Lamotrigine use in Pregnancy and Risk of Orofacial Clefts II

First published: 16/02/2015

Last updated: 01/04/2024

Study Finalised

Administrative details

EU PAS number

EUPAS8618

Study ID

28515

DARWIN EU® study

No

Study countries

- Belgium
- Croatia
- Denmark
- Finland
- France
- Germany

Ireland
Italy
Malta
Netherlands
Norway
Portugal
Spain
Sweden
Switzerland
United Kingdom

Study description

Following a US Federal Drugs Agency alert in 2006 concerning an increased risk of orofacial cleft associated with first trimester exposure to the new anti-epileptic drug (AED) lamotrigine, the EUROCAT AED database was created in 2007 to evaluate this signal using EUROCAT data. The original database included data from 19 registries covering a population of 4 million births, 1995-2005. The database was used to conduct a case-control study evaluating the risk of orofacial clefts in relation to lamotrigine exposure. The study found no evidence of a specific increased risk of isolated orofacial clefts relative to other malformations due to lamotrigine monotherapy. In order to estimate the risk of orofacial clefts relative to other malformations more precisely and to explore whether lamotrigine exposure may be associated with other malformations, a follow-up study was commissioned. This involved 5 yearly updates (2009, 2010, 2011, 2012, and 2013). The final study included data from 21 registries and covered over 10 million births. No evidence of an increased risk of orofacial clefts relative to other malformations associated with lamotrigine exposure in the first trimester was found.

Study status

Finalised

Research institutions and networks

Institutions

Centre for Maternal, Fetal and Infant Research (MFIR), Ulster University

United Kingdom (Northern Ireland)

First published: 31/01/2023

Last updated: 27/03/2026

Institution **Educational Institution** **ENCePP partner**

Networks

European Surveillance of Congenital Anomalies (EUROCAT)

- Austria
- Belgium
- Croatia
- Czechia
- Denmark
- Finland
- France
- Germany
- Hungary
- Ireland
- Italy

Malta
Netherlands
Norway
Poland
Portugal
Spain
Sweden
Switzerland
United Kingdom

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Network **ENCePP partner**

EUROmediCAT

Contact details

Study institution contact

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Study contact

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Primary lead investigator

Helen Dolk

Primary lead investigator

Study timelines

Date when funding contract was signed
Actual: 07/05/2009

Study start date
Actual: 17/08/2009

Data analysis start date
Actual: 29/10/2009

Date of final study report
Planned: 15/03/2015

Actual: 15/03/2015

Sources of funding

- EU institutional research programme
- Pharmaceutical company and other private sector

More details on funding

GSK, DG Sanco

Regulatory

Was the study required by a regulatory body?

No

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

Not applicable

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 investigate more precisely whether first trimester exposure to lamotrigine (LTG) monotherapy is specifically associated with an increased risk of orofacial clefts (OCs) relative to other malformations, in a follow-up study involving 5 yearly updates (2009, 2010, 2011, 2012, and 2013).

Study Design

Non-interventional study design

Other

Non-interventional study design, other

Case-malformed control study

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(N03AX09) lamotrigine

lamotrigine

Medical condition to be studied

Cleft lip and palate

Cleft palate

Population studied

Short description of the study population

Pregnant women who had first trimester exposure to the new anti-epileptic drug (AED) lamotrigine.

Age groups

- Preterm newborn infants (0 – 27 days)
- Term newborn infants (0 – 27 days)
- Infants and toddlers (28 days – 23 months)

Special population of interest

Pregnant women

Estimated number of subjects

10.061.059

Study design details

Outcomes

Odds of lamotrigine exposure among OC registrations (cases) was compared with the odds of lamotrigine exposure among malformed non-OC registrations (controls). Explore whether lamotrigine exposure may be associated with other malformations, and in particularly, assess independent evidence for the association with club foot signalled in the original study.

Data analysis plan

Crude odds ratios (ORs) were calculated as well as ORs adjusted for maternal age, and adjusted for registry

Documents

Study publications

Janneke Jentink, Maria A Loane, Helen Dolk, Ingeborg Barisic, Ester Garne, Joan…

Jentink J, Dolk H, Loane MA, Morris JK, Wellesley D, Garne E, de Jong-van den B…

Dolk H, Jentink J, Loane M, Morris J, de Jong–van den Berg LT. Does lamotrigine…

Dolk H, Wang H, Loane M, Morris J, Garne E, Addor MC, Arriola L, Bakker M,Baris…

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 source(s)

European network of population-based registries for the epidemiological surveillance of congenital anomalies

Data sources (types)

Disease registry

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

Unknown