INTERNATIONAL LEAGUE AGAINST EPILEPSY (ILAE)
Commission on European Affairs (CEA)

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To the kind attention of the members of the:
Coordination Group for Mutual Recognition and Decentralised Procedures – Human, EMA,
and the Pharmacovigilance Risk Assessment Committee (PRAC), EMA

Dear Sirs/Madams,

We are writing on behalf of the International League against Epilepsy (ILAE), the main association for professionals treating epilepsy around the world, and in response to the press release of 10th October 2014 from the Pharmacovigilance Risk Assessment Committee (PRAC) of the EMA. We are aware that the British Chapter of the ILAE and other organisations have already submitted their comments to EMA but the present letter reflects the views of the ILAE as expressed by its relevant Commissions with competence on this issue, i.e. the Commission on European Affairs (CEA), the Commission on Medical Therapies, and the Task Force on AED Trials and Regulatory Affairs. As indicated in the press release headline, the PRAC recommendations aim to strengthen the restrictions on the use of valproate in women and girls, but there are in our view some statements in need of clarification as well as recommendations that raise concerns. We restrict ourselves to comments related to the use of valproate for the treatment of epilepsy.

We fully share the opinion expressed by PRAC that "doctors who prescribe valproate provide women with full information to ensure understanding of the risks and to support their decisions…" and "…that women and health care professionals need to be better informed about the risks of valproate exposure in the womb…"

Needless to say, every therapeutic decision should be based on a careful risk-benefit assessment of available treatment alternatives. In this, teratogenic risks as well as the risks associated with an ineffective treatment must be considered for women of child-bearing potential just as for other people with epilepsy. Epilepsy is a serious condition where uncontrolled seizures can cause harm and even premature death. A recent audit of maternal deaths in the UK suggests that this risk might be even greater in conjunction with pregnancy. A 10-fold increase in mortality was noted in pregnancy in women with epilepsy compared to women without epilepsy (Edey et al.,

2014). Most of these deaths were Sudden Unexpected Death in Epilepsy (SUDEP) demonstrating the importance of complete seizure control.

While for focal epilepsies several effective treatment alternatives exist that have less teratogenic potential than valproate (Tomson and Battino 2012), treatment choices are much more limited for women with idiopathic (genetic) generalized epilepsies (IGE), estimated to account for approximately 25% of people with epilepsy. The randomized SANAD study demonstrated that valproate is significantly better at controlling seizures in IGE than possible alternatives such as lamotrigine and topiramate (Marson et al 2007). Observations from pregnancy registries also suggest superior seizure control during pregnancy with valproate compared to lamotrigine (Battino et al., 2013). We have insufficient evidence about the effectiveness of levetiracetam in IGE and this drug is not approved by EMA for initial monotherapy of seizure types associated with IGE.

Against this background, the ILAE wishes to make the following comments to the PRAC press release.

The PRAC recommendations that *"Valproate should not be used to treat epilepsy or bipolar disorder in girls and in women who are pregnant or who can become pregnant unless other treatments are ineffective or not tolerated"* needs clarifications:

1. Is the recommendation that *"valproate should not be used to treat epilepsy or bipolar disorders in girls"* in general, or just *"girls and women who are pregnant or who can become pregnant"*? Many young girls with epilepsy will be under treatment for a few years only and their treatment withdrawn before they enter the age of child-bearing potential. Should they be denied valproate as first line treatment even if that was the most appropriate choice otherwise?
2. How should *"unless other treatments are ineffective or not tolerated"* be interpreted? Is it necessary to demonstrate the ineffectiveness or poor tolerability of other treatments in every individual patient as the subsequent sentence indicates, and if so how many and which other treatments? Or could the experience of ineffectiveness of the treatment alternatives in other women with the same seizure disorder be sufficient?
3. Should attempts to switch to other, potentially less effective treatments, be mandatory in women that have achieved seizure control on valproate as their first treatment, if they consider pregnancy? Should this trial be made regardless of the dose of valproate? The risks of malformations (Tomson et al., 2011, Tomson and Battino 2012) as well as adverse cognitive development (Meador et al., 2013) with valproate are dose dependent and low valproate doses have been associated with outcomes similar to other treatments. We are aware that with current knowledge it is not possible to define safe doses of valproate but this is also true for other treatment alternatives.

The PRAC further states, "*Women for whom valproate is the only option after trying other treatments, should use effective contraception...*"

1. What is meant by effective contraception?
2. Is the intention with this statement that women for whom valproate is the only option should always be advised against becoming pregnant regardless of dose and their own wish after complete information?

In justification for the proposed restrictions, the PRAC writes: *"Recent studies have shown a risk of developmental problems of up to 30 to 40% in pre-school children exposed to valproate in the womb..."* This unreferenced statement needs clarification.

1. Is it meant to indicate developmental problems in up to 30 to 40% of valproate exposed children, or is "30 to 40%" an estimate of the level of effect on a specific measure of the development of individual children?
2. The expression "up to…." is difficult to interpret as it only indicates the maximum level of effect, and that the effect could be anything below 30 to 40%. The to date most comprehensive prospective study of cognitive development reported IQ in children exposed to low dose of valproate comparable to IQ in children exposed to other antiepileptic drugs (Meador et al., 2013). A more precise and clear estimate of the potential effects on child development would have been of value in the press release.

The ILAE welcomes further consideration of the risks and benefits of the use of valproate for the treatment of epilepsy of women of childbearing potential and agrees that current knowledge of the teratogenic potential of valproate justifies special precautions and restrictions. Our concern is that restrictions need to be formulated so that they do not risk causing harm. Girls and women with epilepsy need easy access to effective treatment for their epilepsy just as much as boys and men. The proposed recommendations of valproate as only a last resort medication for "girls and women who are pregnant or can become pregnant" will force girls and women with IGE to first try treatments that may be less effective or without sufficient evidence of efficacy and thus expose them to the risks associated with uncontrolled seizures.

All treatment decisions involve a discussion of benefits and harms of treatment options. In our view there are situations where the benefits of valproate can outweigh the risks specifically for some girls and women with IGE where valproate should not be seen only as a last resort treatment but rather as one of the first-line options. The ILAE would welcome the opportunity for further discussions of the proposed recommendations with EMA.

Thank you for your kind attention to the above matters.

References

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