Official Communication from the ENTIS Scientific Committee **April 2022**

Re: Product literature (SmPC and PIL) pregnancy section updates for pregabalin containing products

Dear Reader(s),

The European Network of Teratology Information Services, ENTIS, has noticed the recent changes to SmPC section 4.6 “Pregnancy” for medicinal products containing pregabalin. With this letter, we want to raise some points of concern.

ENTIS acknowledges that product literature statements primarily reflect the way a medicinal product is legally authorised to be marketed[1]. However, statements contained within these documents have much wider influences, potentially impacting the prescribing practices of healthcare professionals, and patient confidence.

Product literature (SmPCs and PILs) pregnancy sections have been updated for several pregabalin containing medicinal products in the EU and other regions in which ENTIS members operate (including the UK). These updates utilise evidence provided from an unpublished non-peer reviewed study made available on the EU PAS register[2].

We agree with the overall conclusion from the study report (*“The present study is consistent with the earlier evidence from published population-based studies of an absence of substantially increased risks of congenital malformations.”),* and believe it is critical that these findings be carefully communicated in order to support clinical risk-benefit decision making around pregabalin use in pregnancy. However, upon critical review of this study, some findings appear counter-intuitive, and we believe there are issues with confounding.

After adjustment, the results indicate small increased risks of major malformation among first trimester pregabalin exposed infants in comparison with active comparators exposed to lamotrigine and/or duloxetine, with no measurable increased risk in comparison with population unexposed comparators. Substantial alterations to the crude prevalence ratio estimates were observed after application of the propensity-score adjusted analysis, suggesting significant residual confounding for the latter comparison. We consider this to be particularly important given the potential for maternal pregabalin misuse/recreational abuse[3,4], and the associated concomitant risk factors for adverse pregnancy outcome, many of which will have been unmeasured in this study. Against active comparator groups, crude null-results were **amplified** upon adjustment. This is not discussed to any noticeable extent in the study report on the EU PAS register. A potential factor here may be that in many countries, the prescription of pregabalin for various chronic pain conditions is common, but not so much for duloxetine. Lamotrigine does not hold these indications. The “active comparator” groups may therefore not be all that comparative in terms of underlying diagnoses and severity of disease or symptoms. As such, concomitant risk factors for adverse pregnancy outcome may also differ considerably, and this may be a contributing factor to the counterintuitive findings observed.

Specifically for the product information of the Lyrica® brand (updates applied 7th March 2022), there are several statements that we believe are insufficiently substantiated and potentially misleading for prescribers and pregnant women alike:

1. On the SmPC, *"Data from a Nordic observational study of more than 2700 pregnancies exposed to pregabalin in the first trimester showed a higher prevalence of major congenital malformations (MCM) among the paediatric population (live or stillborn) exposed to pregabalin compared to the unexposed population (5.9% vs. 4.1%)."* However, after adjustment of the prevalence ratio (using a propensity-score method), at the level of 95% confidence, there was no clinically meaningful difference, and no difference using traditional interpretation of statistical significance, in the prevalence of MCM among the pregabalin exposed in comparison with the unexposed population (aPR 1.14, 95% CI; 0.96 to 1.35).

2. The above point is re-stated in the next paragraph of the SmPC, also with the adjusted prevalence ratio statistics quoted. To readers with a basic understanding of medical statistics, this could result in confusion as the statistics contradict the statement (as discussed above), *"The risk of MCM among the paediatric population exposed to pregabalin in the first trimester was slightly higher compared to unexposed population (adjusted prevalence ratio and 95% confidence interval: 1.14 (0.96-1.35))."*

3. The discussion of the crude study results continues on the PIL where it states, *"Pregabalin use during the first 3 months of pregnancy may cause birth defects in the unborn child that require medical treatment. In a study reviewing data from women in Nordic countries who took pregabalin in the first 3 months of pregnancy, 6 babies in every 100 had such birth defects. This compares to 4 babies in every 100 born to women not treated with pregabalin in the study."* Again, whilst these statements are crudely accurate, the statistics quoted do not consider that after adjustment, there was no clinically relevant risk of malformation at the level of 95% confidence. Additionally, the absolute risks suggested by the comparisons against the disease-matched comparators are likely lower than the 6 per 100 cases quoted. Finally, use of the phrase, "*..may cause birth defects,"* in the PIL could also be considered misleading. We suggest a more accurate sentence "*..may be associated with a very small increased risk of birth defects."*

4. A final point of consideration is that although the Toft *et al.* study is the largest available to date, there may still be important methodological limitations that could have contributed to the results. TIS centres routinely consider all published data when counselling on the risks and benefits of medication use in pregnancy. ENTIS strongly advocates including the results from a previous major study in the overall assessment of the fetal safety of pregabalin (see Patorno et al.[5]).

The ENTIS organisation Scientific Committee are concerned that the above statements in the pregabalin product literature will result in confusion and misinformed clinical risk-benefit decision making around pregabalin use in pregnancy. We would urge the PRAC to consider re-wording the SmPC/PIL in order to prevent miscommunication.

ENTIS representatives are experienced in risk/benefit communication relating to medicines use in pregnancy. We would be grateful if the EMA would consider ENTIS as a key-stakeholder to be consulted prior to recommendations about medicines use in pregnancy, particularly where changes to the product literature are planned for medicinal products.

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