Medicines Adverse Reactions Committee

Meeting date	1/12/2022	Agenda item	3.2.2
Title	**Pregabalin and risks in pregnancy**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**	**Sponsor**	
pregabalin	Pregabalin Pfizer capsule, 25 mg, 75 mg, 150 mg, 300 mg Pregabalin-AFT oral solution, 20mg/mL	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics AFT Pharmaceuticals Ltd	
PHARMAC funding	Pregabalin Pfizer capsules (all strengths) fully funded		
Previous MARC meetings	Gabapentin and **pregabalin** safety review 184th meeting on 3 December 2020 The committe was asked to consider three safety issues: misuse, abuse and dependence; opioid-related death and respiratory depression; and use in elderly patients.		
International action	MHRA: • Drug Safety Update article published on 19 April 2022: 'Pregabalin (Lyrica): findings of safety study on risks during pregnancy' [2]. • UK Summary of Product Characteristics updated (July 2022) to include information from a Nordic observational study about the risk of major congenital malformations (MCM) associated with pregabalin exposure in pregnancy. • Safety leaflet published on 19 April 2022: 'Pregabalin and risks in pregnancy' [3]. EMA: Has updated SmPC in line with MHRA (August 2022). [redacted]		
Prescriber Update	Spotlight on gabapentin and pregabalin for neuropathic pain March 2021		
Classification	Prescription medicine		
Usage data	QLIK: • Pharmaceutical Dispensing PoC: for period 1 Jan 2017 to 31 Dec 2019, pregabalin was dispensed to 8911 females aged 10-49 years. • Pharmaceutical Dispensing in Pregnancy PoC: for period 2010-2019, pregabalin was dispensed to 24 individuals during the first trimester (16) and/or in the one month prior to pregnancy (14) – all in 2019.		
Advice sought	**The Committee is asked to advise:** • Whether the available information supports the need for the pregabalin data sheet to be updated to include information on the risk of MCM • Whether any communication in addition to MARC's Remarks in *Prescriber Update* is needed on this topic		

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1 PURPOSE

To review the safety of pregabalin use in pregnancy following the publication of an observational study and updates to prescribing information in some other countries.

2 BACKGROUND

The Commission on Human Medicines (CHM) in the UK recently reviewed the safety of antiepileptic drug (AED) use during pregnancy. The Medicines and Healthcare products Regulatory Authority (MHRA) published a Public Assessment Report on this review on 7 January 2021 [1].

The risk of congenital malformation and neurodevelopmental disorders associated with valproate exposure in pregnancy is well documented. The MHRA's review focused on other types of AEDs, examining the available clinical data on the risk of major congenital malformations (MCM), neurodevelopmental disorders and delay, and other reproductive toxic effects based on published scientific literature. The overarching findings of the review were that lamotrigine and levetiracetam are the safer AEDs to use during pregnancy. At this point no concerns were raised regarding the safety of pregabalin.

After a further review, on 19 April 2022, the MHRA issued a drug safety update advising that pregabalin may slightly increase the risk of major congenital malformations (MCM) if used in the first trimester of pregnancy [2]. The safety update cited a Nordic observational study of more than 2,700 pregnancies that were exposed to pregabalin in the first trimester [4]. The UK Summary of Product Characteristics (SPC) for pregabalin was updated to provide information on the study findings.

2.1 Pregabalin

2.1.1 Indication and mechanism of action

Pregabalin is an antiepileptic drug. In New Zealand it is indicated for:

- The treatment of neuropathic pain in adults
- As adjunctive therapy in adults with partial seizures with or without secondary generalisation.

In some countries, there is also a third approved indication for pregabalin: treatment of generalised anxiety disorder (GAD) in adults.

The data sheet for Pregabalin Pfizer [5] describes the mechanism of action as follows:

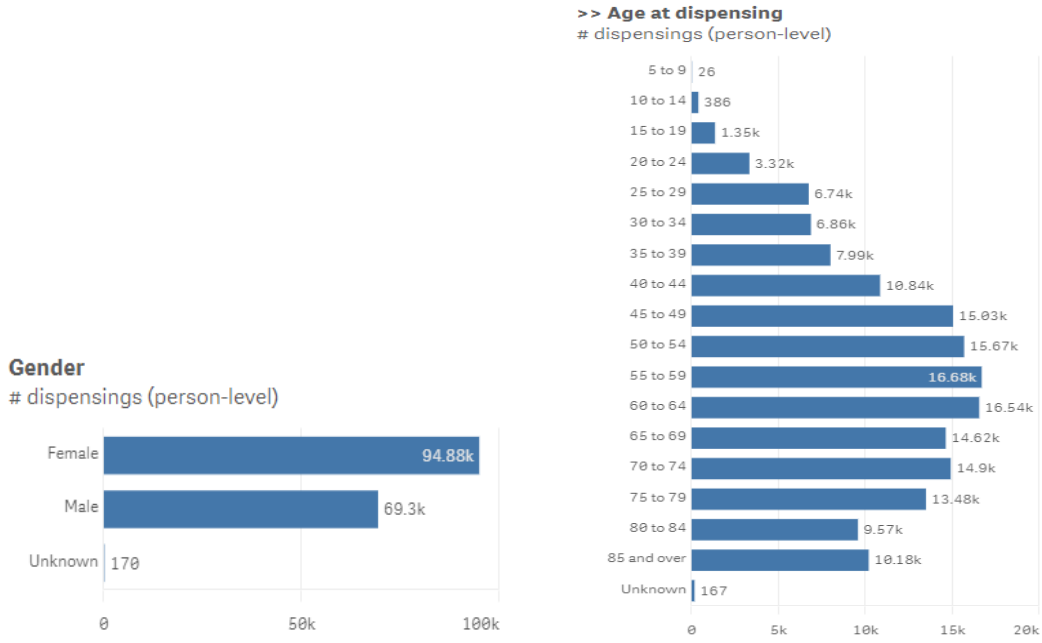
> *In vitro studies show that pregabalin binds to an auxiliary subunit (α2-δ protein) of voltage-gated calcium channels in the central nervous system, potently displacing [3H]-gabapentin. Two lines of evidence indicate that binding of pregabalin to the α2-δ site is required for analgesic and anticonvulsant activity in animal models: (1) Studies with the inactive R-enantiomer and other structural derivatives of pregabalin and (2) Studies of pregabalin in mutant mice with defective drug binding to the α2-δ protein. In addition, pregabalin reduces the release of several neurotransmitters, including glutamate, noradrenaline, and substance P. The significance of these effects for the clinical pharmacology of pregabalin is not known.*
>
> *Pregabalin does not show affinity for receptor sites or alter responses associated with the action of several common drugs for treating seizures or pain. Pregabalin does not interact with either GABAA or GABAB receptors; it is not converted metabolically into GABA or a GABA agonist; it is not an inhibitor of GABA uptake or degradation.*
>
> *Pregabalin prevents pain-related behaviours in animal models of neuropathic and post-surgical pain, including hyperalgesia and allodynia.*
>
> *Pregabalin also shows efficacy in animal models of seizures, including maximal electroshock tonic extensor seizures in mice or rats, threshold clonic seizures from pentylenetetrazol,*

behavioural and electrographic seizures in hippocampal kindled rats, and tonic and clonic seizures in DBA/2 audiogenic mice. Pregabalin does not reduce the incidence of spontaneous absence seizures in Genetic Absence Epilepsy in Rats from Strasbourg (GAERS).

2.1.2 Usage of pregabalin in NZ

In 2019 (the latest date for which Medsafe has access to population level data), the total number of dispensings of pregabalin in New Zealand (NZ) was 164,750, and the number of people who had pregabalin dispensed was 34,790. Figure 1 shows the gender and age-groups that were dispensed pregabalin in 2019 (source Qlik).

Figure 1. Gender and age of people who were dispensed pregabalin in New Zealand in 2019.



The table shows how pregabalin dispensings have changed over year 2018-2020 (source: Pharmaceutical collection, MoH):

Table 1. Trends in pregabalin dispensings from 2018 to 2020.

Year	Number of dispensings	Number of people receiving a dispensing
2018	56,783	17,255
2019	164,348	34,790
2020	260,772	45,192

Between 1 Jan 2017 and 31 Dec 2019, pregabalin was dispensed to 8,911 females aged 10-49 years In NZ (6,850 of these dispensings occurred during 2019) in New Zealand (Pharmaceutical Dispensing PoC, Qlik).

In the period 2010-2019, pregabalin was dispensed to 24 individuals during the first trimester (16) and/or in the one month prior to pregnancy (14) – all in 2019 (Pharmaceutical Dispensing in Pregnancy PoC, Qlik).

2.1.3 Prescribing patterns for pregabalin – general use and in pregnancy

Indication is not required information on prescriptions in New Zealand. However, published international data, shows that in the general population (men and women of all ages), pregabalin is mostly used for treatment of neuropathic pain and least used for control of epilepsy.

An observational study used register data of dispensed drugs and recorded diagnoses for all patients in Stockholm, Sweden, who filled at least one prescription of pregabalin between July 2005 and December 2009. A total of 165,882 prescriptions with pregabalin were dispensed during the study period. To determine the proportion of patients having a history of GAD, neuropathic pain or epilepsy, information concerning diagnoses in the year before the first dispensed pregabalin prescription was included. A total of 18,626 patients were initiated on pregabalin between July 2006 and December 2009, and 63% of them were women. Only 40% of those 18,626 patients, had a recorded approved indication within 1 year of dispensing: 36% were neuropathic pain, 3.6% GAD and 1.3% epilepsy. One-third (34%) of the patients only purchased one prescription of pregabalin and the proportion purchasing pregabalin 1 year after initiation was 42.1% for epilepsy, 36.3% for GAD, 21.5% for neuropathic pain and 25.6% for those without any of the included diagnoses [6].

A recent study analysed utilisation patterns of pregabalin in Germany to investigate potential misuse. The study included 53,049 people (60% females) insured at one of three regional sickness funds, who initiated treatment with pregabalin during 2014-2016 and received at least three prescriptions of the medicine during the observation period of 1 year. The aim of the study was to identify misuse, but it also contains information on which indications pregabalin were prescribed for (only considering diagnoses that had occurred no more than 3 months prior to the prescription). Neuropathic pain was the most frequent indication (approximately 41,000 patients or 77%). General anxiety disorder and epilepsy were prevalent in 3068 and 1968 patients, respectively. About 18% of patients (9283) had none of these diagnosed indications, and 6% of patients (3293) were diagnosed with several conditions [7].

The Nordic observational study states in their background section that pregabalin is prescribed to approximately 0.5 per 1000 pregnant women in Europe [4]. This number is based on data from a study in the United Kingdom (UK), France and Italy [8] and a study from Denmark [9]. However, in several countries the use has risen during the last decade, and in the UK the prevalence of pregabalin prescribing during pregnancy was > 2 per thousand pregnancies in 2015-2016 [8]. In the Nordic observational study, 21% of the pregnant women exposed to pregabalin in the first trimester had a known indication identifiable by a hospital diagnosis in the previous year. Four percent of those diagnoses were epilepsy, 72% were neuropathic pain and 24% were GAD [4].

2.2 Risk of major congenital malformation (MCM)

In June 2020, Pfizer released the findings of a post-authorisation safety study (PASS), which was undertaken as a commitment to the EMA [4]. See section 3.1.1 for a review of the Nordic observational study. The main findings were:

- In crude percentages: 5.9% of infants born to women who took pregabalin in the first 3 months of pregnancy had physical birth abnormalities, compared to 4.1% of infants born to women who were unexposed to AEDs. Crude prevalence ratio: 1.32 (95% CI 1.13-1.55). After adjustment of the prevalence ratio (aPR), the difference was not significant: 1.13 (95% CI 0.97-1.33).
- The study also showed a slightly higher risk of physical birth abnormalities (aPR) in unborn babies exposed to pregabalin compared to lamotrigine 1.36 (95% CI 1.07–1.72) and duloxetine 1.37 (95% CI 1.06–1.77).
- Restricting to monotherapy only marginally changed the results: 1.14 (95% CI 0.96-1.35) for pregabalin monotherapy compared to unexposed; 1.29 (95% CI 1.01–1.65) compared to lamotrigine monotherapy and 1.39 (05% CI 1.07–1.82) compared to duloxetine monotherapy.

On 19 April 2022, the MHRA published a review of pregabalin and risks in pregnancy [3], with the following information about the risks for unborn babies exposed to pregabalin and the following advice for people taking pregabalin who are planning a pregnancy or who may be pregnant (Figure 2):

Figure 2. MHRA Guidance: Pregabalin and risks in pregnancy (published 19 April 2022 [3])

What are the risks to unborn babies who are exposed to pregabalin?

- Physical birth abnormalities can be caused by many different things. In the UK it is estimated that 2 or 3 babies in every 100 births are born with physical abnormalities. The risk (or chance) of physical birth abnormalities is raised by certain medical conditions and in some cases the risk can be increased by certain medicines taken during pregnancy. Some physical birth abnormalities may need medical treatment.
- We have carefully reviewed the results of a new study from 4 European countries. The study showed that taking pregabalin during early pregnancy was associated with a slightly increased chance of having a baby who is born with a physical birth abnormality. It is important to note that this study could not show that pregabalin was the cause of the physical birth abnormalities.
- The study focused on women who took pregabalin during pregnancy. In this study, 6 babies in 100 born to women who took pregabalin in the first 3 months of pregnancy had physical birth abnormalities, compared to 4 babies in every 100 born to women who were not treated with pregabalin or other epilepsy medicines in early pregnancy.
- The study also showed a higher risk of physical birth abnormalities in unborn babies exposed to pregabalin compared to another medicine for epilepsy (called lamotrigine) and another medicine for anxiety and some forms of pain (called duloxetine).

If you are planning a pregnancy, or think you may be pregnant

- It is vitally important that you talk to a healthcare professional about treatments for your health conditions during pregnancy. If you have a condition that requires long-term treatment, it is especially important to ask your doctor whether any changes are needed to your medicines.
- Untreated epilepsy, pain, or anxiety could be harmful to you and your unborn baby. It is important that you talk to your healthcare professional before stopping pregabalin or making any changes to your usual medicines.
- If you're planning a pregnancy, before you stop using contraception you should see your GP, specialist, or nurse to jointly decide the best course of action in your individual situation. They will discuss with you the options and the potential risks, including the risks of different treatments and the risk of your medical condition not being treated. You and your healthcare professional may agree that pregabalin is the safest option for you during pregnancy.
- If you think you may be pregnant and are currently taking pregabalin, you should set up an appointment with your GP, specialist or nurse at your earliest opportunity, to discuss any concerns you may have. However, do continue to take pregabalin as prescribed until you can speak to them.

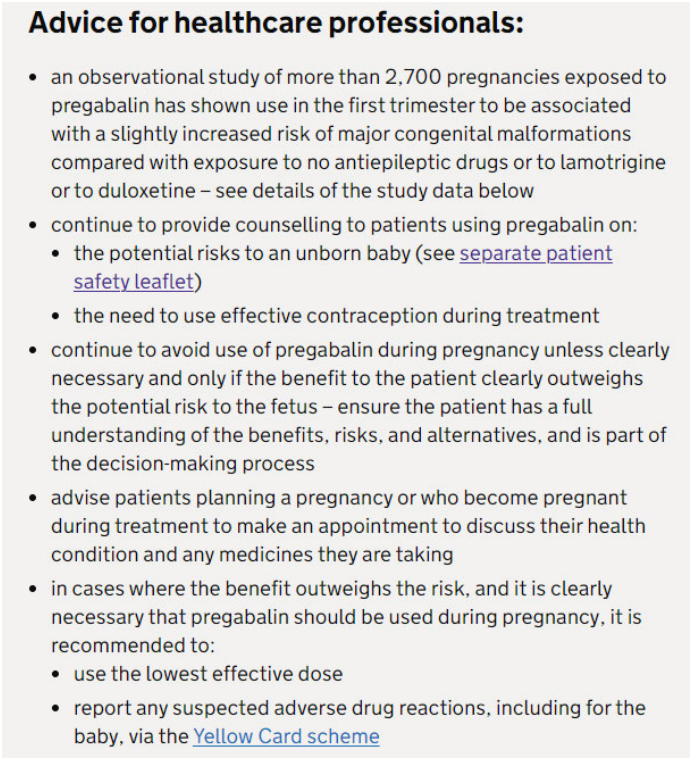
- When planning a pregnancy, taking folic acid is generally recommended before you become pregnant and in early pregnancy to support your baby's development. Talk to your healthcare professional who can recommend the right dose of folic acid for you.
- Always read the Patient Information Leaflet that accompanies your medicine. If you have any questions or concerns about pregabalin, talk to your healthcare professional.

If you are taking pregabalin for epilepsy

- If you have epilepsy, never stop taking medicines such as pregabalin without medical advice. Suddenly stopping epilepsy medicine may cause your seizures to start again or happen more often and last longer than before. Different epilepsy medicines are associated with different risks in pregnancy. Information on this to help patients and their families is in our Guidance on Epilepsy Medicines and Pregnancy.

MHRA also published a more detailed review of the Nordic observational PASS study as a Drug Safety Update [2], including advice for healthcare professionals, on the same day. Figure 3 shows the advice for health care professionals.

Figure 3. Advice given to healthcare professionals in the published MHRA Drug Safety Update on pregabalin [2].



Advice for healthcare professionals:

- an observational study of more than 2,700 pregnancies exposed to pregabalin has shown use in the first trimester to be associated with a slightly increased risk of major congenital malformations compared with exposure to no antiepileptic drugs or to lamotrigine or to duloxetine – see details of the study data below
- continue to provide counselling to patients using pregabalin on:
  - the potential risks to an unborn baby (see separate patient safety leaflet)
  - the need to use effective contraception during treatment
- continue to avoid use of pregabalin during pregnancy unless clearly necessary and only if the benefit to the patient clearly outweighs the potential risk to the fetus – ensure the patient has a full understanding of the benefits, risks, and alternatives, and is part of the decision-making process
- advise patients planning a pregnancy or who become pregnant during treatment to make an appointment to discuss their health condition and any medicines they are taking
- in cases where the benefit outweighs the risk, and it is clearly necessary that pregabalin should be used during pregnancy, it is recommended to:
  - use the lowest effective dose
  - report any suspected adverse drug reactions, including for the baby, via the Yellow Card scheme

Reminder for prescribers of ANY antiepileptic drug:

- at initiation and as part of the recommended annual review for patients with epilepsy, discuss the risks associated with antiepileptic drugs and with untreated epilepsy during pregnancy and review their treatment according to clinical condition and circumstances – see advice for antiepileptic drugs in pregnancy
- urgently refer anyone planning a pregnancy or who is suspected to be pregnant for specialist advice on their antiepileptic treatment
- if a patient is planning to have a baby, offer 5mg per day of folic acid before any possibility of pregnancy

Further information in the Drug Safety Update:

- At the time of the publication of safety advice following the CHM review in 2021 [1], it was noted that due to conflicting data, no firm conclusions could be drawn on the potential teratogenic effect of pregabalin.
- Fuller data is now available from a Nordic observational study of more than 2,700 pregnancies exposed to pregabalin in the first trimester [4] (see section 3.1.1)
- MHRA has reviewed the results of this study alongside a recent European review of the same findings. The review concluded that pregabalin use during the first trimester of pregnancy may cause a slightly increased risk of MCM in the unborn child. Therefore, they have decided to update the SmPC for pregabalin.
- The exposure data from the study indicated that the proportion of women using pregabalin in pregnancy had increased over the 10-year period (up to 2015/2016) and that exposure to pregabalin in pregnancy was most frequent in the first trimester.
- MHRA refer to the findings as above and as described in section 3.1.1.
- They note a risk of confounding, for example by indication.
- MHRA adds: 'although the risk estimates in the study are modest and some are not statistically significant, this is the largest population-based study currently available and there is an indication of a slight increased risk of major congenital malformations with use of pregabalin in the first trimester. It is important for patients to receive this information and consider it carefully with their prescriber'.

2.3 Data sheets

2.3.1 New Zealand [5]

The Pregabalin Pfizer data sheet (last updated 2 February 2022) contains the following information:
In section 4.4 (Special warnings and precautions for use):

> Women of childbearing potential/contraception:
>
> Pregabalin use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus. Women of childbearing potential must use effective contraception during treatment (see section 4.6).

In section 4.6 (Fertility, pregnancy and lactation) regarding pregnancy:

> Pregnancy Category: B3
>
> Limited clinical data on the use of pregabalin in pregnant women is available. PREGABALIN PFIZER should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus.

In a pre- and post-natal study in rats, pregabalin treatment resulted in offspring developmental toxicity at exposures (plasma AUC) ≥5 times the expected human exposure at the maximum recommended clinical dose of 600mg/day.

Offspring development was unaffected at 2 times the expected maximum human exposure.

Labour and delivery

The effects of PREGABALIN PFIZER on labour and delivery in pregnant women are unknown. In a pre- and post-natal development study in rats, pregabalin prolonged gestation and induced dystocia at exposures (plasma AUC) approximately 50 times the expected human exposure at the maximum recommended clinical dose of 600mg/day. These effects were not observed at an exposure that was approximately 12 times the expected human exposure.

2.3.2 United Kingdom [10] and EMA [11]

The Summary of Product Characteristics (SmPCs) for Lyrica (last updated by MHRA in July 2022 and by EMA on 25 August 2022) both contain the following information:

In Section 4.4 (Special warnings and precautions for use):

Women of childbearing potential/Contraception

Lyrica use in the first trimester of pregnancy may cause major birth defects in the unborn child. Pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the foetus. Women of childbearing potential have to use effective contraception during treatment (see section 4.6).

In section 4.6 (Fertility, pregnancy, and lactation) regarding pregnancy):

Women of childbearing potential/Contraception

Women of childbearing potential have to use effective contraception during treatment (see section 4.4).

Pregnancy

Studies in animals have shown reproductive toxicity (see section 5.3). Pregabalin has been shown to cross the placenta in rats (see section 5.2). Pregabalin may cross the human placenta.

Major congenital malformations

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%).

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]) and compared to population exposed to lamotrigine (1.29 [1.01–1.65]) or to duloxetine (1.39 [1.07–1.82]).

The analyses on specific malformations showed higher risks for malformations of the nervous system, the eye, orofacial clefts, urinary malformations and genital malformations, but numbers were small and estimates imprecise.

Lyrica should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the foetus).

The EMA package leaflet for Lyrica contains the following information [11]:

Pregnancy and breast-feeding

> Lyrica should not be taken during pregnancy or when breast-feeding, unless you are told otherwise by your doctor. 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.
>
> Abnormalities of the face (orofacial clefts), the eyes, the nervous system (including the brain), kidneys and genitals have been reported. Effective contraception must be used by women of childbearing potential. If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

2.3.3 United States [12]

The US product labelling for pregabalin (Lyrica) does not currently include information about the risk of MCM associated with exposure in pregnancy.

Comment: note that the updated SmPC states that the risk of MCM after exposure to pregabalin in the first trimester was slightly higher compared to the unexposed population and then refer to a non-significant adjusted prevalence ratio: 1.14 (95% CI 0.96-1.35).

3 SCIENTIFIC INFORMATION

3.1 Published literature

3.1.1 Pfizer Nordic observational PASS study, 2020, unpublished [4]

A Population-based Cohort Study of Pregabalin to Characterize Pregnancy Outcomes

Objective and background

The non-interventional Post-Authorisation Safety (PASS)-study was based on data from registries in 4 Nordic countries: Denmark, Finland, Norway and Sweden. The study aimed to describe the use of pregabalin in pregnancy and to compare the risk of major congenital malformations, adverse birth outcomes and post-natal neurodevelopmental outcomes in pregnancies exposed to pregabalin, lamotrigine (AED comparator) and duloxetine (non-AED comparator). The study is unpublished, but 2 study reports ('Abstract report' and 'Full study report') are publicly available. Reference [4] links to both study reports, and the Full study report is also attached as Annex 1.

In each of the Nordic countries, all live births and stillbirths are recorded in the birth registries from gestational week 22 (before 1 July 2008, the Swedish birth register recorded stillbirths born from gestational week 28). The records can be linked to the individual's unique national person identifier. For births recorded in the birth registries, a maternal unique identifier is a variable in the record of the offspring, enabling exact linkage between a given offspring and maternal history of medication dispensing or diagnoses before or during pregnancy.

Methods

The study population consisted of all pregnancies, identified in the respective administrative registries from 01 January 2005 to 31 December 2015 in Denmark, Finland, and Norway and from 01 July 2006 to 31 December 2016 in Sweden.

All birth outcomes were presumed to have occurred as of the date of delivery. To allow for delayed reporting/diagnosis, diagnoses of congenital malformations were included if recorded until 1 year of age. For neurodevelopmental postnatal outcomes, liveborn children were followed up to a minimum of 1 year and a maximum of 10 years postnatally in Denmark, Finland, and Norway and up to a maximum of 11.5 years postnatally in Sweden.

Exposure was defined by at least one dispensing of one pregabalin, lamotrigine and-or duloxetine during the first trimester or during any trimester. Figure 4 below lists the primary and secondary outcomes of the study.

Figure 4.

Covariates considered for adjustment (inclusion in propensity score model) included for example: smoking, obesity, hospital recorded morbidity in last 12 months and maternal medication use (according to a specific list of medicines).

Descriptive statistics of the use of pregabalin, lamotrigine and duloxetine in pregnancy, and the distributions of the maternal and offspring characteristics were calculated. Prevalence, crude and propensity-score adjusted prevalence ratios were estimated for the birth outcomes comparing pregnancies exposed to pregabalin during relevant exposure period (first trimester only for MCM) versus the comparison groups. Incidence rate, crude and propensity-score adjusted hazard ratios were also estimated for the neurodevelopmental outcomes. The crude and the adjusted country-specific estimates of association were reported separately as well as combined in a meta-analysis.

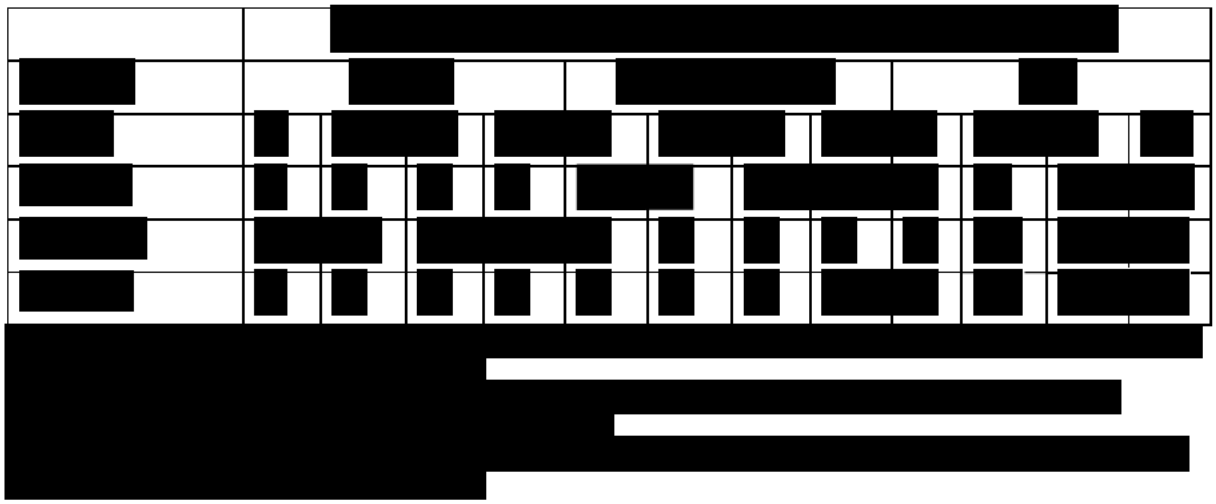
Results

The total number of users of pregabalin in a pregnancy ending in a live birth or stillbirth in the study period was 325/666,146 (0.048%) in Denmark, 965/643,088 (0.16%) in Finland, 307/657,451 (0.046%) in Norway, and 1,275/1,152,002 (0.11%) in Sweden. In all countries, lamotrigine was used more frequently than pregabalin with an overall use in 0.32% of pregnancies in Denmark, 0.15% in Finland, 0.29% in Norway, and 0.26% in Sweden. Duloxetine was used more frequently than pregabalin in

Denmark (0.12% vs. 0.048%) and Sweden (0.14% vs. 0.11%) but less frequently in Finland (0.11% vs. 0.16%) and Norway (0.02% vs. 0.046%).

The distribution of those with a potential indication for pregabalin use, inferred by recorded disease diagnosis, differed between countries, with generalised anxiety disorder (GAD) being the most recorded diagnosis of potential indication in Finland, Norway, and Sweden, and neuropathic pain as the main recorded diagnosis of potential indication in Denmark. The prescribing patterns for lamotrigine and duloxetine differed from the one for pregabalin. See also table below:

Table 2. Pattern of prescribing of the 3 medicines to pregnant women.



The proportion of users of pregabalin in pregnancy was similar among the Nordic countries, in the range of 0.06-0.15 % pregnancies exposed and, in general, use increased over the decade of the study. Lamotrigine use in pregnancy also increased during the study period while duloxetine exposure was stable. Pregabalin was predominantly used in monotherapy in pregnancy (84-88%).

The maternal age distribution was similar in the four countries. Prevalence of smoking was 28-40% of the pregabalin-exposed births and 6-15% in AED-unexposed births. Most of the comorbidities and medicine use was markedly more prevalent in the pregabalin-exposed than in the unexposed births. Births exposed to the active comparators had covariate profiles more similar to those of the pregabalin-exposed than to the unexposed births.

Major malformations

Table 3 below shows country-specific and combined crude and propensity score adjusted prevalence ratios of any major congenital malformations in first trimester pregabalin-exposed pregnancies vs. comparators.

Table 3. Crude, adjusted and MH adjusted MCM prevalence rations for pregabalin vs comparators**

The meta-analysis found a higher prevalence of MCM in the babies (live or stillborn) exposed to pregabalin in the first trimester of pregnancy (crude percentage 5.9%) compared with those not exposed to pregabalin or any other antiepileptic drug (crude percentage 4.1%). After adjustment, the prevalence ratio (aPRs) in the standard meta-analysis for first trimester pregabalin-exposed vs. unexposed was no longer significant: 1.13 (95% CI 0.97-1.33).

The aPRs in the meta-analysis compared to lamotrigine and duloxetine were: lamotrigine, 1.36 (95% CI 1.07-1.72); duloxetine, 1.37 (95% CI 1.06-1.77); lamotrigine or duloxetine, 1.24 (95% CI 1.00–1.54). Restricting to pregabalin, lamotrigine, and duloxetine monotherapy only marginally changed the results: for first trimester pregabalin monotherapy vs.: unexposed, 1.14 (95% CI 0.96-1.35); lamotrigine monotherapy, 1.29 (95% CI 1.01-1.65); duloxetine monotherapy 1.39 (95% CI 1.07-1.82); lamotrigine or duloxetine monotherapy 1.24 (95% CI 1.00-1.54).

The report describes that a few noticeable associations were observed regarding specific malformations. However, no correction for multiple comparisons was conducted and the estimates were imprecise due to low number of exposed outcomes (including frequent zeros). See also table 4 below (results from the meta-analysis):

Table 4: Potential associations found in the meta-analysis regarding specific malformations.

The report states that there was an observed increased risk of eye malformations in Sweden (referring to tables that are not accessible). Therefore, the analysis was repeated with different follow-up times. The aPR (95% CI) of eye malformations up to 1 year of follow-up was 2.71 (95% CI 1.22–6.02). Up to 2 years of follow-up the estimate was 1.12 (95% CI 0.53–2.34), up to 3 years 1.13 (95% CI 0.56–2.25), up to 4 years 1.09 (95% CI 0.55–2.18), and up to 5 years 1.19 (0.62–2.28).

Birth outcomes

Results for the meta-analysis of stillbirth showed an aPR of 1.72 (95% CI 1.02-2.91) for pregabalin-exposed compared to unexposed, and 1.87 (95% CI 0.81-4.32) compared to lamotrigine, 1.46 (95% CI 0.57-3.72) compared to duloxetine, and 2.71 (95% CI 1.25-5.90) compared with the combined lamotrigine and duloxetine group. In the post-hoc meta-analysis including countries with zero events, stillbirth was no longer significantly associated with pregabalin exposure.

Results for the meta-analysis for low birth weight, preterm birth, SGA (small for gestational age), low Apgar score at 5 minutes, and microcephaly for pregabalin-exposed compared to unexposed of 1.05 (95% CI 0.91–1.21), 1.13 (95% CI 0.99–1.29), 1.21 (95% CI 1.01–1.44), 1.18 (95% CI 0.95–1.48), and 1.09 (95% CI 0.88–1.36) respectively, but with estimates closer to null effect for comparison to the active comparators. The prevalence of SGA was slightly elevated in the pregabalin-exposed compared to offspring unexposed to AEDs, it was not elevated in comparison with the active comparators. Pregabalin monotherapy compared to unexposed showed similar aPRs.

Postnatal neurodevelopmental outcomes

In the meta-analyses of the neurodevelopmental outcomes, adjusted hazard ratio for ADHD were for pregabalin-exposed vs: unexposed, 1.32 (95% CI 1.04–1.67); lamotrigine, 1.09 (95% CI 0.79–1.52); duloxetine, 1.11 (95% CI 0.76–1.61); duloxetine or lamotrigine, 1.20 (95% CI 0.89–1.63). Crude estimates suggested markedly stronger associations indicating that confounder adjustment at least partly explained this association. For ASD and ID, the point estimates were close to unity.

Authors' conclusions

The authors concluded that the results do not provide strong evidence of human teratogenicity, or effects on birth outcomes and post-natal neurodevelopmental outcomes after pregabalin exposure. However, in line with previous studies, a small increased risk of adverse birth outcomes in the pregabalin-exposed group compared with unexposed or active comparator groups cannot be completely ruled out, and the associated estimates remain imprecise despite inclusion of data from four countries. The high prevalence of smoking during pregnancy (28–40% of the pregabalin-exposed births compared to 6–15% in AED-unexposed births), a known risk factor associated with adverse birth outcomes, was considered a confounding factor.

The available information on pregabalin exposure lacks sufficient numbers of exposed cases and, despite detailed propensity score adjusted estimates, residual confounding could not be excluded in this observational study. None of the outcomes were observed with a maximum upper CI in the Mantel-Haenszel meta-analyses greater than 1.76 (excluding specific malformations and stillbirths with imprecise estimates due to low number of cases).

The present study is consistent with the earlier evidence from published population-based studies of an absence of substantially increased risks of congenital malformations, adverse birth outcomes, or postnatal neurodevelopment in pregabalin-exposed fetuses in identifiable pregnancies. Several estimates in this study were imprecise due to the low number of events and the results should be interpreted with caution.

Comment: this is the largest population-based study currently available, and data comes from registries that capture all births which should reduce the risk of bias by self-referral, recall, or access to health care.

The study uses dispensings of medicines as a proxy of actual medicine intake, which is better than using the measure of issued prescriptions, but still does not guarantee that the medicine was actually taken.

The study uses active comparators and has selected comparators with the same indications as pregabalin. However, as the prescribing pattern differs between the 3 medicines and the indications are very different, there is a high risk of confounding, especially by indication. There are also differences in prescribing between the countries.

Many of the results are based on few events, including zero events.

For the postnatal neurodevelopmental outcomes, the follow-up time may for many individuals be too short.

3.1.2 Coulm, 2022, Gynécologie Obstétrique Fertilité & Sénologie [13]

Prégabaline et malformations congénitales: une fausse alerte

The *Centre de Référence sur les Agents Tératogènes* (CRAT), a member of the European Network of Teratology Information Services (ENTIS), reviewed Pfizer's population-based study of pregabalin risks in pregnancy [4]. The review, titled Prégabaline et malformations congénitales: une fausse alerte (Pregabalin and congenital malformations: a false alarm), identified several flaws in the study analysis, and concluded that there was no overall risk in major congenital malformation (MCM) in infants who were exposed to pregabalin during the first trimester, compared to unexposed infants. Note that this publication is only available in French (Annex 2), but a Google translation of section 4 and 5 in the publication is attached to this report as Annex 3.

The issues raised include:

- After adjustment, there was no increase in the overall risk of MCM in infants exposed to pregabalin in the 1st trimester, compared to unexposed infants.

- There was no significant difference in the risk of MCM, crude prevalence ratio, in infants exposed to pregabalin compared to those exposed to lamotrigine, duloxetine or to lamotrigine and/or duloxetine, but after adjustment there was a small increase in risk of MCM.
- Lamotrigine and duloxetine were selected as comparator drugs to limit the possibility of indication bias. However, the indications and practical use of these medicines are not entirely comparable. Pregabalin is widely used in neuropathic pain, less so for duloxetine, and not at all for lamotrigine. The prevalence of risk factors for congenital malformations may be different between these groups, which may account for the association becoming significant after adjustment, raising the possibility of residual confounding.

Limitations already identified by the authors in the study include:

- Small numbers make the estimates imprecise
- The significant association found for pregabalin and ocular malformations after 1 year was not found after longer time. It is possible that children exposed *in utero* to pregabalin are followed more closely, resulting in earlier diagnoses of ocular malformations compared to unexposed children. Such case identification bias could potentially account for other types of MCM in exposed children.
- The study only reports on MCMs at the system organ class level (eg, central nervous system, urogenital, etc). There is no information on the exact nature of the MCMs identified in the study.

The authors concluded that the results of the Pfizer post-authorisation safety study are consistent with previous publications and support an absence of association between *in utero* exposure to pregabalin and the occurrence of MCM.

Comment: In April 2022, the European Network of Teratology Information Services (ENTIS) Scientific Committee wrote to the EMA [14], raising concerns with the changes in the product information for pregabalin based on the 'unpublished, non-peer reviewed' Nordic observational study [4]. Main concerns:

- Alterations to the crude prevalence ratio estimates were observed after application of the propensity score adjusted analysis, suggesting significant residual confounding in the latter comparison. They consider this especially important given the potential for maternal pregabalin misuse/recreational abuse which was unmeasured in the study.
- Crude null results were amplified upon adjustment against active comparator groups, which may signal that the active comparators were not that comparative in terms of underlying diagnoses and severity of disease symptoms. As such, concomitant risk factors for adverse pregnancy outcome may also differ considerably.
- They criticise the updated wording in the product information (see section 2.3.2, section 4.6, title 'Major congenital malformations'), saying that the statistics regarding MCM contradicts the first statement on MCM in this text. They also criticise some of the wording in the package leaflet in line with the SmPC, see section 2.3.2. They are concerned that the updates will result in confusion and misinformed clinical risk-benefit decision making.

3.1.3 Winterfeld et al, 2016, Neurology [15]

Pregnancy outcome following maternal exposure to pregabalin may call for concern

Objective and methods

This was a multicenter, observational prospective cohort study comparing pregnancy outcomes in women exposed to pregabalin with those of matched controls (not exposed to any medicines known to be teratogenic or to any antiepileptic drugs). Data from eight Teratology Information Services (TIS) in different countries was analysed. Case and control patients included in the study were women who themselves or whose physician contacted one of the centres between 2004 and 2013. The study was made by the European Teratology Information Services network.

Maternal characteristics (age, tobacco use, alcohol consumption, medical and obstetric history) and information on medicine exposure (indication, timing in pregnancy, duration, dose, and concomitant medicines) were collected at initial contact. After the expected date of delivery, follow-up was achieved through a structured telephone interview or mailed questionnaire to the patient or her health care professional.

The primary outcome of interest was the rate of major birth defects (MBDs). Two independent specialists blinded to information on drug exposure classified birth defects as major or minor using 2 standard classifications.

Results

A total of 164 pregabalin exposed cases and 656 controls were included. Significantly more patients in the pregabalin than in the control group reported tobacco use. The indication for pregabalin treatment was reported for 160 patients and included pain (most often neuropathic pain, n=115), psychiatric disorders (depression, anxiety disorder, bipolar disorder, psychosis, n=39), epilepsy (n=5), and restless legs syndrome (n=1).

The median daily pregabalin dose was 150 mg. Pregabalin therapy started before pregnancy in 77% of the patients and discontinued at a median gestational age of 6 weeks. Sixty-one percent of the patients continued pregabalin treatment beyond week 6 of gestation and 33% beyond week 7. First trimester pregabalin exposure occurred in 96% of the patients and median duration of gestational exposure was 6 weeks (IQR 4–10). In the pregabalin group, 22 (13%) patients were concomitantly treated with another antiepileptic drug. Pregnancy outcomes are presented in Table 5 and the bullet points below.

Table 5. Pregnancy outcomes.

- A significantly higher rate of major birth defects in the pregabalin group persisted after exclusion of chromosomal aberration syndromes, see table 5. Separate analysis of cases with exposure during first trimester of pregnancy (116 patients): (7/116 [6.0%] vs 12/580 [2.1%]; odds ratio 3.0, (95% CI 1.2–7.9), p=0.03.
- The structural anomalies were distributed in 4 organ systems: CNS (n=4), skeletal (n=2), cardiac (n=2), and skin or vascular (n=1).
- The rate of CNS malformations was higher in the exposed group than that observed in the control group. However, all 4 cases were concurrently exposed to other substances and genetic causes have not been formally investigated.
- For the subgroup of 19 patients with pregabalin monotherapy during first trimester, the association with overall MBDs remained significant but became nonsignificant after exclusion of chromosomal or genetic anomalies.
- The rate of live births was lower in the pregabalin group, primarily due to a higher rate of both elective and medical pregnancy terminations. In the Cox proportional cause specific hazards model, pregabalin exposure was associated with a significantly higher risk of pregnancy termination.
- Crude spontaneous abortion rate was higher in the pregabalin group. In the Cox proportional cause specific hazards model, pregabalin exposure was not associated with a significantly higher risk of spontaneous abortion.

The authors discuss that overall, the pregabalin-exposed pregnancies that resulted in malformations were exposed to more medicines and had more complicated medical conditions than those in the comparison group.

Major limitations of the analysis include lack of data on specific malformations, potential selection and detection bias due to self-referral, different information sources for outcome data (health care professionals and patients), low precision, small sample sizes, limited data on folate use and previous/genetic history of pregnancy complications and confounding by indication. For the full study, see Annex 4.

Comment: The authors state that after adjustment for concomitant treatment with antiepileptic drugs, benzodiazepines, antidepressants, alcohol consumption, or twin pregnancy, the OR for major birth defects did not change but do not provide any other adjusted estimates.

This study raises a signal of a potential increase of major birth defects in association with pregabalin use during pregnancy. However, the results are based on very few cases and have a high level of uncertainty because of the study limitations. The authors also call for further confirmation through independent studies.

3.1.4 Patorno et al, 2017, Neurology [16]

Pregabalin use early in pregnancy and the risk of major congenital malformations

Objective and methods

The objective of this cohort study was to assess whether first-trimester exposure to pregabalin is associated with an increased risk of major congenital malformations, as suggested by Winterfeld U et al [15]. The data source was the US Medicaid Analytic eXtract (MAX), for the years 2000 to 2010. The cohort included all pregnancies in women 12 to 55 years of age that resulted in live births for Medicaid beneficiaries. Pregnancies with a documented chromosomal abnormality or exposure to other teratogenic medicines during the first trimester were excluded.

Exposure was defined as at least one filled prescription for pregabalin during the first trimester of pregnancy. The reference group were women with no dispensings for pregabalin or other anticonvulsant medications during the 3 months before the start of pregnancy or during the first trimester. A secondary analysis included women on monotherapy with pregabalin.

The primary outcome was the presence of a nonchromosomal structural major malformation in the infant, defined on the basis of 13 defined inpatient or outpatient ICD-9 diagnoses and procedure. The following covariates were considered: maternal age at delivery, race/ethnicity, year of delivery, smoking, multiple gestation, maternal conditions (n=20 covariates), concomitant medication use (n=19), and general markers of burden of disease (n=8). Sensitivity analyses were done by redefining the exposure to ≥2 prescriptions filled during the first trimester and by basing the outcome on infant claims only.

The reproducibility of the results was tested by a replication analysis in MarketScan, a large nationwide dataset that contains the claims of commercially insured patients in the United States. The adjusted estimates from the MAX and the MarketScan populations were then added to the crude estimates of the study by Winterfeld U et al, and a pooled RR using the DerSimonian and Laird random-effects model was estimated. The crude estimates provided by the multicenter study were considered to be adjusted because the authors had reported that adjustment did not change those point estimates.

Results

There were 1,323,432 pregnancies in the study cohort and 477 of those were exposed to pregabalin during the first trimester. Women exposed were older, more frequently white, had higher prevalence of indications for use and other comorbidities and more frequently used pain/psychotropic medicines. The median dose of pregabalin was 150 mg/d in all indications. Of the pregnancies, 353 were exposed to pregabalin alone.

Table 6 shows absolute and relative risk of major congenital malformations associated with first-trimester exposure to pregabalin any use and monotherapy compared with unexposed women.

Table 6.

The adjusted RR for major congenital malformations for the 174 infants exposed in MarketScan (and 427,304 unexposed) was 1.03 (95% CI 0.56–1.90) with consistent results for those exposed to pregabalin monotherapy. The pooled RR was 1.33 (95% CI 0.83–2.15) for pregabalin any use and 1.02 (95% CI 0.69–1.51) for pregabalin monotherapy. No pregabalin-exposed infant in either population had a diagnosis of cerebral enlarged ventricles or brain anomalies. The sensitivity analysis results were consistent with the main findings.

Limitations identified included that filled prescriptions were used as measurement (however, the aim of the sensitivity analysis of 2 filled prescriptions was to make sure that the medicine was actually taken), the outcome was based on coded diagnoses in claims, the cohort was restricted to live births and that there were no stratified analyses by dose or indication of use.

The authors concluded that the findings suggest that maternal use of pregabalin during the first trimester is not associated with a significantly increased risk of congenital malformations, although a modest increase in risk cannot be ruled out. Their opinion was that residual confounding or chance finding in the setting of a small sample size was likely attributable to the reported large increase in the study by Winterfeld et al [15]. For the full study, see Annex 5.

Comment: This study included more pregnancies exposed to pregabalin compared to the study by Winterfeld U et al [15]. It was population based and not restricted to those who contacted a TIS. The actual exposure of pregabalin is however more unclear in this study as it measured filled prescriptions (which is not the same as actual medicines taken) while information on medicine exposure is provided by the medical history taken at first contact with TIS and at follow-up.

3.1.5 Blotière et al, 2019, Neurology [17]

***Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic* drugs**

Objective and methods

The objective of this French study was to assess the association between exposure to monotherapy with 10 different antiepileptic drugs (AEDs) during the first 2 months of pregnancy and the risk of 23 major congenital malformations (MCMs) in live births. They detected MCMs up to 24 months after birth.

Data came from the French National Health Insurance claims information system, covering 99% of the 67 million inhabitants in France. The system mainly links 2 nationwide datasets: the French national health insurance database (DCIR) and the French hospital discharge database (PMSI). Dispensed

medicines are included in DCIR while PMSI contains detailed medical information on all admissions to public and private hospitals, including deliveries.

All pregnancies ending between January 2011 and March 2015 with at least 20 weeks of gestation were eligible for inclusion. Twin pregnancies, those who could not be linked to neonatal data, pregnancies with teratogenic infections or those exposure to teratogenic medicines were excluded. Women were considered to be exposed when an AED had been dispensed between 1 month before and 2 months after the beginning of pregnancy. The reference group were pregnant women with no reimbursement for AEDs. A sensitivity analysis was conducted to account for possible misclassification of exposure at the beginning of pregnancy including women who had an AED dispensed at least once during the first 2 months of pregnancy.

Cofactors such as maternal age at birth, folic acid supplementation (at least 1 dispensing between 1 month before and 3 months after the start of pregnancy but not counting OTC folic acid), pregestational diabetes and diagnosis of epilepsy or mood disorders were identified.

Results

The cohort included 1,886,825 pregnancies and 1,870,234 (99.1%) of these ended in a live birth. 8,794 were exposed to AED monotherapy which was pregabalin in 1,671 (19.0%) of the pregnancies.

Baseline characteristics for women exposed to pregabalin compared to unexposed women: older, more frequently had low incomes and pregestational diabetes was more frequent. They were not more commonly reimbursed for folic acid than the unexposed women.

One significant association was found for pregabalin exposure: the risk of coarctation of aorta (OR 5.8, 95% CI (1.6–14.9)) based on 4 cases. In the sensitivity analysis, exposure to pregabalin became associated with an increased risk of craniosynostosis (no numbers are given in the article, but in the supplements: (OR 8.1, 95% CI (1.7–23.7)) based on 3 cases. Note that for MCMs with fewer than five cases per treatment group, crude ORs with exact CI were reported.

The authors discuss that studies of pregabalin during pregnancy have shown contradictory results. Regarding limitations of this study, they note that there is a risk of exposure misclassification, especially for AED classes that are often discontinued before conception, which could explain why certain associations were no longer significant in the sensitivity analysis. In particular, pregabalin was often discontinued before conception; the number of women exposed decreased from 1,671 to 918 when the dispensing window was reduced to the first 2 months of pregnancy.

The authors conclude that the result for pregabalin suggests that prenatal exposure was associated with an increased risk of 1 specific MCM, but as a result of possible exposure misclassification or confounding and the small number, the association needs to be interpreted with caution and confirmed by in-depth studies with a sample size allowing more definitive conclusions.

Comment: the results are based on very few cases. Parental history of MCMs and smoking were not adjusted for, and alcohol intake was only measured with a proxy.

3.1.6 Mostacci et al, 2018, J Neurol Neurosurg Psychiatry [18]

Emilia-Romagna Study on Pregnancy and Exposure to Antiepileptic drugs (ESPEA): a population-based study on prescription patterns, pregnancy outcomes and fetal health

Objectives and methods

The objective of this Italian retrospective observational study was to assess the prevalence of AED exposure in pregnant women and the comparative risk of terminations of pregnancy (TOPs), spontaneous abortions, stillbirths, major birth defects (MBDs), neonatal distress and small for gestational age (SGA) infants following intrauterine AED exposure.

Data came from 2 data bases: certificate of delivery assistance (Certificato di Assistenza al Parto—CedAP) and the hospital discharge card (Scheda di Dimissione Ospedaliera (SDO) in a region with about 4,5 million inhabitants. All women residents who had a delivery or underwent an abortion in a hospital in this region, between 1 January 2009 and 31 December 2011 were included.

Exposure was measured by prescriptions of an AED. All the MBDs reported by paediatricians during the first week of the infant's life or detected during the first year of life (from hospital discharge cards) were identified.

Results

The study included 145,243 pregnancies, 611 of those women were exposed to an AED during pregnancy and in 353 cases the exposure occurred in the first trimester. Fourteen of these babies were exposed to pregabalin. During the observational period, 2,302 cases of newborns with MBDs were reported. In one report of ventricular septal defect, the baby had been exposed to pregabalin during the first trimester.

Comment: The numbers of pregabalin exposed babies are too small in this study for any conclusions to be drawn.

3.2 CARM data

As of 21 October 2022, the Centre for Adverse Reactions Monitoring (CARM) had not received any reports of congenital malformations associated with exposure to pregabalin *in utero*. The database was searched using the reaction terms 'abortion' and 'drug exposure in pregnancy' under reproductive female disorders, foetal disorders and neonatal/infancy disorders and no reports were identified.

4 DISCUSSION AND CONCLUSIONS

Pregabalin is indicated for use in neuropathic pain and epilepsy in New Zealand. In some counties it is also indicated for generalised anxiety disorder. Prescribing data suggest that more females than men are prescribed pregabalin and the main use is in neuropathic pain with only minor use in epilepsy.

Studies have shown that pregabalin is sometimes used in pregnancy, and data from New Zealand also confirms this, albeit to a low degree. The data sheet states that 'pregabalin should not be used during pregnancy unless the benefit to the mother clearly outweighs the potential risk to the fetus'. In the individual benefit-risk assessment, it is important to consider which alternative treatments are available for treatment of the indication and the appropriateness of these for the pregnant women.

The risk of MCM following pregabalin treatment in the first trimester has been analysed in few studies with contradictory results. The study by Winterfeld U et al [15] raised a signal for an increased risk of major birth defects, but this association was not confirmed in the study by Patorno E et al [16].

The largest population-based study, the Nordic observational study, is not published, even if the study report was published online in June 2020 [4]. This study showed a higher percentage of infants born to women who took pregabalin in the first trimester had physical birth abnormalities compared to infants born to women unexposed to AEDs. However, this difference was not significant after adjustment of the prevalence ratio. The study also showed a slightly higher risk of MCM in babies exposed to pregabalin compared lamotrigine or duloxetine.

The Nordic observational study, as well as the other studies, may be prone to a high level of methodological limitations and confounding. For example, it is hard to compare effects when the medicines studied have different profiles of prescribing within the approved indications. Also, the studies include different populations (all pregnancies during a specific time or pregnancies that actively contacted a TIS center) and the results are often based on very small numbers of exposed/ events.

Overall, the available data is sparse and uncertain which makes it hard to be able to confidently state whether treatment with pregabalin increases the risk of malformations, even if it currently does not indicate a significant increase in risk that is ensured.

For that reason, pregabalin should, if possible, be avoided during pregnancy, which is already stated in the data sheet. The text can be further strengthened, for example if results from the Nordic observational study are considered strong enough to be included, in line with the updates made in UK and EMA product information. If so, attention should be given to the formulation of the text, for example to not state results that are not significant as evidence for slight differences between patient groups.

5 ADVICE SOUGHT

The Committee is asked to advise:

- Whether the available information supports the need for the pregabalin data sheet to be updated to include information on the risk of MCM
- Whether any communication in addition to MARC's Remarks in *Prescriber Update* is needed on this topic

6 ANNEXES

Annex 1: Full study report Nordic Observational PASS study.

Annex 2: Coulm B (French)

Annex 3: Coulm B (English translation)

Annex 4: Winterfiel U et al.

Annex 5: Patorno E et al.

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