Annex II

Scientific conclusions

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On 08 March 2017 France triggered a procedure under Article 31 of Directive 2001/83/EC, and requested the PRAC to assess the impact on the concerns regarding the effectiveness of the risk minimisation measures on the benefit-risk balance of medicinal products containing substances related to valproate and issue a recommendation on whether the marketing authorisation(s) of these products should be maintained, varied, suspended or revoked.

The PRAC adopted a recommendation on 08 February 2018 which was then considered by the CMDh, in accordance with Article 107k of Directive 2001/83/EC.

Overall summary of the scientific evaluation by the PRAC

In the course of the consultations that PRAC had in this procedure, some additional concerns have arisen, other than the well-known and documented harm to the foetus during *in utero* exposure. The potential impact of paternal use of valproate, the potential effect on the third generation offspring and the potential effects on mitochondria (mitochondrial toxicity) were discussed.

Regarding exposure via seminal fluid, estimation was made of the area under curve (AUC) for valproate in a woman following vaginal exposure to valproate via seminal fluid of a man treated with valproate. This resulted in a value which was more than 25,000 times lower than the AUC in a woman treated orally with an equal dose (single oral dose 500 mg). It can be concluded that it is extremely unlikely that valproate, when used by a male patient, could cause adverse effects to the embryo/foetus by this route. The PRAC requested the conduct of a retrospective observational study to further characterise this theoretical risk.

Genetic changes can be divided in gene mutations and chromosome aberrations. It seems theoretically possible that gene mutations in sperm cells could be transmitted to the offspring. However, tests for gene mutations were negative. Therefore, this type of transmission is not likely to occur for valproate. The PRAC therefore recommends that other tests could be performed (e.g. *in vitro* mouse lymphoma assay) to further explore this hypothesis. Several tests for chromosome damage were positive. Severe chromosome damage is expected to lead to death of sperm cells / reduced fertility and not to transmission of mutations to the offspring. It is unknown whether slight chromosome damage might be transmitted to the offspring. Further investigation is recommended by PRAC.

The epigenetic mechanism refers to the possibility that changes in the gene expression in the gametes are transmitted to the gene expression in the embryo (for example by changes in DNA methylation). Theoretically this is possible by changes to the gene expression in sperm cells of adult males or by changes to the developing germ cells in the embryo. In one experiment it was shown that a change in gene expression (one gene) in male mice after exposure to a histone deacetylases (HDAC) inhibitor (not valproate) was observed also in the offspring of these mice (Jia et al, 2015)[1], so possible in principle. It was shown in a transgenerational experiment in mice that administration of valproate during pregnancy (day 10) produced autism-like symptoms and increased expression of several proteins in the brains up to the third generation offspring. This was not shown for teratogenic effects as malformations in the first generation offspring was not observed in the second and third generation offspring (Choi et al, 2016)[2]. Although several limitations exist, the study suggests that there was some transgenerational effect. The PRAC agrees that more research is necessary to evaluate whether

[1] Jia H, Morris CD, Williams RM, Loring JF, Thomas EA. HDAC inhibition imparts beneficial transgenerational effects in Huntington's disease mice via altered DNA and histone methylation. Proc Natl Acad Sci U S A. 2015 Jan 6;112(1):E56-64.

[2] Choi CS, Gonzales EL, Kim KC, Yang SM, Kim JW, Mabunga DF, et al. The transgenerational inheritance of autism-like phenotypes in mice exposed to valproic acid during pregnancy. Sci Rep. 2016 Nov 7;6:36250

valproate indeed may induce transgenerational alterations of gene expression to the offspring and the types of consequent effects.

Furthermore, in a literature overview regarding effects on mitochondria, known side effects were described such as liver toxicity, Reye-like syndrome, pancreatitis and immune deficiency (leukopenia). There is no clear evidence that mitochondrial dysfunction caused by valproate is associated with the development of autism. The PRAC is of the opinion that the currently available data do not warrant further investigation regarding the potential association between mitochondrial dysfunction and autism.

In the previous European review (2014)[3], several educational measures for patients and healthcare professionals (HCPs) were recommended. Nevertheless, as shown in the data reviewed in this procedure educational measures did not reach the targeted audience in a satisfactory rate in order to have any significant impact on prescriptions.

Usage data from the ongoing joint drug utilisation study (DUS) as well as other data (surveys, national surveys, anecdotal evidence etc.) that have been evaluated in the current referral indicate that valproate is still used by a considerable proportion of WCBP in different MSs for both epilepsy and bipolar disorder indications.

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, stake holders 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 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. To obtain additional robust information on the switch and discontinuation of valproate, the PRAC requested the conduct of an observational study to identify and evaluate the best practices for switching of valproate in clinical practice.

Regarding pregnancy/family planning in epilepsy, the PRAC also highlighted that, 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. 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.

In view of the above, the PRAC recommended amendments to the product information, in particular to contraindicate its use to women of childbearing potential that do not fulfil the conditions of a pregnancy prevention program, and communication to healthcare professionals through a direct healthcare professional communication (DHPC). A pregnancy prevention programme will be implemented accordingly to prevent valproate exposure during pregnancy given that significant risk of lifelong harm is associated with its use. Educational measures are necessary in order to ensure that healthcare professionals and patients are informed about the risks associated with valproate in

[3] http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Valproate_and_related_substances/human_referral_prac_000032.jsp&mid=WC0b01ac05805c516f

pregnant women and women of childbearing potential and on the measures necessary to minimise the risk of exposure on valproate in pregnancy. The PRAC re-iterate that a single version of educational materials is disseminated in each member state, where appropriate. The MAHs are encouraged to collaborate and liaise with the national competent authorities to facilitate the dissemination of the agreed educational material.

The PRAC recommended the improvement of a HCP guide to make sure that valproate prescribers are aware of the risks associated with the use of this product in female children, women of childbearing potential and pregnant women and requested that the patients are also informed about these risks appropriately. The guide should explain the pregnancy prevention programme and the conditions to be met prior to starting treatment with valproate. At least annual re-assessment of the need for valproate therapy and consideration of alternative treatment options in female children who experienced menarche and women of childbearing potential should be included. In addition, the guide should familiarise the prescribers with key actions to mitigate the risks associated with the use of valproate in exposed girls and women by using the patient guide and the risk acknowledgment form. The HCP guide should include the recommendation to inform the parents of young girls using valproate about the need to contact their specialist once their daughter has experienced menarche, information on need for switching when pregnancy planning, on the need to go through the risk acknowledgement form and the patient card, at least annually.

The PRAC recommended that a patient card to be made available in all MSs and for all patients who receive valproate. Information on the patient card should be brief and concise regarding the efficacy of the product but also the harm to an unborn child when taken during pregnancy. The use of effective contraception without interruption during the all course of treatment should be included as well as a reminder for annual re-assessment. Advice on non-interruption of treatment as well as the need to contact the doctor when a pregnancy is planned or suspected should also be included. This patient card should be attached at the outer carton to prompt as a reminder the discussion between the pharmacist and the patient at the time of the product dispensing.

The PRAC recommended that the patient guide for female children, adolescents and women who are being prescribed valproate is further developed and improved. The patient guide should provide comprehensive information on risks to the unborn child due to *in utero* exposure to valproate and related substances, the details of the pregnancy prevention programme to avoid valproate exposure during pregnancy and the required actions in terms of pregnancy or intention to become pregnant. In order to provide adequate information, it should be tailored for different situations in the life-time of a woman and be age-appropriate: the first prescription, women continuing valproate treatment and not trying to have a child, women of childbearing potential continuing valproate treatment and considering trying to have a child, pregnant women (unplanned pregnancy) whilst continuing valproate treatment. This guide should be handed over to the patient.

The PRAC also reviewed the annual risk acknowledgement form which should be used and documented at initiation and during each annual review of valproate treatment by a specialist.

The PRAC taking into account all the evidence as well the areas where information is limited requested several measures in order to further characterise the risks, increase the awareness of the risks, restrict the use and measure the effectiveness of the currently proposed measures. The current ongoing drug utilisation study (DUS) should be adapted and continued to assess the effectiveness of the updated risk minimisation measures including the pregnancy prevention programme conditions and to further characterise the prescribing patterns for valproate. A survey among HCP to assess their knowledge and behaviour with regard to the new product information restrictions and whether they received the direct healthcare professional communication (DHPC) and educational materials, and another survey among patients to assess the receipt of the educational materials should be performed. A post-authorisation

safety study (PASS) using data preferably from existing registries should be performed to further characterise the foetal anticonvulsant syndrome in children with valproate *in utero* exposure as compared to other anti-epileptic drugs. In addition in an effort to increase the knowledge on the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring, a retrospective observational study is recommended. Further, an observational study to evaluate and identify the best practice for discontinuation and switching of valproate treatment will be conducted.

The MAHs are strongly encouraged to collaborate on the requested measures and to perform joint studies.

Among the requests from the patients and family members who were consulted was the implementation of a visual reminder on the outer package to warn the women on the harm to the unborn baby and to also promptly advise them to use effective contraception. The PRAC agreed that such visual reminder on the outer carton is important to warn the patient on the risk and to prompt to consult a physician and requested the inclusion of a visual reminder on the outer packaging. In addition to the boxed text this may include a symbol/pictogram, with the details to be adapted at national level.

In view of the safety issues in discussion and the whole set of conditions for the risk minimisation aiming at minimising exposure in pregnancy, all MAHs need to have in place a risk management plan.

The medicinal products will continue to be listed in the additional monitoring list.

Grounds for PRAC recommendation

Whereas,

- The Pharmacovigilance Risk Assessment Committee (PRAC) considered the procedure under Article 31 of Directive 2001/83/EC for medicinal products containing substances related to valproate.
- The PRAC considered the totality of the data submitted for valproate and related substances with regard to the teratogenic and neurodevelopmental risks, the use in clinical practice and the effectiveness of the risk minimisation measures in place. This included the responses submitted by the marketing authorisation holders in writing as well as the outcomes of the scientific advisory groups in neurology and psychiatry. In addition, the PRAC considered the views of patient organisations, patients, families and carers, and the views of healthcare professionals in a public hearing and dedicated meeting.
- The PRAC confirmed the known risk of intra-uterine exposure to valproate and related substances, associated with an increased risk of developmental disorders and congenital anomalies in the offspring. No new significant information was identified regarding this risk.
- The PRAC concluded that the risk minimisation measures in place have not been sufficiently effective to prevent unintended *in utero* exposure to valproate and related substances in all indications.
- 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) in women/girls of childbearing potential unless the conditions of the pregnancy prevention programme are complied with.

- The PRAC considered that the pregnancy prevention programme should reflect that in 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. 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.
- For their use in pregnancy for the treatment of epilepsy, the PRAC concluded that these medicinal products are contraindicated unless there is no suitable alternative treatment option. For their use in the treatment of bipolar disorders and prophylaxis of migraine these products are contraindicated in pregnancy.
- In addition, the PRAC recommended other changes to the product information such as warnings and precautions for use and updated information on the risks related to exposure during pregnancy to better inform the healthcare professionals and patients.
- The PRAC also concluded that there was a need to update the educational materials aimed to fully inform patients and healthcare professionals on the risks to the unborn child when exposed *in utero* to valproate, and to implement some further risk minimisation measures such as a visual reminder on the outer packaging, a patient card and an acknowledgment form to raise awareness about the risks and the need for contraception. PRAC also recommended post-authorisation studies to assess the effectiveness of the risk minimisation measures. Core elements of a direct healthcare professional communication were agreed, together with the timelines for its distribution.
- The PRAC also reviewed the available scientific evidence on the risk of malformations and neurodevelopmental disorders to offspring after paternal exposure, the risk of malformations and neurodevelopmental disorders to the third generation offspring and considered that further research is needed before conclusions can be drawn. The PRAC requested the conduct of post-authorisation studies.

In view of the above, the Committee considers that the benefit-risk balance of medicinal products containing substances related to valproate remains favourable subject to the agreed conditions to the marketing authorisations, and taking into account the agreed amendments to the product information and other risk minimisation measures.

The Committee, as a consequence, recommends the variation to the terms of the marketing authorisations for medicinal products containing substances related to valproate.

CMDh position

Having reviewed the PRAC recommendation, the CMDh agrees with the PRAC overall conclusions and grounds for recommendation.

Detailed explanation of the scientific grounds for the differences from the PRAC recommendation

The CMDh acknowledges correspondence received from a MAH (Laboratoires Aguettant, France) of medicinal products containing valproate injectable (intravenous; IV) formulations, and requesting further clarity for the implementation of the pharmacovigilance activities and risk minimization measures adopted by the PRAC for these IV formulation indicated for the temporary management of epilepsy when administration via oral route is not possible.

The MAH requests CMDh to clarify the implementation of the PRAC outcome for injectable forms by further differentiating the routine/additional risk minimization activities to be considered for the non-injectable products and those also applicable to the injectable products.

The CMDh therefore clarified that the amendments to the product information and the other routine measures to inform on the risk to the foetus when valproate is taken in pregnancy to all Healthcare professionals (HCP) and patients are applicable to all medicinal products containing valproate and related substances, irrespective of the route of administration. In addition all products should have in place a risk management plan.

For the following risk minimisation measures, the CMDh clarified that:

Regarding the visual reminder on the outer packaging, it is considered that it is crucial to remind to the HCPs that valproate should not be administered to women of childbearing potential (WCBP) who do not fulfil the pregnancy prevention plan requirements, or to pregnant patients, thus initiating a discussion about the risks of valproate with the patient. This may be particularly important as the prescribers of IV formulations of valproate are expected to be different from the usual prescribers targeted during the implementation of additional risk minimisation measures. The visual reminder is considered important and required to be implemented on the outer packaging of any valproate formulation and presentation.

With regards to the educational materials (i.e. HCP guide and patient guide), these are also considered relevant for the injectable forms of products containing valproate and related substances and therefore should be implemented. Indeed, the HCP guide will provide a reminder to the HCP of the conditions that apply for the administration of valproate (e.g. pregnancy prevention plan), the need to discuss the risks with the patient and check her pregnancy status. Additionally, as the IV valproate formulations will likely be administered by different HCPs than the usual treating physicians, having a HCP guide in place for these products is crucial and therefore such HCP guide will also be provided to prescribers of IV formulation of valproate containing products. For the female patients, there may be situations in which valproate treatment is initiated with the IV formulation (before discharge on valproate oral administration). An early communication of complete information about the risks of valproate is considered essential.

Regarding the circulation of the DHPC, all MAHs are encouraged to collaborate in order to prepare and circulate a single DHPC in each Member State and all MAHs marketing products containing valproate and related substances are required to participate in the dissemination of the information, regardless of the route of administration of their medicinal product(s). The information through the DHPC about risks and the new contraindications and other risk minimization measures is applicable to all formulations.

With regards to the patient card, the CMDh clarifies that the information is intended to act as a reminder for long-term use of valproate. As the injectable formulations are indicated only for short use, the patient card is most likely to be of limited value. Additionally, such patient card is to be attached to the packaging of valproate and related substances containing medicines, and serve as an additional reminder during the dispensing. In cases of patients for whom treatment is initiated with IV valproate formulations and then transferred to oral forms of valproate products, the patient card will be disclosed at the time of dispensing the oral valproate-containing products. Therefore, it is considered that the patient card is not required for injectable formulations products containing valproate and related substances.

The annual risk acknowledgement form for injectable formulations of valproate and related substances containing products is intended to act as a periodic reminder and acknowledgement of the risks of valproate for women of childbearing potential (WCBP). Since the injectable formulations are indicated for short-term use with a short treatment duration, this annual risk acknowledgement form is not considered relevant therefore not applicable. Finally, as the patients will be transferred eventually to non-injectable form of valproate, it is considered that the annual review will be carried out as part of RMMs recommended for oral treatment where the annual risk acknowledgment form will then be used. Consequently, the annual risk acknowledgment form is not required for the injectable formulations.

With regards to the other pharmacovigilance activities and the studies are required to further investigate potential risks with products containing valproate and related substances and to measure the effectiveness of the RMMs, the CMDh clarified that these studies would not be relevant for the injectable products as the information that could be collected for these products would be limited and unlikely to be meaningful in view of the short duration of use, often in urgent situations and only when the oral formulations cannot be administered. Therefore, the adapted PASS study on the drug utilisation, the two surveys targeting HCPs or patients, the PASS from registries in order to characterise the foetal anticonvulsant syndrome in children with anti-epileptic drugs *in utero* exposure, the retrospective observational study on the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders including autism in offspring and, the observational study to evaluate and identify the best practice for discontinuation and switching of valproate treatment, are not applicable to the injectable formulations.

Overall conclusion

The CMDh, as a consequence, considers that the benefit-risk balance of medicinal products containing substances related to valproate remains favourable subject to the amendments to the product information and to the conditions described above.

Therefore the CMDh recommends the variation to the terms of the marketing authorisations for medicinal products containing substances related to valproate.