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Final Study Report

Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing valproate: utilisation and prescribing trends

Version 3.0

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Summary information

Title	Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing valproate: utilisation and prescribing trends
Version identifier of the final study report	3.0
Date of last version of the final study report	20 June 2022
EU PAS register number	EUPAS31001
Active substance	Valproic acid (ATC N03AG01, including valproate semisodium and sodium valproate), Valpromide (ATC N03AG02)
Medicinal product	Valproic acid (ATC N03AG01, including valproate semisodium and sodium valproate), Valpromide (ATC N03AG02)
Product reference	Not applicable
Procedure number	Not applicable
Joint PASS	Not applicable
Research question and objectives	This report describes a pharmacoepidemiological study using longitudinal data collected in five electronic health care databases from four EU countries and the UK to investigate the use of valproate-containing medicinal products authorised in the EU before and after implementation of the 2018 revised risk minimisation measures for pregnancy prevention in clinical practice, and effectiveness of the 2018 intervention. The research objectives were: Objective 1: To determine drug utilisation and prescription patterns of valproate-containing medicinal products in females of childbearing potential, and to investigate whether significant changes in prescribing patterns occurred (pre-/post-intervention). Objective 2: To determine prescribers' compliance with the recommendations in the SmPC for valproate-containing medicinal products, by indication, age group, duration of use, and database. Objective 3: To determine, in so far as is possible, patients' use of effective contraception in compliance with recommendations in the SmPC for valproate-containing medicinal products, by indication, age group, method of contraception and database. Objective 4: To determine drug utilisation and prescription patterns over time for alternative medicines prescribed in females of childbearing potential and female becoming pregnant where valproate-containing medicinal products had previously been prescribed or discontinued, by indication, age group and database. Objective 5: Based on the results of the above, to estimate the effectiveness of the 2018 risk minimisation measures for valproates.
Countries of study	Denmark, Italy, the Netherlands, Spain, and United Kingdom.
Principal investigators	Prof Dr Olaf Klungel, Universiteit Utrecht, Utrecht, the Netherlands Prof Dr Miriam Sturkenboom, University Medical Center Utrecht, Utrecht, the Netherlands

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Marketing authorisation holder(s)	Not applicable

Table of contents

List of tables

List of figures

1. Abstract

Title

Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing valproate: utilisation and prescribing trends

Keywords

Sodium valproate, congenital abnormalities, contraceptive agents, pregnancy, risk minimisation measures (RMMs), bipolar disorder, epilepsy, migraine prophylaxis.

Rationale and background

In March 2018, the European risk minimisation measures (RMMs) with a Pregnancy Prevention Program (PPP) for valproate-containing medicines was updated. A pharmacoepidemiological study was conducted using longitudinal data collected in five electronic health care databases from four EU countries and the UK to investigate the use of valproates authorised in the EU before and after implementation of the 2018 revised measures for pregnancy prevention in clinical practice, and effectiveness of the 2018 intervention.

Objectives

Objective 1: To determine drug utilisation and prescription patterns of valproate-containing medicinal products in females of childbearing potential, and to investigate whether significant changes in prescribing patterns occurred (pre-/post-intervention).

Objective 2: To determine prescribers' compliance with the recommendations in the Summary of Products Characteristics (SmPC) for valproate-containing medicinal products, by indication, age group, duration of use, and database.

Objective 3: To determine patients' use of effective contraception in compliance with recommendations in the SmPC for valproate-containing medicinal products, by indication, age group, method of contraception, and database.

Objective 4: To determine drug utilisation and prescription patterns over time for alternative medicines prescribed in women who became pregnant, where valproate-containing medicinal products had previously been prescribed or discontinued, by indication, by age group and by database.

Objective 5: Based on the results of the above, to estimate the effectiveness of the 2018 RMMs for valproates.

1.1 Abstract Objective 1

Aim: To determine drug utilisation and prescription patterns of valproates in women of childbearing potential, and to investigate whether significant changes in prescribing patterns after the 2018 EU RMMs occurred, using longitudinal data collected from five electronic health care databases from four EU countries and the UK.

Methods: We performed an observational times series study including all female subjects of childbearing age (aged 12 to 55 years) from the corresponding databases in Denmark (Danish National Registers, DNR), Italy (ARS Tuscany), the Netherlands (PHARMO Database Network), Spain (Base de datos para la Investigación Farmacoepidemiológica en Atención Primaria, BIFAP), and UK

(Clinical Practice Research Datalink, CPRD) between 01 January 2010 to 31 December 2020. The incident use, prevalent use and rate of discontinuation thereof was estimated per month in each data source, in addition to the change in level and trend in use after the implementation of the 2018 EU RMMs, using an interrupted time series (ITS) analysis design.

Results: There were 69,533 valproate users out of a total of 9,699,371 female subjects of childbearing age from the five participating centres during the study period. The median follow-up time of the study population ranged between 3.5-10.0 years and the mean age at the start of follow-up was always ≥30 years in different centres. The monthly incidence rate of valproate use ranged between 0.01-0.47 per 1000 persons months across databases and the prevalence rate ranged between 1.2-7.7 per 1000 female subjects. While the observed rates were similar for DNR, PHARMO, BIFAP and CPRD, the rates of prevalent use were much higher in ARS Tuscany. We observed a statistically significant declining trend in prevalent use of valproates in all countries/regions, for which an ITS analysis could be performed, but no significant decreasing trend in incidence rates after the 2018 RMMs compared to the period before. The monthly rate of valproate discontinuers ranged between 1-8% across all databases, and in no database we observed a significant increase in trend or level of valproate discontinuation after the 2018 intervention compared to time prior.

Conclusion: We observed declining trends in prevalent use of valproates after the 2018 RMMs across all databases. However, there were no declining trends in incidence rate of valproates in none of databases. The rate of discontinuation of valproates was not affected by the 2018 RMMs.

1.2 Abstract Objective 2

Aim: To determine prescribers' compliance with the recommendations in the SmPC for valproates (sections 4.4, 4.6), in form of prescribing pregnancy tests or contraceptive coverage before a treatment episode with valproates, using longitudinal data collected from five electronic health care databases from four EU countries and the UK.

Methods: We performed an observational times series study including all female subjects of childbearing age (aged 12 to 55 years) who used valproates from the corresponding databases in Denmark (DNR), Italy (ARS Tuscany), the Netherlands (PHARMO Database Network), Spain (BIFAP), and UK (CPRD) between 01 January 2010 to 31 December 2020. First, we separately estimated the proportion of valproate users with a record of a pregnancy test within the 90 days i) before and ii) after the date of valproate prescribing or dispensing per month. We estimated the change in level and trend in these proportions after the implementation of the 2018 EU RMMs. Second, we estimated the proportion of valproate users with a record of contraceptive (prescribed or dispensed with a prescription, or identified through medical events or procedures records) in 90-days before the prescription, or prescribed/dispensed during a contraceptive episode. We then estimated the change in level and trend in this proportion after the implementation of the 2018 EU intervention, using an ITS analysis design.

Results: We included 69,533 female valproate users from the five participating centres during the study period, with a median follow-up time between 4.4-11.0 years and the mean age at the start of follow-up ≥34 years. Due to the limited data on pregnancy tests from all databases, modelling of any trend change in proportion of valproate prescriptions or dispensings with an adherent pregnancy test before versus after 2018 RMMs was not possible. The rate of recorded contraceptive coverage at the start of valproate treatment was low across all centres, as only 0.5-23% of valproate prescriptions/dispensings each month were accompanied by a contraceptive prescription in 90-days before, and only between 0.5-25% of new valproate treatment episode had started during contraceptive use. There was no increasing trend in compliant valproate prescriptions/ dispensings with a contraceptive coverage after the 2018 RMMs across the studied databases, and the only increase in level was observed in PHARMO.

Conclusion: We found in general low rates of recorded adherent contraceptive coverage with valproate use across all studied regions/countries, and there was no increased trend in compliant

valproate prescriptions/dispensings with a contraceptive coverage after the 2018 RMMs compared to time prior. Due to limited data availability, rates of adherent pregnancy tests and the trend change after the intervention could not be studied.

1.3 Abstract Objective 3

Aim: To determine patients' use of effective contraception in compliance with recommendations in the SmPC for valproates (sections 4.4, 4.6), in form of the overall outcome of pregnancy events, using longitudinal data collected from five electronic health care databases from four EU countries and the UK.

Methods: We performed an observational times series study including all female subjects of childbearing age (aged 12 to 55 years) who used valproates from the corresponding databases in Denmark (DNR), Italy (ARS Tuscany), the Netherlands (PHARMO Database Network), Spain (BIFAP), and UK (CPRD) between 01 January 2010 to 31 December 2020. We estimated the incidence of new pregnancies during a period of valproate use per month and the change in level and trend in this rate after the implementation of the 2018 EU intervention, using an ITS analysis design.

Results: We included 69,533 female valproate users from the five participating centres during study period, with a median follow-up time between 4.4-11.0 years and the mean age at the start of follow-up ≥34 years. In general, we observed a substantial number of concurrent new valproate prescriptions/dispensings during a pregnancy time window in ARS Tuscany (386 pre- and 40 post 2018 intervention), BIFAP (330 pre and 20 post) and CPRD (204 pre and 56 post), while there were fewer concurrent events in PHARMO (27 pre and 0 post). However, the rates of concurrent events declined for most databases after the 2018 intervention. There was no data on pregnancy counts available from DNR.

Conclusion: Despite the declining rates after the 2018 intervention, high counts and rates of concurrent pregnancy events with a valproate prescription/dispensing were observed across most studied countries/regions.

1.4 Abstract Objective 4

Aim: To determine drug utilisation and prescription patterns over time for alternative medications prescribed in women of childbearing potential and pregnant women where valproates had previously been prescribed or discontinued, using longitudinal data collected from five electronic health care databases from four EU countries and the UK.

Methods: We performed an observational times series study including all female subjects of childbearing age (aged 12 to 55 years) who used valproates from the corresponding databases in Denmark (DNR), Italy (ARS Tuscany), the Netherlands (PHARMO Database Network), Spain (BIFAP), and UK (CPRD) between 01 January 2010 to 31 December 2020. We estimated the rates of alternative medication prescriptions/dispensings for the indications epilepsy, bipolar disorder, and migraine among valproate users and the rate of switching from valproate to an alternative medicine per month. Then, the change in trend of switches from valproate to alternative medications before and after the implementation of the 2018 EU intervention was estimated, using an ITS analysis design.

Results: We included 69,533 female valproate users from the five participating centres during study period, with a median follow-up time between 4.4-11.0 years and the mean age at the start of follow-up ≥34 years. We found an increasing trend in rates of alternative medicine use for epilepsy and bipolar diseases indications of valproates across the study period in most databases (i.e., DNR, ARS Tuscany, PHARMO and CPRD), while the rates for migraine were mostly steady. The monthly rate of switch from a valproate to an alternative medication was similar across all DAPs and ranged

between 1-8%. Running an ITS analysis was not possible for most of the included databases due to the low frequency of switching, but there was a significant increase in trend in switching rates from valproates to alternative medicine after the 2018 RMMs in ARS Tuscany.

Conclusion: Although the trend in alternative medication use for most indications of valproates (epilepsy and bipolar disorder) was increasing during the study period, the only significant increase in trend in switching rates from valproates to alternative medications after the 2018 RMMs was observed in ARS Tuscany.

1.5 Abstract Objective 5

Aim: To draw conclusions on the effectiveness of the 2018 EU RMMs for valproates.

Methods: Evidence generated from Objectives 1-4, weighed by the strengths and limitations of the analyses, was used to draw conclusions on the effectiveness of the RMMs, per country and across European countries included in the study.

Results: We found a generally declining trend in prevalence rate of valproate use after the 2018 RMMs in almost all databases (Objective 1), but also no increasing trend in compliant valproate prescriptions/dispensings with a contraceptive coverage (Objective 2). There was a substantial number of occurrences of pregnancy events (as the final endpoint) concurrently with valproate exposure across most included databases, but the rates declined after 2018 (Objective 3). Furthermore, we observed a significant increase in switching rates from valproates to alternative medications only in few regions (such as ARS Tuscany) (Objective 4). Noteworthy, these findings should be interpreted in context of the limitations that we faced, such as an inability to investigate some objectives due to limited data availability on pregnancy test or over-the-counter use of some contraceptives, and the occurrence of COVID-19 pandemic, which has shortened and impacted our post-intervention period and limited our ability to run ITS analyses for some objectives and some databases.

Conclusion: Based on the findings on various objectives in this study, we can conclude that there was a small impact of the 2018 RMMs on valproate use and prescribing in the studied European countries/regions. Considering the limitations of this study (such as not studying all PPP elements, the included databases had important limitations, and the study period after 2018 intervention was rather short), the results of other currently ongoing studies are needed to have a clearer picture of the appropriate implementation of 2018 RMMs on valproate use in Europe.