EMA tender EMA/2017/09/PE, Lot 2

Impact of EU label changes and pregnancy prevention programme for medicinal products containing valproate and related substances: risk awareness and adherence

Protocol

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Table of contents

Background

Valproate and related substances (valproic acid, sodium valproate, magnesium valproate, valproate semisodium and valpromide) are licensed for the treatment of epilepsy and manic episodes in patients with bipolar disorder in Europe, and in some EU Member States also for migraine prophylaxis. The teratogenic risk and congenital malformations and neurodevelopmental disorders associated with the use of valproate in pregnant women are well established. The risk is dose dependent with no threshold dose under which no risk exists.

Due to the risk of malformations and neurodevelopmental disorders of children exposed in utero a review in 2014 concluded that valproate and related substances should not be used to treat epilepsy in female children, women in childbearing age and pregnant women unless alternative treatments are ineffective or not tolerated. Manic episodes in bipolar disorder should only be treated with valproate when lithium is contraindicated or not tolerated and the prophylaxis of migraine attacks has been contraindicated both in pregnancy as in women in childbearing age who are not using effective methods of contraception.

Warnings and precautions with updated information on the risks related to exposure during pregnancy were included in the product information of all medicinal products containing valproate and related substances, including development of educational materials for patients and healthcare professionals.

Despite these warnings and precautions a post-authorisation safety study (PASS) requested by the European Medicines Agency's Pharmacovigilance Risk Assessment Committee (PRAC) showed a persisting high level of exposure to valproate and related substances among childbearing age women. Moreover, the PRAC noted there was insufficient adherence to the educational measures for patients and healthcare professionals introduced in 2014.

On 21 March 2018 the CMDh, advised by the PRAC, endorsed new measures to avoid further exposure of babies to valproate-related products. The new measures include a ban on the use of such medicines for migraine or bipolar disorder during pregnancy, and a ban on treating epilepsy during pregnancy unless there is no other effective treatment available.

Furthermore, the medicines must not be used in any woman or girl able to have children unless the conditions of a new pregnancy prevention programme (PPP) are met. The programme is designed to ensure that patients are made fully aware of the risks and the need to avoid pregnancy. As part of the PPP, the PRAC required:

- the assessment of the potential for pregnancy in all female patients undergoing valproate treatment
- the understanding and acknowledgment of the risks of congenital malformations and neurodevelopmental disorders,
- the need for pregnancy testing prior to initiation and during treatment,
- the need to use effective contraception without interruption during the entire duration of treatment with valproate,
- the need for at least annual treatment reviews by a specialist,
- the need for consultation on planning pregnancy and switching to alternative treatment options prior to conception and before contraception is discontinued,
- and the need for urgent physician consultation in case of pregnancy during valproate treatment.

A visual warning of the pregnancy risks (in the form of boxed text with other possible elements such as a warning symbol) must also be placed on the packaging of the medicines and warnings included on patient cards attached to the box and supplied with the medicine each time it is dispensed. The PRAC revised the

educational materials which include a healthcare professional guide, a patient guide tailored to age and situations in a woman's life-time, a patient reminder card (attached to the outer carton to support pharmacist advice at dispensing) and an annual risk acknowledgement form with a checklist for prescribers and for patients or carers. These materials should be made available in all EU Member States where valproate and related substances are licensed. The PRAC also required a direct healthcare professional communication (DHPC) to ensure healthcare professionals and patients are informed about the risks associated with valproate in pregnant women and women of childbearing potential and on the new measures necessary to minimise the risk of exposure on valproate in pregnancy.
Finally the PRAC imposed new post-authorisation safety studies (PASS) to assess risk minimisation effectiveness, including prescribing and switching patterns in clinical practice and patient and healthcare professional awareness of the PPP and revised educational materials.

Aims of the study

1) To assess the extent of the influence of recommendations from regulatory authorities on patients', prescribers' and pharmacists' awareness about the risk of adverse teratogenic effects and neurodevelopmental disorders to children of women exposed to valproate and related substances during pregnancy, and to investigate whether knowledge, attitudes and practices have been affected.

2) To evaluate health care professionals' (physicians and pharmacists) knowledge and adherence to the pregnancy prevention programme and risk minimisation measures for women of childbearing age intending to use medicinal products containing valproate or related substances, with a focus on receipt of and awareness about educational materials, contraindications, provision of patient cards, annual review and risk assessments and their influence on valproate exposure during pregnancy.

3) To assess patient knowledge and adherence to the pregnancy prevention programme and risk minimisation measures, with a focus on educational materials, need for pregnancy testing prior, during and after treatment initiation, use of effective contraception throughout treatment, consent for risk acknowledgment forms.

Methods

Setting

This is a multi-country study in eight European countries: Belgium, Denmark, Greece, Latvia, Portugal, The Netherlands, Slovenia and Spain. The countries have a wide geographic spread and variation in health care systems and cultures. In each country a web-based questionnaire will be conducted among users and former users of valproate and related products, and among health care professionals: prescribers (general practitioners, psychiatrists and neurologists), midwives and pharmacists (hospital and community). All valproate and related products included in this study are listed in ANNEX 1. Estimates of use of valproate and related products are listed in ANNEX 2.

Study design

WP1 – Health care professional study
Relevant health care professionals will be identified in each country (see *population*). HCPs will be invited to fill in the web-based questionnaire (see *questionnaires*). Data from the questionnaires will be anonymised and collected in a central database and analysed for differences between countries. Determinants for adherence to the measures implemented per country will be analysed.

WP2 – Patient study
Women in childbearing age (aged 15-50) who are at risk of using valproate and related products will be identified in each country (see *population*) and invited to complete the web-based questionnaire (see *questionnaires*). Data from the questionnaires will be anonymised and collected in a central database and analysed for differences between countries. Additionally, in at least two countries (Netherlands and Portugal) telephone interviews will be held with 6-8 patients (per country) with a range in age and varied educational background; including, when possible, both individuals who have used valproate and related products during pregnancy, and women who discontinued its use before getting pregnant.

Population
WP1 Health care professionals
Prescribers (both GPs and specialists) will be included if they have treated at least 1 woman in the childbearing age with valproate and related products in the past year. Community pharmacists will be included and hospital pharmacists may be included. Midwives may be included, if they have had experience with at least one woman treated with valproate and related products.

A convenience sample of prescribers and pharmacists (as well as midwives, when relevant) will be included in each country. Regardless of the size of country, we aim that each country will need to complete and deliver for each study at least 150 healthcare professional questionnaires (at least 30 each for GPs and pharmacists with an additional 60 questionnaires from specialists). The expected response rate is 20-40%, and we aim for 1200 completed questionnaires for all 8 countries in total. This will mean 375-750 HCPs will have to be approached in each country.

HCPs will be recruited through the following strategies:
- through professional organizations by sending out requests to mailing lists, where possible with a recommendation from the board of the professional organization;
- through pre-existing networks of HCPs that are in place in the participating countries;
- Through advertising on (professional) websites and media aimed at the particular HCPs.

Each partner in a participating country may adjust the recruiting strategy best fitted to the local contacts and healthcare organization. Recruiting should be aimed at broad inclusion of HCPs in order to ensure the probability of an unbiased and representative sample. Where administrative health data are available (for instance, from provincial administration services in Navarra, Spain) we will analyse information about responders and non-responders, to assess selective sampling. We will compare key characteristics of respondents with those of the general population of patients or healthcare professionals.

WP2 Patients
Inclusion criteria for patients are:

- female
- aged between 15-50 years
- having used valproate or related products in the past 5 years or are currently using.

For each country we will aim to obtain 50 completed patient questionnaires. With an estimated response rate of 20%, this means that 250 patients (meeting the inclusion criteria) should be approached per country.

Recruitment Strategies
Each country will select the most suitable strategy or combination thereof. Recruiting should be aimed at broad inclusion of patients in order to increase the probability of an unbiased and representative sample. Where administrative health data are available we will analyse information about responders and non-responders, to assess selective sampling.

Recruitment strategies can include:

- asking pharmacists to select current and past users from pharmacy information systems, to contact patients and request them to fill in the web-based questionnaire;
- asking physicians to select current and past users from prescriber dossiers, to contact patients and request them to fill in the web-based questionnaire;
- approaching potential participants through patient organisations;
- advertising on online patient forums, and social media.

Detailed information about the various recruitment strategies is available per country on Annex 6.

Questionnaires

WP1 Health care professionals
An electronic survey including questions on the influence of regulatory recommendations on HCP awareness about the teratogenic and neurodevelopment effects of valproate and related substances will be used to gauge their perspective and to assess effects on knowledge, attitudes and practices. The survey has been prepared including questions to ascertain: awareness of the regulatory recommendations; whether physicians have prescribed such products; how health professionals comprehend the regulatory message; and why it is being used. If respondents are aware and understand, physicians will be asked whether it has had an effect on their prescribing behaviour (e.g. has it affected their pharmacotherapeutic choices) and asked about their information provision to patients. If they are unaware or do not understand the message conveyed then a new field will pop up which will explain the rationale for the regulatory recommendation and respondents will be asked to foresee how this new knowledge is likely to impact their future prescribing and information provision behaviours.

Topics to include in the questionnaire will cover:
(1) Awareness about regulatory recommendation regarding the use of valproate and related products by women in childbearing age
(2) Effect of regulatory recommendation on prescribing patterns
(3) Awareness of the contraindication for not using these products during pregnancy
(4) Likelihood of implementing pregnancy prevention programme and risk minimisation measures when prescribing these products, such as provision of patient guides, use of healthcare professional guides,

implementation of annual risk acknowledgement forms, seeking informed consent from patients using valproate and related products.
(5) Implementation and effect of annual reviews and risk assessment by specialists
(6) Provision of patient information when dispensing valproate and related products.
(7) Advice on discontinuation of valproate medication and guidance on contacting specialist in case of a planned or suspected pregnancy
(8) Use of healthcare professional guidelines

In the questionnaire for pharmacists additional questions on adherence of pharmacists to the need to provide the patient card and to advise patients in case of planned or suspected pregnancy at each dispensing has been added.

See:
ANNEX 3 – Questionnaire for medical specialists and GPs
ANNEX 4 – Questionnaire for pharmacists

Patients
The patient questionnaire has been developed to include the following topics:
(1) Awareness of a regulatory recommendation regarding the use of valproate and related products in women of childbearing age
(2) Effect of recommendation on use of medicine
(4) Provision of patient guide by prescriber, or patient card by pharmacist
For patients currently using valproate and related products:
(5) Use of pregnancy test prior to treatment, during treatment, after stopping treatment
(6) Effective contraception use
(7) Provision of informed consent to prescriber enabling data collection on valproate and related products' use.

See:
ANNEX 5 – Questionnaire for patients

Interviews
We will conduct telephone interviews in the Netherlands and Portugal with 6-8 patients aged 18 years or older, from a convenience sample, with a range in age and varied educational background; including both individuals who have used valproate and related products during pregnancy, and women who discontinued its use before getting pregnant. The patients to be included in the interviews will be recruited from participants that filled in the web-based questionnaire and indicated that they are willing to be interviewed. The interviews will be semi-structured based on the same topics and themes as the questionnaires. The interviews will be facilitated by experienced researchers in participating countries. Audio recordings will be transcribed verbatim.

Analysis
Workplan 1 and 2 will generate descriptive statistics, describing the distribution of characteristics of patients and HCPs for the variables included in the questionnaires. Univariate linear regression and bivariate regression analysis will be conducted to assess effect of single or multiple variables, including HCP characteristics (age, gender, country, specialism, years of experience) and patient characteristics (age, diagnosis, past use of valproate and related products, type of prescriber, country) on outcomes (awareness and/or use of pregnancy prevention measures). For the qualitative data, the analysis involves an inductive

content analysis based on a close line-by-line reading of the responses and developing a conceptual coding scheme based on the major themes in the interview guides. Transcripts will be categorized individually by two coders in each country in native languages. Coders from all countries will meet prior to the analysis to predefine categories and codes to be used. They meet again to evaluate the categories identified and to write up the results using illustrative quotes.

The descriptive statistics and its results from workplan 1 and 2, will provide insight into the key determinants of awareness and use of pregnancy prevention measures, whereas the qualitative interviews will shed light into the rationale for decision-making by patients. Both aspects will be further described in the final report and manuscript.

Information storage and management
All anonymized surveys will be hosted in a server of the University of Utrecht, The Netherlands, and will be kept for 10 years.

Study Timelines and milestones

The study started with an online kick-off meeting organised by the Study Coordinator, during which all those involved in the project will become familiar with their counterparts in other countries and the study coordinators. The Coordinating Team is responsible for hosting and preparing the content discussions, which will cover communication aspects, data management, and compliance with timelines and feedback procedures. An email-distribution list was established to share information among all those involved and telephone and skype meetings will be scheduled on a regular basis to oversee project implementation and progress.

The development of the study plan was initiated by the Coordinating Team, but National Teams will be invited to review and provide input. A similar procedure was implemented for the study protocol.

The National Team based in Copenhagen developed the first draft of the healthcare and patient questionnaires. These were subsequently reviewed by the Coordinating Team and the National Teams. The Danish team pilot tested the questionnaires and improved those when needed. Once a final questionnaire is agreed upon, other national teams will be invited to adapt it to their national settings and to translate them. The following step will include seeking Ethical Approval providing the already translated final questionnaires.

All National Teams are also invited to start recruiting respondents from July onwards, as this is the most limiting factor for a successful implementation. Recruitment of participants and implementation of the survey are likely to overlap for some months. Halfway through the questionnaire implementation and through the data analysis, the coordinating team will organize telephone meetings to receive feedback on project progress.

Between March and June 2020, all the data packages are expected to have been delivered to the Coordinating Team, that will then take the lead on the reporting, drafting both the preliminary report and the preliminary manuscript. Both documents will also be reviewed by the national teams, and if deemed necessary, by the European Medicines Agency responsible staff.

The **timeline** described below provides an overview of the study chronology together with main tasks, including responsible teams, identifying also the main milestones (indicating project progress) and deliverables.

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Timing:
3 = March 2019 - 10 = October 2020

Milestones:
M1: Milestone 1: Final version of questionnaires ready to be sent out
M2: Milestone 2: Recruitment of Respondents completed
M3: Milestone 3: Coordinating team receives all the data from NTs
M4: Milestone 4: Draft Report has been written and agreed upon by NTs and CT
M5: Milestone 5: Draft Manuscript has been written and agreed upon by NTs and CT

Deliverables:
D1: Deliverable 1 Preliminary Study Plan
D2: Deliverable 2 Study Protocol
D3: Deliverable 3 Study Report
D4: Deliverable 4 Manuscript

People involved:
Coordinating Team (CT)
Study Coordinator (C)
National Teams (NTs)
The Steering Committee (SC)

	2019										2020							
TIMELINE	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Project inception																		
Organization kick-off meeting		SC																
Installation Steering Committee		SC																
Attending kick-off meeting		NT CT SC																
Development of preliminary study plan	CT	CT NT **D1**																
Development of instructions for recruitment forms and of harmonized consent forms					CT	CT	CT											
Writing and reviewing of protocol			CT	CT NT	CT NT **D2**	CT NT												
Development of questionnaire health care professionals		CT	CT NT	CT NT														
Development of questionnaire patients		CT	CT NT	CT NT														
Hosting web-based questionnaires		CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT	CT			
Pilot testing of questionnaire healthcare professionals				DK	DK	NL												
Pilot testing of questionnaire patients				DK	DK													
Inventory of products and relevant professionals		CT	NT	NT	NT													

	2019										2020							
TIMELINE	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Tailoring questionnaire patients to national setting & translation							NT **M1**											
Seeking Ethical Committee Approval						NT	NT	NT										
Recruitment of respondents healthcare professionals					NT	NT	NT	NT	NT	NT	NT	NT	NT	NT **M2**				
Recruitment of respondents patients					NT	NT	NT	NT	NT	NT	NT	NT	NT	NT **M2**				
Monitoring progress	C	C	C	C	C	C	C	C	C	C	C	C	C	C				
Data collection and analysis																		
Implementation questionnaire healthcare professionals							NT	NT CT	NT	NT CT	NT	NT	NT	NT CT				
Implementation questionnaire patients							NT	NT CT	NT	NT CT	NT	NT	NT	NT CT				
Monitoring progress/SC									SC									
Recruitment of patients for interviews in two key countries						NL, NT 2	NL, NT 2	NL, NT 2	NL, NT 2	NL, NT 2	NL, NT 2	NL, NT 2						
Interviews patients in two key countries										NL NT2	NL NT2	NL NT2	NL NT2	NL, NT 2	NL, NT 2			
Data analysis questionnaires									NT	NT CT	NT	NT	NT	NT	NT	NT CT **M3**		
Data analysis interviews												NL	NT	NT	NT	NT CT **M3**		
Monitoring progress					C	C	C	C	C	C	C	SC	C	C	C	SC	C	

TIMELINE	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Reporting																				
Drafting preliminary report														C	C	CT	CT	CT; NT **M4**		
Review of draft report																	CT NT	CT NT		
Delivery of final report																	C	CT	CT **D3**	
Drafting manuscript																	CT	CT	CT **M5**	
Manuscript review																	NT CT	CT	NT CT	CT
Manuscript delivery																		CT		CT **D4**

ANNEX 1 - INVENTORY OF VALPROATE RELATED PRODUCTS IN THE PARTICIPATING COUNTRIES

Belgium

ATC Code	INN	Dosage form and Strength	Brand Name
N03AG01	valproic acid	valproic acid (controlled release) •300 mg •500 mg	Convulex®; Depakine® Chrono(+sodium valproaat); Valproate Sandoz®(+sodium valproaat) • tabl. verl. afgifte (deelb.); Valproate EG® • tabl. verl. afgifte (deelb.)
N03AG01	sodium valproate	oral valproate •150 mg •300 mg •500 mg injection/infusion •300 mg / 1 ml •300 mg / 3 ml •300 mg / 5 ml •1 g / 10 ml •400 mg	Convulex®; Depakine®• inj./inf. oploss. (pdr. + solv.) i.v. [flac. + amp.]• maagsapresist. tabl.• oploss.• siroop • tabl. verl. afgifte (deelb.); Valproate Mylan® • inj./inf. oploss. i.v. [amp.]

Denmark

Information retrieved from https://pro.medicin.dk/Laegemiddelgrupper/Grupper/233020

ATC	INN	Brand name	Route of administration
N03AG01	Sodium Valproate	Delepsine® Orion Pharma	Gastro-resistant tablets 100 mg
N03AG01	Sodium Valproate	Delepsine® Orion Pharma	Gastro-resistant tablets 300 mg
N03AG01	Sodium Valproate	Delepsine® Orion Pharma	Gastro-resistant tablets 500 mg
N03AG01	Sodium Valproate	Delepsine® Orion Pharma	Modified release tablets 300 mg
N03AG01	Sodium Valproate	Delepsine® Orion Pharma	Modified release tablets 500 mg
N03AG01	Sodium Valproate	Delepsine® Orion Pharma	Oral drops, soloution 200 mg/ml
N03AG01	Sodium Valproate	Delepsine® Orion Pharma	Oral solution 60 mg/ml
N03AG01	Sodium Valproate	Delepsine® Orion Pharma	suppositories 300 mg
N03AG01	Sodium Valproate	Depakine Retard Parallelimport	Modified release tablets 500 mg
N03AG01	Sodium Valproate	Deprakine® Sanofi	Gastro-resistant tablets 300 mg

N03AG01	Sodium Valproate	Deprakine® Sanofi	Gastro-resistant tablets 500 mg
N03AG01	Sodium Valproate	Deprakine® Sanofi	Modified release tablets 300 mg
N03AG01	Sodium Valproate	Deprakine® Sanofi	Modified release tablets 500 mg
N03AG01	Sodium Valproate	Orfiril® Desitin	Gastro-resistant tablets 300 mg
N03AG01	Sodium Valproate	Orfiril® Desitin	Gastro-resistant tablets 600 mg
N03AG01	Sodium Valproate	Orfiril® Desitin (Orifarm)	Gastro-resistant tablets 600 mg
N03AG01	Sodium Valproate	Orfiril® Desitin	Modified release tablets 300 mg
N03AG01	Sodium Valproate	Orfiril® Desitin	Modified-release capsules 150 mg
N03AG01	Sodium Valproate	Orfiril® Desitin (Orifarm)	Modified-release capsules 150 mg (Orifarm)
N03AG01	Sodium Valproate	Orfiril® Desitin (Paranova Danmark)	Modified-release capsules 150 mg
N03AG01	Sodium Valproate	Orfiril® Desitin	Modified-release capsules 300 mg
N03AG01	Sodium Valproate	Orfiril® Desitin (2care4)	Modified-release capsules 300 mg
N03AG01	Sodium Valproate	Orfiril® Desitin (Orifarm)	Modified-release capsules 300 mg
N03AG01	Sodium Valproate	Orfiril® Desitin (Paranova Danmark)	Modified-release capsules 300 mg
N03AG01	Sodium Valproate	Orfiril® Desitin	Modified-release granules 500 mg
N03AG01	Sodium Valproate	Orfiril® Desitin	Modified-release granules 1000 mg
N03AG01	Sodium Valproate	Orfiril® Desitin	Oral soloution 60 mg/ml
N03AG01	Sodium Valproate	Orfiril® Desitin	Injections 100 mg/ml
N03AG01	Sodium Valproate	Orfiril® Desitin	Injections 100 mg/ml
N03AG01	Sodium Valproate	Valproat "Life Medical" Life	Injections and infusions 100 mg/ml
N03AG01	Sodium Valproate	Valproat "Life Medical" Life	Injections and infusions 100 mg/ml

All valproate in DK is sodium valproate (no valproic acid, magnesium valporate, or valporate semisodium). N03AG02 valpromide is not sold in DK

Greece

ATC	INN	Brand
N03AG01	Valproic acid	DEPAKINE-CHRONO
N03AG01	Sodium valproate	DEPAKINE
N03AG01	Valproate semisodium	DEPAKINE-CHRONO
N03AG02	Valpromide	HEXAQUIN

Latvia

ATC	INN	Brand	Strength
N03AG01	Valproic acid	Convulex	150 mg
N03AG01	Valproic acid	Convulex	300 mg
N03AG01	Valproic acid	Convulex	500 mg
N03AG01	Sodium valproate, Valproic acid	Depakine Chrono	300 mg
N03AG01	Sodium valproate, Valproic acid	Depakine Chrono	500 mg
N03AG01	Valproate semisodium	Convulex	100 mg/ml
N03AG01	Valproate semisodium	Convulex retard	300 mg
N03AG01	Valproate semisodium	Convulex retard	500 mg
N03AG01	Valproate semisodium	Depakine	57,64 mg/ml
N03AG01	Valproate semisodium	Convulex	50 mg/ml
N03AG01	Valproate semisodium	Convulex	300 mg/ml

Portugal

ATC	INN	Brandname	Dosage Form	Strength
N03AG01	Valproic acid	Ácido Valpróico Generis	Prolonged-release tablet	300 mg
N03AG01	Valproic acid	Ácido Valpróico Generis	Prolonged-release tablet	500 mg
N03AG01	Valproic acid	Ácido Valpróico Generis	Powder and solvent for solution for injection	400 mg/4 ml
N03AG01	Valproic acid	Ácido Valpróico Neogen	Solution for injection	100 mg/ml

N03AG01	Valproic acid	Ácido Valpróico Neogen	Solution for injection	100 mg/ml
N03AG01	Valproic acid	Ácido Valpróico Ratiopharm 300 mg Comprimidos de libertação prolongada	Prolonged-release tablet	300 mg
N03AG01	Valproic acid	Ácido Valpróico Ratiopharm 500 mg Comprimidos de libertação prolongada	Prolonged-release tablet	500 mg
N03AG01	Valproic acid	Depakine	Powder and solvent for solution for injection	400 mg/4 ml
N03AG01	Valproic acid	Depakine	Oral solution	200 mg/ml
N03AG01	Valproic acid	Depakine	Syrup	40 mg/ml
N03AG01	Valproic acid	Depakine Chrono 300	Prolonged-release tablet	300 mg
N03AG01	Valproic acid	Depakine Chrono 500	Prolonged-release tablet	500 mg
N03AG01	Valproic acid	Depakine Chronosphere	Modified-release granules	100 mg
N03AG01	Valproic acid	Depakine Chronosphere	Modified-release granules	1000 mg
N03AG01	Valproic acid	Depakine Chronosphere	Modified-release granules	250 mg
N03AG01	Valproic acid	Depakine Chronosphere	Modified-release granules	50 mg
N03AG01	Valproic acid	Depakine Chronosphere	Modified-release granules	500 mg
N03AG01	Valproic acid	Depakine Chronosphere	Modified-release granules	750 mg
N03AG01	Valproic acid	Diplexil	Gastro-Resistant tablet	500 mg
N03AG01	Valproic acid	Diplexil	Coated tablet	200 mg
N03AG01	Valproic acid	Diplexil	Solution for injection	100 mg/ml
N03AG01	Valproic acid	Diplexil	Oral solution	200 mg/ml
N03AG01	Valproic acid	Diplexil 1000	Prolonged-release granules	1000 mg
N03AG01	Valproic acid	Diplexil 150	Prolonged-release capsule	150 mg
N03AG01	Valproic acid	Diplexil 300	Prolonged-release capsule	300 mg

N03AG01	Valproic acid	Diplexil 500	Prolonged-release granules	500 mg
N03AG01	Valproic acid	Epixival	Solution for injection	100 mg/ml
N03AG01	Valproic acid	Epixival	Solution for injection	100 mg/ml
N03AG01	Valproic acid	Valproato de sódio G.E.S.	Powder and solvent for solution for injection	400 mg/4 ml
N03AG01	Valproate semisodium	Diplexil-R	Gastro-Resistant tablet	250 mg
N03AG01	Valproate semisodium	Diplexil-R	Gastro-Resistant tablet	500 mg

Slovenia

ATC	**INN**	**Product**
N03AG01	Valproic acid	Depakine chrono 300 mg SR tablets
		Depakine chrono 500 mg SR tablets
		Depakine 300 mg/ml oral solution

Spain

ATC	**INN**	**Brandname**	**Marketing Authorisation Holder**
N03AG01	Sodium valproate	Depakine 200 mg comprimidos gastrorresistentes	Sanofi Aventis, S.A.
N03AG01	Sodium valproate	Depakine 500 mg comprimidos gastrorresistentes	Sanofi Aventis, S.A.
N03AG01	Sodium valproate	Depakine 200 mg/ml solución oral	Sanofi Aventis, S.A.
N03AG01	Sodium valproate	Depakine 100 mg/ml polvo y disolvente para solución inyectable	Sanofi Aventis, S.A.
N03AG01	Sodium valproate	Acido Valproico GES 400 mg polvo y disolvente para solución inyectable EFG	G.E.S. Genéricos Españoles Laboratorio, S.A.
N03AG01	Sodium valproate, Valproic acid	Depakine Crono 300 mg comprimidos recubiertos	Sanofi Aventis, S.A.
N03AG01	Sodium valproate, Valproic acid	Depakine Crono 500 mg comprimidos recubiertos	Sanofi Aventis, S.A.

The Netherlands

ATC	INN	Brand	Marketing Authorisation Holder
N03AG01	Sodium valproate, Valproic acid	Depakine Chrono 300, tabletten met gereguleerde afgifte 300 mg	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate, Valproic acid	Depakine Chrono 500, tabletten met gereguleerde afgifte 500 mg	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate, Valproic acid	Depakine Chronosphere 100 mg, granulaat met gereguleerde afgifte	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate, Valproic acid	Depakine Chronosphere 1000 mg, granulaat met gereguleerde afgifte	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate, Valproic acid	Depakine Chronosphere 250 mg, granulaat met gereguleerde afgifte	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate, Valproic acid	Depakine Chronosphere 500 mg, granulaat met gereguleerde afgifte	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate, Valproic acid	Depakine Chronosphere 750 mg, granulaat met gereguleerde afgifte	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate	Depakine Enteric, maagsapresistente tabletten 150 mg	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate	Depakine Enteric, maagsapresistente tabletten 300 mg	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate	Depakine Enteric, maagsapresistente tabletten 500 mg	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate	Depakine i.v. 400, poeder voor injectievloeistof 400 mg	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate	Depakine suikervrije stroop, drank 200 mg/5 ml	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate	Depakine vloeistof voor kinderen, vloeistof voor oraal gebruik 300 mg/ml	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate	Natrii valproas, maagsapresistente tabletten 300 mg	Sanofi - Aventis Netherlands B.V.
N03AG01	Sodium valproate	Natriumvalproaat Apotex 150 mg, maagsapresistente tabletten	Apotex Europe B.V.
N03AG01	Sodium valproate	Natriumvalproaat Apotex 300 mg, maagsapresistente tabletten	Apotex Europe B.V.
N03AG01	Sodium valproate	Natriumvalproaat Apotex 300 mg/5 ml, drank	Apotex Europe B.V.
N03AG01	Sodium valproate	Natriumvalproaat Apotex 600 mg, maagsapresistente tabletten	Apotex Europe B.V.
N03AG01	Sodium valproate, Valproic acid	Natriumvalproaat Chrono CF 300 mg, tabletten met verlengde afgifte	Centrafarm B.V.

N03AG01	Sodium valproate, Valproic acid	Natriumvalproaat Chrono CF 500 mg, tabletten met verlengde afgifte	Centrafarm B.V.
N03AG01	Sodium valproate, Valproic acid	Natriumvalproaat Chrono Sandoz 300 mg, tabletten met verlengde afgifte	Sandoz B.V.
N03AG01	Sodium valproate, Valproic acid	Natriumvalproaat Chrono Sandoz 500 mg, tabletten met verlengde afgifte	Sandoz B.V.
N03AG01	Sodium valproate, Valproic acid	Natriumvalproaat chrono 300 mg Teva, tabletten met gereguleerde afgifte	Teva Nederland B.V.
N03AG01	Sodium valproate, Valproic acid	Natriumvalproaat chrono 500 mg Teva, tabletten met gereguleerde afgifte	Teva Nederland B.V.
N03AG01	Sodium valproate	Orfiril CR 1000 mg, granulaat met gereguleerde afgifte	Pharmachemie B.V.
N03AG01	Sodium valproate	Orfiril CR 150 mg, capsules met gereguleerde afgifte	Pharmachemie B.V.
N03AG01	Sodium valproate	Orfiril CR 300 mg, capsules met gereguleerde afgifte	Pharmachemie B.V.
N03AG01	Sodium valproate	Orfiril CR 500 mg, granulaat met gereguleerde afgifte	Pharmachemie B.V.
N03AG01	Sodium valproate	Orfiril 100 mg/ml, oplossing voor injectie	Pharmachemie B.V.
N03AG01	Valproic acid	Propymal Enteric 150 mg, maagsapresistente capsules	Apotex Europe B.V.
N03AG01	Valproic acid	Propymal Enteric 300 mg, maagsapresistente capsules	Apotex Europe B.V.
N03AG01	Valproic acid	Propymal Enteric 450 mg, maagsapresistente capsules	Apotex Europe B.V.
N03AG01	Valproic acid	Propymal Enteric 600 mg, maagsapresistente capsules	Apotex Europe B.V.

ANNEX 2 - INVENTORY OF MAIN PRESCRIBERS AND ESTIMATES OF USE OF VALPROATE RELATED PRODUCTS IN THE CONTRIBUTING COUNTRIES

Data was sought among countries to ascertain who were the main prescribers of retinoid-related products within the countries participating in our study. Similarly, we invited participating researchers to estimate of the prevalence of the use of valproic acid (or related products) by women of childbearing age in their country. When possible, stratified by age groups. Not all participating countries were able to provide data and the type data obtained varies greatly as shown in the tables below.

Belgium

INN	**ATC Code**	**Dosage form and strength**	**Brandname**	**Total prescribed DDD in 2017**	**Prescribers**	***Rough estimate of patients within Belgium target population (♀≤40y chronic users and therapy compliant)***
valproic acid	N03AG01	Oral valproic acid (controled release) •300 mg •500 mg	Convulex®; Depakine®Chrono (+sodium valproate); Valproate Sandoz® (+sodium valproate); Valproate EG®	11211000	70,8% general practitioners 20,0% neurologists	*2764*
sodium valproate	N03AG01	Oral valproate •150 mg •300 mg •500 mg injectie/infusie •300 mg / 1 ml •300 mg / 3 ml •300 mg / 5 ml •1 g / 10 ml •400 mg	Convulex®; Depakine® Valproate Mylan®			

		Volume (DDD) per 1000 inhabitants/day – 2014 (% of total DDD for this subgroup)		
		Females 0-20 years	**Females 21-40 years**	**Females 41-60 years**
ANTIEPILEPTICS	N03	2,491 (2%)	8,607 (7%)	16,986 (13%)

Denmark

ATC	**INN**	**Number of users 2017, primary sector, Denmark , female, 18-44 year old**
N03AG01	Sodium Valproate	1800

Greece (no data available)

Latvia

	Age group				
	Females 0-14 years	**Females 15-44 years**	**Females 45-54 years**	**Females ≥ 55 years**	**All Females**
Volume (DDD) per 1000 inhabitants/day In 2018	0.03	0.19	0.1	0.23	1.5

Portugal

Data were procured from the National Health System billing centre. These data cover only reimbursed medicines dispensed in ambulatory to patients of the National Health System. They do not include medicines used in hospital settings.

INN	**Packages 2008**	**Packages 2009**	**Packages 2010**	**Packages 2011**	**Packages 2012**	**Packages 2013**	**Packages 2014**	**Packages 2015**	**Packages 2016**	**Packages 2017**	**Packages 2018**
Valproic acid	441.048	462.153	474.501	494.578	508.174	528.253	538.576	531.061	516.677	507.496	499.671
Sodium valproate	103.726	113.640	123.858	138.627	159.277	185.377	204.180	208.078	219.444	230.272	235.056

Age Group	**INN**	**Number of packages dispensed to women**	**Number of packages dispensed to men**	**Total Amount of packages dispensed**
10 - 14 years	Valproic acid	10.767	16.509	27.276
	Sodium valproate	1.042	2.843	3.885
15 - 19 years	Valproic acid	8.874	15.949	24.823
	Sodium valproate	2.708	4.667	7.375
20 - 24 years	Valproic acid	8.475	14.650	23.125
	Sodium valproate	2.877	5.669	8.546
25 - 29 years	Valproic acid	9.322	15.438	24.760
	Sodium valproate	3.437	5.939	9.376
30 - 34 years	Valproic acid	10.028	16.529	26.557
	Sodium valproate	4.930	6.801	11.731
35 - 39 years	Valproic acid	12.692	19.964	32.656

	Sodium valproate	7.123	8.423	15.546
40 - 44 years	Valproic acid	16.683	23.178	39.861
	Sodium valproate	10.846	11.558	22.404
45 - 49 years	Valproic acid	19.315	21.863	41.178
	Sodium valproate	13.239	11.832	25.071
50 - 54 years	Valproic acid	20.988	20.528	41.516
	Sodium valproate	14.846	11.030	25.876

Slovenia

The 1-year prevalence in 2018 for use by women in Slovenia of ATC codes N03AG01, N03AG02 is as follows:

Age group	No of women	Percent	Population of Slovenia - women
0-11	176	5.5	124,141
12-17	105	3.3	54,047
18-30	310	9.7	134,439
31-40	443	13.9	140,111
41-50	494	15.5	143,835
50 and more	1655	52.0	443,243
Total	**3183**	**100.0**	**1,039,816**
Total 12-55y	**1648**	**51.8**	**548,734**

Spain

This data is for the Navarre region only, based on health administration data. The total population of Navarre was of 647.554 inhabitants on 01/01/2018, from which 322.807 are women.

Active Ingredient	ATC Code	Amount active principle and dosage form	Brandname	Total DDD prescribed in 2018	Prescribers	*Estimated number of users (*

		200mg comp (5%)				
Valproate semisodium	N03AG01			0	no prescription	*0*
Valpromide	N03AG02			0	no prescription	*0*

Use of Valproic Acid by women

Age Groups	18 & 19	20-29	30-39	40-49	Other	Total all age groups
Number of users	3.067	16.197	19.689	42.437	131.463	212.853
Percentage of total users	1,44%	7,61%	9,25%	19,94%	61,76%	

Key Prescribers of Valproic Acid

Medical Specialties	Percentage prescribing N03AG01 – Valproic Acid
Unknown	0,54%
Anaesthesiology	0,27%
Vascular surgery	0,13%
Dermatology	0,13%
Endocrinology	0,13%
Geriatrics	0,27%
Aviation Medicine	0,13%
Family and Community Medicine	**62,28%**
General Medicine	1,74%
Intensive Care Medicine	0,13%
Internal Medicine	2,01%
Nephrology	0,27%
Neurosurgery	0,13%
Neurology	3,62%
Gynaecology and Obstetrics	0,27%
Medical Oncology	0,13%
Radio-Oncology	0,27%
Otorhinolaryngology	0,13%
Paediatrics	**14,50%**
Psychiatry	**10,34%**
Rehabilitation	0,13%
Emergency	2,42%
Total	100,00%

The Netherlands

Estimation for the total health-insured population, source: GIPDatabank.nl

N03AG01 Valproic Acid (Dekapine chrono ®)	2013	2014	2015	2016	2017
DDD's	13.127.700	12.923.900	12.755.900	12.710.500	12.350.000
Users	60.609	59.496	57.880	56.384	54.017
Prescriptions	683.220	699.420	700.050	701.350	669.030

Female users in 2017							
	0-4	5-14	15-24	25-44	45-64	65-74	75 +
N03AG01 Valproicacid	196	985	1.360	4.253	10.905	4.198	2.599

ANNEX 3 Questionnaire for GPs and medical specialists - Valproate

(Text in green refers to issues mentioned in the research plan to make sure all these issues are covered, it will not appear in the questionnaire)
(Text in blue refers to **skip patterns** and other instructions for national coordinators)

Dear Doctor,

As you are certainly aware, the knowledge about a medicine is not only built up during its research and development, but also once the drug is available on the market and being used by a larger group of patients. We are conducting an international survey funded by the European Medicines Agency to monitor how information about drug safety is being conveyed to women across the European Union who are using certain medications.

Our study concerns the use of valproate or <similar drugs available in your country >. Below is a list of medications that are oral retinoids and are approved in (include country): <insert trade names for the available drugs>

You are invited to fill in this questionnaire given that you are in contact with patients who use valproate or <similar drugs available in your country >.

We are particularly interested in knowing more about the information you have received about this medicine and how that might have influenced your prescribing and the guidance you have provided to female patients in the past and will be providing in the future.

This is an international study, which includes research centres across eight European Member States. In (include country) this research is being led in by (include name of centre).

We estimate that it will take approximately 10 minutes to answer the questions below. The information provided will inform the European Medicines Agency pharmacovigilance activities and will contribute to increased knowledge about how to better advise patients about the use of valproate or <similar drugs available in your country >.

Your participation is voluntary. Answers will be registered anonymously and handled in accordance with the General Data Protection Regulation (or GDPR) (EU) 2016/679 of 27 April 2016.

□ I hereby declare to have read and understood the information provided above and accept free-willingly to participate. I allow my response to be recorded and analyzed by the researchers.
□ I would like to receive information about the results of this study by e-mail. Please provide your e-mail_____

Baseline characteristics

Q1.What is your year of birth?
- Year _ _ _ _

Q2.What is your sex?
- Male
- Female
- Would rather not say

Q3.What is your current professional category?
- General Practitioner/Family doctor
- Psychiatrist
- Neurologist
- Other, please specify _____

Q4.How long have you practiced in your current field?
- 0-5 years
- 6-10 years
- 11-20 years
- 21-30 years
- 31 years or longer

Q5.On average how frequently do you consult with women of reproductive age who are taking valproate or < similar drugs available in your country >?
- 4 times per month (once a week) or more
- 2-3 times per month
- Once a month or less
- Never

If "Never", the respondent is thanked and the survey stops here.
Message: Thank you for your interest in participating, but given that you do not consult with women of reproductive age who are likely to take valproate-related products your input is outside the scope of this study.

Q6. In your practice, have you ever suspected or witnessed malformations or developmental problems in the newborn, that may have been caused by medicines' use during pregnancy?
- Yes
- No
- I am not sure

If "Yes" go to Q7, if others go to Q8

Q7. Were the suspected malformations and/or developmental problems related to the use of valproate or < similar drugs available in your country >?
- Yes
- No
- I am not sure

(3) Awareness of the contraindication for not using these products during pregnancy

Q8. When did you learn about the teratogenic risks of valproate or < similar drugs available in your country > if taken during pregnancy?

- Just now, when answering this questionnaire
- Within the last 2 years
- Within the last 5 years
- Longer than 5 years ago

If "Within the last 2 years" or "Within the last 5 years" or "Longer than 5 years ago" go to Q9, if "Just now, through this questionnaire", go to Q10.

Q9. Where did you obtain that information? (Choose all that apply)

- Health authorities
- Drug Regulatory Agencies
- Professional societies
- Colleagues
- Professional journals
- Manufacturers (e.g. printed or electronic materials)
- Internet
- Symposia or conferences
- During academic training
- During post-academic training/continuous professional education
- Other, please specify: _____

(1) Awareness about regulatory recommendations regarding the use of valproate and related products by women in childbearing age
(4) How likely is the healthcare professional to implement pregnancy prevention programme and risk minimisation measures when prescribing these products, such as provision of patient guides, use of healthcare professional guides, implementation of annual risk acknowledgement forms, seeking informed consent from patients using valproate and related products.

Q10. Think about **the last time you prescribed valproate o**r < similar drugs available in your country > **to a woman of reproductive age** or consulted with a woman who uses valproate or < similar drugs available in your country >. Did you apply any of the pregnancy prevention measure described below, which were established in 2018? (one option per row)

		Yes, I did apply it	I have seen it but did not apply it	No, I have never seen/done it	I am not sure
Q10a	Consult Health professional guide* (Please click the link to see an example)	1.1	1.2	1.3	1.4
Q10b	Deliver the Patient guide* to the patient (Please click the link to see an example)	2.1	2.2	2.3	2.4
Q10c	Review the Risk acknowledgement form/checklist* with the patient (Please click the link to see an example	3.1	3.2	3.3	3.4

Q10d	Ask the patient to sign the Risk acknowledgement form/checklist*	4.1	4.2	4.3	4.4
Q10e	Deliver a Patient reminder card * (Please click the link to see an example)	5.1	5.2	5.3	5.4
Q10f	Consult the Direct to Healthcare Professional Communication letter* (Please click the link to see an example)	6.1	6.2	6.3	6.4

*Clicking on the link opens an explanation with a visual example of the specific measure used in the country
** Each country adapts (leaves or deletes what is in the brackets) depending on the country situation

All the answers are registered first, then:
Consider Q10a first, and for those who did not tick 1.1 (i.e. tick 1.2, 1.3, 1.4) insert Q11a, and then move to the next questions that follows
Then consider Q10b, and for those who did not tick 2.1 (i.e. tick 2.2, 2.3, 2.4) insert Q11b, and then move to the next questions that follows
Then consider Q10c, and for those who did not tick 3.1 (i.e. tick 3.2, 3.3, 3.4) insert Q11c, and then move to the next questions that follows
Then consider Q10d, and for those who did not tick 4.1 (i.e. tick 4.2, 4.3, 4.4) insert Q11d, and then move to the next question that follows
Then consider Q10e, and for those who did not tick 5.1 (i.e. tick 5.2, 5.3, 5.4) insert Q11e, and then move to the next question that follows
Then consider Q10f, and for those who did not tick 6.1 (i.e. tick 6.2, 6.3,6.4) insert Q11f, and then move to Q12

Q11a. In the future, how likely are you to consult the "Healthcare professional guide or Pharmacist guide"* when prescribing valproate or < similar drugs available in your country > to reproductive age women or consulting with women taking valproate or < similar drugs available in your country >?

- Very unlikely
- Unlikely
- Neither unlikely nor likely
- Likely
- Very likely

If "Very unlikely" or "Unlikely", go to Q11a_ad

Q11a_ad. Please explain why not_____

Q11b. In the future, how likely are you deliver the "Patient guide" * when prescribing valproate or < similar drugs available in your country > to reproductive age women or consulting with women taking valproate or < similar drugs available in your country >?

- Very unlikely
- Unlikely
- Neither unlikely nor likely
- Likely
- Very likely

If "Very unlikely" or "Unlikely", go to Q11b_ad

Q11b_ad. Please explain why not_____

Q11c. In the future, how likely are you to review the "Risk acknowledgement form/checklist" * with your patient when prescribing valproate or < similar drugs available in your country > to reproductive age women or consulting with women taking valproate or < similar drugs available in your country >?

- Very unlikely
- Unlikely
- Neither unlikely nor likely
- Likely
- Very likely

If "Very unlikely" or "Unlikely", go to Q11c_ad

Q11c_ad. Please explain why not_____

Q11d. In the future, how likely are you to ask your patient to sign the "Risk acknowledgement form/checklist" * when prescribing when prescribing valproate or < similar drugs available in your country > to women of reproductive age or consulting with women taking valproate or < similar drugs available in your country >?

- Very unlikely
- Unlikely
- Neither unlikely nor likely
- Likely
- Very likely

If "Very unlikely" or "Unlikely", go to Q11d_ad

Q11d_ad. Please explain why not_____

Q11e. In the future, how likely are you to deliver the "Patient reminder card" * when prescribing valproate or < similar drugs available in your country > to reproductive age women or consulting with women taking valproate or < similar drugs available in your country >?

- Very unlikely
- Unlikely
- Neither unlikely nor likely
- Likely
- Very likely

If "Very unlikely" or "Unlikely", go to Q11e_ad

Q11e_ad. Please explain why not_____

Q11f. In the future how likely are you to read the "Direct to Healthcare Professional Communication letter"* when prescribing valproate or < similar drugs available in your country > to women of reproductive age or consulting with women taking valproate or < similar drugs available in your country >?

- Very unlikely
- Unlikely
- Neither unlikely nor likely
- Likely
- Very likely

If "Very unlikely" or "Unlikely", go to Q11f_ad

Q11f_ad. Please explain why not_____

Q12. In your opinion, reproductive age women are those of age (choose all that applies):

- 15-17 years old
- 18-44 years old
- 45-50 years old
- 51-55 years old

Other, please explain_____

(2) Effect of regulatory recommendation on prescribing patterns

Q13. Have your prescribing and counselling to women of reproductive age changed since the implementation of pregnancy prevention measures for valproate or < similar drugs available in your country > established in 2018 (e.g. Health professional guide, Patient guide, Risk acknowledgment form, Direct to healthcare professional communication letter)?

- Not at all
- Probably not
- Not sure
- Probably yes
- Certainly yes

If "Probably yes" or "Certainly yes" go to Q14, if others go to Q16

Q14. Which pregnancy prevention measures established in 2018 have had impact on your prescribing patterns and counselling to women of reproductive age? (Please select all that apply)

- Health professional guide*
- Patient guide*
- Reviewing Risk acknowledgement form/checklist*
- Signing Risk acknowledgement form by patient
- Patient reminder card*
- Direct to Healthcare Professional Communication letter*

Q15. Please describe briefly how your provision of information/counseling/prescribing has changed?

_____
_____
_____
_____
_____

(8) Identifying barriers preventing the implementation of the regulatory recommendations

Q16. Which barriers hinder the implementation and/or use of the pregnancy prevention measures established in 2018 (e.g. Health professional guide*, Patient guide*, Risk acknowledgment form*, Direct to healthcare professional communication letter*etc? Please include at least one example.

_____
_____
_____
_____
_____

(7) Advice on discontinuation of valproate medication and guidance on contacting specialist in case of a planned or suspected pregnancy
(5) Implementation and effect of annual reviews and risk assessment by medical specialists

Q17. We are interested in getting to know a bit more about your current practice of valproate or < similar drugs available in your country > prescribing, follow-up, pregnancy testing and contraception counseling for women of reproductive age who take the medication. Please indicate what describes your practice best (one option per row)

		Strongly Agree	Somehow agree	Somehow disagree	Strongly Disagree	Not relevant to me
	Prescribing					
Q17a	I don't prescribe valproate or <similar drugs available in your country >					
Q17b	I don't prescribe valproate or <similar drugs available in your country > to women of reproductive age					
Q17c	I am selective when prescribing valproate or <similar drugs available in your country > to women of reproductive age					
Q17d	I discontinue valproate or <similar drugs available in your country > in women who are planning to become pregnant or suspect they might be pregnant.					
Q17e	I refer women who use valproate or <similar drugs available in your country > and who are planning to become pregnant or suspect being pregnant to a specialist.					
	Follow up					
Q17f	I hold monthly follow-up consultations with women of reproductive age who are taking valproate or <similar drugs available in your country >					
	Pregnancy testing					
Q17g	I make sure that women of reproductive age take a pregnancy test before starting treatment with valproate or <similar drugs available in your country >					
Q13h	I make sure that women of reproductive age who use valproate or <similar drugs available in your country > take monthly pregnancy tests					
Q17i	I make sure that women of reproductive age who use valproate or <similar drugs available in your					

	country > take pregnancy tests regularly once they stop treatment					
Q17j	I discuss the results of pregnancy tests with women of reproductive age who are or were taking valproate or <similar drugs available in your country >					
	Contraception counseling					
Q17k	When prescribing valproate or <similar drugs available in your country to women of reproductive age, I inform them about the importance of effective contraception					
Q17l	I prescribe effective contraception to women of reproductive age who take valproate or <similar drugs available in your country >					
Q17m	When prescribing valproate or <similar drugs available in your country >, to women of reproductive age I advise them to contact their general practitioner or specialist to discuss effective contraception					

Q18. Are there any additional points/suggestions/concerns you would like to raise, in what concerns the prescribing/counselling/implementation of pregnancy prevention measures valproate or <similar drugs available in your country >?

_____
_____
_____
_____
_____

Thank you for participating!

ANNEX 4 Questionnaire **for pharmacists – Valproate**

(Text in green refers to issues mentioned in the research plan to make sure all these issues are covered, it will
(Text in green refers to issues mentioned in the research plan to make sure all these issues are covered, it will not appear in the questionnaire)
(Text in blue refers to **skip patterns** and other instructions for national coordinators)

Dear Pharmacist,

As you are certainly aware, the knowledge about a medicine is not only built up during its research and development, but also once the drug is available on the market and being used by a larger group of patients. We are conducting an international survey funded by the European Medicines Agency to monitor how information about drug safety is being conveyed to women across the European Union who are using certain medications.

Our study concerns the use of medications containing valproate . Below is a list of medications that contain valproate and are approved in (include country): <insert trade names for the available drugs>

You are invited to fill in this questionnaire given that you are in contact with patients who use medication containing valproate.

We are particularly interested in knowing more about the information you have received about this medicine and how that might have influenced the counselling you have provided in the past and will be providing in the future.

This is an international study, which includes research centres across eight European Member States. In (include country) this research is being led in by (include name of centre).

We estimate that it will take approximately 10 minutes to answer the questions below. The information provided will inform the European Medicines Agency pharmacovigilance activities and will contribute to increased knowledge about how to better advise patients about the use of medications containing valproate.

Your participation is voluntary. Answers will be registered anonymously and handled in accordance with the General Data Protection Regulation (or GDPR) (EU) 2016/679 of 27 April 2016.

□ I hereby declare to have read and understood the information provided above and accept free-willingly to participate. I allow my response to be recorded and analyzed by the researchers.
□ I would like to receive information about the results of this study by e-mail. Please provide your e-mail_____

Baseline characteristics

Q1. When were you born?
- Year__ __ __ __

Q2. What is your sex?
- Male
- Female
- Would rather not say

Q3. What is your current professional category?

- Hospital pharmacist
- Community pharmacist
- Other, please specify _____

Q4. How long have you practiced in your current field?
- 0-5 years
- 6-10 years
- 11-20 years
- 21-30 years
- 31 years or longer

Q5a. How frequently do you dispense valproate or <similar drugs available in your country > for women of reproductive age?
- Once a week or more
- Twice a month
- Once a month or less frequently
- Never

If "Never", the respondent is thanked for interest and stops here
Message: Thank you for your interest in participating, but given that you do not dispense valproate to women of reproductive age your input is outside the scope of this study.

Q5b. How frequently do you provide information to women of reproductive age about valproate or <similar drugs available in your country >?
- Once a week or more
- Twice a month
- Once a month or less frequently
- Never

Q6. In your practice, have you ever suspected or witnessed malformations or developmental problems in the newborn, that may have been caused by medicines' use during pregnancy ?
- Yes
- No
- I am unaware

If "Yes" go to Q7, if others go to Q8

Q7. Were the suspected malformations and/or development problems related to the use of valproate or <similar drugs available in your country >?
- Yes
- No
- I am unaware

(3) Awareness of the contraindication for using these products during pregnancy

Q8. When did you learn about the teratogenic effects of valproate or <similar drugs available in your country > taken during pregnancy?
- Just now, when answering this questionnaire
- Within the last 2 years
- Within the last 5 years

- More than 5 years ago

If "Within the last 2 years" or "Within the last 5 years" or "Longer than 5 years ago" go to Q9, if "if "Just now, when answering this questionnaire", go to Q10.

Q9. Where did you obtain that information? (Choose all that apply)

- Health authorities
- Drug regulatory agencies
- Professional societies
- Colleagues
- Professional journals
- Manufacturers (e.g. printed or electronic material)
- Internet
- Symposia or conferences
- During academic studies
- During post-academic training/continuous professional education
- Other – please elaborate: _____

(1) Awareness about regulatory recommendation regarding the use of valproate and related products by women in childbearing age
(4) How likely is the healthcare professional to implement pregnancy prevention programme and risk minimisation measures when prescribing these products, such as provision of patient guides, use of healthcare professional guides, implementation of annual risk acknowledgement forms, seeking informed consent from patients using valproate and related products.

Q10.Think about **the last time you dispensed valproate** or <similar drugs available in your country > **to a woman of reproductive age.** Did you apply any of the pregnancy prevention measure described below, which were established in 2018?

		Yes, I applied it	I have seen it, but did not apply it	No, I have never seen it before	I am not sure
Q10a	Consult the Healthcare professional guide or Pharmacist guide (Please click the link to see an example)*	1.1	1.2	1.3	1.4
Q10b	Consult the Pharmacist checklist* (Please click the link to see an example)	2.1	2.2	2.3	2.4
Q10c	Alert the patient to the warning sign not to use that medication during pregnancy which is included in the outer packaging * (Please click the link to see an example)	3.1	3.2	3.3	3.4
Q10d	Deliver a Patient reminder card* (Please click the link to see an example)	4.1	4.2	4.3	4.4
Q10e	Consult the Direct to healthcare professional communication (DHPC)* (Please click the link to see an example)	5.1	5.2	5.3	5.4

*Clicking on the link opens an explanation with a visual example of the specific measure used in the country

All the answers are registered first, then:
Consider Q10a first, and for those who did not tick 1.1 (i.e. tick 1.2, 1.3, 1.4) insert Q11a, and then move to the next questions that follows
Then consider Q10b, and for those who did not tick 2.1 (i.e. tick 2.2, 2.3, 2.4) insert Q11b, and then move to the next questions that follows
Then consider Q10c, and for those who did not tick 3.1 (i.e. tick 3.2, 3.3, 3.4) insert Q11c, and then move to the next questions that follows
Then consider Q10d, and for those who did not tick 4.1 (i.e. tick 4.2, 4.3, 4.4) insert Q11d, and then move to the next questions that follows
Then consider Q10e, and for those who did not tick 5.1 (i.e. tick 5.2, 5.3, 5.4) insert Q11e, and then move to Q12

Q11a. In the future, how likely are you to consult the "Healthcare professional guide or Pharmacist guide" * when dispensing valproate or <similar drugs available in your country > to women of reproductive age?

- Very unlikely
- Unlikely
- Neither unlikely nor likely
- Likely
- Very likely

If "Very unlikely" or "Unlikely", go to Q11a_ad

Q11a_ad. Please explain why not_____

Q11b. In the future how likely are you to consult the "Pharmacist checklist" * when dispensing valproate or <similar drugs available in your country > to women of reproductive age?

- Very unlikely
- Unlikely
- Neither unlikely nor likely
- Likely
- Very likely

If "Very unlikely" or "Unlikely", go to Q11b_ad

Q11b_ad. Please explain why not_____

Q11c. In the future, how likely are you to alert to the warning sign* included in the outer packaging, when dispensing valproate or <similar drugs available in your country > to a woman of reproductive age?

- Very unlikely
- Unlikely
- Neither unlikely nor likely
- Likely
- Very likely

If "Very unlikely" or "Unlikely", go to Q11c_ad

Q11c_ad. Please explain why not_____

Q11d. In the future, , how likely are you to deliver the "Patient reminder card" * when dispensing valproate or <similar drugs available in your country > to a woman of reproductive age next time?

- Very unlikely
- Unlikely
- Neither unlikely nor likely
- Likely
- Very likely

If "Very unlikely" or "Unlikely", go to Q11d_ad

Q11d_ad. Please explain why not_____

Q11e. In the future, how likely are to read or consult the "Direct to Healthcare Professional Communication letter" * on valproate or <similar drugs available in your country > when dispensing this medication to women of reproductive age?

- Very unlikely
- Unlikely
- Neither unlikely nor likely
- Likely
- Very likely

If "Very unlikely" or "Unlikely", go to Q11e_ad

Q11e_ad. Please explain, why not_____

Q12. In your opinion, women of reproductive age are those within the following age ranges: (Select all that apply)

- 15-17 years old
- 18-44 years old
- 45-50 years old
- 51-55 years old
- Other, please explain_____

(6) Provision of patient information when dispensing valproate and related products.
(7) Advice on discontinuation of valproate medication and guidance on contacting specialist in case of a planned or suspected pregnancy

Q13a. We want to know more about the information you provide when dispensing or <similar drugs available in your country > to women of reproductive age. (Select all that apply)

		Never	Seldom	Often	Always
Q13a.	I inform or remind patients about the importance of effective contraception				
Q13b.	I advise patients to stop taking the medication, if they suspect being pregnant				
Q13c.	I advise patients to contact their doctor, if they suspect being pregnant				
Q13d.	I highlight the importance of testing for pregnancy before and during the treatment.				

Q13b. Are there differences in the counselling that you provide when dispensing a first prescription of valproate to women of reproductive age when compared to refill prescriptions?

- Yes

- No

If "Yes", go to Q13b_ad

Q13b ad. Please explain what differs:

Q14. Has the information you provide to women of reproductive age when dispensing valproate or <similar drugs available in your country > changed since the implementation of the pregnancy prevention measures established in 2018 (i.e. the Health professional guide*, the Pharmacy checklist*, the Patient guide*, the warning sign on the outer packaging*, the Patient reminder card, the Direct to Healthcare Professional Communication letter*)?

- Not at all
- Probably not
- Not sure
- Probably yes
- Certainly yes

If "Probably yes" or "Certainly yes" go to Q15, if others go to Q17.

Q15. Which pregnancy prevention measures established in 2018 have had impact on the information you provide when dispensing valproate or <similar drugs available in your country > to women of reproductive age? (Please select all that apply)

- Healthcare professional guide or Pharmacist guide*
- Pharmacist checklist*
- Warning sign on the outer packaging not to take medication during pregnancy *
- Patient reminder card*
- Direct to Healthcare Professional Communication letter*

Q16.Please describe briefly how your provision of information/counseling has changed?

_____
_____
_____
_____
_____

(8) Identifying barriers preventing the implementation of the regulatory rec

Q17. Which barriers hinder the implementation and/or use of the pregnancy prevention measures established in 2018 (i.e. Health professional guide*, Pharmacist checklist*, Warning sign on outer packaging*, Patient reminder card*, Direct to Healthcare Professional Communication letter*)
in your country? Please include at least one example.

_____
_____
_____
_____
_____

Q18. Are there any additional points/suggestions/concerns you would like to raise, in what concerns the dispensing/counselling/implementation of pregnancy prevention measures for valproate or <similar drugs available in your country >?

_____
_____
_____
_____
_____

Thank you for participating!

Not relevant issues
(2) Effect of regulatory recommendation on prescribing patterns
5) Implementation and effect of annual reviews and risk assessment by medical specialists

ANNEX 5 Questionnaire for patients - Valproate

(The text in green refers to items included in the research plan. These will not be included in the final questionnaire)
(The text in blue offers instructions (to skip questions) or additional information for national coordinators. The general rule is selecting one response per question, unless indicated otherwise)

The knowledge about a medicine is not only built up during its research and development, but also once the drug is available on the market and being used by a larger group of patients. We are conducting an international survey on behalf of the European Medicines Agency to monitor how women across the European Union are using certain medications.

Our study concerns the use of medications containing valproate . Below is a list of medications that contain valproate and are approved in (include country): <insert trade names for the available drugs>

You are invited to fill in this questionnaire as we assume you are using or have recently used a medication containing valproate.

We are particularly interested in knowing more about the information you have received about your medicine and how that has influenced your decisions.

This is an international study, which includes research centres across eight European Member States. In (include country) this research is being led in by (include name of centre).

We estimate that it will take approximately 10 minutes to answer the questions below. The information provided will inform the European Medicines Agency and contribute to increased knowledge about how to better advise patients about the use of medications containing valproate.

Your participation is voluntary and will not affect your current use of health care services. Answers will be registered anonymously and handled in accordance with the General Data Protection Regulation (or GDPR) (EU) 2016/679 of 27 April 2016.

I hereby declare to have read and understood the information provided above and accept free-willingly to participate.

I would like to receive information about the results of this study.

Baseline characteristics

Q1a. What is your gender?
- Male
- Female
- Would rather not say

Only females will continue, others are thanked and the survey stops here < include here standard text>
The message to be included states: Thank you for your interest in completing this survey, but your gender is outside the scope of our study.

Q1b. When were you born?
- Year: __ __ __ __

Only those who born between 1969 and 2004 continue, others are thanked and the survey stops here < include here standard text> The message to be included states: Thank you for your interest in completing this survey, but your age is outside the scope of our study.

Q1c. Are you currently pregnant?

- Yes
- No
- Not sure

Only those who tick "No" continue. Those who tick "Yes" OR "Not sure" are thanked and the survey stops here due to ethical issues, as they might be unaware about the risks. They are thanked for their interest and advised to contact a GP or a medical specialist < include here standard text> The message to be included states: Thank you for your interest in completing this survey, but given that you are or might be pregnant, we would like to advise you to visit your GP or medical specialist to ensure the safe and effective use of your medication.

Q1d. Which level of education have you completed? (Select all that apply)

- Primary school
- Secondary school
- Professional school
- University, undergraduate
- University, postgraduate
- Other, please explain_____

Q2. Please indicate, by ticking the relevant box, whether you are currently taking or have ever taken any of the medication containing valproate (one option per row)

Medication*	I have used it before	I am using it currently	I have never used it	I don't remember
Delepsine	1.1	1.2	1.3	1.4
Deprakine	2.1	2.2	2.3	2.4
Orfiril	3.1	3.2	3.3	3.4
Valproat "Life Medical"	4.1	4.2	4.3	4.4

*Each country adapts the list in accordance to what is approved in this country

For every answer under "I have used it before" go to Q3.1/Q3.2/Q3.3/Q3.4, respectively, before proceeding to Q4. For every answer under "I am using it currently" go to to Q4. All All those who do not choose "I have used it before" OR do not choose "I am using it currently" are thanked and the survey stops. The message to be included states: Thank you for your interest in completing this survey. Unfortunately, your input is outside the scope of our study, as you have never used or do not recall using medicines containing valproate.

Q3.1/Q3.2/Q3.3/Q3.4. When did you stop taking this medication?

- In 2018 or in 2019
- In 2017 or earlier
- I don't know

(3) Awareness of the contraindication for not using these products during pregnancy

Q4. Do you know that medications containing valproate can cause malformations and developmental defects in the foetus when taken during pregnancy?

- Yes
- No
- Not sure

If "Yes" go to Q5, if others go to Q6

Q5. How did you learn about this? (Select all that apply)

- I was informed by a General Practitioner
- I was informed by a Neurologist
- I was informed by a Psychiatrist
- I was informed by a Pharmacist or Pharmacy Technician
- I found information on the Internet
- I read the patient information leaflet provided with the medication
- I found information on the outer medication package
- I received a guide
- I received a reminder card
- I completed a form and became aware of this risk
- Other, please specify: _____

(1) Awareness of a regulatory recommendation regarding the use of valproate and related products in women of childbearing age
(4) Provision of patient guide by a prescriber, or of the patient card by a pharmacist to patients currently using oral retinoids

Q6. In connection to **your use of** medications containing valproate, have you ever (select all that apply):

Q6a	… received a "Patient guide"* (Please click the link to see an example)	
Q6b	… received a "Patient reminder card"* (Please click the link to see an example)	
Q6c	… reviewed a "Risk acknowledgement form/checklist"* (Please click the link to see an example)	
Q6d	…signed a "Risk acknowledgment form/checklist"* (Please click the link to see an example)	
Q6e	… read the patient information leaflet included in the medication package* (Please click the link to see an example)	
Q6f	…seen a warning sign on the outer medication package not to use during pregnancy* (Please click the link to see an example)	
Q6g	… discussed the use of contraception to prevent pregnancy with a healthcare professional	
Q6h	…had a medication containing valproate changed to other medication because you planned to become or became pregnant	

*Clicking on the link opens an explanation with a visual example of the specific measure used in the country

All the answers are registered first, then:
For those who tick Q6a, insert Q7a, and then move to the next questions that follows
For those who tick Q6b, insert Q7b, and then move to the next questions that follows
For those who tick Q6c, insert Q7c, and then move to the next questions that follows
For those who tick Q6d, insert Q7d, and then move to the next questions that follows

For those who tick Q6e, insert Q7e, and then move to the next questions that follows
For those who tick Q6g, insert Q7g, and then move to the next questions that follows
For those who tick Q6h, insert Q7h, and then move to the next questions that follows

Q7a. Who provided you with a "Patient guide"*? (Select all that apply)
- A General Practitioner
- A Neurologist
- A Psychiatrist
- A Pharmacist or Pharmacy Technician
- I received if from another source, please explain_____
- I don't remember

Q7b. Who provided you with a "Patient reminder card" (Select all that apply)
- A General Practitioner
- A Neurologists
- A Psychiatrist
- A Pharmacist of Pharmacy Technician
- I received if from another source, please explain_____
- I don't remember

Q7c. With whom have you reviewed a "Risk acknowledgement form/checklist"? (Select all that apply)
- A General Practitioner
- A Neurologist
- A Psychiatrist
- Other healthcare professional, please explain_____
- I don't remember

Q7d. With whom did you sign a "Risk acknowledgement form/checklist"? (Select all that apply)
- A General Practitioner
- A Neurologist
- A Psychiatrist
- Other healthcare professional, please explain_____
- I don't remember

Q7e_1. Have you read in the package leaflet that you should not use the medication during pregnancy?
- Yes
- No
- Don't remember

Q7e_2. Have you ever visited the internet site using this QR code*? (Please click the link to see an example of what it is)
- Yes
- No
- Never seen this QR code
- Don´t remember

Q7g. With whom did you discuss contraception use? (Select all that apply)
- A General Practitioner
- A Neurologist

- A Psychiatrist
- A Pharmacist or Pharmacy Technician
- Another health care professional: _____
- Don't remember

Q7h. What was the name of your new medication: _____

(5) Use of pregnancy test prior to treatment, during treatment, after stopping treatment

We are interested knowing more about your use of **pregnancy tests** when taking medication containing valproate.

Q8. Did you ever take a pregnancy test just before starting using your medication containing valproate?
- Yes
- No
- Don't remember
- Not relevant, please explain (e.g. not sexually active, fertility problems, menopause etc)_____

Q9. Do/did you regularly take pregnancy tests because you use/d medication containing valproate?
- Yes
- No
- Don't remember
- Not relevant, please explain (e.g. not sexually active, fertility problems, menopause etc)_____

If "Yes" go to Q9a, if others go to Q10

Q9a. How often do/did you take it?
- Monthly or more frequently
- Every second months or less often

Q10. Did you ever take a pregnancy test just after stopping using medications containing valproate?
- Yes
- No
- Don't remember
- Not relevant, please explain (e.g. not sexually active, fertility problems, menopause etc)_____

If "Yes" go to Q10a, if others go to Q11.

Q10a. How often did you take it?
- Monthly or more frequently after stopping the medication.
- Every other months or less often.

(6) Eventual use of valproate or related products during pregnancy

We are interested in getting to know whether you took medication containing valproate **during pregnancy.**

Q11. Have you ever been pregnant? (select all that apply)
- Yes, within the period 2018-2019
- Yes, in 2017 or earlier
- No
- Not sure

If "Yes, within the period 2018-2019" go to Q12; If "yes, in 2017 or earlier" go to Q13; if others go to Q14

Q12. Did you ever use medication containing valproate while pregnant within the period 2018-2019?
- Yes
- No
- Don't remember

(for those who were pregnant in 2017 or earlier)

Q13. Did you ever use medication containing valproate during pregnancy within the period 2017 and earlier?
- Yes
- No
- Don't remember

(7) Effective contraception use

Q14. Do you currently use any birth control/contraception methods?
- Yes
- No
- Not relevant, please explain (e.g. not sexually active, fertility problems, menopause etc)_____

If "Yes" go to Q15, if others go to Q17

Q15. Which birth control/contraception do you currently use? (Select all that apply)

Birth control pills	
Birth control patch	
Intrauterine device (copper or hormonal)	
Diaphragm	
Condom	
Injectables (Depo-Provera)	
I am sterilized (tied tubes)	
My partner is sterilized (vasectomy)	
Emergency contraception	
Temperature or rhythm methods	
Interrupted intercourse (withdrawal, pull-out method)	

Other method(s), please specify:	

Q16. Please choose the option that best describes your agreement with the following statement:
"I am/was particularly careful to use birth control/contraception because I am/was taking medication containing valproate

- Highly agree
- Agree
- Neither agree nor disagree
- Disagree
- Highly disagree

(3) Effect of recommendation on use of medicine

Q17. Has your use of medication containing valproate changed since 2018 (e.g. are you more careful to avoid pregnancy when taking this medicine, did you stop using it, did you reduce intake/dose)?

- Not at all, it did not change and I use/d it the same way as in 2018 or earlier
- I am not sure
- Yes, it changed since 2018
- Can't say as I stopped the medication before 2018

If "Certainly yes", go to Q18, if others go to Thank you

Q18. Could you please briefly describe these changes?

_____
_____
_____
_____
_____

Thank you very much for your participation!

ANNEX 6 - RECRUITMENT STRATEGIES (PER COUNTRY)

BELGIUM

Patients

- Final-year pharmacy students (n=120) of Ghent University performing their community pharmacy internship will be asked to paste a sticker containing a weblink/QR code to the questionnaire on every package of valproate related product they dispense during their internship. As soon as a sufficient number of patients is recruited, students will be informed that they can stop the stickering.
- Pocket cards and/or stickers will be available upon request from pharmacists, GP's, neurologists to provide to patients.

Healthcare professionals

GPs, neurologists

- An e-mail will be sent to a list of GPs, neurologists known to the public providing the link to the questionnaire.
- A master thesis student at the Pharmaceutical Care Unit of Ghent University will visit randomly selected GP's, neurologists with the questionnaire and will provide pocket cards and/or stickers they can provide to patients.

Community pharmacists

- Community pharmacists acting as internship supervisor in the Ghent University community pharmacy internship program will be sent an e-mail containing information about this study and a weblink to the questionnaire.
- The Belgian Pharmaceutical Association (APB) will soon launch a campaign about pregnancy. Information about this study and a weblink to the questionnaire will be included in the promotional material towards community pharmacists participating in the campaign.

DENMARK

To recruit relevant health care professionals and patients in Denmark, a convenient sampling strategy will be employed. E-mails with links to questionnaires as well as invitations to respond to it will be sent using mailing lists of selected professional societies. In addition, Facebook interest groups will be approached in order to post invitations and links.
For the valproate study, the Danish Neurological Society (https://neuro.dk/wordpress/om-dns/) and the Danish Epilepsy Society (http://epilepsiselskabet.dk/) will be contacted to recruite neurology specialists, the Danish Society for General Practitioners (https://www.dsam.dk/flx/english/hippokrates/denmark/) will be contacted to recruite general practitioners, and the Danish Pharmacy Association (https://www.apotekerforeningen.dk/) will be contacted to recruit pharmacists. Administration offices of the societies will first be approached by e-mail and subsequently by phone in order to introduce the study and identify contact persons with

access to e-mail list of the society members, where the invitations to the study and the links to the relevant questionnaires can be sent to.
Additionally, the administrators of the following Facebook groups will be contacted with the information about the study inviting them to send the link to the specialist/GP questionnaire to the group's members: Young neurologists (https://www.facebook.com/groups/476214675763415/), Epilepsy association (https://www.facebook.com/search/top/?q=epilepsiforeningen&epa=SEARCH_BOX)
To recruit patients, similar approach will be utilized for the following Facebook groups to distribute the patient questionnaire: Forum for people with epilepsy in Denmark (and relatives) (https://www.facebook.com/groups/epilepsi/), The epilepsy corner (https://www.facebook.com/Epilepsihjornet/), The epilepsy association (https://www.facebook.com/epilepsiforeningen/), Epilepsy for young people (https://www.facebook.com/groups/4163999018/)

GREECE

Recruitment of General Practitioners and Specialists

- Physicians will be approached (phone or e-mail) through professional societies (neurologists, general practitioners). Apart from those societies, where physicians are distinguished based on their specialty, contact will also be made with unions where physicians belong according to where their practice is located. Those associations will be asked to either promote the questionnaire to the mailing list of their members or provide us the mailing list in order to promote the questionnaires ourselves. The mail sent will also contain a brief description of the study.
- Social media groups and website that are physician-relevant will be utilized for the promotion of the questionnaire. Contact (e-mail or phone) will be made with the administrators in order to provide their support by making an announcement with a brief description of the study and a link to the questionnaire.
- After permission from the organizing committee, we can attend medical conferences or seminars, especially those that are directed to neurologists, psychiatrists or general practitioners, and ask attending physicians to fill in the questionnaire in a laptop/tablet of ours.

Recruitment of Pharmacists

- In Greece, there is the Panhellenic Pharmaceutical Association, as well as regional pharmaceutical associations. Contact will be made through phone or e-mail with those and we will ask them to promote a brief description of the study accompanied by the link to the questionnaire to their members' mailing list.
- Social media groups and website that are pharmacist-relevant will be utilized for the promotion of the questionnaire. Contact (e-mail or phone) will be made with the administrators in order to provide their support by making an announcement with a brief description of the study and a link to the questionnaire.
- After permission from the organizing committee, we can attend pharmaceutical conferences or seminars and ask attending pharmacists to fill in the questionnaire in a laptop/tablet of ours.

- Undergraduate pharmacy students that are doing/ have done their internship will be asked to ask the pharmacist responsible for the practice to fill in the questionnaire.
- We can contact via phone or e-mail companies that provide pharmacies with professional software and ask them to insert a notification containing a brief description of the study and a link to the questionnaire to their next update.

Recruitment of Patients

- We will contact organizations that are relevant with epilepsy, such as http://www.epilepsy-greece.gr/index.php, so they can send an e-mail to their members, containing a brief description of the study and the link to the questionnaire.
- Administrators of social media groups, where it is probable that epilepsy and acne patients are members, will be contacted and asked to post a brief description of the study and the link to the questionnaire, thus inviting patients to participate.
- Healthcare professionals that have been recruited can be asked to distribute leaflets/ pocket cards with a study description and a short link to the questionnaire to patients receiving the medications under study. Another possible way for recruiting patients through healthcare professionals is by giving them forms where the patient will be asked to fill in their e-mail address. After a short time, we will collect those forms and make a patient mailing list.

LATVIA

- Story about the problem with these medicines in the university's website & social media & press release + invitation with survey links to participate (both to HCP and patients).
- We will create easy to remember survey links in Latvian (e.g. go-to.patientvalproatesurvey).
- GPs and specialists will be reached out through mailing lists of professional societies. Preliminary we have spoken to representatives of these societies and received support. Links to survey will be also posted in closed professional FB groups. If there will be any professional meetings at the time of recruitment we will ask to present the study and invite GPs/specialists to fill the survey.
- Pharmacists and pharmacy assistants will be approached via public pharmacy emails and through the mailing list of pharmacist society. If there will be any professional meetings at the time of recruitment we will ask to present the study and invite pharmacists and pharmacy assistants to fill the survey. Link will be posted in closed professional FB group.
- Patients will be approached via patient groups – email lists and social media. Some of the specialists have public blogs and Instagram accounts – we will ask them to share invitations there.
- We will prepare a small flyer with basic description of the study and survey link (separate for valproate and retinoid study) that can be handed out to patients in pharmacy and doctors office. Preliminary we have identified several pharmacists and doctors that could be involved in this.

- Plan B for patient recruitment if we are unable to reach the necessary number of patient respondents is to contract doctors or nurses to review patient records and reach out to patients that use valproates and reach out to these patients with invitation to fill the survey. Preliminary we have discussed this at the institute as a possibility but have not identified specific doctors, nurses or clinics. We have budgeted some finances for this. However, we will need a separate ethics approval for this.

THE NETHERLANDS

Patients

- Patients will be recruited through pharmacies by adding an information leaflet with each dispensing of a relevant medication
- Final-year pharmacy students of Utrecht University performing their community pharmacy internship will assist in recruitment of patients

Healthcare professionals

Community pharmacists

- The UPPER network of pharmacists (n=1400) will be asked to participate through an email-list.

Pharmacists can participate by filling in the questionnaires, and also by recruiting other health care professionals and patients.

GPs, neurologists, psychiatrists and midwives

- GPs, neurologists, psychiatrists and midwives will be recruited through participating pharmacies. The pharmacists will contact HCP in their own network and provide them with information on the study
- Multiple GP networks will be contacted directly through email-lists
- Neurologists and psychiatrists will be recruited through their professional societies.

PORTUGAL

Recruiting GPs and specialists:

- Invitation through Portuguese physicians' societies (*Colégios de especialidade*), namely: neurology, psychiatry, gynaecology, pediatrics and GP. The invitation will include a text explaining the study and the link to the survey.
- HCP will be informed that for each survey completed, we will donate a small account (e.g. 2€) to a Humanitarian Association (e.g. Medecins sans Frontieres). (<u>if possible</u>, in accordance with the host institution's cash rules - we are waiting for confirmation.)
- At the end of the study, we will offer participants a free training session to present the results and with expert speakers addressing drug safety issues.

Recruiting pharmacists:

- Invitation through the Portuguese pharmaceutical society and through the national pharmacy association. The invitation will include a text explaining the study and the link to the survey.
- HCP will be informed that for each survey completed, we will donate a small account (e.g. 2€) to a Humanitarian Association (e.g. Banco Farmacêutico). (if possible, in accordance with the host institution's cash rules - we are waiting for confirmation.)
- At the end of the study, we will offer participants a free training session to present the results and with expert speakers addressing drug safety issues.

Recruiting patients:

- Invitation through the communitarian pharmacists during drug dispensing (we asked the Portuguese pharmaceutical society and the national pharmacy association for collaboration with this issue). The invitation will include a text explaining the study and the link to the survey (Additionally, we'd like to create a sticker with a QR code that refers to the online questionnaire that would be pasted in the dispensed packages by the pharmacists.)
- If needed, invitation through patients' associations: Epilepsy*;* Depressive and bipolar patients (Note: this strategy may introduce an information bias which is why it should only be adopted if the first strategy does not allow the necessary number of patients to be recruited).
- In both cases, patients will be informed that for each survey completed, we will donate a small account (e.g. 2€) to a Humanitarian Association. (if possible, in accordance with the host institution's cash rules - we are waiting for confirmation.)

SLOVENIA

Recruiting GPs and specialists:

- Email and postal mail to directors of
  clinics (psychiatric, gynaecology) to spread the email/invitation to their employees
  community health centers to spread the email/invitation to their employees
  reminder call few days after (e)mail has been sent.
- Contacting private GPs and specialists directly via email and postal mail
- Invitation through the national medical chamber

Recruiting pharmacists:

- Invitation through the Slovene pharmaceutical society
- Invitation through the network of student practice supervisors in community and hospital pharmacies
- Direct approach through acquaintances

Recruiting patients:

- Direct invitation by the patient's physician or pharmacist – preparation of leaflets to be distributed to patients?
- Invitation through patient groups (email, social media, etc)

SPAIN

Patients

- Patients will be recruited through their Health Center professionals working in the primary care setting. The list of female patients that are/were treated with medicines containing valproic acid will be obtained centrally by the Navarre Health Service Information Services. Each GP will be provided the list of their patients meeting the inclusion criteria. Doctors will contact the patients to invite them to participate in the study and will also email them the link to the surveys.

Healthcare professionals

Community pharmacists

- Community pharmacists will be recruited through the Pharmacy Association. All pharmacies in the province will receive an email including the link to the surveys and also receive information about the study beforehand.

GPs, neurologists, psychiatrists and midwives

- An e-mail will be sent to all GPs, neurologists, midwives in the Navarre Health Service database providing the link to the questionnaire.