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Lamotrigine and risk of oral clefts

Dear

Following discussions with the Irish Medicines Board, GlaxoSmithKline (GSK) would like to inform you about important new safety information regarding Lamictal®.

- An increased risk of oral clefts associated with the use of Lamictal® during early pregnancy has recently been detected in one pregnancy registry.
- The product information for Lamictal® will be updated with this new information.
- The possible risk of oral clefts should be balanced against the needs for treatment. Sudden discontinuation of antiepileptic therapy may lead to breakthrough seizures with serious consequences for both the mother and the foetus and should be avoided.

Emerging data from the North American Anitepileptic Drug (NAAED) Pregnancy Registry suggest an association between Lamictal (lamotrigine) and an increased risk of non-syndromic oral clefts. Specifically, the NAAED Pregnancy Registry detected an elevated incidence of isolated, non syndromic cleft palate deformity occurring in infants exposed to lamotrigine monotherapy during the first trimester of pregnancy compared to the reference population used in this Registry.[1] Recently published data from the Registry report three cases of isolated, non syndromic cleft palate and two cases of isolated, non syndromic cleft lip without cleft palate in infants from 564 first trimester lamotrigine monotherapy exposures giving a rate of 8.9 per 1000.[2] This compares with a prevalence rate of 0.37 per 1000 seen in the general population of the Brigham and Women's Hospital (BWH) Surveillance Program (relative risk in lamotrigine-treated patients vs. BWH general population of 24; 95% CI 10.0-57.4). For reference, the overall rate of major malformations reported by the NAAED registry was 15/564 (2.7%, 27 per 1000) and not different from the reference population.

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The prevalence of oral clefts noted in the NAAED registry is also higher than the background prevalence of non-syndromic oral clefts reported in the literature, including studies from the United States, Australia and Europe. While different studies have differing results due to geographic and case ascertainment variations, the reported range is 0.50 to 2.16/1000 [3-17].

Whereas this finding has not been confirmed by other studies, GlaxoSmithKline (GSK) is in discussion with regulatory authorities around the world about these newly reported data and other relevant information, including outcomes in over 2000 pregnancies from other pregnancy registries, to further understand the significance of this finding. GSK is working with the Irish Medicines Board to update the prescribing and patient information to reflect these new data.

At this time, patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy. The possible risk of oral clefts associated with the use of lamotrigine during early pregnancy should be balanced against the needs for treatment. Sudden discontinuation of antiepileptic therapy may lead to breakthrough seizures with serious consequences for both the mother and the foetus and should be avoided. It should be noted that other antiepileptic drugs have also been associated with congenital malformations.

Any suspected adverse drug reactions should be notified to GSK and/or the Irish Medicines Board in the usual way.

Should you have any questions or require additional information, please contact GlaxoSmithKline on 1 800 244 255.

Yours sincerely,

Martina Dempsey

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