Valproate: risk awareness survey in women of childbearing age

Protocol

1 Title Page – Protocol

Full/long title of study	Valproate: survey on awareness of teratogenicity risk and impact of risk minimisation measures in women of childbearing age.
Short title	Valproate: risk awareness survey in women of childbearing age.
Protocol identification	Valproate Survey v2.0
Sponsor	Federal Agency for Medicines and Health Products (FAMHP)
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Statistical team	Stat-Gent University Ghent
Protocol version	Version 1.0
HMA-EMA Catalogue of real-world data (former EU PAS register) number	To be added upon protocol endorsement
Date of last revision of protocol	11/10/2024

This study will be performed in compliance with the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice (GCP) and local Ethic Committee and appropriate guidelines.

2 Signature page

Sponsor Representative

Jamila Hamdani _____ _____ _____

Name Signature Date

DECLARATIONS

INVESTIGATOR (S)

I agree to conduct this study in accordance with the design and specific provisions of this protocol and will only make changes in the protocol after notifying the sponsor.

I understand that I may terminate or suspend enrolment of the study at any time if it becomes necessary to protect the best interests of the study subjects. This study may be terminated by CUB – Hôpital Erasme, with or without cause.

I agree to personally conduct or supervise this investigation and to ensure that all associates, colleagues, and employees assisting in the conduct of this study are informed about their obligations in meeting these commitments.

I will conduct the study in accordance with Good Clinical Practice, the Declaration of Helsinki, and the moral, ethical and scientific principles that justify medical research. The study will be conducted in accordance with all relevant laws and regulations relating to clinical studies and the protection of patients.

I will ensure that the requirements relating to Ethics Committee review and approval are met. I will provide CUB – Hôpital Erasme with any material which is provided to the EC for Ethical approval.

I agree to maintain adequate and accurate records and to make those records available for audit and inspection in accordance with relevant regulatory requirements.

I agree to promptly report to the EC any changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without EC approval, except where necessary to ensure the safety of study participants.

Dr Martine Sabbe _____ _____ _____

Name Signature Date

3 Protocol synopsis

Name of Sponsor	Federal Agency for Medicines and Health Products (FAMHP) - Directorate General POST authorisation – Entity Pharmacovigilance - Evaluation
Name of Active Ingredient	Valproate (sodium valproate, valproic acid) [N03AG01]
Medicinal product	Depakine®, Valproate EG®, Valproate Viatris®
Title of Study	Valproate: survey on awareness of teratogenicity risk and impact of risk minimisation measures in women of childbearing age.
Studied period	Expected start: March 2025 Expected completion: December 2025
Overall Objectives	To assess effectiveness of the risk minimisation measures in avoiding exposure to valproate during pregnancy.
Specific Objectives	To assess patients' awareness of the developmental toxicity to children when women are exposed to valproate during pregnancy To identify the main sources of information and preferred sources that patients use to learn about the risks of valproate during pregnancy. To describe the distribution of valproate use among women of childbearing age according to age group and indication To evaluate the reported receipt of risk minimisation tools such as information leaflets, patient cards and signed confirmation documents. To assess whether patients have discussed with a competent HCP (physician, pharmacist) the risks associated with using valproate during pregnancy, the need to use an effective contraceptive method during treatment with valproate and the risks associated with stopping treatment without medical advice. To assess whether patients have been recommended a pregnancy test before start of valproate treatment and current use of contraception.
Study Design	Cross-sectional survey
Number of patients planned	2033 patients for the 18-39 group 2400 patients for the 40-49 group

	Total: 2433 patients
Main criteria for inclusion	The target population consists of women of childbearing age who have received at least one prescription for valproate during 2024
Statistical considerations	The statistical analysis will be purely descriptive. Analyses will be presented in the form of frequency and percentage tables.
Committees	Ethics Committee – CUB – Hôpital Erasme, Collège Intermutualiste National/ Nationaal Intermutualistisch College (CIN-NIC) Informatieveiligheidscomité/Comité de sécurité de l'information (IVC/CSI)
Data protection officer	michel.brouyere@fagg-afmps.be

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5 Study Glosssary

List of main abbreviations and definitions of terms used in the study protocol.

ADHD	Attention Deficit Hyperactivity Disorder
ANSEM	Agence nationale de sécurité du médicament et des produits de santé (France)
CIN-NIC	Collège Intermutualiste National/ Nationaal Intermutualistisch College
CUB	Cliniques Universitaires de Bruxelles
DHPC	Direct Healthcare Professional Communication
EC	Ethics Committee
EMA	European Medicines Agency
FAMHP	Federal Agency for Medicines and Health Products
HCP	Health Care Professional
IVC/CSI	Informatieveiligheidscomité/comité de sécurité de l'information
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
PPP	Pregnancy Prevention Programme
PRAC	Pharmacovigilance Risk Assessment Committee
RIZIV-INAMI	Rijksinstituut voor ziekte- en invaliditeitsverzekering/Institut national d'assurance maladie-invalidité
RMM	Risk Minimisation Measures
SmPC	Summary of Product Characteristics
WIT	Work Instruction

6 Ethics

- This protocol, any protocol amendments, informed consent form and other relevant documents (eg. recruitment advertisements) will be submitted to the Erasme Hospital Ethics Committee for formal approval to conduct the study. The decision of the EC concerning the conduct of the study will be made in writing to the investigator. All correspondence with the IRB/IEC should be retained in the Investigator File.
- The study will be conducted in accordance with legal and regulatory requirements (Belgian law of 7 May 2004, Patient rights (08/2002), Private life (RD 2001), HBM (Human Body Material, law of 19 December 2008)), as well as the Guidelines for Good Clinical Practice (International Conference on Harmonization 1996), and the last version of Declaration of Helsinki (World Medical Association).
- *Participation to the survey is absolutely voluntary. This will be explained in the introductory letter sent to the patients. No personal identifier will be collected. Completion of the questionnaire is without explicit consent: the fact of completing the questionnaire and sending it back to the FAMHP expresses the consent. The questionnaire is to be administered to patients aged 18 years or older (minimum age of participants set to 18 years or older in the questionnaire).*

7 Abstract

Rationale and Background: Valproate, a medication used primarily for epilepsy and bipolar disorder, has been associated with significant teratogenic and neurodevelopmental risks when used during pregnancy. Despite the implementation of risk minimization measures (RMMs) by regulatory agencies, there remains a substantial number of women of childbearing age who are unaware of these risks. This study aims to evaluate the effectiveness of these RMMs and the level of awareness among women who are prescribed valproate.

Research questions and Objectives: The objective of this survey is to assess the effectiveness of RMMs in preventing valproate exposure during pregnancy. Specific objectives include evaluating patients' awareness of the developmental toxicity risks associated with valproate, identifying the main sources of information about these risks, describing the distribution of valproate use among women of childbearing age, and assessing the receipt and understanding of risk minimization tools.

Study design: This cross-sectional survey will be conducted in 2025, among women aged 18-49 who have received at least one prescription for valproate during 2024. A total of 4,433 participants will be randomly selected from mutual insurance company databases, with 2,033 participants from the 18-39 age group and 2,400 from the 40-49 age group. Data will be collected through self-administered questionnaires, which will include questions on awareness of valproate risks, sources of information, discussions with healthcare professionals, and adherence to RMMs such as the use of contraception and receipt of educational materials.

Analysis: The survey will provide descriptive statistics on the awareness and understanding of valproate risks among the study population. It will also evaluate the effectiveness of RMMs by examining the proportion of respondents who have received and understood risk minimization tools, discussed valproate risks with healthcare professionals, and adhered to recommended contraceptive measures. The data will be presented in frequency and percentage tables, with subgroup analyses by age group and indication for valproate use.

Conclusion: This study will offer valuable insights into the current state of awareness and effectiveness of RMMs among women of childbearing age who are prescribed valproate. The findings will inform future regulatory actions and communication strategies to enhance patient safety and reduce the risk of valproate exposure during pregnancy.

8 Objectives

8.1 Overall objective

To assess effectiveness of the risk minimisation measures in avoiding exposure to valproate during pregnancy.

8.2 Specific objectives

- To assess patients' awareness of the developmental toxicity to children when women are exposed to valproate during pregnancy
- To identify the main sources of information and preferred sources that patients use to learn about the risks of valproate during pregnancy.
- To describe the distribution of valproate use among women of childbearing age according to age group and indication
- To evaluate the reported receipt of risk minimisation tools such as information leaflets, patient cards and signed confirmation documents.
- To assess whether patients have discussed with a competent HCP (physician, pharmacist) the risks associated with using valproate during pregnancy, the need to use an effective contraceptive method during treatment with valproate and the risks associated with stopping treatment without medical advice.
- To assess whether patients have been recommended a pregnancy test before start of valproate treatment and current use of contraception.

9 Background Information and Scientific Rationale

Valproate and related substances (sodium valproate, valproic acid, valproate semi sodium, valpromide and valproate magnesium - hereafter all referred to as valproate) are indicated in the treatment of epilepsy and bipolar disorders. In some EU member states, valproate-containing medicines are also authorised for the prevention of migraine attacks but this indication is not approved in Belgium.

The teratogenic potential of valproate valproate has been known since the 1980s (Dalens, 1980), while evidence suggesting neurodevelopmental risks for foetuses exposed to valproate *in utero* started to emerge in the early 2000s (Moore, 2000; Cummings, 2011) . Consequently, warnings on the developmental toxicity risks associated with valproate use during pregnancy were gradually introduced in the product information of valproate-containing medicines to inform healthcare professionals (HCPs) and women of childbearing age with epilepsy or bipolar disorder about these risks. Despite these warnings, a significant number of pregnancies remained exposed to valproate, while women of childbearing age using valproate seemed to remain mostly unaware of the risks.

Following several publications alerting on the risks of major congenital malformations and neurodevelopmental disorders in children exposed to valproate *in utero (*Meador, 2008, Vajda, 2010) the UK Medicines Agency (MHRA) triggered in October 2013 a first European referral procedure under the Article 31 of Directive 2001/83/EC to reassess the benefit-risk balance of valproate use during pregnancy. Using information from all available sources and consultation of relevant experts, the review concluded that 10.7% of children of epileptic women exposed to

valproate monotherapy during pregnancy suffered from major congenital malformations (vs 2-3% in the general population). Moreover, 30-40% of children born to mothers exposed to valproate during pregnancy experienced neurodevelopmental disorders (i.e. talking and walking later, lower intellectual abilities, poor language skills or memory problems). Increased risks of autism spectrum disorders and infantile autism (respectively 3-fold and 5-fold higher than in the general population) were also found in children exposed to valproate in utero, while an increased risk of developing attention deficit hyperactivity disorder (ADHD) was suspected (Cohen, 2013) but considered unclear.

The European Medicines Agency (EMA) issued recommendations in October 2014 following the review, contraindicating valproate in prophylaxis of migraine attacks during pregnancy and in women of childbearing age not using effective contraception (EMA, 2014). Prescribers were also advised not to use valproate in pregnant women, women of childbearing age or young girls with epilepsy unless other treatments were ineffective or not tolerated. In bipolar disorder, valproate was no longer to be prescribed unless lithium was contraindicated. In cases where valproate treatment was still necessary, the EMA further recommended that patients should be carefully informed about these risks, that contraception should be used and that the treatment should be supervised by an experienced physician. Strengthen warnings and precautions on the risks related to valproate exposure during pregnancy were added to the product information, risk minimisation measures (RMMs – i.e. educational materials for patients and HCPs) were implemented and a direct healthcare professional communication (DHPC) was circulated to inform HCPs about these new recommendations. A drug utilisation study and a Joint prescribers' survey were also requested from the MAHs to assess the effectiveness of the newly implemented RMMs.

These effectiveness studies converged at suggesting that the RMMs implemented at the end of the 2014 referral procedure failed to mitigate the developmental toxicity risks of valproate, as well as to meaningfully decrease the number of women of childbearing age and pregnancies unduly exposed to valproate (Toussi, 2021a, Toussi, 2021b). Meanwhile, evidence demonstrating the teratogenicity and neurodevelopmental disorders risk of valproate kept accumulating in the scientific literature.

Consequently, the French Medicines Agency (ANSM) triggered in March 2017 a second European referral procedure under the Article 31 of Directive 2001/83/EC to reassess the benefit-risk balance of valproate use during pregnancy. Recommendations following this second re-evaluation procedure were issued in March 2018 (EMA, 2018). Overall, the magnitudes of the teratogenic and neurodevelopmental disorders risks of valproate were confirmed. Additional risks following paternal exposure to valproate before conception and risk for the third generation offspring (both possibly resulting from epigenomic modifications) were also discussed during the referral, but fall out of scope of the present study. New measures were considered necessary to better transmit risks information to patients in a timely manner and to strengthen the previous prescription restrictions in order to avoid exposure of pregnancies to valproate unless absolutely necessary. Previously-decided contraindications regarding the indications in bipolar disorder and prophylaxis of migraine were maintained. Among new restrictions, valproate-containing medications were also contraindicated in girls and women of childbearing age unless the conditions of a pregnancy prevention programme (PPP) were met. The PPP involves the appraisal of the patient's potential to become pregnant, the use of pregnancy tests before starting and during valproate treatment, adequate counselling about the risks of valproate to women of childbearing age and the use of an Annual Risk Acknowledgement Form to attest that the information has been given by the prescriber and understood by the patient, the use of effective contraception throughout valproate treatment and the review of valproate treatment annually by a specialist.

Multiple RMMs were also decided at the end of the second European referral procedure. These included updated warnings and highlights on the developmental toxicity risks in the product information, the use of a visual warning including a pictogram on the packaging of valproate-containing medicines, a patient alert card containing key messages on these risks and which is attached to/added inside the packaging as well as updated educational material for HCPs and patients. Several studies were also imposed to the MAHs marketing valproate in order to better characterise the risks of valproate during pregnancy or to assess the effectiveness of the new prescription restrictions/RMMs decided at the end of the second referral procedure. A database

study in Denmark, Italy, Spain, the Netherlands, and the UK showed only a limited impact of the RMMs on valproate use (Abtahi, 2023).

In Belgium, the FAMHP performed a survey in November 2018 in order to assess if female patients were aware of the teratogenic and neurodevelopmental risks associated with the use of valproate during pregnancy, as well as their knowledge of the RMMs implemented after the European referrals. The results, based on answers from nearly 700 women of childbearing age between 19-49 year-old, showed that 27% of them still ignored the risks of using valproate during pregnancy (FAMHP, 2019). Recommendations regarding the prescription of valproate also appeared poorly respected among HCPs, as 34% of the responders used valproate for prophylaxis of migraine, an indication not approved in Belgium. Among those who declared being aware of the developmental toxicity risks of valproate, 47% had been informed by their specialist, 33% by their general practitioner (GP), 16% by their pharmacist and 11% by the media. The survey also highlighted very inefficient circulation of the risk minimization material, as only 8.4% of responders who were aware of the risks of valproate declared receiving the Patient information leaflet and 4.7% had signed the Annual Risk Acknowledgement Form. A survey in Belgium in 2020 evaluated implementation of RMMs for oral retinoid and valproate among 317 patients, physicians and pharmacists (Bertels, 2022). The majority of patients failed to comply with the PPP and a large number of healthcare providers is unaware of the available educational materials. To note is that implementation of the patient card in Belgium took some time following the referral. The patient card is not present for the injectable forms of valproate.

The present survey intends to re-assess the awareness of the teratogenic/neurodevelopmental disorders risks among women in childbearing age along with the use/distribution of the available risk minimisation and information material. Evaluating the effectiveness of measures taken to reduce risks associated with the use of medicines is part of the FAMHP's mission and legal obligations. By conducting the survey of women of childbearing age, it is possible to assess whether the information materials are used by prescribers and understood by women. Results of these study can guide communication strategies of the FAMHP regarding valproate risks and inform ongoing discussions on the RMMs at the Pharmacovigilance Risk Assessment Committee of the EMA.

Legal Basis

The specific legal basis for conducting this survey is Directive 2001/83, Art 107h (Directive2001/83/EC, 2001):

> *Section 3 – Signal detection. Article 107h*
>
> 1. Regarding medicinal products authorised in accordance with this Directive, national competent authorities in collaboration with the Agency, shall take the following measures:
>
> (a) monitor the outcome of risk minimisation measures contained in risk management plans and of the conditions referred to in Articles 21a, 22 or 22a

This Directive has been put into the Belgian Legislation (Arrêté royal relatif aux médicaments à usage humain, 2006):

> *Art. 69. [1 § 1er. En ce qui concerne les médicaments autorisés conformément à la loi sur les médicaments et au présent arrêté, l'AFMPS, en collaboration avec l'EMA, prend les mesures suivantes :*
>
> *a) elle surveille les résultats des mesures de réduction des risques prévues dans les plans de gestion des risques, ainsi que des conditions visées à l'article 6, § 1ersepties, à l'article 6, § 1erocties et à l'article 6, § 1er nonies de la loi sur les médicaments;*

The effectiveness of the risk minimisation activities of valproate is the main objective of this survey and in line with art. 69 a). The educational materials for patients (= the risk minimizations measures) are listed in the risk management plans of valproate products (EMA, 2018).

10 Investigational Plan

10.1 Design

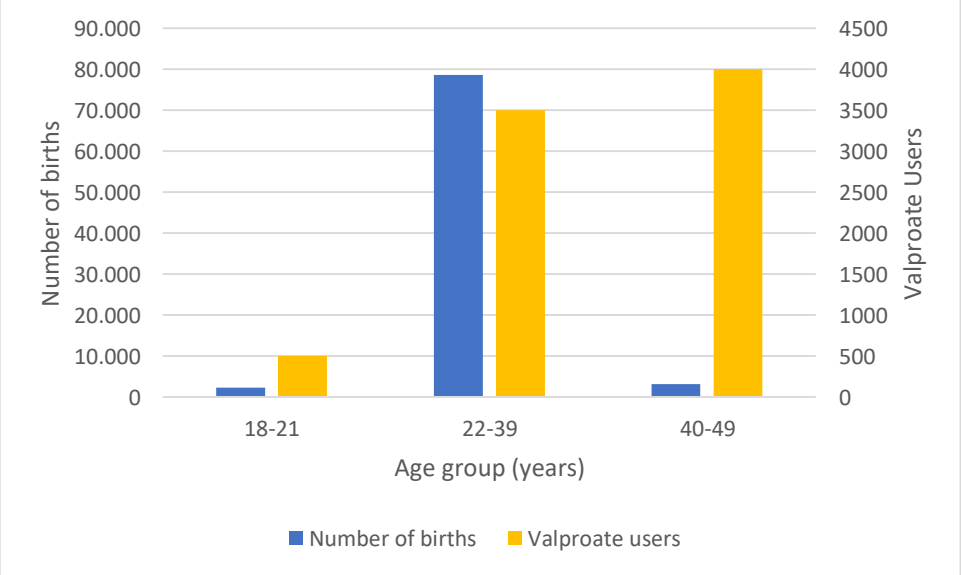
Cross-sectional survey based on a questionnaire with closed questions sent to a sample of women of childbearing age registered with a mutual insurance company in Belgium.

The patient questionnaire has been developed to include the following topics (See: Appendix 16.2 – Questionnaire for patients):

- Awareness of the possible adverse effects on children born to women exposed to valproate during pregnancy and source of this information.
- If patients have discussed with a competent HCP (physician, pharmacist) the risks associated with using valproate during pregnancy, the need to use an effective contraceptive method during treatment with valproate and the risks associated with stopping treatment without medical advice.
- Provision of a Risk acknowledgment form by the prescriber or information card by pharmacist
- Current contraception use

The sample of patients to whom a questionnaire will be sent will be drawn randomly, with a sufficient sample size for the age group < 40 years, as this is the age group where the largest number of children is born. The largest number of valproate users is in the age group 40-49 years (around 500, 3,500 and 4,000 in the 18-21, 22-39 and 40-49 age groups respectively, according to estimates of INAMI data in 2022).

Figure 1: Number of children born from Belgian mothers by age of mother and estimated number of valproate users, 2022



Source Number of births: Statbel, Statistics Belgium, Birhts and fertility 2022, https://statbel.fgov.be/en/themes/population/natality-and-fertility#figures

Source Valproate users, 2022: RIZIV/INAMA

Sampling will be carried out similarly as the study conducted in 2018, as follows:

The mutual insurers identify patients in their databases who meet the survey's eligibility criteria. All mutual insurers are taking part. The FAMHP collaborates for this with the Collège

Intermutualiste National/ Nationaal Intermutualistisch College (CIN-NIC), the association of the mutual insurers.

The CIN-NIC consolidates the list of patients for all the mutual insurers. The CIN-NIC sends the FAMHP the total number of patients identified.

Using statistical software, the FAMHP draws 4433 numbers at random: 2033 numbers for the sample in 18- 39 group and 2400 numbers for the sample in the 40-49 group.

The FAMHP sends the list of numbers to the CIN-NIC, which matches the numbers on the consolidated list of patients with the FAMHP list of numbers.

A CIN-NIC consultant doctor sends the FAMHP doctor the list (first name, surname, address, language regime) of the women selected via the eHealthBox.

The FAMHP uses the address list to prepare the mailing by post. Each envelope will contain the letter of invitation to participants, the survey questionnaire and a "return paid by recipient" envelope. The file containing the names and addresses of the patients will then be destroyed under the supervision of the DPO.

The FAMHP will use this data (name, first name, address) only for sending correspondence. It may not use them for analysis purposes. The data will not be kept longer than necessary for sending the questionnaires by post to the patients. The instructions provided clearly state that respondents should not include their name and address either on the return envelope or on the questionnaire. Thus, no personal information is expected by return.

Valproate and related products available in Belgium and number of users are listed in Appendix 16.4.

10.2 Study size

The study is intended to be powered to have a precision (half width of 95% confidence interval) for the proportion of women using valproate that is aware of the risks.

Since the majority of pregnancies is in the group under 40, that precision is required in both subgroups (under 40 and 40-49).

The sampling can be performed stratified (x sampled from under 40, y sampled from 40-49). This ensures the intended distribution of questionnaires between the groups (this is on questionnaires sent, not on questionnaires responded)

Give the large sample size, the main advantage of the stratified design, is that the subgroup-sample sizes can be targeted according to what is expected.

- In the 2018 questionnaire, 80% of the women was aware in the under 40-group versus 67% in the 40-49 group.
- Given these numbers, the currently assumed 75% seems conservative for the under 40 group, but not for 40-49. As variability increases with proportions closer to 50%, this should be accounted for.

In Figure 1, the calculations in SAS Proc Power as presented in the current protocol under assumed proportion of 75%, are repeated and extended to an assumed 65%. It is clear the required sample sizes differ significantly.

Assuming that 75% and 65% are reasonable but conservative assumptions on the proportions in the Under-40 and 40-49 groups, we advise a stratified sampling scheme. Following the drop out assumptions from the current protocol, this would require:

- 305/0.15 = 2033 patients sampled in the Under 40 group (85% probability of having at least the required precision)
- 360/0.15 = 2400 patients sampled in the 40-49 group (90% probability of having at least the required precision)

Total sample is estimated at 4433 patients.

Since the number of responses will be relatively large, there is no real need to implement mid-p confidence intervals. The impact of adjusting for the finite size of the population would also be very limited, so standard Wilson score-confidence intervals may be used within each stratum (age-subgroup).

When pooled estimates are required, within-stratum results can be weighted by their known size in the population (numbers per age-group are available from the sampling process).

Figure 1 Results from SAS Proc Power - Probability of obtaining the required half width given the 'real' proportions and the sample size

The POWER Procedure
Wilson Score Confidence Interval for Binomial Proportion

Fixed Scenario Elements	
Method	Exact
Alpha	0.05
CI Half-Width	0.05
Number of Sides	2

Computed Prob(Width)			
Index	Proportion	N Total	Prob(Width)
1	0.65	285	<.001
2	0.65	295	<.001
3	0.65	300	0.001
4	0.65	305	0.003
5	0.65	325	0.061
6	0.65	345	0.446
7	0.65	355	0.791
8	0.65	360	0.916
9	0.65	365	0.973
10	0.65	385	>.999
11	0.75	285	0.518
12	0.75	295	0.696
13	0.75	300	0.770
14	0.75	305	0.862
15	0.75	325	0.992
16	0.75	345	>.999
17	0.75	355	>.999
18	0.75	360	>.999
19	0.75	365	>.999
20	0.75	385	>.999

10.3 Description of population

The target population consists of women of childbearing age who have received at least one prescription for valproate during 2024.

The specific inclusion criteria were as follows:

Sex: female

Age: between 18 and 49 years on 31/12/2024

Having received one of the following medicines, all strengths and galenic forms combined, between 01/12/2024 and 31/12/2024:

- Depakine®
- Valproate EG®
- Valproate Viatris®
- Valproate Mylan®

For the sake of convenience, in the remainder of this document, the above medicines containing sodium valproate or valproic acid will be referred to as 'valproate'.

Study time period: Q2 2025

10.4 Strategies for participant recruitment

Patients will be recruited trough the list of patients for the CIN-NIC. This ensures the inclusion of patients as a representative sample.

10.5 Variables

The variables of interest are defined in the survey questions. The questionnaire consists of binary (yes/no) and multiple choice nominal (single-punch).

10.6 Data collection methods and tools

Data will be collected in self-administered questionnaires. The questionnaire will be developed by FAMHP PE staff and will be based on the one used in a similar previous survey carried out in 2018. Some modifications were applied in order to make the tool more robust to the effect of potential biases (eg, deletion of relatively irrelevant options) and to include some questions regarding the pregnancy prevention programme. A comparison of the questions in the 2018 and the 2025 survey is provided in Appendix 16.5.

The first two questions are screening questions to confirm the eligibility of respondents. The following questions ask about the condition for which the valproate is used. The following questions deal with the respondent's level of information on the risk associated with the use of valproate during pregnancy and risk minimisation measures.

The questionnaire is available in two languages: Dutch and French. The questionnaire was first developed in French and then translated to Dutch. Back-translation was used to check the consistency between the versions. Preliminary versions of the questionnaire will be reviewed by two FAMHP colleagues to assess their interpretability. The questionnaires will then be pre-tested with 18 women of childbearing age (9 Dutch-speaking and 9 French-speaking). Following the results of the pre-test, changes will be made if necessary to improve the readability and/or clarity of the questions.

The questionnaires will be sent by post to the patient's home address and in the language declared to the mutual insurance company (French or Dutch). The questionnaire will be preceded by a short introductory letter explaining the context of the survey and its objectives. Respondents are reminded that the survey is entirely voluntary and anonymous, but that their participation is strongly encouraged. A stamped envelope (or postage paid by the recipient) will also be enclosed with the address for receipt at the FAMHP to facilitate the return of the completed questionnaire and encourage participation in the survey.

The patient information letter and full questionnaire can be found in Appendix 16.1 and 16.2

10.7 Data management

The questionnaires will be received by FAMHP staff who will analyse the data and disseminate the results. The questionnaires will be numbered so that they can be monitored and encoded progressively. Data entry will be carried out by 2 teams of double entry encoders. Double encoding ensures quality control as well as checking for logical errors. Once the database is closed, it will be secured and saved on a server at the FAMHP following the working instructions (WIT) VIG/071/WIT/E. Analysts will have read-only access to the database in order to secure and prevent modification of the raw data. Full access to the database will be restricted to the PIs and any activity carried out after the closing date will be traced.

10.8 Data Quality Assurance

The PI will ensure there are adequate quality and number of monitoring activities conducted by the study team. This will include adherence to the protocol and ensure adequate data quality.

Any amendments to the study protocol will be clearly documented and justified.

The results of the analyses and the study report will be peer reviewed by at least one member of the pharmaco-epidemiology team.

If the study is ended prematurely, the PI will notify all responsible parties, including the reasons for the premature termination.

10.9 Statistical Analysis

10.9.1 Planned analyses

The statistical analysis will be purely descriptive. Analyses will be presented in the form of frequency and percentage tables.

The participation rate will be calculated dividing the number of returned questionnaires by the number of invitations sent.

The study population will be described by age group (18-39, 40-49 years) and condition treated (epilepsy, bipolar disorder, migraine, other).

The following indicators will be calculated :

Proportion of respondents aware of the risks of valproate on the development and/or health of children exposed to these drugs *in utero*. The numerator will be derived from question 4.

Proportion of respondents who received information about contraception, risks to the unborn child, the importance of not stopping valproate treatment without the doctor's advice. The numerator will be derived from question 9, 10, 14.

Proportion of respondents who received an information leaflet, patient card and/or a risk information acknowledgement form. The numerator will be derived from question 6,7, 8.

The denominator will be defined by the number of valid responses provided by respondents meeting the eligibility criteria (age 18-49 years old, taking valproate in the defined period).

The proportions will be presented with two-sided 95% confidence intervals estimated using the mid-p method.

The primary analysis will be done on the overall study population. Additionally, subgroup analyses will be performed by age group and indication.

Missing values will not be imputed.

10.10 Limitations of the research methods

The survey cannot firmly establish a link between women's awareness of the risk associated with valproate and their use of the information tools provided by the regulatory agencies. This is because other sources of information are possible, and a patient may have misperceived or misremembered the message conveyed by the tools provided. Recollection of the risks of valproate and the discussion of educational material may also vary according to the women taking part and the time elapsed between becoming aware of the risks and responding to the survey.

Various biases are also possible and should be considered when interpreting the results.

Selection bias

Women who take part in the survey may have different characteristics to those who do not (education, language, interest in pregnancy, etc.).

Information bias

Women who have experienced difficulties may remember or report valproate use (or the information they received) in a different way to those who have not.

10.11 Study timelines and milestones

	2024							**2025**												**2026**		
	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3
Writing/reviewing of protocol	X	X	X	X	X	X																
Development of questionnaire	X	X	X	X																		
Pre-testing questionnaire				X	X																	
Seeking approval (APD, EC, NIC)				X	X	X																
Setting up paper questionnaires for distribution							X	X														
Recruitment of respondents									X	X	X	X	X									
Sending reminder										X												
Data entry													X	X								
Data cleaning and analysis															X	X	X	X				
Writing and reviewing of study report and scientific publication																		X	X	X	X	X

10.12 Protocol Amendments

If amendments to the protocol (modifying sense or objectives or modifying the undergone constraints or the risks incurred by the subjects) turn out to be necessary, they will be subjected at first opinion of the promoter of the study. After agreement by the promoter, these amendments will then be submitted to the opinion of the EC having examined the initial protocol.

11 Finance and Insurance

Insurance not deemed necessary as this is not a clinical trial.

The survey is financed by an internal budget of pharmaco-epidemiology of the FAMHP.

12 Protection of human subjects

A request to the informatieveiligheidscomité/comité de sécurité de l'information (IVC/CSI) will be made for exchange of the personal data between the CIN-NIC and the FAMHP.

FAMHP is the data controller.

FAMHP Data Protection Officer is Michel Brouyère - Chief information security officer (CISO)/ Data protection officer (DPO) michel.brouyere@fagg-afmps.be / dpo@fagg-afmps.be

The study will be collecting the following personal data: name, address and language of the patients, only to distribute the survey. These personal data will not be linked to the responses. Only the principal investigator and administrative support team of the FAMHP (see title page) will have access to these personal data to prepare the distribution of the survey. Personal data will be destroyed one week after sending out of the survey, under supervision of the DPO, with a report of the destruction.

Collected data from the questionnaire are not linked to the patients' name or address. Respondents do not provide any personal information in their answers to the questionnaire. The questionnaires are returned to the FAMHP and processed in such a way that the answers cannot be linked to the respondents. This anonymisation eliminates any personal identification and the data is therefore no longer considered personal data within the meaning of the GDPR. Simply returning the questionnaire constitutes implicit consent to participate in the study.

The data processors are the investigators (see title page) and Stat-Gent of the Ghent University.

13 Dissemination of Results and Publication Policy

- A summary of the results will be published on the website of the FAMHP similarly to the 2018 survey (FAMHP, 2019) available to HCP and public/patients.
- A scientific report will be prepared by the investigators and results will be shared with EMA, the Ethical committee and the CIN-NIC.
- A scientific publication will be prepared by the investigators, with acknowledgement of the participation of the patients and the CIN-NIC.

14 Archiving

Study-related documents (including correspondence between responsible parties, protocol, SAP, questionnaires, scripts for statistical analyses, outputs and logs of statistical analyses, study report, …) will be archived at the end of the study during 10 years, from the study end. Details about storage/archiving of data are provided in the WIT number VIG/071/WIT/E.

15 Study Report

A scientific report will be prepared by the investigators and results will be shared with EMA, the Ethical committee and the CIN-NIC in Q1 2026.

16 Literature References

Abtahi S, Pajouheshnia R, Durán CE, Riera-Arnau J, Gamba M, et al. Impact of 2018 EU Risk Minimisation Measures and Revised Pregnancy Prevention Programme on Utilisation and Prescribing Trends of Medicinal Products Containing Valproate: An Interrupted Time Series Study. Drug Saf. 2023 Jul;46(7):689-702. doi: 10.1007/s40264-023-01314-3. Epub 2023 Jun 9. PMID: 37294532; PMCID: PMC10252161.

Arrêté royal relatif aux médicaments à usage humain, Partie 1 : Médicaments à usage humain (art. 1 à 140). 14 Décembre 2006. [Available from: Banque de données Justel]

Bertels X, Mehuys E, Boussery K, Lahousse L. The implementation of risk minimization measures to prevent teratogenic pregnancy outcomes related to oral retinoid and valproate use in Belgium. Acta Clin Belg. 2022 Oct;77(5):815-822. doi: 10.1080/17843286.2021.1983708. Epub 2021 Sep 26. PMID: 34569444.

Directive 2001/83/EC of the European Parliament and the Council of 6 November 2001 on the Community code relating to medicinal products for human use. [Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02001L0083-20190726]

Dalens B, Raynaud EJ. Teratogenicity of valproic acid. J Pediatr 1980; 97: 332-333

Cohen MJ, Meador KJ, Browning N, et al. Fetal antiepileptic drug exposure : Adaptive and emotional/behavioral functioning at age 6 years. Epilepsy Behav 2013 ; 29 (2) : 308-15

Cummings C, Stewart M, Stevenson M, et al. Neurodevelopment of children exposed in utero to lamotrigine, sodium valproate and carbamazepine. Arch Dis Child 2011; 96 (7): 643-7.

Meador K, Reynolds MW, Crean S, et al. Pregnancy outcomes in women with epilepsy : a systematic review and meta-analysis of published pregnancy registries and cohorts. Epilepsy Res 2008; 81 (1): 1-13.

Moore SJ, Turnpenny P, Quinn A, Glover S, Lloyd DJ, Montgomery T, Dean JC. A clinical study of 57 children with fetal anticonvulsant syndromes. J Med Genet. 2000 Jul;37(7):489-97.

Toussi M, Shlaen M, Coste F, de Voogd H, Dimos V, Kaplan S. Effectiveness of risk minimisation measures for valproate: A drug utilisation study in Europe. Pharmacoepidemiol Drug Saf. 2021 (a) Mar;30(3):292-303. doi: 10.1002/pds.5166. Epub 2020 Nov 23. PMID: 33108674; PMCID: PMC7894134.

Toussi M, Isabelle B, Tcherny-Lessenot S, de Voogd H, Dimos V, Kaplan S. Effectiveness of risk minimisation measures for valproate: A cross-sectional survey among physicians in Europe. Pharmacoepidemiol Drug Saf. 2021 (b) Mar;30(3):283-291. doi: 10.1002/pds.5119. Epub 2020 Nov 20. PMID: 33216434; PMCID: PMC7894483.

Vajda FJ, Hitchcock AA, Graham J, O'Brien TJ, Lander CM, Eadie MJ. The teratogenic risk of antiepileptic drug polytherapy. Epilepsia. 2010 May;51(5):805-10. doi: 10.1111/j.1528-1167.2009.02336.x. Epub 2009 Oct 8. PMID: 19817810.

European Mediciens Agency. CMDh agrees to strengthen warnings on the use of valproate medicines in women and girls. 21/11/2014 [Available from: https://www.ema.europa.eu/en/news/cmdh-agrees-strengthen-warnings-use-valproate-medicines-women-girls]

European Medicines Agency. PRAC recommends new measures to avoid valproate exposure in pregnancy. 09/02/2018 [Available from: https://www.ema.europa.eu/en/medicines/human/referrals/valproate-related-substances-0]

Federal Agency for Medicines and Health Products (FAMHP). Valproate: knowledge of the risks associated with taking during pregnancy - Results of the 2018 FAMHP survey. 25/06/2019. [Available from : https://www.famhp.be/en/news/valproate_knowledge_of_the_risks_associated_with_taking_during_pregnancy_results_of_the_2018]

Other Studies

Surveys among Health Care Professionals and Patients to assess their knowledge and behaviour with respect to the new (2018) Risk Minimisation Measures for valproate use in Europe. Final study report version 1.0 dated 28 July 2021. EUPAS34465. https://redirect.ema.europa.eu/resource/34466

Impact of EU label changes and revised pregnancy prevention programme for medicinal products containing valproate: utilisation and prescribing trends. EUPAS31001. https://redirect.ema.europa.eu/resource/49706

Impact of EU label changes and pregnancy prevention programme for medicinal products containing valproate and related substances: risk awareness and adherence (ValproateRiskAware). EUPAS32405. https://redirect.ema.europa.eu/resource/49662

DARWIN EU® Drug utilisation of valproate-containing medicinal products in women of childbearing potential. EUPAS50789. https://redirect.ema.europa.eu/resource/84554

17 Appendix

17.1 Patient information letters (French and Dutch version)

(a) Patient information letter-FR



Agence fédérale des médicaments et des produits de santé
Avenue Galilée 5/03
1210 BRUXELLES
www.afmps.be

DG POST autorisation/Division Vigilance/
Cellule Pharmacovigilance/Évaluation

Date
JJ.MM.AAAA

Objet – Participation à une enquête

Chère Madame,

Nous souhaitons solliciter votre participation à une enquête organisée par l'Agence fédérale des médicaments et des produits de santé (AFMPS). L'AFMPS est l'institution publique responsable de la qualité, la sécurité et l'efficacité des médicaments disponibles en Belgique. Elle définit les conditions d'utilisation des médicaments, par exemple en approuvant le contenu des notices. Elle a aussi pour rôle d'évaluer si les patients sont informés sur les conditions d'utilisation de certains traitements.

Vous êtes invitée à participer à cette enquête si un médicament à base de valproate vous a été prescrit pendant l'année 2024. Il s'agit d'un des produits suivants : Depakine, Valproate EG, Valproate Mylan, Valproate Viatris.

Si aucun de ces médicaments ne vous a été prescrit en 2024, veuillez ne pas répondre à cette enquête.

Cependant, si l'un de ces médicaments vous a été prescrit et que vous acceptez de participer à l'enquête, nous vous invitons à remplir le questionnaire annexé à cette lettre.

Si en répondant au questionnaire, vous avez des questions concernant votre traitement, discutez-en avec votre médecin traitant ou le médecin prenant en charge votre pathologie. En aucun cas vous ne devez arrêter votre traitement sans en avoir discuté avec votre médecin.

Comment envoyer le questionnaire?

Renvoyez le questionnaire rempli à l'AFMPS en utilisant l'enveloppe prévue (port payé par le destinataire) avant le xx xxxx 2025.

Protection des données personnelles Votre participation à l'enquête est entièrement volontaire. Veuillez **ne pas** indiquer votre nom ni sur le questionnaire ni sur l'enveloppe de retour, afin de protéger vos données personnelles.

Nous vous remercions chaleureusement pour votre participation à cette enquête. Les résultats de l'enquête seront disponibles d'ici environ six mois sur le site de l'AFMPS. Nous espérons rencontrer votre intérêt.

Très sincèrement,

Dr Martine Sabbe
Médecin épidémiologiste à l'AFMPS/Team PharmacoEpidémiologie

Annexe : Questionnaire d'enquête sur les médicaments contenant du valproate

(a) <u>Patient information letter-NL</u>

Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten
Galileelaan 5/03
1210 BRUSSEL
www.fagg.be

DG POST vergunning/afdeling Vigilantie/
cel Farmacovigilantie/Evaluatie

Datum
DD.MM.JJJJ

Betreft - Deelname aan een bevraging

Geachte mevrouw

We nodigen u uit om deel te nemen aan een bevraging van het Federaal Agentschap voor Geneesmiddelen en Gezondheidsproducten (FAGG). Het FAGG is de overheidsinstelling die instaat voor de kwaliteit, de veiligheid en de doeltreffendheid van geneesmiddelen en gezondheidsproducten. De instelling bepaalt onder andere de gebruiksvoorwaarden van geneesmiddelen, bijvoorbeeld door de inhoud van bijsluiters goed te keuren. Daarnaast gaat het FAGG ook na of patiënten correct werden geïnformeerd over de gebruiksvoorwaarden van bepaalde behandelingen.

We nodigen u uit om aan deze bevraging deel te nemen als u in de loop van het jaar 2024 een geneesmiddel met valproaat voorgeschreven kreeg. Het gaat om één van de volgende geneesmiddelen: Depakine, Valproaat EG, Valproaat Mylan en Valproaat Viatris.

Als u geen van deze geneesmiddelen werd voorgeschreven in 2024, gelieve de vragenlijst dan niet in te vullen.

Als u een van deze geneesmiddelen wel werd voorgeschreven en u ermee instemt om deel te nemen aan de bevraging, nodigen wij u uit om de vragenlijst in te vullen die bij deze brief is gevoegd.

Hebt u tijdens het invullen van de vragenlijst vragen over uw behandeling, bespreek die dan met uw huisarts of met de arts die uw aandoening behandelt. U mag in geen geval uw behandeling stopzetten zonder er met uw arts over te spreken.

Hoe verstuur ik de vragenlijst?
Stuur de ingevulde vragenlijst vóór xx xxxx 2025 terug naar het FAGG met de bijgeleverde briefomslag (kosten worden betaald door de ontvanger).

Bescherming van persoonsgegevens
Uw deelname aan de bevraging is geheel vrijwillig. Vermeld uw naam **niet** op de vragenlijst of op de retouromslag om uw persoonsgegevens te beschermen.

Wij danken u van harte voor uw medewerking aan deze bevraging. De resultaten zullen binnen ongeveer zes maanden beschikbaar zijn op de website van het FAGG. Hopelijk heeft deze brief uw belangstelling gewekt.

Met oprechte dank

Dr. Martine Sabbe

Arts-epidemioloog bij het FAGG/team FarmacoEpidemiologie

Bijlage: Bevraging over geneesmiddelen met valproaat

17.2 Questionnaires (French and Dutch version)

(a) Questionnaire-FR

Questionnaire d'enquête sur les médicaments contenant du valproate

Ce questionnaire est destiné aux femmes qui utilisent l'un des produits suivants :

Depakine, Valproate EG, Valproate Viatris , Valproate Mylan

Merci de répondre à ce questionnaire. Nous estimons qu'il vous faudra environ 5 à 10 minutes pour répondre aux questions ci-dessous. Si vous ne pouvez pas y répondre seule, cette enquête peut également être complétée par une personne aidante de votre choix.

Ce questionnaire est anonyme. Nous vous demandons de ne pas y indiquer votre nom ni d'écrire de remarques en dehors des espaces prévus en pointillés.

Si vous avez des questions par rapport à votre traitement au valproate, discutez-en avec votre médecin traitant.

Si vous avez des questions ou des commentaires sur cette enquête, veuillez contacter le Dr. Martine Sabbe par e-mail à Martine.Sabbe@afmps.be.

Merci d'avance de votre participation.

1. **Êtes-vous une femme âgée de 18 à 49 ans ?**
   ☐ Oui
   ☐ Non (Si non, il est inutile de compléter ce questionnaire)

2. **Avez-vous pris un médicament contenant du valproate (Depakine, Valproate EG, Valproate Viatris, Valproate Mylan) au moins une fois au cours des 12 derniers mois ?**
   ☐ Oui
   ☐ Non (Si non, il est inutile de compléter ce questionnaire)

3. **Pour quelle(s) maladie(s) prenez-vous/avez-vous pris ce médicament ?**
   (Plusieurs réponses possibles)
   ☐ Épilepsie
   ☐ Troubles bipolaires
   ☐ Migraine
   ☐ Autre(s) : ……

4. **Savez-vous que le valproate peut avoir un effet défavorable sur le développement et/ou la santé des enfants nés de femmes ayant pris ce médicament pendant leur grossesse ?**

   ☐ Oui

   ☐ Non (Si non, veuillez passer à la question 9)

5. **Comment avez-vous été informée des risques liés à la prise du valproate pendant la grossesse ?** *(Plusieurs réponses possibles)*

   ☐ Médecin

   ☐ Pharmacien(ne)

   ☐ Notice du médicament

   ☐ Logo sur la boîte du médicament

   ☐ Carte patient distribuée lors de la délivrance du médicament

   ☐ Feuillet d'information du patient

   ☐ Accusé de réception annuel d'information de risques à signer

   ☐ Média (journaux, radio, internet, réseau social …)

   ☐ Autre

6. **Votre médecin ou votre pharmacien(ne) vous a-t-il(elle) remis un feuillet d'information sur les risques du valproate pour l'enfant à naître ?**

   ☐ Oui

   ☐ Non

   ☐ Je ne m'en souviens pas/Pas sûre

   ☐ Pas pertinent (pas sexuellement active/infertilité/ménopause …)

7. **Savez-vous qu'une carte patient concernant les risques du valproate pour l'enfant à naître est attachée à la boîte de votre médicament contenant du valproate ?**

   ☐ Oui, le (la) pharmacien(ne) me l'a signalé lors de la délivrance de mon médicament

   ☐ Oui, mais je l'ai trouvée toute seule

   ☐ Non, ou je ne m'en souviens pas

   ☐ Pas pertinent (pas sexuellement active/infertilité/ménopause …)

8. **Votre médecin vous a-t-il remis un document à signer confirmant que vous avez reçu l'information sur le risque en cas de grossesse ?**

   ☐ Oui

   ☐ Non

   ☐ Je ne m'en souviens pas/Pas sûre

☐ Pas pertinent (pas sexuellement active/infertilité/ménopause …)

9. Votre médecin ou votre pharmacien(ne) a-t-il(elle) discuté avec vous des risques du valproate pour l'enfant à naître ?

☐ Oui

☐ Non

☐ Je ne m'en souviens pas/Pas sûre

☐ Pas pertinent (pas sexuellement active/infertilité/ménopause …)

10. Votre médecin ou votre pharmacien(ne) a-t-il(elle) discuté avec vous de l'utilisation d'une contraception efficace pendant le traitement par le valproate ?

☐ Oui

☐ Non

☐ Je ne m'en souviens pas/Pas sûre

☐ Pas pertinent (pas sexuellement active/infertilité/ménopause …)

11. Votre médecin a-t-il proposé un test de grossesse avant de vous (re)prescrire du valproate ?

☐ Oui

☐ Non

☐ Je ne m'en souviens pas/Pas sûre

☐ Pas pertinent (pas sexuellement active/infertilité/ménopause …)

12. Utilisez-vous actuellement des méthodes de contraception ?

☐ Oui

☐ Non

☐ Pas pertinent (pas sexuellement active/infertilité/ménopause …)

Si « Oui » veuillez passer à la question 13, sinon passez à la question 14.

13. Quelle(s) méthode(s) de contraception utilisez-vous (ou utilisiez-vous) durant votre traitement par valproate ? (Sélectionnez toutes celles qui s'appliquent)

☐ Pilules contraceptives

☐ Patch contraceptif

☐ Dispositif intra-utérin/stérilet (cuivre ou hormonal)

☐ Diaphragme

☐ Préservatif

☐ Je suis stérilisée (ligature des trompes)

☐ Mon partenaire est stérilisé (vasectomie)

☐ Contraception d'urgence

☐ Méthodes de température ou d'abstinence périodique

☐ Rapport sexuel interrompu (méthode du retrait)

☐ Autre

14. Votre médecin ou votre pharmacien(ne) a-t-il(elle) discuté avec vous de l'importance de ne jamais arrêter le traitement par valproate sans avis médical ?

☐ Oui

☐ Non

☐ Je ne m'en souviens pas/Pas sûre

15. Par quel(s) moyen(s) préférez-vous être informée sur les risques liés à la prise du valproate pendant la grossesse ? (Plusieurs réponses possibles)

☐ Médecin

☐ Pharmacien(ne)

☐ Notice du médicament

☐ Logo sur la boîte du médicament

☐ Carte patient distribuée lors de la délivrance du médicament

☐ Feuillet d'information du patient

☐ Accusé de réception annuel d'information de risques à signer

☐ Média (journaux, radio, internet, réseau social …)

☐ Autre

16. À quelle tranche d'âge appartenez-vous ?

☐ 18-21 ans

☐ 22-30 ans

☐ 31-39 ans

☐ 40-49 ans

Nous vous remercions d'avoir répondu à ce questionnaire.

(a) Questionnaire-NL



Bevraging over geneesmiddelen met valproaat

Deze vragenlijst is bedoeld voor vrouwen die een van de volgende producten gebruiken: Depakine, Valproaat EG, Valproaat Viatris, Valproaat Mylan

Bedankt voor het invullen van deze vragenlijst.
Het beantwoorden van de onderstaande vragen duurt ongeveer 5 tot 10 minuten. Lukt het niet om de vragenlijst alleen te beantwoorden? Vraag dan aan iemand om je te helpen bij het invullen.
Deze vragenlijst is anoniem. Vermeld nergens uw naam en schrijf ook geen opmerkingen behalve op de daartoe voorziene stippellijnen.
Hebt u vragen over uw behandeling met valproaat? Bespreek dit dan met uw behandelende arts.
Voor vragen of opmerkingen over deze vragenlijst kunt u contact opnemen met Dr. Martine Sabbe via e-mail aan Martine.Sabbe@fagg.be.
Alvast bedankt om deel te nemen!

1. **Bent u een vrouw tussen 18 en 49 jaar?**
   ☐ Ja
   ☐ Nee (Is het antwoord 'nee', dan hoeft u deze vragenlijst niet in te vullen)

2. **Hebt u in de afgelopen 12 maanden minstens één keer een geneesmiddel gebruikt dat valproaat bevat (Depakine, Valproaat EG, Valproaat Viatris, Valproaat Mylan)?**
   ☐ Ja
   ☐ Nee (Is het antwoord 'nee', dan hoeft u deze vragenlijst niet in te vullen)

3. **Voor welke ziekte(n) neemt u dit geneesmiddel?** (Meerdere antwoorden mogelijk)
   ☐ Epilepsie
   ☐ Bipolaire stoornissen
   ☐ Migraine
   ☐ Andere: .....

4. **Weet u dat valproaat nadelige gevolgen kan hebben voor de ontwikkeling en/of de gezondheid van kinderen van vrouwen die dit geneesmiddel tijdens de zwangerschap hebben gebruikt?**
   ☐ Ja

☐ Nee (Is het antwoord 'nee', ga dan naar vraag 9)

5. **Hoe werd u geïnformeerd over de risico's van het gebruik van valproaat tijdens de zwangerschap?** *(Meerdere antwoorden mogelijk)*

☐ Arts

☐ Apotheker

☐ Bijsluiter van het geneesmiddel

☐ Logo op het doosje van het geneesmiddel

☐ Patiëntenkaart uitgedeeld bij de aflevering van het geneesmiddel

☐ Informatiefolder voor de patiënt

☐ Jaarlijks ontvangstbewijs van risico-informatie

☐ Media (kranten, radio, internet, sociale netwerken, enz.)

☐ Andere

6. **Heeft uw arts of apotheker u een informatiefolder gegeven over de risico's van valproaat voor het ongeboren kind?**

☐ Ja

☐ Nee

☐ Ik weet het niet meer/niet zeker

☐ Niet relevant (niet seksueel actief/onvruchtbaarheid/menopauze ...)

7. **Wist u dat er een patiëntenkaart over de risico's van valproaat voor het ongeboren kind aan het doosje van uw geneesmiddel met valproaat is bevestigd?**

☐ Ja, de apotheker heeft me hierover geïnformeerd bij de aflevering van mijn geneesmiddel

☐ Ja, maar ik heb die zelf gevonden

☐ Nee, of ik weet het niet meer

☐ Niet relevant (niet seksueel actief/onvruchtbaarheid/menopauze ...)

8. **Heeft uw arts u een document laten ondertekenen waarin wordt bevestigd dat u informatie hebt gekregen over de risico's in geval van zwangerschap?**

☐ Ja

☐ Nee

☐ Ik weet het niet meer/niet zeker

☐ Niet relevant (niet seksueel actief/onvruchtbaarheid/menopauze ...)

9. Heeft uw arts of apotheker de risico's van valproaat voor het ongeboren kind met u besproken?

☐ Ja

☐ Nee

☐ Ik weet het niet meer/niet zeker

☐ Niet relevant (niet seksueel actief/onvruchtbaarheid/menopauze ...)

10. Heeft uw arts of apotheker het gebruik van doeltreffende anticonceptie tijdens de behandeling met valproaat met u besproken?

☐ Ja

☐ Nee

☐ Ik weet het niet meer/niet zeker

☐ Niet relevant (niet seksueel actief/onvruchtbaarheid/menopauze ...)

11. Heeft uw arts u een zwangerschapstest voorgesteld voordat hij/zij valproaat (opnieuw) voorschreef?

☐ Ja

☐ Nee

☐ Ik weet het niet meer/niet zeker

☐ Niet relevant (niet seksueel actief/onvruchtbaarheid/menopauze ...)

12. Gebruikt u momenteel anticonceptie?

☐ Ja

☐ Nee

☐ Niet relevant (niet seksueel actief/onvruchtbaarheid/menopauze ...)

Is het antwoord 'Ja', ga naar vraag 13, anders naar vraag 14.

13. Welke anticonceptiemethode(n) gebruikt(e) u tijdens uw behandeling met valproaat? (Selecteer alles wat van toepassing is)

☐ Anticonceptiepil

☐ Anticonceptiepleister

☐ Spiraaltje (koper of hormonaal)

☐ Diafragma

☐ Condoom

☐ Ik ben gesteriliseerd (afbinding van de eileiders)

☐ Mijn partner is gesteriliseerd (vasectomie)

☐ Noodanticonceptie

☐ Temperatuurmethode of periodieke onthouding

☐ Coïtus interruptus (terugtrekmethode)

☐ Andere

14. Heeft uw arts of apotheker met u besproken dat u nooit zonder medisch advies uw behandeling met valproaat mag stopzetten?

☐ Ja

☐ Nee

☐ Ik weet het niet meer/niet zeker

15. Hoe wilt u het liefst worden geïnformeerd over de risico's van het gebruik van valproaat tijdens de zwangerschap? (Meerdere antwoorden mogelijk)

☐ Arts

☐ Apotheker

☐ Bijsluiter van het geneesmiddel

☐ Logo op het doosje van het geneesmiddel

☐ Patiëntenkaart uitgedeeld bij de aflevering van het geneesmiddel

☐ Informatiefolder voor de patiënt

☐ Jaarlijks ontvangstbewijs van risico-informatie

☐ Media (kranten, radio, internet, sociale netwerken, enz.)

☐ Andere

16. Tot welke leeftijdscategorie behoort u?

☐ 18-21 jaar

☐ 22-30 jaar

☐ 31-39 jaar

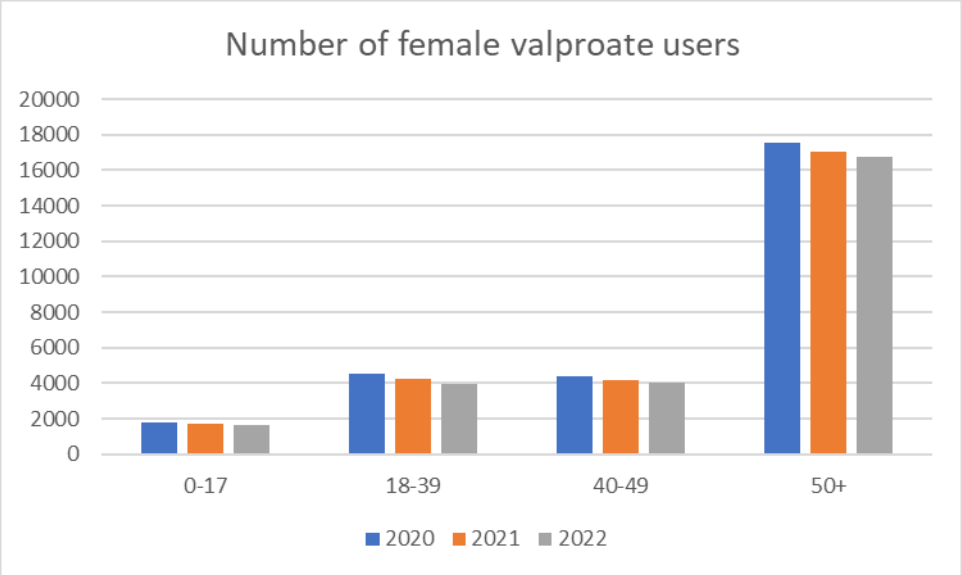
☐ 40-49 jaar

Bedankt voor het invullen van deze vragenlijst.

17.3 Valproate and related products in Belgium and number of users

INN	ATC Code	Dosage form and strength	Brandname	Indication
valproic acid	N03AG01	Oral valproic acid (controled release) •300 mg •500 mg	Depakine® Chrono Valproate Retard EG®	Depakine®: Epilepsy Valproate Retard EG®: Epilepsy Bipolar disorder (maniac episode) when lithium is contra-indicated. Treatment can be considered to be continued.
sodium valproate	N03AG01	Oral valproate (tablets, syrup) •300 mg •500 mg •300 mg / 1 ml •300 mg / 5 ml injectie/infusie •300 mg / 3 ml •1 g / 10 ml •400 mg	Depakine® Valproate Viatris®	Depakine®: Epilepsy Valproate Viatris®: Epilepsy

Number of female valproate users in Belgium (RIZIV, INAMI data)



Agegroup	2020	2021	2022
0-17	1762	1732	1639
18-39	4527	4233	3992
40-49	4389	4184	3994
50+	17576	17070	16737

17.4 Key differences in questions between the 2018 and 2025 survey

Title and Introduction:

2025 Version: narrows down the list of products used or relevant at the time, due to changes in market availability.

2025 Version specifically mentions that the questionnaire can be completed by the respondent or their caregiver. Allowing caregivers to complete the questionnaire acknowledges that some respondents may need assistance, ensuring more accurate and complete data collection. This was provided as feedback on some of the responses in 2018.

Information Sources about sources of information of valproate risk:

2025 Version: Lists various sources of information about the risks of valproate during pregnancy, including media, doctors, and pharmacists. The 2018 versions had a similar list but included more specific types of doctors (e.g., gynecologist, neurologist, psychiatrist). This level of detail was not deemed necessary in the current survey.

Documentation and Discussion of risk:

2025 Version: Similar questions but the 2018 survey included additional details about other medications received before valproate. This is considered not relevant for the current survey.

2025 Version: Includes the option in the answers that the question does not apply as the patient is not sexually active/is infertile/menopaused. This is based on feedback received from the 2018 Survey.

Contraception:

2025 Version: Asks detailed questions about the use of contraception and methods used. This is to evaluate the adherence to the Pregnancy Prevention Programme as detailed in the patient leaflet and risk minimisation materials.

Preferred Information Sources:

2025 Version: Asks how the respondent prefers to be informed about the risks. Understanding how participants prefer to receive information allows for more effective communication strategies, ensuring that important safety messages are delivered in the most accessible and impactful way.