, EMA would like to put forward, for ease of reference and for the purpose of completeness, a number of preliminary remarks related to the **intent of pregnancy prevention programmes** and the **nature of the allegations against EMA**.

a. Pregnancy prevention programmes (PPP)

In respect of pregnancy prevention programmes (PPP),[7] EMA would like to clarify that PPPs are well established and effective regulatory tools, not unique to valproate-containing medicinal products in the EU. On the contrary, PPPs were introduced for several medicines inducing risk of harm for the foetus. This set of measures was for instance put in place for the use of thalidomide in patients with certain cancers in order to avoid the occurrence of extensive and severe malformations that were observed with its use in the 1960s. Such programmes have also been implemented since 1988 for Roaccutane (isotretinoin, a retinoid) to avoid pregnancies in women taking oral isotretinoin, as reflected in the product information worldwide. In 2018 the PRAC reinforced this pregnancy prevention programme in all retinoid-containing medicinal products for oral use, following an extensive referral review.[8]

Helpful guidance in respect of PPPs can be found in the "Guideline on good pharmacovigilance practices; Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2)", wherein the term PPP is defined as:

> "*a set of interventions aimed at* ***minimising pregnancy exposure during treatment with a medicinal product with known or potential teratogenic effects****. The scope of such a programme is to ensure that female patients are not pregnant when starting therapy and do not become pregnant during the course of and/or soon after stopping the therapy. It could also*

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https://www.ema.europa.eu/en/documents/other/summary-ema-public-hearing-valproate-pregnancy_en.pdf.

[7] In the present document, the term "PPP"/"PPPs" and the term "pregnancy prevention programme" in lowercase will be used when reference is made to pregnancy prevention programme(s) in general. The term "Pregnancy Prevention Programme" with capitalisation will be used when reference is made to the specific programme that was put in place for valproate-containing medicinal products by virtue of the respective Commission Implementing Decision.

[8] For more information on the PPP for retinoid-containing medicinal products, see: https://www.ema.europa.eu/en/documents/referral/retinoid-article-31-referral-prac-recommends-updating-measures-pregnancy-prevention-during-retinoid_en.pdf.

target male patients when use of a medicinal product by the biological father might have a negative effect on pregnancy outcome. ***A PPP combines the use of educational tools with interventions to control appropriately access to the medicine***" (emphasis added).[9]

Further, and as set out in the (draft) "Guideline on good pharmacovigilance practices; Product- or Population-Specific Considerations III: Pregnant and breastfeeding women",[10]

"*When a medicinal product with known* ***teratogenic effect*** *is intended for use in women of childbearing potential, implementing* ***a pregnancy prevention programme (PPP) may be appropriate****. Scenarios when a PPP may be needed include* ***chronic*** *conditions where treatment may be started long before the patient becomes of child-bearing potential or is considering pregnancy.*

The nature of the PPP will depend on the ***indication****, the* ***duration of use of the medicine****, and* ***whether or not alternatives to the medicine are available*** *(e.g. delaying pregnancy, delaying treatment or using an alternative medication or other kind of treatment)*" (emphasis added).

In view of the above, it is clear that a PPP aims at minimising the exposure of the unborn child to a medicine that would entail severe risks. In order to minimise such exposure, a set of measures are put in place, intended to better inform healthcare professionals and women about those risks and further reduce exposure of unborn children to the teratogenic medicine. These measures also guide women who intend to become pregnant to continue treatment on alternative medication that might be less harmful for the unborn child.

b. Nature of the allegations

EMA would like to note that certain allegations set out in the complaint relate to the scientific evaluation of measures taken to mitigate the risks of valproate-containing medicinal products. In accordance with established "ombudsprudence", the Ombudsman refrains from questioning "*the merits of scientific evaluations carried out by specialised scientific agencies. The Ombudsman's inquiry therefore does not cover the substantive medical and scientific assessment of the safety and efficacy of* [medicinal products]*. Moreover, it is crucial that scientific bodies are allowed to carry out their work in full serenity, free from undue external pressure. This is all the more important as regards the assessment of the safety and efficacy of medicines*".[11]

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[9] In this respect, see: Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2), page 8; available at: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xvi-risk-minimisation-measures-selection-tools_en-3.pdf.

[10] In this respect, see: (in public consultation) Guideline on good pharmacovigilance practices (GVP) – Product- or Population-Specific Considerations III: Pregnant and breastfeeding women, page 20; available at: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-good-pharmacovigilance-practices-product-population-specific-considerations-iii_en.pdf.

[11] For this quote, see: Decision of the European Ombudsman of 3 June 2020 in case 222/2020/EWM on how the European Medicines Agency dealt with the authorisation of the medicine Kalydeco for use by children with a specific form of cystic fibrosis, paragraph 13. In addition, and by direct analogy, see: Decision of the

With that said, EMA would like to take the opportunity to provide information and clarifications in respect of the outcome of the referral procedure that is criticised by the complainant.

III. In respect of the complainant's allegation that the "Pregnancy Prevention Programme" prevents women from becoming pregnant and in respect of the complainant's criticism of the term used to describe said programme

In the complaint, the complainant appears to take issue with the Pregnancy Prevention Programme of valproate-containing medicinal products and with the term used to describe this programme.

EMA would like to explain the reasons for which it does not consider the term "pregnancy prevention programme" to be offensive or dictatorial.

As already noted in **IIa** above, the general aim of a PPP is to minimise exposure of the unborn child to a medicine that carries severe risks by avoiding pregnancy whilst under treatment. Regardless of the above, any decision for family planning remains with the woman. In respect of the specific aim of the programme for valproate, it bears recalling that the Pregnancy Prevention Programme states regarding pregnancy planning

> "*Pregnancy planning*
>
> *For the indication epilepsy, if a woman is planning to become pregnant, a specialist experienced in the management of epilepsy, must reassess valproate therapy and consider alternative treatment options. Every effort should be made to switch to appropriate alternative treatment prior to conception, and before contraception is discontinued (see section 4.6). If switching is not possible, the woman should receive* ***further counselling regarding the valproate risks for the unborn child to support her informed decision making regarding family planning***" (emphasis added).[12]

The Pregnancy Prevention Programme for valproate-containing medicines clearly sets out to achieve its aims by ensuring that women of childbearing potential use effective contraception and at the same time are well informed of the risks of taking valproate during pregnancy for the unborn child, including through a discussion with their treating physician of the availability of alternative treatments that would not pose such severe risks to an unborn child. Thus, the Pregnancy Prevention Programme allows for women who intend to be pregnant to consult their physician as soon as they plan a pregnancy to ensure timely discussion and switching to alternative treatment options prior to conception and before contraception is discontinued.

European Ombudsman of 3 April 2014 closing the inquiry into complaint 857/2012/(ER)PMC against the Research Executive Agency, paragraph 7.

[12] In this respect, see: Annex III to the respective Commission Implementing Decision, page 54; available at: https://ec.europa.eu/health/documents/community-register/2018/20180531140837/anx_140837_en.pdf.

As explained *supra*, the intent of the Pregnancy Prevention Programme is also to ensure that women are, in any event, fully apprised of the relevant risks of taking valproate-containing medicinal products during pregnancy and that, if they would like to become pregnant, they do so in a manner that minimises the risk of exposure of the unborn child to valproate. The provision of information aims to address, in particular, the evidence which indicated that, despite the measures undertaken in the context of the 2013-14 referral, women were not informed sufficiently and at the right moment in time.[4] This point was also highlighted by patients' associations during the public hearing for valproate-containing products.[13] Therefore, in view of the serious risk for the unborn child and in view of the fact that the measures undertaken in the context of the 2013-14 referral were not sufficient, further measures in the form of a PPP were required.

Turning to the **wording of the term** "Pregnancy Prevention Programme", EMA would like to highlight that this is a well-known and widely used technical term by which such measures are known and understood by the scientific community. This term is also included in the relevant EMA guidance, such as the "Guideline on good pharmacovigilance practices" which underwent public consultation before its publication. EMA is not aware of any previous concerns or objections related to the wording of this term.

IV. In respect of the complainant's criticism of the statement that "*valproate must not be used in girls and women able to become pregnant unless the terms of a pregnancy prevention programme are followed*"

As the 2017-18 referral was initiated in order to establish further measures to ensure the risk-benefit balance of valproate-containing medicinal products remained positive for all treated populations, a number of risk minimisation measures were either newly adopted or further tightened.

The complainant's complaint appears to pertain, in particular, to the part of the respective Commission Implementing Decision that instructed Members States to add the following text in Section 4.3 of the SmPC of valproate-containing medicinal products:

> "***Section 4.3 Contraindications***
> *[…]*
> *Treatment of epilepsy*
>
> - *in pregnancy unless there is no suitable alternative treatment (see section 4.4 and 4.6).*

[13] In this respect, see: Public hearing on valproate – Written interventions (EMA/645752/2017), page 12; available at: https://www.ema.europa.eu/en/documents/other/public-hearing-valproate-written-interventions_en.pdf, wherein it was reported that "*A 2016 survey (Epilepsy Action, Epilepsy Society, Young Epilepsy) of 2,700 women with epilepsy showed that **almost half (48%) of women did not know that taking valproate in pregnancy could harm their unborn baby**. More concerning was that **1 in 5 (20%) women currently taking the drug did not know it can, in a minority of cases, harm the development and physical health of their unborn child should they become pregnant**. Epilepsy Action strongly believes the **current measures are not enough** – women still are not aware of the problems associated with valproate and therefore unborn babies continue to be put at risk of avoidable lifelong difficulties and complications*" (emphasis added).

- *in women of childbearing potential,* ***unless the conditions of the pregnancy prevention programme are fulfilled*** [emphasis added] (see section 4.4 and 4.6)".

As explained in the Guideline on Summary of Product Characteristics, contraindications aim to cover "*Situations where the medicinal product* ***must not be given*** *for safety reasons*" (emphasis added).[14] Almost all medicines will have some contraindications, and some have many. Because these represent situations in which the use of the medicine may be extremely harmful or even fatal, they need to be expressed strongly and unambiguously. For those reasons, the product information of medicines routinely employs peremptory language (such as the use of the term "*must*") in order to warn healthcare professionals and patients, in unequivocal terms, of the situations in which a medicine should not be taken.

In the case of valproate, the PRAC concluded that the minimisation measures for medicinal products containing valproate or related substances should be strengthened through contraindication in all indications (epilepsy, bipolar disorders and prophylaxis of migraine).[15] Introduction of this contraindication and the employment of the corresponding language in the product information aimed at ensuring clear and unambiguous messaging for better adherence of healthcare professionals and patients with the recommended risk minimisation measures.[16]

Similar language is used in Sections 4.4 and 4.6 of the SmPC of valproate-containing medicinal products (titled "Special warnings and precautions for use" and "Fertility, pregnancy and lactation"), to provide optimal information to HCPs and patients.

Further to the above considerations, the use of the verb "*must*" is used in order to ensure that patients and healthcare professionals are apprised of the serious risks that exposure to valproate during pregnancy would entail for an unborn child.

V. In respect of the complainant's allegation that "[signing] an *Annual Risk Awareness Form is exaggerated and unnecessary. Signing a Risk Awareness Form once should be enough for records to show that the patient has understood the risks*"

In the complaint, it is alleged that the requirement for the signing of an Annual Risk Awareness Form is exaggerated and unnecessary and, as further claimed in the complaint, it should supposedly be sufficient that a patient signs the Risk Awareness Form only once (in her lifetime).

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14 In this respect, see: Notice to Applicants, Volume 2C, A Guideline on Summary of Product Characteristics, Section 4.3; available at: https://ec.europa.eu/health//sites/health/files/files/eudralex/vol-2/c/smpc_guideline_rev2_en.pdf).

15 PRAC Assessment report of the Referral procedure. https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-prac-assessment-report_en.pdf

16 In this respect, see: Public hearing on valproate – Written interventions (EMA/645752/2017), page 10; available at: https://www.ema.europa.eu/en/documents/other/public-hearing-valproate-written-interventions_en.pdf, where in it was reported by one stakeholder that "*An audit of Parisian hospitals revealed an edifying observation: Paris* ***doctors are not aware of the new recommendations issued by the EMA****. I quote: "The* ***major lack of information*** *by Paris' Hospital* ***doctors on the new prescription conditions*** *for valproate results from multiple malfunctions at all levels* […]*"* (emphasis added).

This measure was also part of the measures to minimise this risk in the referral in 2014, although it was only stated that the form needed to be given to the patient regularly (not necessarily annually), and its signing was not stipulated. Following several surveys by FACS Forum and other patients organisations, it was found that, by December 2016 (2 years after the introduction of those measures), and **at best**, only 56% of patients questioned were given the new safety information and discussed its content with their treating physician.[17] This was a highly unsatisfactory outcome in view of the level of risk, and it showed that many patients were not informed sufficiently of the risks. In addition, this outcome also indicated that a discussion on this topic between the patient and the healthcare professional did not always take place. It was reported by patients that the form and the patient booklet (which needs to accompany the form) were in some cases sent to patients by post, without any opportunity for face-to-face consultation with the treating physician.

The reasons why annual signing of a Risk Awareness Form for valproate-containing medicinal product is considered by EMA's safety committee (PRAC) as a proportionate risk minimisation measure are the following:

First, it should be borne in mind that the conditions of epilepsy and bipolar disorder, for which valproate-containing medicinal products are indicated, are chronic and may occur at young age. Patients may need to take medicinal products for a substantial part of their lives and may start at different stages of their lives. Some women will start valproate treatment before puberty, long before they are in a position or in any need to consider pregnancy. Those women's personal situation regarding childbearing will change as time goes by and may vary throughout their lives, regardless of age. Therefore, it was deemed necessary to ensure that patients are informed regularly about the risks in line with a personal situation that may also change regularly. Furthermore, it is a measure that not only provides information to patient but also fosters an appropriate discussion between the patient and the treating physician. This measure has been proposed in close cooperation and according to the preferences of the consulted stakeholders.

Second, the medical condition of epilepsy may be associated with impairment of memory or cognitive impairment in some cases. Accordingly, it may be helpful to provide regular reminders of the severe risks. It bears noting that this point was also specifically brought up in the written interventions that were submitted by stakeholders to the Agency in the context of the public hearing.[18]

Third, this risk minimisation measure should be seen against the heightened need to minimise the risks to unborn children. The fact, which was shared by several patient groups, is that the measures taken during the previous referral did not provide sufficient and precise information for women and caretakers to help them take well-informed decisions for what is often a life-long condition, and information should be shared not only once but throughout the long-term treatment.

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17 In this respect, see: Written submission to EMA by the FACS Forum (20 April 2017) (**Attachment 1**).

18 In this respect, see: Public hearing on valproate – Written interventions (EMA/645752/2017), page 10; available at: https://www.ema.europa.eu/en/documents/other/public-hearing-valproate-written-interventions_en.pdf.

Finally, the right to treatment is not impeded by signing a Risk Awareness Form. On the contrary the discussion to be had on alternative medications is explicitly included in the acknowledgment form that PRAC recommended.[19] Should the woman decide that she would like to become pregnant, she will be able to discuss with the treating physician her alternative treatment options which might provide a safer alternative when used during pregnancy.

Further to the above considerations, EMA submits that the Annual Risk Awareness Form is a measure that is suitable and proportionate to the aim it pursues; namely providing information of the severe risks of this medicinal product to an unborn child, and helping the patients prepare for a pregnancy in the best informed way.

VI. In respect of the complainant's criticism of the statement on the need for effective contraception whilst taking valproate

When a PPP is in place, this entails that contraceptive method(s) to minimise the risk for pregnancies are used. In the absence of contraception, such programme would be ineffective to mitigate the risks of exposure of women of childbearing potential to the respective medicinal products.

Guidelines on this may require that patients should have a negative pregnancy test before starting the treatment.[20] The patients may also have to undergo regular pregnancy tests. Regarding contraception while on treatment with known teratogenic products, it is suggested that patients should agree to use effective contraception.[21] Obviously, failure to comply –unintentionally or not– with the instructions relevant to a contraceptive method results in a high risk of pregnancy.

In the case of valproate the PRAC recommended that:

> *"At least one effective method of contraception (preferably a user independent form such as an intra-uterine device or implant) or two complementary forms of contraception including a barrier method should be used"*.[22]

Of note, injectable preparations, implants, intrauterine system or devices may be contraceptive methods to be used which are considered to be independent of the patient's individual compliance.

The above considerations serve to show that contraception forms an inseparable part of any PPP.

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19 In this respect, Annual Risk Awareness Form, as recommended by PRAC in the context of the 2017-18 referral procedure (**Attachment 2**).

20 Kanelleas A, Thornton S, and J. Berth-Jones. Suggestions for effective contraception in isotretinoin therapy. Br J Clin Pharmacol. 2009 Jan; 67(1): 137–138. doi: 10.1111/j.1365-2125.2008.03235.x.

21 Contraception for women using known teratogenic drugs or drugs with potential teratogenic effects (February 2018); available at: https://www.fsrh.org/news/fsrh-ceu-statement-on-contraception-for-women-using-known/.

22 See page 53 of Annex III – product information – https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-annex-iii_en.pdf.

Last, and without prejudice to the above, it bears noting that there may be cases where there is no need for (medical) contraception based on certain life-style choices (e.g. when a patient is not sexually active, or the prescriber considers that there are compelling reasons to indicate that there is no risk of pregnancy). Ultimately the choice of contraception is up to the woman in close discussion with her treating physician. If after such discussion it is concluded that there is no need for contraception, this is a personal well-informed decision which needs to be re-evaluated regularly.

For that reason, the PRAC stipulated in the information regarding contraception that:

> "*Individual circumstances should be evaluated in each case, when choosing the contraception method involving the patient in the discussion, to guarantee her engagement and compliance with the chosen measures*".[22]

VII. Interactions between EMA and the complainant

In the complaint, it is also suggested that EMA did not deal with the complaint in an appropriate manner.[23]

EMA would like to summarise its correspondence with the complainant to show how her complaint was dealt with in an appropriate, professional and courteous manner.

On **11 November 2019**, EMA received the first complaint from the complainant on the matter of the 2017-18 referral procedure. The complainant noted in particular that, following the implementation of the risk minimisation measures of the 2017-18 referral, she had had difficulties obtaining her medication. In addition, the complainant objected to the name of the PPP and the use of the verb "*must/must not*" in reference to the use of contraception, a woman becoming pregnant, and the prescription of the medicine. Further, the complainant noted that she had borne a healthy child in 2018 while receiving valproate, and, in her opinion, measures such as divided doses and the use of folic acid were adequate for this to be done safely.[24]

On **21 November 2019**, EMA responded that the term PPP has been used for teratogenic medicines for some years (thalidomide). In addition, since the term accurately describes the purpose of such programmes, which is to help women taking such medicines avoid becoming pregnant in a manner that would be unsafe for the unborn child, EMA noted that it did not consider the term insulting or inappropriate. Further, it was noted that the risk minimisation measures that were introduced as a result of the 2017-18 referral procedure were strengthened, since the previous measures (as introduced in the context of the 2013-14 referral procedure) had not been sufficiently effective. EMA also emphasised that, in exceptional circumstances, a woman who is aware of the risks to her baby may still decide to get pregnant. In that case, this plan should be discussed with the treating physician

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23 In the complaint, it is specifically stated that: "*The EMA have NOT once addressed what they will do with my complaint, they have simply 'closed it'. This is unacceptable by ANY complaints process*".

24 In this respect, see: **Attachment 3** (containing the complainant's message of 11 November 2019 and EMA's response of 21 November 2019). (ASK-223)

to ensure that the best (tailor-made) medical advice is provided to the patient. Last, EMA noted that the scientific assessment could not conclude that folate supplementation and altered dosage patterns would be enough to prevent harm.[24]

On **10 December 2019**, EMA received a further message from the complainant, wherein the previous objections to the terminology of the PPP and to the use of the verb "*must*" in the SmPC were reiterated. In addition, it was noted in the message that "*it was insulting to require annual signing of a risk awareness form*". Further, the complainant informed EMA that she would be instituting a separate complaint with the NCA of the United Kingdom (namely, with the Medicines and Healthcare products Regulatory Agency). [25]

On **12 December 2019**, EMA responded to the complainant's follow-up message (of 10 December 2019) noting that both the risk minimisation measures of the strong wording in the SmPCs of valproate-containing medicinal products and the annual review were specifically requested by patient groups during the procedure. In addition, EMA highlighted that no one had an absolute right to prevent a woman from becoming pregnant and reiterated that the Pregnancy Prevention Programme did not attempt to do so.[25]

On **12 December 2019**, the complainant responded thanking EMA for the quick response. Still, the complainant noted that, regardless of the source of the recommendations, they remained offensive and she required the terminology to be changed.[26]

Further to a review of the message of 12 December 2019, EMA considered that the new follow-up message did not add anything of substance to the complainant's messages of 11 November 2019 and of 10 December 2019.

On **17 December 2019**, EMA corresponded again with the complainant to reiterate that the previous considerations (as set out in its messages of 21 November 2019 and 10 December 2019) stood, and that, accordingly, EMA had nothing further to add to its previous messages.[26]

On **17 December 2019**, the complainant sent a further message to EMA, noting that she did not consider the matter closed and was not satisfied with the responses to date. She felt that the EMA had not treated the matter as a complaint.[27]

On **15 January 2020**, EMA responded to confirm that the "*[complainant's] points have been handled as a complaint according to [EMA's] procedure (https://www.ema.europa.eu/en/about-us/legal/complaints)*". It was confirmed again that EMA had no additional considerations in response to the points raised by the complainant.

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25 In this respect, see: **Attachment 4** (containing the complainant's message of 10 December 2019 and EMA's response of 12 December 2019). (ASK-65784)

26 In this respect, see: **Attachment 5** (containing the complainant's message of 12 December 2019 and EMA's response of 17 December 2019). (ASK-65849)

27 In this respect, see: **Attachment 6** (containing the complainant's message of 17 December 2019 and EMA's response of 15 January 2020). (ASK-65958)

On **15 January 2020**, the complainant responded noting that she had not been told what action EMA intended to take in response to her complaint and that therefore she was making a complaint to the Ombudsman.[28]

On the **same day**, the complainant sent a supplementary message to further note that "*as a patient,* [she is] *telling the EMA, that* [she refuses] *to sign another Risk Assessment Form or to be 'enrolled' into the insulting Pregnancy Prevention Programme due to this matter as* [she refuses] *to be dictated to*".[29]

EMA did not respond to the two messages of 15 January 2020, as no new information was brought forward in those two messages. In addition, EMA had already addressed all substantive points of the complaint in the complainant's two messages of 11 November 2019 and of 10 December 2019.

Further to the above considerations, EMA considers that it provided extensive and detailed responses to the substantive points raised in the complainant's messages. Acknowledging that the matter at hand must be a source of concern for the complainant, EMA provided its responses to those substantive points in a **very short timeframe**.[30] Further, in all its interactions with the complainant, EMA used courteous, respectful and informative language.

In view of the above, EMA would like to submit respectfully that the allegation that the complaint to EMA was not handled in an appropriate manner is unfounded.

VIII. In respect of the effectiveness of the measures that were adopted in the context of the 2017-18 referral

As part of the outcomes of the 2017-2018 referral procedure, several steps were adopted by PRAC in order to measure the effectiveness of the risk minimisations measures imposed. Among those several "post-authorisation safety studies" (PASS), including a drug utilisation study (DUS) to monitor, among other aspects, whether these strengthened measures indeed have the desired effect of reducing exposure in women of childbearing potential. The collection and analysis of such data takes some time (results are expected to become available from the end of September 2020 to the end of February 2024), and EMA does not yet have enough information to assess the effects.[31] PRAC is being involved in assessing the protocol of these studies, the interim and final study results.

However, while the data from official and commissioned studies is not yet available for analysis by EMA, we are aware of some independent studies suggesting a positive trend in reducing exposure in

[28] In this respect, see: **Attachment 7** (containing the complainant's message of 20 January 2020). (ASK-66531)

[29] In this respect, see: **Attachment 8** (containing the complainant's supplementary message of 20 January 2020). (ASK-66545)

[30] In particular, the complaint of 11 November 2019 was responded to on 21 November 2019, while the complainant's message of 10 December 2019 was responded to on 12 December 2019.

[31] Studies imposed by PRAC as conditions to the MAHs of valproate-containing medicinal products for assessing the effectiveness of the risk minimisation measures (https://www.ema.europa.eu/en/documents/referral/valproate-article-31-referral-annex-iv_en.pdf).

women of childbearing potential.[32] This is an important signal that the strengthened risk minimisation measures appear to be effective in preventing exposure of the unborn child to valproate during pregnancy and therefore avoiding risk of malformations or neuro-developmental disorders for the child.

IX. Concluding remarks

Taking all these into account, **the Agency considers that its recommendations in the context of the 2017-18 referral are both proportionate and scientifically justified**. These recommendations were based on scientific evidence of the seriousness of the risks to the unborn child and on the need for more effective measures than the ones imposed in the 2014 referral procedure, and came after extensive consultation, in writing and in a public hearing, with different patient organisations and representatives. The advantage of this consultation process was that it has allowed the comprehensive inclusion of patients' views in the decision-making procedure for the valproate referral.

Finally, we should also like to note that, while we were unable to agree with the substance of [redacted] complaint, we understand the frustrations that restrictions in the supply of a medicinal product may entail. With that in mind, the Agency staff members have made effort to deal with the merits of her complaint in a courteous, timely and professional way.

We can also confirm that **no other person or patient has expressed any concerns on the terminology used in the most recent measures**.

We hope that the above considerations address all the questions that have been raised in your letter and in the complaint. We remain at your disposal to provide any clarifications and further information that may be needed.

Kind regards,

Prof. Guido Rasi
Executive Director
European Medicines Agency

[32] In this respect, see : French study on use of Antiepileptics including valproate finalised in April 2019 (in French and English) available at: (https://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Antiepileptiques-au-cours-de-la-grossesse-Etat-actuel-des-connaissances-sur-les-risques-de-malformations-et-de-troubles-neuro-developpementaux-Point-d-information). (page 23 of Document in English);

Attachments

Attachment 1: Written submission to EMA by the FACS Forum (20 April 2017)

Attachment 2: Annual Risk Awareness Form, as recommended by PRAC in the context of the 2017-18 referral procedure

Attachment 3: ASK-223 – Correspondence between EMA and the complainant

Attachment 4: ASK-65784 – Correspondence between EMA and the complainant

Attachment 5: ASK-65849 – Correspondence between EMA and the complainant

Attachment 6: ASK-65958 – Correspondence between EMA and the complainant

Attachment 7: ASK-66531 – Correspondence between EMA and the complainant

Attachment 8: ASK-66545 – Correspondence between EMA and the complainant