EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

31 August 2023
EMA/490185/2023
Pharmacovigilance Risk Assessment Committee (PRAC)

PRAC non-interventional imposed PASS final study report assessment report

Active substance: valproate

Procedure no.: EMEA/H/N/PSR/J/0036

Note

Assessment report as adopted by the PRAC and considered by the CMDh with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

In order to fulfil the obligation to submit the results of an imposed non-interventional PASS in accordance with Article 107p of Directive 2001/83/EC, Sanofi-Aventis Recherche & Développement, on behalf of a consortium of MAHs, submitted on 12 August 2021 a post-authorisation safety study (PASS) final study report for valproate to the European Medicines Agency (EMA).

The submission provided the final study report version 1.0 of the surveys among health care professionals (HCP) and patients to assess their knowledge and behaviour with respect to the new (2018) risk minimization measures (RMM) for valproate use in Europe.

Marketing authorization conditions – Post referral EMEA-H-A31-1454:

Article I. Survey among HCP to assess knowledge of HCP and behaviour with regard to PPP as well as receipt/use of DHPC and educational materials

Article II. Survey among patients to assess knowledge of the patients with regards to PPP as well as receipt/use of educational materials.

PASS information

Title	Surveys among health care professionals and patients to assess their knowledge and behaviour with respect to the new (2018) Risk Minimisation Measures for valproate use in Europe
Version identifier of the final study report	Final – Version 1.0
Date of last version of the final study report	28 July 2021
EU PAS register number	EUPAS34465
Active substance	Valproate and related substances: - ATC code: N03AG01 - ATC code: N03AG02
Medicinal product	Valproate and related substances*: - magnesium valproate - sodium valproate - valproic acid - sodium valproate/valproic acid - valproate semisodium - valpromide *All substances will be summarised under the term "valproate"
Product reference	MAH study number VALNAC09348
Procedure number	EMEA/H/N/PSR/J/0036
Marketing authorisation holder(s)	APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH; BIOGARAN; BIOMO PHARMA GMBH; CONSILIENT HEALTH LIMITED, CRESCENT PHARMA, DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; HEXAL AG; LUPIN HEALTHCARE (UK) LTD; MYLAN SAS; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; PHARMASWISS CESKA REPUBLIKA S.R.O.; SANOFI R&D; STADA ARZNEIMITTEL AG; TECNIFAR S.A.; TEVA PHARMACEUTICALS EUROPE; WOCKHARDT UK LIMITED.

Title	Surveys among health care professionals and patients to assess their knowledge and behaviour with respect to the new (2018) Risk Minimisation Measures for valproate use in Europe
Joint PASS	Yes
Research question and objectives	Research question: What is the impact of the implementation of the new (2018) risk minimisation measures (RMMs) and pregnancy prevention programme (PPP) on the knowledge and behaviour of health care professionals (HCPs) who prescribe or dispense valproate and of patients treated with valproate in Europe? The objectives of the surveys are to assess the following items related to the new (2018) additional RMM (aRMM), among HCPs and women of childbearing potential (WCBP): • Awareness related to both receipt and reading of the new aRMM materials for valproate-containing medicines; • Knowledge of the risks associated with exposure to valproate-containing medicines during pregnancy and of the measures recommended to minimise those risks; • Behaviour with respect to the measures imposed by the new (2018) aRMMs, including measures of the PPP.
Country(-ies) of study	France, United Kingdom (UK), Sweden, Poland, Germany and Spain
Author	

2. Final assessment conclusions and actions

PRAC extensively discussed the results of the surveys among patients and health care professionals (HCPs - general practitioners [GPs], neurologists, psychiatrist, pediatricians, gynecologists and pharmacists) evaluating the impact of routine and additional risk minimisation measures (aRMM) distribution (direct HCP communication [DHPC] and educational materials [EM]) and the pregnancy prevention programme (PPP) implementation, as triggered within the referral procedure concluded in 2018, on knowledge and behaviour of HCPs who prescribe or dispense and patients receiving valproate in Europe. The overall success for effectiveness of both routine and aRMM, including PPP implementation, was assessed using three dimensions: awareness, knowledge and behaviour.

Summary of PASS Survey results

Despite a very low response rate among HCPs (i.e. varying between 1.6% in France to 7.7% in Spain) and patients, the pre-defined sample size was met. Further clarification has been provided by the consortium of MAH's on patient's recruitment and the potential for selection bias. Among patients recruited by HCPs, nearly all patients were recruited by HCPs who participated in the HCP survey (94%, n=497). The high percentage of patients recruited via participating HCPs might have led to selection bias, as physicians might have selected patients that were more knowledgeable on the PPP. Furthermore, these physicians might have been more aware of the importance of aRMM and PPP and

may have provided better information to their patients. This is further substantiated by additional analyses which showed that patients recruited via HCPs (68% of all patients) scored substantially better in all three dimensions than patients recruited via consumer panels (32% of all patients). Selection bias could have resulted in an overestimation of the results of the patient survey. This further justifies the need for a discussion on ways to further improve patient knowledge and awareness on the PPP.

Although predefined success rates for any of the selected three dimensions were not reached, neither for HCPs or patients, PRAC concluded that, still, successful and less successful areas could be identified from these results.

Of note, in the patient survey, success rates in each dimension were slightly higher for epilepsy patients as compared to patients with bipolar disorders (BP), and substantially lower for patients with other or unknown indications. For the HCPs, the highest proportions of successful HCPs were found among gynaecologists, followed by pharmacists and the prescribing physicians (GPs, neurologists, psychiatrist, pediatricians). Among the prescribing physicians, the highest proportions of successful HCPs were found for neurologists and psychiatrists. GPs and paediatricians were the least successful on each of the three dimensions.

Awareness (HCPs and patients):

The DHPC and HCP guide were the aRMM received by most of the HCPs, including the vast majority of neurologists and psychiatrists (80%). Comparable proportions were observed for reading them, indicating that, if received, these materials were also read. As prescribing physicians (GPs, neurologists, psychiatrist, pediatricians) were the only target group for the patient guide, PRAC considered the low proportion of these HCPs indicating receipt of the patient guide worrisome (37% of GPs, 53% of neurologists, 63% of psychiatrists and 30% of paediatricians), as they should provide this guide to their patients. The annual risk acknowledgment form (ARAF), to be completed by specialists, was recalled as received by 58% of neurologists, 54% of psychiatrists and 29% of paediatricians. The consortium of MAHs explained in their responses how all relevant HCPs from target groups were identified in different countries, using a robust method for identification of the relevant HCPs. Regarding the reasons for insufficient recall of aRMM receipt by the HCPs, the consortium of MAHs suggested that the EM may not be identified within the high volume of post mail and may be neglected, since perceived as an advertisement. No further suggestions could be identified by the consortium on how the receipt of different materials and DHPC could be improved; however, proposals to increase awareness and knowledge have been provided (see below). In addition, the preferred way of HCPs and patients for receiving and accessing information on the valproate PPP will be further investigated in a category 3 qualitative study focusing on barriers and reasons why certain measures part of the PPP are not always followed in clinical practice (see below).

Furthermore, from these results it appeared that GPs also received the ARAF, while the ARAF should only be used by specialists. The consortium of MAHs clarified that this has been done in agreement with national competent authorities (NCA) in some member states (MSs), and that the observed high proportion of GPs using the ARAF did not compromise the annual visit needed with a specialist. In addition, PRAC noted that, out of 60% of patients reporting discussing the ARAF with the prescriber, 30% of them did not understand its contents. This will be further investigated in the qualitative study.

Successfulness of distribution of patient card by attaching it to the packaging, as recommended in the 2018 referral outcomes, is difficult to assess considering that some MAHs are still in the process of its implementation. The patient card has also been distributed separately (with other EM) several times, before and during the survey in all countries where this study was conducted. While over 70% of pharmacists stated that they delivered and discussed the content of the patient card with new patients, or during each dispensing visit, 57% of the patients read the patient card but only 36% answered that

the pharmacist had discussed the content of the patient card with them. Reasons why the content of the patient card may not always be discussed with the patients will be further investigated in the qualitative study.

The patient guide was received by majority of epileptic (82%) and BP patients (75%). However, PRAC agreed that the reasons for 50% of patients not reading the guide, while these patients indicated to have read the patient card, requires further investigation in the qualitative study.

For both HCPs and patients updated analyses indicated higher scores for the awareness dimension . For HCPs, the median score increased from 50% [IQR: 20, 80%] to 71% [IQR: 40-100]. No major change in the overall success rate for HCPs (using the pre-defined success criteria) was observed with the adjusted analyses. The updated analyses of the patient survey showed only slightly higher scores of the awareness dimension. The revised awareness analyses did not impact the overall success rate of the patient survey.

Knowledge and behaviour (HCPs):

For different areas PRAC noted a sufficient proportion of HCPs who knew prescribing conditions or PPP measures and behaved correctly: 'Annual follow up visit with valproate prescriber', 'Referral to specialist (psychiatrist/neurologist) when planning for pregnancy or when pregnant', 'Prescribing conditions regarding use of valproate in pregnancy in patients with epilepsy', 'Contraindication in WBCP unless PPP condition are met'. Furthermore, although not tested within the "behaviour" dimension, majority of all HCPs knew that: 'Initiation and supervision of valproate treatment should be performed by a specialist (neurologist, psychiatrists)' (>85% within all type of HCPs), childbearing potential should be evaluated for all premenopausal females who are capable of becoming pregnant (70% - 81 %) and women of childbearing potential (WCBP) have to be counselled about the risk of valproate in pregnancy (also if sexually inactive) (77%-94%). PRAC agreed these areas are well implemented and do not warrant further actions or investigations at this moment.

PRAC also noted that a sufficient proportion of HCPs knew the prescribing conditions or PPP measures but behaved incorrectly in the following areas: second line indication of valproate in epilepsy and BP in girls and WCBP and performance of pregnancy test.

While 92% of neurologists (~75% of other prescribers) knew that valproate should not be used as a first line treatment in girls or WCBP with epilepsy, the behaviour question showed that 57% of neurologists (~72% of other relevant prescribers) would still prescribe valproate as a first line treatment to a 10 year old girl with epilepsy. 88% of psychiatrists, answered the knowledge question regarding the second line treatment of valproate in girls and WBCP with bipolar disease correctly. Unfortunately, there was no question in the behaviour dimension to test if the second line indication of valproate in girls and WCBP is adhered to. However, considering responses for the epilepsy indication, PRAC concluded on the need for further investigation of reasons why specialists may prescribe valproate as first line treatment in WCBP in epilepsy or BP.

While the majority of prescribing HCPs were aware that pregnancy tests must be done before starting valproate, and repeated as needed during treatment (70% - 83%), only 47% of paediatricians, 59% of neurologists, 67% of GPs and 69% of psychiatrists conducted a pregnancy test at initiation of valproate treatment, and as needed during the treatment. For these areas of relatively high knowledge, but reported behaviour not in line with PPP measures, PRAC agreed that a qualitative study should be performed to investigate barriers and reasons for not following PPP recommendations.

PRAC also noted that the proportion of HCPs with correct answers for behaviour (not tested in knowledge dimension) was insufficient for: prescribing of effective contraceptive methods (especially in sexually inactive WBCP), use of ARAF, providing patients with the patient guide, pharmacists discussing the patient card with patients, recommend pregnant patients to continue valproate

treatment until the next visit with their specialist. PRAC confirmed these areas should be further investigated in the new qualitative category 3 study.

Furthermore, the majority of HCPs were insufficiently knowledgeable of: strict contraindication of valproate in pregnancy for BP; risk of valproate on congenital malformations, delays in early development, childhood autism and that lower doses of valproate and folic acid supplementation cannot prevented these risks; among GPs: a specialist must be consulted to advise on the need of valproate withdrawal or switch when a women is pregnant or planning a pregnancy. Therefore, PRAC agreed that the consortium of MAHs should discuss strategies on how knowledge within these areas can be improved (see below).

Knowledge and behaviour (patients):

The information obtained from the patient survey on knowledge and behaviour was analysed and, where possible, linked to each other or to HCP behaviour . PRAC considered that, although criteria for success for the dimensions of "knowledge" and "behaviour" have not been met also among patients, successful and unsuccessful aspects could be identified by focussing on the most relevant questions of the survey.

PRAC noted the following areas, which can be considered successful, among women included in the survey:

- Knowledge on the risks of congenital malformations and neurodevelopmental disorders (NDD)
- Knowledge on the use of valproate in pregnancy in patients with BP
- Use of contraceptive methods
- Annual follow up visits
- When a women wish to become pregnant: contact a doctor
- In case of suspected pregnancy: urgently contact a doctor

In addition, PRAC agreed that the following areas require further improvement among WCBP treated with valproate:

- Knowledge on the use of valproate in pregnancy in patients with epilepsy
- Performance of pregnancy test
- When a women wishes to become pregnant: knowledge on the discontinuation of contraception and valproate seems insufficient
- In case of unplanned or suspected pregnancy: knowledge on the immediate discontinuation of valproate seems insufficient

Country trends

PRAC noted that, when looking at country trends, the highest proportions of success among HCPs were more frequently reported in the United Kingdom (UK), and the lowest proportions in Spain (and Poland and Sweden, to a lesser extent). The same trends across countries were observed for patients. These trends might partly be explained by the lag-time from distribution of materials to survey conduct.

Other results of aRMM effectiveness

When study results of the current HCP survey were compared to the 2016 HPC survey conducted by the consortium of MAHs, similar patterns were obtained. In both surveys GPs and pediatricians scored

significantly lower than other prescribing physicians on receipt of the aRMMs and knowledge of prescribing conditions. Although still an insufficient proportion of HCPs reported receipt of different aRMMs in 2021, the proportion of HCPs who received the aRMM improved considerably compared to the situation in 2016. In addition, both surveys showed that prescribing HCPs recalling EM and/or DHPC receipt had a better knowledge on valproate prescribing conditions .

With the responses to the first request for supplementary information (RfSI), the consortium of MAH's provided a literature review and identified 10 relevant studies. In general, the patterns identified within these studies are comparable with the findings of the PASS. However, several studies showed substantially lower results on awareness of the EMs. For example, within the Epilepsy Ireland survey[1], only 30% of the patients received a patient guide, while the corresponding proportion in the PASS survey in 6 other countries was 73%. Corresponding figures for the patient card were comparable between the Epilepsy Ireland survey and the PASS survey (60.6%). In the Irish survey, the majority of the patients did not sign the ARAF (62% had not been asked to sign, 16% did not remember). It should be noted that not all countries required a signed ARAF, and the awareness of the ARAF amongst patients with epilepsy indication was higher in the PASS survey (62.0% discussed the information in ARAF with their prescriber and 70% received the ARAF). Furthermore, in the ValproateRiskAware study[2] (performed in Belgium [only Flanders], Denmark, Greece, Latvia, Portugal, the Netherlands, Slovenia and Spain) receipt of patient EM was even lower compared to both Epilepsy Ireland survey and PASS survey (only 7% of the patients recalled receiving the patient guide, 2% the patient card and 2% the ARAF).

Furthermore, the literature review of the consortium of MAHs also provided some complementary findings and/or potential new barriers to be evaluated in the qualitative study:

- The Valproate Risk Aware study suggested that patients mainly preferred information coming from the verbal conversation with HCPs. Within the qualitative study it will be evaluated what are the preferred ways to receive information on the PPP (besides aRMM).
- Strict and relative contraindications during pregnancy for BP and epilepsy, respectively, were confusing for GPs whereas neurologists were well aware of the relative contraindication in the epilepsy indication during pregnancy (Hughes et al 2021[3]). No new information became available from literature on the knowledge regarding the contraindication during pregnancy for the BP indication amongst psychiatrists. The PASS survey showed that only 17% of the psychiatrist answered the question on the absolute contraindication in BP correctly, which is worrisome, and knowledge regarding the absolute contraindication during pregnancy should be improved amongst psychiatrists. Knowledge regarding the strict and relative contraindications during pregnancy for BP and epilepsy should also be increased amongst GPs. The HCP guide should be improved on this aspect.
- A survey among 215 HCPs from UK (Angus-Leppan et al 2020[4]) found that the recommendation for effective contraception was not always well accepted by patients (with or without intellectual disabilities - ID), mainly because of risks of AEs related to contraception and lack of sexual activity. Furthermore, in one study HCPs indicated that counselling on contraception is perceived as inappropriate when there is no sexual activity. In the study of Watkins et al. 2021[5] 36% of the included HCPs from the UK and 24% of the HCPs from the European Union (EU) stated that there is specific guidance for people with intellectual disabilities who are not sexually active. Of note, there are no specific recommendations for people with intellectual disabilities in the product information (PI). However, it is possible there is need for such guidance for HCPs to aid them in

[1] www.epilepsy.ie/sites/www.epilepsy.ie/files/2020%20Epilepsy%20Ireland%20Valproate%20Survey%20results%20FINAL.pdf
[2] www.encepp.eu/encepp/openAttachment/studyResult/40652
[3] https://doi.org/10.1080/14740338.2021.1933429
[4] https://onlinelibrary.wiley.com/doi/abs/10.1111/ane.13231
[5] https://onlinelibrary.wiley.com/doi/full/10.1111/ane.13337

the implementation of the PPP. Further understanding of the potential barriers with regard to use of contraception in sexually inactive patients (including use of contraception in patients with ID) should be explored in the qualitative study.

- Half of the HCPs (GPs, neurologists) from a study in UK (conducted in April-July 2019)[6] declared having limited resources for the identification of WCBP treated with valproate as well as the ARAF completion. Furthermore, >31% of the HCPs reported that the ARAF was found as dissatisfactory by patients (time-consuming, tick-box exercise, invasive, etc.) and 40% of clinicians were dissatisfied or strongly dissatisfied with the ARAF themselves. Unfortunately, the term "invasive" was not further specified. When the protocol of the qualitative study is submitted, the MAH should discuss how the potential barriers identified from the literature review will be taken on board in this study.
- NHS data on antiepileptic use in females aged 0 to 54 in England from the UK Medicines and Pregnancy Registry[7], covering the period April 2018- September 2021, showed that valproate exposed pregnancies still occur in UK despite the PPP. Reasons for prescribing valproate, including the indication, remain however unknown. Proportion of female patients 0-54 years that received prior treatment in the 12 months before valproate initiation seems around 50%. However, it appeared that 50% of all females were aged 45-54. Since the proportion of new users without prior therapy among girls and women up to 45 years of age cannot be reliably estimated from the NHS publication, findings of the PASS survey (HCPs know that valproate should not be used as first line treatment in WCBP but act sometimes differently) can therefore not be confirmed or rejected. Based on the NSH report no new areas for improvement of knowledge and behaviour could be identified in addition to those already flagged.

Stakeholder meeting

Upon request from PRAC, a stakeholder (virtual) meeting was conveyed on 1 February 2023 to explore, together with representatives of HCP organisations and learned societies and representatives of patient and carers, and discuss the current status of implementation of the valproate PPP in clinical practice, including challenges and opportunities for effective implementation. It was also discussed whether non-regulatory tools (e.g. alerts in clinical decision support softwares, continued education) and measures undertaking by MS in collaboration with professional organisations could contribute to optimize the implementation of RMM.

A summary of the stakeholder meeting is noted below.

Receipt of materials and stock maintenance

Patient organisations and individual patients report that not all patients have received the material intended for patients (patient guide, ARAF). When received, patients generally report the materials developed for them as useful. The following input was provided regarding the different tools for patients:

- The **patient guide** was described as being very comprehensive and to contain all required information. However, it was also mentioned that the patient guide is text heavy, very difficult to read and assimilate and contains a lot of information for patient/parent/carer to take in. In the current procedure, a new core version of the patient guide, with simplified text and more graphics has been agreed. A further update, to include a dedicated section for young girls/adolescents has been also recommended by PRAC.

[6] https://onlinelibrary.wiley.com/doi/abs/10.1111/ane.13231
[7] https://digital.nhs.uk/data-and-information/publications/statistical/mi-medicines-and-pregnancy-registry/antiepileptic-use-in-females-aged-0-to-54-in-england-april-2018-to-september-2021

- The **patient card** is described as very accessible and easy to read. The card is useful for the patient as a reminder to be kept with them. However, it was also noted that patients overlook the card as it does not clearly stand out from the rest of the outer packaging.
- Similarly, the **visual reminder** on the outer packaging has also been perceived as useful by patients and patient's organizations. However, as for the patient card, it was noted that patients can overlook the information on the outer packaging. It is therefore considered important that pharmacists are involved in communicating the risks at the time of dispensing valproate.
- Regarding the content of the **ARAF**, it was mentioned that the targeted division in 3 patient categories (young girl, sexually active potential pregnancy and pregnant) is considered very clear.

Repeated and periodic sending of information about risks and RMM was considered crucial. The distribution of risk minimisation measures, including the frequency of distribution, is subject to national policies in each EU MS. It is therefore recommended that the consortium of MAHs agrees with the national competent authorities (NCAs) the distribution of the revised version of the HCP and patient guide (new core versions recommended by PRAC in the current procedure), as well as periodic re-distribution of materials.

Although HCPs report that the patient EM are perceived as useful by patients themselves, some HCPs questioned the directive tone of voice used in the materials, which may be perceived as intrusive and not respectful to personal/religious beliefs. They also mentioned the ARAF as a very formal and authoritarian tool that does not match with how physicians generally communicate risk and RMM to patients. These aspects could be potential barriers for use of the materials by HCPs in clinical practice. This will be further investigated in the planned qualitative study, which will look into why specialists do not feel the need to use the ARAF, or why the ARAF is not discussed. Improving the EM by collaborating with HCPs/HCPs organisations in the development of these materials was mentioned by HCP organisations as a mean to improve HCP support for these RMM.

Stock of EM is generally maintained either by printing materials from an online resource and/or by refill of stock by the MAHs. A centralized online information source where all materials (including the ARAF) would be made available was mentioned as a helpful resource. Valproate aRMM are generally published on NCA websites, although this may be subject to different national policies. Further collaboration between patients, professional organisations and NCAs to develop additional channels to distribute information/aRMM should be explored at national level. A QR code on the outer packaging linking to this centralized website was mentioned as an aid for easy access of the patient materials. Of note, following the 2018 referral, a QR code linking to the valproate patient guide has been included in the package leaflet (PL).

Integration of RMM in clinical guidelines and prescribing/dispensing software

To what extent the RMMs for valproate have been integrated in clinical guidelines differs among MS. Similarly, integration of the RMM as alerts in prescribing or dispensing software varies between EU countries. Both patient and HCP organisations consider that integration in clinical guidelines and prescribing/dispensing softwares is an important aspect to improve adherence and to facilitate access to aRMMs.

Preferred way to receive RMM

For patients, the preferred way of being informed about risks and RMM is by direct dialogue (face to face) with their HCP, in addition to availability of written materials (both in print and digital). This topic will also be further investigated in the planned qualitative study. It was mentioned that the current valproate materials are predominantly paper-based and other digital opportunities to reach patients

should be explored (e.g. apps, use of video and social media content). It was mentioned that HCPs of different disciplines (specialists, GPs, pharmacists) all have a role in risk communication, although the focus of communication may differ per discipline (e.g. neurologist/gynaecologist to counsel on contraception, GP/nurse most frequent interacting with patients, age-specific information provided by epilepsy nurse or paediatrician, pharmacist to remind about risks at dispensing, etc), which highlights the need for communication and dialogue between HCPs of different disciplines.

HCPs prefer digital access to RMM, for example via alerts in prescribing/dispensing software and/or a centralized website with all valproate RMM information. They consider repeated and periodic communication to be crucial.

A national source of all available, up to date information for patients and HCPs was mentioned as a useful tool.

The preferred way of HCPs and patients for receiving and accessing information on valproate PPP will likewise be further investigated in the qualitative study.

Perceived barriers for effective implementation

Some further information regarding potential barriers that prevent full implementation of RMM in clinical practice were reported by HCP and patient organisations.

- As noted above, the ARAF was mentioned to be a very formal and authoritarian tool that does not match well with risk communication in standard clinical practice.
- Patients not receiving materials or sufficient counselling about valproate risks, contraception, and having limited access to specialists. Design of materials not always user friendly.
- The concept of 'childbearing potential' was mentioned to be generic, broad and not considering situations in which pregnancy is not an option, such as a very severe disease, childhood, and women who are not heterosexually active. Specialists may feel uncomfortable repeatedly addressing possible pregnancy in these situations and consider that this may result in humiliation for patients and/or their caregivers.
- Patients on valproate not promptly communicating pregnancy status to HCPs or not being aware of early pregnancy.
- The RMM do not provide information on the uncertainties regarding switching to alternative treatment options, also taking into account risk of seizures when switching (with impact to patient). Clinical guidelines papers on alternatives were mentioned as helpful tool in this respect.
- Valproate may be considered the best/only treatment option for some patients (with generalized epilepsy), which could explain declining rates of 1st line prescription but not in 2nd/3rd line prescriptions.
- The lack of clinical capacity could impact several PPP aspects , e.g. counselling on need for contraception, discussing therapeutic options, annual review of patients.
- Lack of coordination/limited flow of information or dialogue between HCPs of different disciplines involved in patient care.

Similar points were also identified following the literature review performed by the consortium of MAH's.

Activities to raise awareness on valproate (VPA) risks and RMM and to improve implementation

Patient organisations actively communicate information (both from NCAs as well as their own information) regarding valproate risks and RMM and provide awareness campaigns directed at women using valproate (VPA). Patient organisations also reported having contacted both governmental and professional organisations, both to stress the need for better implementation of existing RMM and to set up stakeholder groups intended to further collaborate on risk awareness, communication and implementation of RMM.

Several HCP organisations were not aware of activities offered in their country. Others do report activities organized by professional organisations that range from including information in scientific product databases/softwares, publications of information on their websites, presentations at meetings/conferences, online training and continuous professional education and awareness campaigns.

Both patient and HCP organisations stress the need for all stakeholders, including NCAs, ministries of health/governmental organizations, HCPs and patients, working together and separately, to support implementation and increase awareness of the risks and RMM. Information regarding RMM should be implemented via multiple ways, including awareness campaigns (addressing both women on VPA and HCPs), professional education and training, as well as open online courses, integration of RMM information in clinical guidelines and prescribing and dispensing software, and engaging in active dialogue with patients. The messages to HCPs and patients should be targeted, complete and consistent, and delivered in collaboration between NCA and HCP or patient organisations. There should also be focus on family planning strategies and counselling on effective contraception to ultimately prevent pregnancy while on valproate treatment. However, it was considered that these type of actions are challenging to coordinate at EU level and further coordination and strategies are needed at national level.

Some other measures to improve adherence to VPA PPP were suggested, such as valproate prescription not being reimbursable by national healthcare system when the product is not prescribed in accordance with the terms and conditions of the marketing authorisation (MA). It was also suggested for NCA to consider measures for prescribers to clearly justify valproate prescriptions in women of childbearing age (i.e., with reference to UK, where implemented a 2-step approach for valproate prescription to be confirmed by 2 separate independent specialists).

As implementation of current measures is not complete; it was noted that focus should turn to preferred methods on how professionals/patients want to receive this information, as previous/ongoing efforts (such as mailings by NCA or professional organizations) seem to have limited impact. To improve impact, alternative means to target groups need to be considered. This will be addressed in the planned qualitative study.

Conclusion on stakeholder meeting

In general, the points raised during the stakeholder meeting are in line with the issues identified from the HCP and patient survey and the literature reviewed in the current procedure, and indicate that the RMM, as agreed in the 2018 referral procedure, may still not be fully implemented across the EU.

In the current procedure, further improvements of the HCP and patient materials have been agreed, and the PI has been updated to put more emphasis on the contraindication during pregnancy. A qualitative study to further investigate barriers and reasons why the PPP measures are not always followed in clinical practice has also been requested (see section below). With this study, PRAC will continue to evaluate whether the existing RMM can be improved or replacement or addition of tools/measures may be necessary to further increase implementation of VPA PPP in clinical practice.

Implementation of VPA RMM is too complex to be fully coordinated at EU level, as national health care system organisations are different across MS. Therefore, further improvement towards full

implementation requires collaboration between all stakeholders and tailored actions at national level. An integrated multidisciplinary approach and shared responsibility of all stakeholders is required, as not all actions for further improvement are within mandate/authority of regulatory authorities or the MAH. See section below (Further actions), for proposed actions for the MAH's consortium as well as other stakeholders.

Study synopsis of qualitative study

The survey findings indicated that, for several domains of self-reported behaviour, both patients and HCPs do not always follow PPP measures, despite knowledge about these measures. Therefore, PRAC concluded by consensus that a qualitative study (to be included in valproate RMP as category 3) is necessary to investigate barriers and reasons why certain measures part of the PPP are not always followed in clinical practice.

Among HCPs the following reasons and barriers should be investigated:

- Why the targeted specialists do not feel the need to use the ARAF or distribute the patient guide to patients.
- Why the ARAF is not discussed/used by specialists during discussion with all patients, in particular when a pregnancy is planned or in case of unplanned pregnancy.
- Why specialists may prescribe valproate as first line treatment in girls with epilepsy, while they do know it is indicated for second line treatment.
- Why specialists do not perform pregnancy tests in all WCBP, while they know that a pregnancy test should be performed at treatment initiation and, when necessary, during valproate treatment.
- Why HCPs do not sufficiently prescribe or counsel on the need of effective contraception in WBCP, especially those who are sexually active or of adolescent age.
- Why pharmacists don't discuss the content of the patient card with their patients.
- Why GPs do not recommend patients to continue treatment with valproate until the next visit with their specialist (psychiatrist/neurologist) in case of unplanned pregnancy.
- What are the preferred ways of HCPs to receive information on the PPP (besides aRMM)

Furthermore, amongst patients:

- The reasons why patients do not read the patient guide and do read the patient card more often.
- Which topics of the ARAF were not well understood by the patient, in case the ARAF was discussed.
- The reasons why the conditions during which valproate may be used in pregnancy in epileptic patients are not well understood.
- What are the preferred ways of patients to receive information on the PPP (besides aRMM)

Furthermore, the literature review of the consortium of MAHs provided some potential new barriers to be further evaluated in the qualitative study:

- For the ARAF: HPCs have limited resources, filling of the ARAF is time-consuming and perceived as a tick-bock exercise.
- Counselling on contraception is perceived as inappropriate when there is no sexual activity.
- Absence of specific recommendations for patients with intellectual disabilities who are not sexual active.

In the study protocol , the MAH should also discuss how the potential barriers identified within the literature review will be taken on board in the study.

For both HCPs and patients a mixed design including two phases i.e. first a qualitative approach (phase 1, focus groups with HCPs and face-to- face interviews with patients) followed by an optional open ended online survey questions (phase 2) was proposed. While this stagged approach was generally supported, PRAC had important suggestions regarding the aims of the second phase . Reasons and barriers for HCPs and patients requiring further understanding, as specified by PRAC, have been included sufficiently among the proposed study objectives for phase 1. The proposed purposive sampling with snow ball sampling techniques can also be endorsed, although further details should be provided in the full study protocol.

The second phase, the proposed optional online survey among HCPs and patients aiming "to identify additional reasons and barriers to further enrich the findings from phase 1", was not supported by PRAC. An online survey would not be the preferred method to collect deeper understanding on barriers, as the possibility to really dig deeper is limited using this (online survey) setting, and much more possible with focus groups and face-to-face interview in the first phase. Data saturation should therefore be reached within in the first phase, whereas the aim and complete design of the second phase require major amendments. The second phase might be used to confirm the results of the first phase, reinforce representativity of HCPs and patients (by conducting the survey in a larger number of countries), collect data on feasibility and as support of ideas to improve PPP effectiveness. PRAC agreed that the second phase should not remain optional but it may be possible that further design of this phase depends on the findings of the first phase.

Further suggestions to be taken into account for the full study protocol of this qualitative study were made regarding the study objectives, details on the target groups being considered in the focus groups and face-to-face interviews, how the focus groups and interviews will be prepared and organised (i.e. minimum number of participants in each target group, how diversity in HCP or patients will be ensured, which countries will be involved in each phase, duration of interviews/focus groups), and preparation of an interview guide. The consortium of MAH should identify MS with different health care systems and processes in view of valproate PPP implementation to ensure representativeness of collected data of the qualitative study first phase. Further explanation on data saturation concept and how this will be monitored and optimised is also needed. In addition, argumentation should be provided on why the hierarchic cluster analysis will be suitable to analyse the focus group and interview data. Finally, comments on the proposed milestones were also provided by PRAC.

The next step for the qualitative study (category 3) are noted below:

1. Since there is no need for PRAC approval of the synopsis , the next milestone is the submission of the full study protocol in a separate procedure, expected in Q2 2023. During its preparation, comments made by PRAC while assessing the synopsis should be considered.
2. The qualitative study (category 3) should be included in valproate RMP, to be updated accordingly in a separate procedure.

Further actions to improve knowledge and awareness among HCP and patient

Results of the survey among HCP and patients showed that, although the definitions of success were not reached, a variation in the level of awareness (receive and use), knowledge and behaviour following implementation of PPP and aRMM have been observed. PRAC agreed on several points (as outlined above) sufficiently implemented and on topics requiring further clarification and improvements, such as implementation of the aRMMs, to ensure all eligible HCPs within the target

groups receive relevant materials. Next, knowledge on valproate risks, teratogenicity and NDD, should be further improved among HCPs and patients. In addition, PRAC agreed that, since the final study report of the ongoing joint DUS for valproate containing products should be submitted in February 2025, the consortium of MAHs was requested to already propose improvements of the aRMM based on this surveys' findings, as these results cannot be awaited.

Revision of the product information

The proposed boxed presentation of the contraindications for use during pregnancy on top of SmPC section 4.6, to emphasize the different contraindication per indication, and using bullet points, is supported by PRAC, considering the knowledge deficiency in this area among psychiatrists observed in the HCP Survey, and the confusion among GPs regarding the contraindications for pregnancy observed in literature. No changes to the PL are proposed. It is advised that any proposal to update the PL to improve readability is substantiated by a user test.

Introduction of 'core version of the HCP guide'

At EU level key elements for the HCP guide are agreed and PRAC usually does not assess and approve the full version of the EM. However, considering the challenges of the aRMM for this product in the past, as well as the results from the HCP and patient surveys indicating a clear need for further improvement of knowledge and the available user test, PRAC recommended to agree on a 'core version of the HCP guide' which can be translated into national versions and adapted to the national preferences in agreement with NCA. Agreement on a 'core version' will facilitate implementation of the changes in the HCP guide in EU MS.

The consortium of MAHs submitted an updated HCP guide to be considered as 'core version' based on the comments from PRAC. This 'core version' include a restructured version of the material by HCP's role and indication, use of color coding and tabs, visualization of information in flow charts and graphs which is supported by HCPs, according to an user test. The guide is easy to navigate, also digitally. This proposal was substantiated with the user test which provided useful information to further improve the guide. A final version of the revised HCP guide should be implemented at national level in agreement with the NCA.

Revised 'core version of the patient guide'

The Consortium of MAHs proposed a user tested revised patient guide which has been simplified and includes all important information for girls and WCBP using valproate. The revised patient guide is slightly restructured (shuffle of two chapters), easier to read, shortened and simplified where needed. The most essential information is presented first under the headings and includes only one safety topic per page. No important information has been deleted. The revised core version of the patient guide is considered acceptable by PRAC. As requested, the consortium of MAHs included a dedicated section for young girls/adolescents, informing about the risk of valproate, actions to take when girls experience their first period as well as other recommendations specific for young girls/adolescents. This section uses simplified language, flow charts and illustrations to present the information in a clear manner, and has been user tested in the appropriate age group. A final version of the revised patient guide should be implemented at national level in agreement with the NCA.

The Consortium of MAHs did not propose changes to the core versions of the ARAF and the patient card, which is endorsed by PRAC.

Broadening of channels and format of information on the PPP and risks of valproate as suggested by the Consortium of MAHs is supported by PRAC, considering the possible various preferences of subgroups of HCPs and patients with various indications. In addition, the awareness of PPP and safety of valproate in WCBP and during pregnancy among HCPs requires refreshment and reminders on a

periodic basis. This would also allow changes in the distribution modalities for which possibilities and preferences of HCPs and patients may change over time.

Further actions for the MAHs of valproate containing products

- The consortium of MAHs should distribute revised versions of the HCP guide, revised patient guide and unrevised ARAF at national level in agreement with NCA. It is recommended to include a cover letter with the materials to highlight the reason for distribution of such revised materials. In addition, NCAs are encouraged to communicate on the revised package of EM and PPP.
- To promote access and awareness of valproate aRMM and PPP in each EU MS, the MAHs should ensure easy access to digital/electronic versions of EM in the local language, with and without QR code included in the packaging material and/or the package leaflet, i.e. via online search on trusted webpages used by patients looking for information on medicines.
- A qualitative study should be conducted to investigate the preferred way of HCPs and patients for receiving and accessing information on the valproate PPP. The need for further actions and specific formats or channels will be reconsidered.

***At national level the MAHs of valproate-containing products should consider, in agreement with NCAs*:**

- Inclusion of the pictogram on the packaging and EM. The results of the PASS survey show that 39% of the patients noticed the pictogram. The pictogram might contribute to improvement of patients awareness. In the RiskAwareStudy the warning symbol on the package was noticed by less than one third (27%) of the patients. However, in the same study, pharmacists have reported the warning on the outer packaging as very helpful, both currently and towards the future, and for both informing patients about risks and as a reminder to verbally alert on the risks around pregnancy and medication use.
- Periodic EM re-distribution to HCPs, since reminders and refreshment of information on the PPP and valproate risks may add to increased knowledge. The results of the HCP survey showed that HCPs who received the EM and DHPC scored better in all three dimensions (awareness, knowledge, behaviour) compared to those who did not recalled the EM or the DHPC. Furthermore, new HCPs may be targeted as well with period re-distribution. The distribution modalities (electronic/digital distribution, paper based distribution, full package or reminder mail) and frequency should be decided at national level in agreement with NCAs.
- Use of a symbol on the envelope or in the email heading to recognize the EM (i.e. to avoid confusion of such materials as promotional), as suggested by the consortium of MAHs, may be helpful and should be decided at national level in agreement with NCAs.

Actions that require further collaboration between all stakeholders

As described by the consortium in the response submitted to PRAC, there are possibilities for MAHs, as well as other stakeholders, learned societies and patient organisations, to contribute to risk minimisation of valproate use in WCBP and pregnant women which unfortunately do not all fall under the full mandate or authority of PRAC/NCA/MAH and in some cases need to be facilitated and ensured by the national health care systems, learned societies and the HCPs. The PRAC would like to remind on

the following activities and encourage collaborations, as previously advised in the PRAC AR of the referral concluded in 2018:

- To explore the possibilities of prescribing and pharmacy dispensing softwares (e.g. pop-up alerts, reminders).
- Collaboration between patient and professional organisations and NCAs to further explore and develop additional channels to distribute information/EM, such as web platforms to publish materials with cross-references to each webpage depending on national particularities .
- To ensure that updated recommendations regarding the use of valproate in WCBP and in pregnancy are incorporated in the curriculum of (continuous) medical education of HCPs.
- MS are encouraged to explore public campaigns, using different channels of communication. These channels may include mass media campaigns, social media, visual displays (leaflets and posters) at relevant places (e.g. clinics, family planning centres).

Further PRAC recommendations to study effectiveness of the aRMM

The final study report of the HCPs and patient surveys, investigating the effectiveness of routine and additional RMM (distribution) and the PPP for valproate, as implemented after the 2018 referral shows that, despite knowledge of risks and prescribing conditions, physicians still reported prescribing valproate to female children and WCBP even if alternative treatment options are available or to some WCBP who do not use effective contraception. In addition, the available interim results of the MAH's consortium DUS and the final results of study EUPAS31001 show that pregnancies continue to occur in WCBP who use valproate after implementation of the new (2018) RMM. The reasons for not adhering to valproate restricted prescribing conditions are currently not fully clear and will be further investigated in a qualitative (category 3) study.

The HCPs and patient surveys and the DUS (another category 1 study) imposed within the 2018 referral, provided complementary data on effectiveness of the measures implemented after such referral. In this procedure, both updates to the PI and to the aRMM for HCPs and patients are recommended to enhance adherence to prescribing conditions and PPP. A new post-authorisation study to further monitor such adherence in clinical practice over time may also be foreseen by PRAC.

The final study report of the MAH's consortium-sponsored DUS should be submitted in February 2025. Therefore, PRAC agreed that the need for further measures, as well as additional studies to investigate effectiveness of measures taken so far, will be determined after assessment of this DUS, when a complete picture on RMM effectiveness has become available.

Scientific conclusions and grounds for variation to the terms of the marketing authorisation(s)

Having considered the PRAC assessment report for the imposed PASS final report (surveys among health care professionals [HCPs] and patients) investigating the effectiveness of the risk minimisation measures (RMM) implemented after the Article 31 referral completed in 2018 for the medicinal product(s) containing valproate and related active substances, the PRAC scientific conclusions are as follows.

The overall success for effectiveness of both routine and additional (RMM), including PPP implementation, was assessed using three dimensions: awareness, knowledge and behaviour. Although the response rate of both HCPs and patients was very low, and predefined success rates for

any of the selected three dimensions were not reached (neither for HCPs or patients), PRAC concluded that, still, successful and less successful areas could be identified from these results and that a variation in the level of awareness, knowledge and self-reported behaviour following implementation of the PPP and additional RMM was observed. Most importantly, the knowledge regarding the contraindication during pregnancy and in WCBP for different indications of valproate was not sufficient. Next, for some of the prescribing conditions, despite sufficient knowledge , PRAC noted a remarkable number of prescribers who reported that they would prescribe valproate not in line with the PPP, e.g. to female children and women of child bearing potential (WCBP) even if alternative treatment options are available, or to some WCBP who do not use effective contraception. Furthermore, the prescribers reported that they would not always conduct pregnancy testing was (i.e. before starting treatment and repeated, as needed, during treatment) and educational materials (EM) did not always reach the targeted audience or were not always used (i.e. ARAF); the patient guide, described as very comprehensive but text heavy and difficult to read. Patients also reported to rather prefer reading the patient card.

The available interim results of the MAH's consortium drug utilisation study (DUS) and the final results of study EUPAS31001, showing that pregnancies continue to occur in WCBP who use medicinal products containing valproate and related active substances, despite implementation of the (new) risk minimisation measures (RMMs) agreed in the framework of the 2018 Article 31 referral, were also taken into account. In addition, PRAC considered the views and suggestions of representatives of HCPs organisations, learned societies and representatives of patient and carers who attended at the stakeholder's (virtual) meeting held in February 2023.

PRAC concluded that the patient and HCP guides agreed withing the 2018 referral should be revised, to further enhance knowledge on valproate risks, teratogenicity and neurodevelopmental disorders, and adherence to prescribing conditions and PPP.

Furthermore, specifically considering the knowledge deficiency among psychiatrists, as observed in the HCPs survey, and the confusion among general practitioners (GPs) regarding the contraindication for use during pregnancy, as observed in the literature, a boxed presentation of the contraindication should be added on top of SmPC section 4.6, using bullet points, to emphasize the different contraindication per indication.

3. Final Recommendations

Based on the review of the PASS final study report version 1.0 dated 29 July 2021, the PRAC considers by consensus that:

☒ The risk-benefit balance of medicinal products containing valproate and related active substances concerned by the PASS final report remains unchanged but recommends that the terms of the marketing authorisation(s) should be varied as follows:

In view of available data regarding the PASS final study report, other (interim) available studies, data from literature, the outcome of the stakeholder's meeting held in February 2023, the PRAC concluded that changes to the product information (PI) and the conditions of the marketing authorisation (MA) for medicinal products containing valproate and related active substances are warranted.

Product information

The following changes to the PI of medicinal products containing valproate and related active substances are recommended (new text **<u>underlined and in bold</u>,** deleted text ~~strike through~~)

Summary of Product Characteristic

- Section 4.6

Pregnancy

Treatment of epilepsy

- **Valproate is contraindicated during pregnancy, unless there is no suitable alternative treatment**
- **Valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.4)**

Treatment of bipolar disorder

- **Valproate is contraindicated during pregnancy**
- **Valproate is contraindicated in women of childbearing potential, unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.4)**

~~Valproate is contraindicated as treatment for bipolar disorder during pregnancy. Valproate is contraindicated as treatment for epilepsy during pregnancy unless there is no suitable alternative to treat epilepsy. Valproate is contraindicated for use in women of childbearing potential unless the conditions of the pregnancy prevention programme are fulfilled (see sections 4.3 and 4.4).~~

Patient leaflet

No changes to the package leaflet (PL) are proposed. The following changes to the conditions of the marketing authorisation(s) of medicinal products containing valproate and related active substances concerned by the PASS final report are also recommended:

Additional risk minimisation measures

- As part of the pregnancy prevention programme (PPP) the following educational measures for valproate and related active substances containing products have been agreed withing the Article 31 referral procedure completed in 2018: HCP guide, patient guide, annual risk acknowledgement form (ARAF), patient card, visual reminder on the outer package. The following changes to the educational measures are recommended:

  Patient guide

  A revised ”core version” of the patient guide is agreed by PRAC. The final version of the revised patient guide should be implemented in each EU Member State (MS) in agreement with the national competent authority (NCA).

  HCP guide

  A new ”core version” of the HCP guide is agreed by PRAC. The final version of the revised HCP guide should be implemented in each EU MS in agreement with the NCA.

  - The following changes to the key elements of the HCP guide are recommended to correct inconsistencies with the SmPC approved in Article 31 referral completed in 2018 (new text **underlined and in bold,** deleted text ~~strike through~~):

Key elements to be addressed in the HCP guide

- The HCP guide should reflect all pregnancy prevention program (PPP) conditions as outlined in the summary of product characteristics (SmPC).

- The role of the different HCPs for implementation of the PPP and educational materials aimed at patients should be provided (as outlined below).
- Information on congenital malformations and developmental disorders including the magnitude of these risks for children exposed to valproate in utero.
- Valproate **should not be used** ~~initiated~~ in female children **unless other treatments are ineffective or not tolerated** ~~only if there is no suitable alternative treatment.~~
- Recommendations for prescribers when valproate is prescribed to female children, in particular the need to:
    - explain the risks of congenital malformations and neurodevelopmental disorders to the parent/caregivers (and children, depending on their age)
    - explain to the parents/caregivers of female girls the importance of contacting the specialist once a female child using valproate experiences menarche
    - reassess the need for valproate therapy at least annually and consider alternative treatment options in female children who experienced menarche
    - make efforts to switch the female children to alternative treatment before they reach adulthood.
- Valproate may be initiated in girls and women of childbearing potential only if the conditions of valproate pregnancy prevention program (as outlined in the SmPC) are fulfilled.
- The need to clearly explain to the patient/caregivers the risks of valproate and required actions (in line with valproate PPP) to minimise these risks to all WCBP using valproate and to ensure that the information is well understood.
- The need to use and document the annual risk acknowledgement form, at initiation and during each annual review of valproate treatment by a specialist.
- The need to provide patient educational tools to each **girl and** WCBP using valproate.
- Guidance on the contraception methods (in line with the SmPC recommendations on contraception).
- Recommendations on switching or discontinuing valproate.
- Recommendations on pregnancy planning.
- Recommendations if valproate is the only suitable treatment for a patient who is (planning to become) pregnant.
- *{To be agreed at a national level:}*

  <A link to the dedicated website, indicating to patients where additional online information about valproate use in WCBP can be found.>

Key information to be included for the role of different HCPs in the HCP guide

a. Valproate should be initiated by specialist

b. The patient guide should be provided to the patients by the prescriber

c. The Annual risk acknowledgment form should be used by the specialist at initiation of valproate treatment and during annual treatment reviews

d. The patient card should be provided by the pharmacists

e. Optional for countries where valproate may be unpacked in pharmacies: Avoid unpacking valproate and in the situations where this cannot be avoided, always provide a copy of a package leaflet, patient card and the outer box if available.

The additional details regarding the role of the HCPs (including all relevant HCPs such as GPs, gynecologists, paediatricians, midwifes, pharmacists, etc.) in the implementation of the PPP and educational materials should be assessed on national level taking into account the differences in health care systems in individual Member States.

Annual risk acknowledgement form (ARAF)

The ARAF should be used and documented at initiation and during each annual review of treatment by a specialist. The core version agreed with the Article 31 referral concluded in 2018 remains valid.

Patient card

The patient card is attached to the outer carton to prompt as a reminder for the discussion between the pharmacist and the patient at the time of product dispensing. The core version agreed with the Article 31 referral concluded in 2018 remains valid.

- The MAH(s) should distribute revised versions of the HCP guide, the revised patient guide and the unrevised ARAF in each EU MS, in agreement with the NCA. It is also recommended to include a cover letter with these materials to highlight the reason for distribution of such revised materials.
- To promote access and awareness of valproate and related active substances additional RMM and PPP in each EU MS the MAH(s) should ensure easy access to digital/electronic versions of the EMs in the local language, with and without a QR code included in the packaging material and/or the package leaflet, i.e. via online search on trusted webpages used by patients looking for information on medicines.

Risk management plan

In addition, the MAH(s) should submit an updated risk management plan (RMP) after finalisation of this PASS procedure, also addressing the following:

- A qualitative study should be included in the RMP as category 3, in order to investigate
    - barriers and reasons why certain measures part of the PPP are not always followed in clinical practice;
    - the preferred ways of HCPs and patients to receive information on the PPP.

This RMP update should be made accordingly in a separate procedure.

4. Other considerations

☒ The recommendations proposed by the PRAC in this report merit careful consideration by CMDh, as they propose e.g. important restrictions of use and/or substantial modifications in the Product Information or Annex II.