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NON-INTERVENTIONAL STUDY REPORT ABSTRACT

Title: A Population-based Study of the Safety of Gabapentin Use During Pregnancy

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Keywords: Gabapentin, birth outcomes, postnatal neurodevelopmental outcomes.

Rationale and background:

Gabapentin (Neurontin®) received first regulatory approval on 05 February 1993 in the United Kingdom (UK) and is currently marketed in 93 countries. In the European Union (EU), gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above, and as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years and above. In addition, gabapentin is used for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults. Per current EU Mutual Recognition Procedure (MRP) Reference Member States (RMS) summary of product characteristics (SmPC), gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus. To date, gabapentin use in pregnancy has been relatively low.

The aim of this non-interventional study is to evaluate the use and safety of gabapentin in pregnancy using data on pregnancies identified from population-based registries in Denmark, Finland, Norway, and Sweden. To reduce confounding by indication or disease severity, in addition to the use of the AED-unexposed pregnancies as a comparator, this study also included, as active comparators, agents with overlapping albeit not identical indications as gabapentin: namely, pregabalin (indications: epilepsy, neuropathic pain), and lamotrigine (indication: epilepsy). This study has been designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the European Medicines Agency (EMA).

Research question and objectives: The study objectives were to describe the use of gabapentin in pregnancy and to estimate the risk of major congenital malformations, birth outcomes other than congenital malformations, and neurodevelopmental outcomes with the use of gabapentin.

The primary objectives of the study were to:

- Describe use of gabapentin, pregabalin, and lamotrigine during pregnancy overall (for any therapeutic use), and by trimester of pregnancy, indication, cumulative dose, and calendar year of delivery. Description of exposure was performed for all pregnancies, including pregnancies with monotherapy exposure (defined as no concomitant administration with other AEDs) and pregnancies with polytherapy exposure (defined as concomitant administration with other AEDs), as well as the subset of only pregnancies with monotherapy exposure.

- Calculate the prevalence of major congenital malformations in pregnancies with first-trimester exposure to gabapentin, pregabalin, lamotrigine, pregabalin or lamotrigine.

- Perform a sensitivity analysis to calculate the prevalence of major congenital malformations that includes stillbirth and pregnancies ending in therapeutic 2nd trimester induced abortion in the definition of prevalence in pregnancies with first-trimester exposure to gabapentin, pregabalin, lamotrigine, pregabalin or lamotrigine.

- Estimate the associations between first-trimester exposure to gabapentin and prevalence of major congenital malformations, as compared with no exposure to AEDs during the first trimester, exposure to pregabalin during the first trimester, exposure to lamotrigine during the first trimester, exposure to pregabalin or lamotrigine during the first trimester.

- Calculate the prevalence of pre-specified birth outcomes including stillbirth, low birth weight, small for gestational age (SGA), preterm birth, low Apgar score, microcephaly, among pregnancies with any trimester exposure to gabapentin, pregabalin, lamotrigine, pregabalin or lamotrigine.

- Estimate the associations between exposure to gabapentin any time during gestation and other pre-specified birth outcomes, including stillbirth, low birth weight, small for gestational age (SGA), preterm birth, low Apgar score, microcephaly, as compared with no exposure to AEDs any time during gestation, exposure to pregabalin any time during gestation, exposure to lamotrigine any time during gestation, exposure to pregabalin or lamotrigine any time during gestation.

The secondary objectives of the study were to:

- Calculate the incidence rates of pre-specified postnatal neurodevelopmental outcomes (attention-deficit hyperactivity disorders, pervasive developmental disorders, learning disorders and intellectual disabilities) with any trimester exposure to gabapentin, pregabalin, lamotrigine, pregabalin or lamotrigine.

- Estimate the associations between exposure to gabapentin any time during gestation and the pre-specified postnatal neurodevelopmental outcomes, as compared with no exposure to AEDs any time during gestation, exposure to pregabalin any time during

gestation, exposure to lamotrigine any time during gestation, exposure to pregabalin or lamotrigine any time during gestation.

Study design: This PASS is a population-based study using national administrative and medical registers from four Nordic countries: Denmark, Finland, Norway, and Sweden.

Setting: Each participating country is a welfare state with tax-supported universal health care, routinely and prospectively collected data on outpatient dispensings, live and still births, hospital diagnoses, migrations and deaths, and individual-level data linkage including exact mother-child linkage (mother's personal identifier is a data field in the child's birth record).

Subjects and study size, including dropouts: The study population consisted of live and stillbirths of single and multifetal pregnancies from 1 January 2005 to 31 December 2017 in Denmark, from 1 January 2005 to 31 December 2015 in Norway and Finland, and between 1 July 2006 and 31 December 2018 in Sweden. In Sweden, women were also required to be resident in Sweden from 1 year prior to LMP until delivery. Births with a record of exposure to a known teratogenic medication (0.17-0.23% of all eligible records across four countries) and births with a chromosomal abnormality diagnosis (0.11-0.34% of all eligible records across four countries) were excluded.

The total number of live births, stillbirths, and births ending in a 2nd trimester induced abortion included in the analyses in the study period (2005-2015 for Denmark, Finland, and Norway and 2006-2016 for Sweden) were 798,688 in Denmark, 654,483 in Finland, 666,449 in Norway, and 1,315,979 in Sweden.

Variables and data sources:
Variables
Exposure to the medications under study is defined as follows:
Gabapentin exposure – at least one maternal dispensing of gabapentin during the first trimester. Gabapentin monotherapy exposure during the first trimester was defined as at least one maternal dispensing of gabapentin during the first trimester and not any other AED. Comparators/reference groups included No exposure to AEDs, pregabalin exposure, lamotrigine exposure, and pregabalin or lamotrigine exposure. For analyses that use pregabalin as the comparator, pregnancies exposed to both gabapentin and lamotrigine in the same relevant exposure window were excluded. For analyses that use lamotrigine as the comparator, pregnancies exposed to both gabapentin and pregabalin in the same relevant exposure window were excluded. For the outcome of major congenital malformations exposures during the first trimester were considered. For all other outcomes exposures any time during gestation were considered.

Primary outcomes:
Birth outcomes
- Major congenital malformations
- Stillbirth
- Low birth weight
- Small for gestational age among singletons

- Preterm birth
- Low Apgar score at 5 minutes
- Microcephaly

Secondary outcomes:
Postnatal neurodevelopmental outcomes:

- Attention-deficit hyperactivity disorders (ADHD);
- Pervasive developmental disorders including autism spectrum disorders (ASD);
- Learning disorders (Specific developmental disorders of speech and language, and Specific developmental disorders of scholastic skills, and Intellectual disabilities [mental retardation]).

Follow-up for the postnatal neurodevelopmental outcomes, when available, was a minimum of 1 year postnatally and for the maximum period available in the dataset for each birth.

Covariables:
Characteristics of the study population included:

- calendar year of delivery;
- maternal age in years at conception;
- marital/cohabiting status;
- smoking during pregnancy;
- obesity (BMI $\geq$ 30 kg/m^2) or a hospital ICD diagnosis of obesity;
- single or multiple gestation;
- hospital-recorded morbidity based on inpatient and outpatient specialist care or proxy medication use in 12 months pre-LMP: migraine or other headache syndromes, other neurologic disorders, depression, bipolar disorder, alcohol abuse or dependence, drug abuse or dependence, hypertension, haematological diseases, diabetes, asthma, liver diseases, renal impairment, rheumatic diseases, disorders of female pelvic organs/genital tract, thyroid disorders, infections (infections were assessed in 90 days pre-LMP). In Finland, in addition to the hospital diagnoses, diagnoses from primary care were also available and used;
- indicators of maternal health care utilisation in the 12 months pre-LMP (number of inpatient and specialised outpatient encounters);

For the outcome congenital malformations: maternal medication use each as a dichotomous variable, defined by at least one dispensing during the first trimester (AEDs, antidepressants, hypnotics, antipsychotics, analgesics, antihypertensives, non-steroidal anti-inflammatory drugs, drugs for peptic ulcer/gastroesophageal reflux, folic acid, drugs for in-vitro fertilization, thyroid hormones, systemic corticosteroids, and anti-infectives for systemic use).

Data sources
Data from national population-based administrative registries in Denmark, Finland, Norway, and Sweden were used in this study. These national registries include patient, birth, prescription, and total population registries. Within each country, records from all registries are linkable at the individual level by a unique personal identifier. For births recorded in the

birth registries, a maternal unique identifier is a variable on the record of the offspring, enabling exact linkage between a given offspring and maternal history of medication dispensing or diagnoses before or during pregnancy. Diagnoses in all countries were registered based on the International Classification of Diseases, 9th revision (ICD-9) or the International Classification of Diseases, 10th revision (ICD-10) coding system and accessed through patient registries. Medications were classified according to the Anatomical Therapeutic Chemical (ATC) coding system and accessed through prescription registers.

Statistical methods
Descriptive statistics of the use of gabapentin, pregabalin, and lamotrigine in pregnancy, and the distributions of the maternal and offspring characteristics were reported. Prevalence, crude and propensity-score adjusted prevalence ratios were estimated for the birth outcomes comparing pregnancies exposed to gabapentin during relevant exposure period (first trimester only for major congenital malformations and any trimester exposure for other birth outcomes and postnatal outcomes) versus the comparator cohorts. Similarly, incidence rate, crude and propensity-score adjusted hazard ratios were estimated for the neurodevelopmental outcomes. Country-specific crude and adjusted estimates of association were first calculated and reported; then these results were pooled using fixed effects meta-analysis and Mantel-Haenszel (MH) method that allowed retaining information from strata with zero exposed events.

Results:
The number of births exposed to any (poly- or monotherapy) gabapentin was 460 in Denmark, 256 in Finland, 486 in Norway, and 806 in Sweden. Monotherapy accounted for most of the exposures both in the first trimester and any time during gestation. The proportion of gabapentin users in any trimester of a pregnancy ending in a live birth or stillbirth in the study period was 0.06% in Denmark, 0.04% in Finland, 0.07% in Norway, and 0.06% in Sweden. The gabapentin-exposed births had higher than unexposed births prevalence of maternal smoking in pregnancy, maternal obesity, Caesarean delivery, most psychiatric comorbidities and history of use of psychiatric and other medication across all countries. After PS computation, stratification and trimming, no covariates had SMD above the balance cut-off of 0.2 across all contrasts in all participating Nordic countries.

Major malformations
Based on 86 events among 1,781 births gabapentin-exposed in first trimester across four Nordic countries, fixed effect meta-analysis for any major congenital malformation showed aPR 0.99 (95 % CI: 0.80-1.23). Similar results were observed in analyses comparing gabapentin-exposed births with active comparators-exposed births in first trimester. For gabapentin-exposed in first trimester vs unexposed to gabapentin and other AED births, the pooled fixed effect aPRs were based on a small number of events and were 2.30 (95% CI: 0.83-6.36) for nervous system malformations, 1.12 (95% CI: 0.80-1.58) for congenital heart defects, 3.99 (95% CI: 0.51-31.41) for respiratory malformations, 1.15 (95% CI: 0.47-2.79) for digestive system malformations, 10.52 (95% CI: 2.45-45.17) for abdominal wall defects, 1.42 (95% CI: 0.86-2.34) for other malformations. The aPRs were attenuated towards the null value in the analyses comparing the risk of site-specific malformations among gabapentin-exposed births vs births exposed to pregabalin: 0.65 (95% CI: 0.14-3.03) for

nervous system malformations, 0.57 (95% CI: 0.32-1.02) for congenital heart defects, not estimable for respiratory malformations, 0.58 (95% CI: 0.17-1.90) for digestive system malformations, not estimable for abdominal wall defects, 0.68 (95% CI: 0.31-1.49) for other malformations. Contrasts with lamotrigine, and lamotrigine and/or pregabalin also resulted in attenuation of the associations.

Other birth outcomes

For stillbirth, pooled adjusted estimate for gabapentin-exposed births vs unexposed births was 1.24 (95% CI: 0.66-2.34) using fixed effects meta-analysis and 1.14 (95% CI: 0.62-2.12) using MH approach. In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aPRs (95% CIs) were 1.07 (0.40-2.87), 1.69 (0.67-4.27), and 1.68 (0.76-3.73) for pregabalin, lamotrigine and pregabalin or lamotrigine, respectively.

For low birth weight, pooled adjusted estimate comparing gabapentin-exposed births vs unexposed births was 1.21 (1.02-1.44). In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aPRs not appreciably attenuated towards the null value.

For preterm birth, pooled adjusted estimate comparing gabapentin-exposed births vs unexposed births was 1.16 (1.00-1.35). In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aPRs attenuated towards the null value.

For being born small for gestational age, pooled adjusted estimate comparing gabapentin-exposed births vs unexposed births was 1.10 (0.83-1.46). In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aPRs not appreciably attenuated towards the null value.

For low five-minute Apgar score, pooled adjusted estimate comparing gabapentin-exposed births vs unexposed births was 1.09 (0.80-1.48). In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aPRs close to the null value.

For microcephaly, pooled adjusted estimate for microcephaly comparing gabapentin-exposed births vs unexposed births was 0.88 (0.62-1.23). In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed no association, however, the 95% Cis were wide.

Postnatal neurodevelopmental outcomes

For hyperkinetic disorders incl. ADHD, pooled aHR comparing offspring with prenatal exposure to gabapentin vs no exposure to AED was 1.12 (95% CI: 0.82-1.51). In analyses comparing offspring with prenatal exposure to gabapentin vs active comparators, pooled fixed effect meta-analyses showed attenuated aPRs.

For pervasive developmental disorders including ASD, pooled aHR comparing offspring with prenatal exposure to gabapentin vs no exposure to AED was 1.03 (0.67-1.58). In analyses comparing offspring with prenatal exposure to gabapentin vs active comparators, pooled fixed effect meta-analyses showed aPRs close to the null value.

For learning disorders including intellectual disability, pooled aHR comparing gabapentin-exposed offspring vs unexposed offspring was 1.06 (0.75-1.49). In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aHRs (95% CIs) 0.99 (0.62-1 .60), 0.84 (0.51-1.38), and 0.80 (0.52-1.22) vs pregabalin, lamotrigine, and pregabalin and/or lamotrigine-exposed births, respectively.

Discussion:
Pooled aPRs for specific malformations suggested that cardiac, nervous system, respiratory, digestive system malformations, and abdominal wall defects may be more prevalent among births gabapentin-exposed vs births unexposed to AED. Importantly, these risk estimates were imprecise and unstable due to the low number of events and were vulnerable to chance findings due to multiple comparisons. For the remaining birth outcomes, comparing prenatal exposure to gabapentin vs no exposure to AEDs, we could not rule out associations with stillbirth, low birth weight, preterm birth and SGA, however, the risk estimates were small in magnitude, imprecise and analyses using active comparators attenuated pooled aPRs towards the null value for these outcomes. We found no evidence of an association between prenatal exposure to gabapentin and postnatal neurodevelopmental outcomes (hyperkinetic disorders incl. ADHD, pervasive developmental disorders including ASD, and learning disorders including intellectual disability).

Residual confounding, especially confounding by indication cannot be fully accounted for by the applied methods as indication was not available. The gabapentin-exposed pregnancies may differ considerably from not only the unexposed but also the active comparators, and residual confounding due to uneven underreporting of confounders in gabapentin or comparator groups may have influenced the results. Validity of routinely collected healthcare data in Nordic national registries has been found to be high. Although misclassification of study variables cannot be ruled out, the positive predictive values, especially for the outcomes, were high. Moreover, there is an agreement between dispensing records and drug use according to general practitioners data for the chronically used medications.

In this post-authorisation safety study based on routinely collected secondary population-based data from four Nordic countries, prenatal exposure to gabapentin was not associated with an increased risk of most adverse birth outcomes or postnatal neurodevelopmental outcomes. The weak associations observed for low birth weight and preterm birth may, at least partially, be due to residual confounding, although could not be ruled out completely.

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