Observational Study to Assess Maternal and Fetal Outcomes Following Exposure to Duloxetine (F1J-MC-B059)

First published: 02/08/2017

Last updated: 15/08/2024

Study Finalised

Administrative details

EU PAS number

EUPAS20253

Study ID

44527

DARWIN EU® study

No

Study countries

- ☐ Denmark
- ☐ Finland
- ☐ Norway
- ☐ Sweden

Study description

There are no published large controlled studies examining the safety of duloxetine in pregnancy. Given the limitations of spontaneous adverse reports and the small sample size of the duloxetine registry, there is currently limited information regarding the safety of duloxetine in pregnancy.To determine whether exposure to duloxetine during pregnancy is associated with an increased risk of adverse maternal and fetal outcomes, including major congenital malformations, perinatal mortality, spontaneous abortion, preterm birth, and Small for Gestational Age (SGA).

Study status

Finalised

Research institutions and networks

Institutions

Department of Epidemiology, Institute of Applied Economics and Health Research (ApHER)

Denmark

First published: 22/02/2013

Last updated: 01/07/2019

Institution | **EU Institution/Body/Agency** | **ENCePP partner**

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Li Hu

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 07/03/2017

Actual: 07/03/2017

Study start date

Planned: 30/05/2018

Actual: 15/10/2018

Date of final study report

Planned: 28/03/2019

Actual: 27/09/2019

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Eli Lilly and Company

Study protocol

B059 05 Protocol (a)_Redacted__s.pdf(2.59 MB)

Regulatory

Was the study required by a regulatory body?

Yes

Is the study required by a Risk Management Plan (RMP)?

Non-EU RMP only

Methodological aspects

Study type

Study type list

Study topic:

Disease /health condition

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Assessment of risk minimisation measure implementation or effectiveness

Data collection methods:

Secondary use of data

Main study objective:

To assess the relative risk of major congenital malformation overall and specific malformation (pre-specified) – comparing first trimester duloxetine exposure to comparators (unexposed, SSRI, venlafaxinevenafaxine/SNRI, duloxetine discontinuator), events to be assessed through first year of life among infants

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Name of medicine

ARICLAIM

CYMBALTA

YENTREVE

Name of medicine, other

Xeristar

Medical condition to be studied

Exposure during pregnancy

Population studied

Short description of the study population

The basis for all the analyses will be data from national birth registers of Denmark and Sweden and national patient registries.

1) Analyses of major congenital malformations

a) Inclusion criteria: 1. Base cohort to include all pregnancies ending in a live birth from the national birth registries of the 2 countries with linked offspring from 2004 to 2015 2. Information on mother available 12 months prior to the LMP until 1 month postdelivery 3. Information on offspring available up to 12 months after the delivery

b) Exclusion criteria: 1. Pregnancies where information on the mother is unavailable from 12 months prior to the LMP until 1 month post-delivery. 2. Pregnancies with a chromosomal abnormality based on at least 1 inpatient or outpatient diagnosis of Q87.1, Q87.4, Q9X (International Classification of Diseases 10th revision [ICD-10]) within the first 12 months of the date of birth. 3. Pregnancies complicated by outpatient exposure to definite teratogens including warfarin, antineoplastic agents, isotretinoin, misoprostol, lithium, and thalidomide from LMP through LMP plus 90 days (i.e., days of exposure overlap with first trimester).

2) Analyses of preterm delivery and SGA

a) This cohort will include all live births with the following inclusion and exclusion criteria:

b) Inclusion criteria: 1. Base cohort will include pregnancies drawn from the Danish and Swedish birth registers with linked offspring 2. Information on

mother available 12 months prior to the LMP until 1 month postdelivery. 3. For the outcomes of preterm delivery and SGA, information on the offspring for at least 1 month after the delivery is required, unless the infant died prior to the end of the first month, in which case age at death will be the time of exclusion from the analyses.
c) Exclusion criteria: 1. Pregnancies where information on the mother is unavailable from 12 months prior to the LMP until 1 month post-delivery. 2. Pregnancies for which information on gestational age is missing or implausible. 3. Offspring where information on birth weight is missing. 4. Pregnancies in which duloxetine is dispensed in the 3 months prior to the LMP but not during the first trimester (to ensure that there is not misclassification of the non-exposed), except for the analyses using these duloxetine discontinuers as the reference group.

3) Analyses of stillbirths
a) This cohort will be similar to that used to study major congenital malformations, with the exception of the inclusion of stillbirths (deaths after 22 weeks of gestation).
b) Inclusion criteria: 1. Base cohort to include all pregnancies drawn from the national birth registries of Denmark and Sweden with linked offspring from 2004 to 2015 2. Information on mother available 12 months prior to the LMP until delivery
c) Exclusion criteria: 1. Pregnancies where information on the mother is unavailable from 12 months prior to the LMP until delivery 2. Pregnancies for which information on gestational age is missing or implausible

4) Analyses of spontaneous and elective abortions
a) The study population used for this outcome will highly depend on the availability of data from the 2 countries and their legislation. It is unclear if

abortion data from both countries will be accessible.
b) Data from Denmark will be available and has previously been used to estimate risk of abortion among duloxetine-exposed pregnant women. The study only included data from 1997 to 2008. Data are not available from Sweden. The information on abortions are available only on an aggregated level and without unique personal identification number. The Swedish government wants to make it possible to register abortions in the National Patient Register but it has not been decided when this will become effective.
c) Base cohort to include all pregnancies from the national birth registries of the 2 countries with linked offspring and all women with a diagnosis of spontaneous or elective abortion from the national hospital registers, from 2004 to 2015.
d) Inclusion criteria: 1. Information on mother available 12 months prior to the LMP until 1 month post-delivery/abortion.
e) Exclusion criteria: 1. Missing information on gestational length or date of abortion

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Age groups

Preterm newborn infants (0 – 27 days)
Term newborn infants (0 – 27 days)
Infants and toddlers (28 days – 23 months)
Adults (18 to < 46 years)
Adults (46 to < 65 years)

Special population of interest

Pregnant women

Estimated number of subjects

1400

Study design details

Outcomes

major congenital malformation, non-live birth (spontaneous abortion, still birth, elective termination)

Data analysis plan

We will compare differences in basic characteristics for the duloxetine exposed and reference group. Focus will be on country of origin, birth year, maternal age, birth order, smoking, comedication, comorbidity and socioeconomy. Baseline characteristics will be compared with chi-square tests for categorical variables. For the chosen outcome, we will calculate absolute risks and unadjusted relative risks with their 95% CI.

Documents

Study report

LY248686 B059 PASS Final study report.pdf_EUPAS_NoCCIreview_Redacted.pdf (3.82 MB)

Data management

ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

Data sources

Data sources (types)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No