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

Impact of EU label changes and revised pregnancy prevention programme for oral retinoid containing medicinal products: risk awareness and adherence

Protocol

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Background

Retinoids are natural or synthetic vitamin A derivatives that regulate cell differentiation, proliferation and apoptosis and include the active substances acitretin, adapalene, alitretinoin, bexarotene, isotretinoin, tazarotene and tretinoin. Oral and topical retinoids are used to treat dermatological conditions like severe acne vulgaris and psoriasis, some oral retinoids are also used to treat skin manifestations of T-cell lymphoma (bexarotene) and acute promyelocytic leukaemia (tretinoin).

Oral retinoids are highly teratogenic and must not be used during pregnancy. A pregnancy prevention programme (PPP) launched in 2003 for isotretinoin has since been introduced for other oral retinoids for the treatment of dermatological conditions. The effectiveness of these PPPs has been closely reviewed and despite a reduction in the number of pregnancies exposed to retinoids cases of pregnancy exposure continued to occur, raising concerns about compliance and the effectiveness of the PPPs in clinical practice. In addition, periodic safety update reports showed inconsistencies between products with the same active substance, between oral and topical retinoids and between European Union (EU) Member States as to the extent of the warnings and the risk minimisation measures in place for pregnancy prevention in women of child-bearing potential (WCBP).
On 22 March 2018, the European Medicines Agency (EMA) Committee for Medicinal Products for Human use (CHMP), advised by the Pharmacovigilance Risk Assessment Committee (PRAC) concluded that that an update of measures for pregnancy prevention is needed.

To ensure healthcare professionals and patients are informed about the risks in pregnant women and women of child-bearing potential, changes to educational materials have been introduced, including a patient reminder card, a physician checklist and risk acknowledgement form, and a pharmacist checklist. These revised materials should effectively encourage contraception use, regular pregnancy testing and inform about the shared responsibility between patients, doctors and pharmacists in adhering to the PPP. To ensure consistent and effective communication for all oral retinoid products distribution via electronic channels such as Quick Response (QR) codes and websites has been recommended. The patient signature on the physician checklist/risk acknowledgement form, the dissemination of the patient reminder card and the pharmacist checklist, the inclusion of an appointment table in the patient reminder card and a pictogram/symbol to accompany the boxed warning to be included in the visual reminder on the outer package to warn patients about the harm to the unborn baby and the need for effective contraception when using the medicinal product.
The EMA required a study to investigate risk awareness and adherence to risk minimisation measures amongst prescribers and users of oral retinoid containing medicinal products authorised in the EU following the implementation of the 2018 revised pregnancy prevention programme in relation to teratogenic effects.

Aims of the study

Primary objective: To determine the extent of awareness of the PPP and of the risk of teratogenic effects in women of childbearing potential and pregnant women exposed to oral retinoid containing medicinal products, by patient and by healthcare professionals, with particular focus on:

1.1. Extent of the influence of recommendations from regulatory authorities on knowledge, attitudes and practices;
1.2. Feasibility of the contraceptive programme, including method of effective contraception and regular pregnancy testing;

Secondary objective:To determine the extent of adherence to the pregnancy prevention programme and risk minimisation measures for oral retinoids intended for use in women of childbearing potential, with particular focus on the following components:

1.3. Receipt and awareness of educational materials for patients (i.e. patient reminder card) and healthcare professionals (i.e. prescriber checklist/risk acknowledgement form, pharmacist checklist);
1.4. Use of effective contraception throughout treatment in line with sections 4.4 and 4.6 of the SmPC, including use of non-prescription or non-reimbursed contraceptives;
1.5. Performance of medically supervised pregnancy testing prior treatment initiation, repeated testing during treatment and one month after stopping treatment (for acitretin only the recommendation is periodically with 1-3 months intervals over a period of 3 years after stopping treatment), including pregnancy test results where available in Member States;
1.6. Obtaining patient signature for prescriber checklist and acknowledgment form where implemented in Member States;
1.7. Implementation of monthly follow-up visits, repeated medically supervised pregnancy testing, limitation of prescription duration to 30-days and 7-day validity where legally possible and implemented in Member States.

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 oral retinoids, and among health care professionals: prescribers (general practitioners, dermatologists), midwives (when relevant) and pharmacists (community). All oral retinoids included in this study are listed in ANNEX 1. Estimates of use of oral retinoids 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 oral retinoids will be identified in each country (see *population*) and 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. 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 oral retinoids 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 oral retinoids in the past year. Hospital and community pharmacists may be included. Midwives may be included, if they have had experience with at least one woman treated with oral retinoids.

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, each country will aim to complete and deliver for each study at least 150 healthcare professional questionnaires (at least 30 each for GPs, pharmacists and midwives (when relevant) 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 t 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 increase 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 oral retinoids in the past 5 years or are currently using.

For each country we will aim to have 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 societies;
- 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 risks of oral retinoids and the revised pregnancy prevention programme 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 oral retinoids by women in childbearing age
(2) Effect of regulatory recommendation on prescribing patterns
(3) Awareness of the contraindication for 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 oral retinoids.
(5) Whether medically supervised pregnancy testing is performed prior to treatment initiation, repeated testing during treatment and one month after stopping treatment (for acitretin only the recommendation is periodically with 1-3 months intervals over a period of 3 years after stopping treatment), including pregnancy test results where available in Member States;
(6) Whether patient signature are sought for prescriber checklists and acknowledgment forms, where implemented in Member States;
(7) Implementation of monthly follow-up visits, repeated medically supervised pregnancy testing, limitation of prescription duration to 30-days and 7-day validity where implemented in Member States;

For prescribers specifically, the feasibility of the PPP and implementation of pregnancy testing before, during and after treatment is of major interest. The questionnaire also addresses treatment recommendations based on test results where available in the eight selected countries.

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

Patients
The patient questionnaire has been developed to include the following topics:

(1) Awareness of the pregnancy prevention programme and risks of teratogenic effects of oral retinoids in women of childbearing age
(2) Awareness of the regulatory recommendations
(3) Effect of recommendation on use of medicine
(4) Provision of patient guide by prescriber, or patient card by pharmacist

For patients currently using oral retinoids:

(5) Use of pregnancy test prior to treatment, during treatment, after stopping treatment
(6) Effective contraception use
(7) Whether signature was obtained for prescriber checklist and acknowledgment form where implemented in Member States

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. 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.

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.

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.

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	NT CT M3	
Data analysis interviews												NL	NT	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 RETINOID RELATED PRODUCTS IN THE PARTICIPATING COUNTRIES

Belgium

ATC	INN	Dosage form and strength	Brandname
D05BB02	acitretin	acitretine oraal •10 mg •25 mg	Neotigason®
D10BA01	isotretinoin	isotretinoïne oraal •5 mg •8 mg •10 mg •16 mg •20 mg	Isocural®; Isosupra®; Isotretinoine®; Roaccutane®

Denmark

Retinoids for acne (systemic treatment)
Information retrieved from https://pro.medicin.dk/Laegemiddelgrupper/Grupper/133080#

ATC	INN	Brandname	Route of administration
D10BA01	Isotretinoin	Accutin® Sandoz	Soft capsules 10 mg
D10BA01	Isotretinoin	Accutin® Sandoz	Soft capsules 20 mg
D10BA01	Isotretinoin	Isotretinoin "Orion" Orion Pharma	Soft capsules 10 mg
D10BA01	Isotretinoin	Isotretinoin "Orion" Orion Pharma	Soft capsules 20 mg
D10BA01	Isotretinoin	Isotretinoin Teva" TEVA	Soft capsules 20 mg
D10BA01	Isotretinoin	Isotretinoin "Teva" TEVA	Soft capsules 20 mg

Retinoids for psoriasis
Information retrived from https://pro.medicin.dk/Laegemiddelgrupper/Grupper/135093

ATC	INN	Brandname	Route of administration
D05BB02	Acitretin	Acitretin "Orifarm" Orifarm Generics	hard capsules 10 mg
D05BB02	Acitretin	Acitretin "Orifarm" Orifarm Generics	hard capsules 25 mg
D05BB02	Acitretin	Neotigason® TEVA	hard capsules 10 mg
D05BB02	Acitretin	Neotigason® TEVA	hard capsules 10 mg
D05BB02	Acitretin	Neotigason® TEVA	hard capsules 10 mg
D05BB02	Acitretin	Neotigason® TEVA	hard capsules 25 mg
D05BB02	Acitretin	Neotigason®	hard capsules 25 mg

		TEVA	
D05BB02	Acitretin	Neotigason® TEVA	hard capsules 25 mg
D05BB02	Acitretin	Neotigason® TEVA	hard capsules 25 mg

Alitretinoin
Information retrieved from https://pro.medicin.dk/Medicin/Indholdsstoffer/3378

ATC	INN	Brand name	Route of administration
D11AH04	Alitretinoin	Toctino GSK Pharma	Soft Capsules 10 mg
D11AH04	Alitretinoin	Toctino GSK Pharma	Soft Capsules 30 mg
D11AH04	Alitretinoin	Toctino GSK Pharma	Soft Capsules 30 mg

Bexarotene (L01XY) and tretinoin (D10AD01) are not marketed in DK.

Greece

ATC	INN	Brandname	Distributor
D05BB02	Acitretin	NEOTIGASON	Actavis Group Ptc ehf
D11AH04	Alitretinoin	CEHADO	GlaxoSmithKline A.B.E.E.
D10BA01	Isotretinoin	A-CNOTREN	Pharmathen A.B.E.E.
		ACCURAN	Nexus Medicals A.E.
		ACNOGEN	Genepharm A.E.
		CURACNE	Pierre Fabre Φάρμακα A.E.
		ISOTROIN	Iasis Pharma Hellas A.B.E.E.
		POLICANO	Alapis A.B.E.E.
		REDUCAR	GAP A.E.
		ROACCUTAN	Roche Hellas A.E.
		ROCNE	Boderm A.E.
		TRETIN	Target Pharma M.E.Π.E.
L01XX14	Tretinoin	VESANOID	Cheplapharm Arzneimittel GmbH

Latvia

ATC	INN	Brand	Dosage form	Strength
D05BB02	Acitretin	Neotigason	hard caps	10 mg
D10BA01	Isotretinoin	Roaccutane	soft caps	10 mg
D10BA01	Isotretinoin	Roaccutane	soft caps	20 mg

Portugal

ATC	INN	Brand name	Dosage form	Dosage
D05BB02	Acitretin	Neotigason	Capsule	10 mg
D05BB02	Acitretin	Neotigason	Capsule	25 mg
D10BA01	Isotretinoin	Isotretinoína Aurovitas	Capsule, soft	10 mg

D10BA01	Isotretinoin	Isotretinoína Aurovitas	Capsule, soft	20 mg
D10BA01	Isotretinoin	Isotretinoína Cantabria	Capsule, soft	10 mg
D10BA01	Isotretinoin	Isotretinoína Cantabria	Capsule, soft	20 mg
D10BA01	Isotretinoin	Isotretinoína Cantabria	Capsule, soft	30 mg
D10BA01	Isotretinoin	Isotretinoína Cantabria	Capsule, soft	5 mg
D10BA01	Isotretinoin	Isotretinoína Mer	Capsule, soft	10 mg
D10BA01	Isotretinoin	Isotretinoína Mer	Capsule, soft	20 mg
D10BA01	Isotretinoin	Isotretinoína Orotrex	Capsule, soft	10 mg
D10BA01	Isotretinoin	Isotretinoína Orotrex	Capsule, soft	20 mg
D10BA01	Isotretinoin	Isotretinoína Orotrex	Capsule, soft	5 mg
L01XX14	Tretinoin	Vesanoid	Capsule, soft	10 mg

Slovenia

ATC	**INN**	**Product**
D05BB02	acitretin	Neotigason 10 mg hard capsules
		Neotigason 25 mg hard capsules
D10BA01	isotretinoin	Roaccutane 10 mg soft capsules
		Roaccutane 20 mg soft capsules
D11AH04	alitretinoin	Toctino 10 mg soft capsules
		Toctino 30 mg soft capsules

Spain

ATC	**INN**	Products description
D05BB02	Acitretin	ACITRETINA IFC 10MG 30 CAPSULAS DURAS EFG |684171|
D05BB02	Acitretin	ACITRETINA IFC 25MG 30 CAPSULAS DURAS EFG |684169|
D05BB02	Acitretin	NEOTIGASON 10MG 30 CAPSULAS |692616|
D05BB02	Acitretin	NEOTIGASON 25MG 30 CAPSULAS |692624|
D10BA01	Isotretinoin	ACNEMIN 10MG 50 CAPSULAS |653728|
D10BA01	Isotretinoin	ACNEMIN 20MG 50 CAPSULAS |653732|
D10BA01	Isotretinoin	DERCUTANE 5MG 50 CAPSULAS BLANDAS |660861|
D10BA01	Isotretinoin	DERCUTANE 10MG 50 CAPSULAS |791780|
D10BA01	Isotretinoin	DERCUTANE 20MG 50 CAPSULAS |791962|
D10BA01	Isotretinoin	DERCUTANE 30MG 30 CAPSULAS BLANDAS |700996|
D10BA01	Isotretinoin	DERCUTANE 30MG 50 CAPSULAS BLANDAS |700998|
D10BA01	Isotretinoin	DERCUTANE 40MG 30 CAPSULAS BLANDAS |660288|
D10BA01	Isotretinoin	FLEXRESAN 10MG 50 CAPSULAS BLANDAS |734822|
D10BA01	Isotretinoin	FLEXRESAN 20MG 50 CAPSULAS BLANDAS |734764|
D10BA01	Isotretinoin	ISDIBEN 10MG 50 CAPSULAS BLANDAS |880674|
D10BA01	Isotretinoin	ISDIBEN 20MG 50 CAPSULAS BLANDAS |880724|
D10BA01	Isotretinoin	ISDIBEN 40MG 30 CAPSULAS BLANDAS |691233|
D10BA01	Isotretinoin	ISOACNE 5MG 50 CAPSULAS BLANDAS |653587|
D10BA01	Isotretinoin	ISOACNE 10MG 50 CAPSULAS BLANDAS |653860|
D10BA01	Isotretinoin	ISOACNE 20MG 50 CAPSULAS BLANDAS |653861|
D10BA01	Isotretinoin	ISOACNE 40MG 30 CAPSULAS BLANDAS |661191|
D10BA01	Isotretinoin	MAYESTA 10MG 50 CAPSULAS BLANDAS |660466|

D10BA01	Isotretinoin	MAYESTA 20MG 50 CAPSULAS BLANDAS |660467|
L01XX14	Tretinoin	VESANOID 10MG 100 CAPSULAS BLANDAS |700610|

The Netherlands

ATC - INN	Product name
D05BB02 - Acitretin	Neotigason 10 mg, capsules
D05BB02 - Acitretin	Neotigason 25 mg, capsules
D05BB02 - Acitretin	Neotigason 10 mg, capsules
D05BB02 - Acitretin	Neotigason 25 mg, capsules
D05BB02 - Acitretin	Acitretine IFC 10 mg, capsules
D05BB02 - Acitretin	Acitretine IFC 25 mg, capsules
D05BB02 - Acitretin	Acitretine CF 10 mg, capsules
D05BB02 - Acitretin	Acitretine CF 25 mg, capsules
D05BB02 - Acitretin	Neotigason 25 mg, capsules
D05BB02 - Acitretin	Neotigason 25 mg, capsules
D11AH04 - Alitretinoin	Toctino 10 mg, capsules, zacht
D11AH04 - Alitretinoin	Toctino 30 mg, capsules, zacht
D11AH04 - Alitretinoin	Toctino 10 mg, capsules, zacht
D11AH04 - Alitretinoin	Toctino 30 mg, capsules, zacht
D11AH04 - Alitretinoin	Alizem 10 mg zachte capsules
D11AH04 - Alitretinoin	Alizem 30 mg zachte capsules
D11AH04 - Alitretinoin	Alitretinoïne IFC 10 mg zachte capsules
D11AH04 - Alitretinoin	Alitretinoïne IFC 30 mg zachte capsules
D11AH04 - Alitretinoin	Artesonin 10 mg zachte capsules
D11AH04 - Alitretinoin	Artesonin 30 mg zachte capsules
D11AH04 - Alitretinoin	Alitretinoïne Regiomedica 10 mg zachte capsules
D11AH04 - Alitretinoin	Alitretinoïne Regiomedica 30 mg zachte capsules
D10BA01 - Isotretinoin	Isotretinoïne Mylan 10 mg, zachte capsules
D10BA01 - Isotretinoin	Isotretinoïne Mylan 20 mg, zachte capsules
D10BA01 - Isotretinoin	Isotretinoïne Aurobindo 10 mg, zachte capsules
D10BA01 - Isotretinoin	Isotretinoïne Aurobindo 20 mg, capsules
D10BA01 - Isotretinoin	Isotretinoïne SUN 10 mg, zachte capsules
D10BA01 - Isotretinoin	Isotretinoïne SUN 20 mg, zachte capsules
L01XX14 - Tretinoin	Vesanoid, zachte capsules 10 mg

ANNEX 2 - INVENTORY OF MAIN PRESCRIBERS AND ESTIMATES OF USE OF RETINOID 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 retinoid related product by women of childbearing age in their country or region. 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)*
acitretin	D05BB02	Oral acitretin •10 mg •25 mg	Neotigason®	not frequently used	N.A.	N.A.
bexarotene	L01XY	bexarotene oral •75 mg	Targretin®	not frequently used	N.A.	N.A.
isotretinoin	D10BA01	Isotretinoin oral •5 mg •8 mg •10 mg •16 mg •20 mg	Isocural® Isosupra® Isotretinoine® Roaccutane®	3099474	76,1% dermatologists	*3482*

		Volume (DDD) per 1000 inhabitants/day– 2014 (% of total DDD for subgroup)		
		Females 0-20 years	**Females 21-40 years**	**Females 41-60 years**
ANTIPSORIATICS	D05	0,09 (1%)	0,331 (5%)	0,633 (10%)
ANTI-ACNE PREPARATIONS	D10	1,169 (19%)	1,323 (22%)	0,27 (4%)

Denmark

ATC	INN	Number of users 2017, primary sector, Denmark , female, 18-44 year old
D10BA01	Isotretinoin	7071
D05BB02	Acitretin	98
D11AH04	Alitretinoin	15

Greece

Researchers in Greece were unable to obtain the necessary data from the Greek Regulatory Agency, despite their request.

Latvia

The researchers estimated that from the total population of 267 users taking isotretinoin for acne in Latvia in 2018, about 160 (60%) would be females in reproductive age. Similarly, from the 94 users taking acitretionin for psoriasis in 2017, there were approximately 47 females in reproductive age (50%).
The estimated defined daily dose for acitretin in 2017 was of 0.01 DDD/1000 inhab/day.
The estimated defined daily dose for isotretionin in 2017 was of 0.07 DDD/1000 inhab/day.

Portugal

Data were procured from the National Health System billing centre. These 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 2010	Packages 2011	Packages 2012	Packages 2013	Packages 2014	Packages 2015	Packages 2016	Packages 2017	Packages 2018
Acitretin	7.688	9.172	9.869	10.809	12.376	12.713	12.702	13.324	13.874
Isotretinoin	46.253	46.620	46.884	56.001	62.345	62.641	65.181	67.251	70.537
Tretinoin	9	6	15	17	7	29	17	29	14

Age Group	INN	Number of packages dispensed to women	Number of packages dispensed to men	Total Amount of packages dispensed
10 - 14 years	Acitretin	12	15	27
	Isotretinoin	3.179	2.621	5.800
15 - 19 years	Acitretin	16	98	114
	Isotretinoin	11.542	17.296	28.838
20 - 24 years	Acitretin	36	143	179
	Isotretinoin	6.451	4.942	11.393
25 - 29 years	Acitretin	23	257	280
	Isotretinoin	4.181	1.917	6.098

30 - 34 years	Acitretin	43	315	358
	Isotretinoin	2.453	1.180	3.633
	Tretinoin		2	2
35 - 39 years	Acitretin	128	533	661
	Isotretinoin	2.092	861	2.953
40 - 44 years	Acitretin	280	604	884
	Isotretinoin	2.079	702	2.781
45 - 49 years	Acitretin	446	897	1.343
	Isotretinoin	1.392	517	1.909
	Tretinoin	1	0	1
50 - 54 years	Acitretin	729	871	1.600
	Isotretinoin	850	409	1.259

Slovenia

The 1-year prevalence of use in 2018 by female age groups using ATC: **D05BB02**, D10AD53, **D11AH04**, D10AD04, **D10BA01**, D10AD5, D05AX05, D10AD01 is as follows:

Age group	Total women users	Percent	Population of Slovenia - women
0-11	0	0.0	124,141
12-17	181	19.1	54,047
18-30	379	40.0	134,439
31-40	104	11.0	140,111
41-50	86	9.1	143,835
50 and more	198	20.9	443,243
Total	**948**	**100.0**	**1,039,816**
Total 12-55y	**806**	**85.0**	**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 year (mention year) 2018	*Estimated number of users (*

alitretinoin	D11AH04			0	*0*
isotretinoin	D10BA01	20mg cap (43%); 40mg cap (33%); 30mg cap (15%);10mg cap (8%);5mg cap (1%)	Acenin / Dercutane/ Flexresan / Isdiben / Isoacne / Mayesta	81275,53	*306*
tretinoin	L01XX14	10mg caps	Vesanoid	No established DDD	*1*

Products used by women per age group	**15-19**	**20-29**	**30-39**	**40-49**	**Other age group**	**Total**
D05BB02 - Acitretin	283	0	60	193	6.252	6.787
D10BA01 - Isotretinoin	13.021	13.559	4.676	2.443	1.525	35.224
L01XX14 - Tretinoin	Not used					

Key Prescribers of Retinoid Products

Medical Specialties	**D05BB02 - Acitretin**	**D10BA01 - Isotretinoin**	**L01XX14 - Tretinoin**
Unknown	0,77%	0,81%	
Allergology	0,77%		
Cardiology		0,40%	
General and Gastro Surgery		0,40%	
Dermatology	**12,31%**	**7,66%**	
Aviation Medicine		0,40%	
Family and Community Medicine	**83,85%**	**82,26%**	100,00%
General Medicine		0,81%	
Paediatrics	0,77%	**4,84%**	
Psychiatry		0,40%	
Rehabilitation			
Traumatology and Orthopeadics		0,81%	
Emergency	1,54%	1,21%	
Total	100,00%	100,00%	100,00%

The Netherlands

D05BB02 – Acitretin	**2013**	**2014**	**2015**	**2016**	**2017**
DDDs	470.820	450.740	450.850	459.770	450.190
DDD's per user	104	104	106	108	110
Users	4.522	4.356	4.264	4.248	4.103

Prescriptions	21.800	21.937	21.629	21.684	21.305
Prescriptions per user	4,82	5,04	5,07	5,10	5,19

D11AH04 – Alitretinoin	**2013**	**2014**	**2015**	**2016**	**2017**
DDDs	19.333	243.370	320.820	354.080	374.020
DDD's per user	80	153	158	168	165
Users	241	1.592	2.028	2.109	2.270
Prescriptions	454	5.484	7.124	7.861	8.564
Prescriptions per user	1,89	3,44	3,51	3,73	3,77

D10BA01 Isotretinoin	**2013**	**2014**	**2015**	**2016**	**2017**
DDDs	2.288.000	2.591.400	2.604.100	2.845.200	2.976.400
DDD's per user	118	119	116	119	120
Users	19.414	21.820	22.423	23.994	24.894
Prescriptions	81.870	97.807	100.520	106.020	114.960
Prescriptions per user	4,22	4,48	4,48	4,42	4,62

L01XX14 – Tretinoin	**2013**	**2014**	**2015**	**2016**	**2017**
DDDs	29.831	31.612			
DDD's per user	402	455			
Users	74	69			
Prescriptions	218	239			
Prescriptions per user	2,94	3,44			

Appendix 3 - Questionnaire for GPs and medical specialists – Oral retinoids

(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 oral retinoids . 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 oral retinoids.

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 inform the European Medicines Agency pharmacovigilance activities and will contribute to increased knowledge about how to better advise patients about the use of oral retinoids.

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

- Dermatologist
- 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 oral retinoids?
- Once a week or more
- 2-3 times per month
- Once a month or less frequently
- 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 oral retinoids 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 oral retinoids?
- 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 oral retinoids 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 studies
- During post-academic training/continuous professional education
- Other, please specify: _____

(1) Awareness about regulatory recommendation regarding the use oral retinoids 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 an oral retinoid to a woman of reproductive age** or consulted with a woman who uses oral retinoids. 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 the 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 (including an appointment table)* ** (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) insert Q11e, and then move to Q12

Then consider Q10f, and for those who did not tick 6.1 (i.e. tick 6.2, 6.3) 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 oral retinoids to reproductive age women or consulting with women taking oral retinoids?

- 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 oral retinoids to reproductive age women or consulting with women taking oral retinoids?

- 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 oral retinoids to reproductive age women or consulting with women taking oral retinoids?

- 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 oral retinoids to women of reproductive age or consulting with women taking oral retinoids?

- 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 oral retinoids to reproductive age women or consulting with women taking oral retinoids?

- 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"* on oral retinoids when prescribing oral retinoids to women of reproductive age or consulting with women taking oral retinoids?

- 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, reproductive age women are those of age (Select all that apply):

- 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 oral retinoids established in 2018 (i.e. Health professional guide or Pharmacist guide*, Pharmacist checklist*, warning sign on outer packaging*, Patient reminder card (including appointment table)* **, 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 acknowledge form by a patient
- Patient reminder card (including appointment table)* **
- 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 (Health professional guide or Pharmacist guide*, Pharmacist checklist*, warning sign on outer packaging *, Patient reminder card (including appointment table)* **, Direct to healthcare professional communication letter*) in your country? Please include at least one example.

_____
_____
_____
_____
_____

(5) Whether medically supervised pregnancy testing is performed prior to treatment initiation, repeated testing during treatment and one month after stopping treatment (for Acitretin only the recommendation is periodically with 1-3 months intervals over a period of 3 years after stopping treatment), including pregnancy test results where available in Member States;
(7) Implementation of monthly follow-up visits, repeated medically supervised pregnancy testing, limitation of prescription duration to 30-days and 7-day validity where implemented in Member States.

Q17. We want to know more about how your prescribing, counselling and monitoring of oral retinoids use by women of reproductive age. Please indicate the option that best describes your practice (one option per row)

		Strongly Agree	Somehow agree	Somehow disagree	Strongly Disagree	Not relevant to me
	Prescribing					
Q17a	I don't prescribe oral retinoids.					
Q17b	I don't prescribe oral retinoids to women of reproductive age.					
Q17c	I am selective when prescribing oral retinoids to women of reproductive age.					
Q17d	I discontinue oral retinoids in women who are planning to become pregnant or suspect they might be pregnant.					
Q17e	I refer women who use oral retinoids 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 oral retinoids.					
	Pregnancy testing					
Q17g	I make sure that women of reproductive age take a pregnancy test before starting treatment with oral retinoids					
Q13h	I make sure that women of reproductive age who use oral retinoids take monthly pregnancy tests					
Q17i	I make sure that women of reproductive age who use oral retinoids 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 oral retinoids					
	Contraception counseling					
Q17k	When prescribing oral retinoids 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 oral retinoids					
Q17m	When prescribing oral retinoids, 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 for oral retinoids?

_____
_____
_____
_____
_____

Thank you for participating!

Not relevant issues
(6) Provision of patient information when dispensing oral retinoids and related products.

Appendix 4 - Questionnaire for pharmacists – Oral retinoids

(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 oral retinoids . 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 oral retinoids.

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 oral retinoids.

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 often do you dispense oral retinoids for women of reproductive age?
- Once a week or more
- A couple of times a month
- Once a month or less frequently
- 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 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 oral retinoids?
- Once a week or more
- A couple of times 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 developmental problems related to the use of oral retinoids?
- Yes
- No
- I am not sure

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

Q8. When did you learn about the teratogenic risks of oral retinoids if 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 oral retinoids 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

Q10. Think about **the last time you dispensed an oral retinoid to a woman of reproductive age.** Did you apply any of the pregnancy prevention measure described below, which were established in 2018?

		Yes, I do it	I have seen it, but did not do it	No, I have never seen/done 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 (including appointment table)* ** (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
** Each country has to adapt (leave or delete what is in the bracket) depending on implementation situation 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 question that follows
Then consider Q10e, and for those who did not tick 5.1 (i.e. tick 5.2, 5.2, 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 oral retinoids 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 the "Pharmacist checklist" * when dispensing oral retinoids 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 oral retinoids to women 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 (including appointment table)**" when dispensing oral retinoids to women of reproductive age?

- 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 oral retinoids 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_____

Q13a. We want to know more about the information you provide when dispensing oral retinoids to women of reproductive age. (Select all that apply)

		Never	Seldom	Often	Always
Q13aa.	I inform or remind patients about the importance of effective contraception				
Q13ab.	I advise patients to stop taking the medication, if they suspect being pregnant				
Q13ac.	I advise patients to contact their doctor, if they suspect being pregnant				
Q13ad.	I highlight the importance of testing for pregnancy				

	before, during and after stopping the treatment				

Q13b. Are there differences in the counselling that you provide when dispensing a first prescription of oral retinoids 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 oral retinoids changed since the implementation of pregnancy prevention measures established in 2018 (i.e. Health professional guide or Pharmacist guide*, Pharmacist checklist*, warning sign on outer packaging*, Patient reminder card (including appointment table)* **, 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 oral retinoids 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 (including appointment table)* **
- 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 recommendations

Q17. Which barriers hinder the implementation and/or use of the pregnancy prevention measures established in 2018 (Health professional guide or Pharmacist guide*, Pharmacist checklist*, warning sign on outer packaging *, Patient reminder card (including appointment table)* **, 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 oral retinoids?

_____
_____
_____
_____
_____

(7) Implementation of monthly follow-up visits, repeated medically supervised pregnancy testing, limitation of prescription duration to 30-days and 7-day validity where implemented in Member States. (prescriptions are only valid for 7 days in **Latvia**, France, Italy and **Slovenia**)

Q19. <only Slovenia and Latvia> Are you aware that prescriptions for oral retinoids are only valid for 7 days?

- Yes
- No
- I am not sure

Thank you for participating!

Not relevant for pharmacists issues
(2) Effect of regulatory recommendation on prescribing patterns
(5) Whether medically supervised pregnancy testing is performed prior to treatment initiation, repeated testing during treatment and one month after stopping treatment (for Acitretin only the recommendation is periodically with 1-3 months intervals over a period of 3 years after stopping treatment), including pregnancy test results where available in Member States;
(6) Whether patient signature is sought for prescriber checklists and acknowledgment forms, where implemented in Member States;

Appendix 5 - Questionnaire for patients - Oral retinoids

(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 oral medication for acne or for psoriasis . 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 oral medication for acne or for psoriasis.

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 oral medication for acne or for psoriasis.

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 you ever taken any of the oral medication for acne listed (one option per row)

Medication*	I have used it before	I am using it currently	I have never used it	I don't remember
Isotretinoin or Accutin	1.1	1.2	1.3	1.4
Acitretin or Neotigason	2.1	2.2	2.3	2.4
Neotigason or Toctino	3.1	3.2	3.3	3.4

*Each country adapts the list in accordance to what is approved in this country. The medications listed are used in Denmark

For every answer under "I have used it before" go to Q3.1/Q3.2/Q3.3, respectively, before proceeding to Q4. All that do not tick "I have used it before" OR do not tick "I am using it currently" are thanked and the survey stops < include here standard text> 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 oral medication for acne.

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

(1) Awareness of the pregnancy prevention programme and risks of teratogenic effects of oral retinoids in women of childbearing age

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

- Yes
- No
- Not sure

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

Q5. Where did you learn about this? (Choose all that apply)

- I was informed by a General Practitioner
- I was informed a Dermatologist
- 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: _____

(2) Awareness of the regulatory recommendations
(4) Provision of patient guide by a prescriber, or of the patient card by a pharmacist to patients
(8) Whether a patient signature was obtained for the prescriber checklist and for the acknowledgment form in the Member States where these measures are implemented.

Q6. In connection to **your use of oral medications for acne**, have you ever (Choose all that apply)

Q6a	… received a "Patient guide"* (Please click the link to see an example)	
Q6b	… received a "Patient reminder card (including appointment table)"* ** (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 acknowledgement 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	… changed to another 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

** Each country adapts (leaves or deletes what is in the brackets) depending on the country situation

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"? (Choose all that apply)

- A General Practitioner
- A Dermatologist
- 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 (including appointment table)"** (Choose all that apply)A General Practitioner

- A Dermatologist
- A Pharmacist or 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"? (Choose all that apply)

- A General Practitioner
- A Dermatologist
- Other healthcare professional, please explain_____
- I don't remember

Q7d. With whom have you signed a "Risk acknowledgement form/checklist"? (Choose all that apply)

- A General Practitioner
- A Dermatologist
- 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 a QR code* (Please click the link to see an example of what it is)?

- Yes
- No
- Never seen a QR code on the leaflet
- Don´t remember

Q7g. With whom did you discuss contraception use? (Choose all that apply)

- A General Practitioner
- A Dermatologist
- 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 in getting to know how you **did or do pregnancy tests** while taking oral medications for acne.

Q8. Have you ever taken a pregnancy test, just before starting oral medications for acne?

- Yes
- No
- Don't remember
- Not relevant, please explain (e.g. not sexually active, fertility problems, menopause eetc)_____

Q9. Do/did you regularly take a pregnancy test because you use/d oral medications for acne?

- 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 oral medications for acne?

- 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
- Every other month or less often after stopping

(6) Eventual use of oral retinoids during pregnancy

We are interested in knowing whether you have used oral medications for acne **during pregnancy**

Q11. Have you ever been pregnant? (Choose all that apply)

- Yes, after 1st if January 2018
- Yes, before the 1st of January 2018
- No
- Not sure

If "Yes, after 1st if January 2018" go to Q12; If "Yes, before the 1st of January 2018" go to Q13; If others go to Q14

Q12. Did you ever use oral medications for acne while pregnant after 1st if January 2018?

- Yes
- No
- Don't remember

Q13. Did you ever use oral medication for acne while pregnant before the 1st of January 2018?

- 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? (Choose 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 oral medications for acne"

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

(3) Effect of recommendation on use of medicine

Q17. Has your use of oral medications for acne 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 as before 2018
- I am not sure
- Yes, it changed since 2018
- Can't say as I stopped taking medication before 2018

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

Q18. Could you please briefly describe what has changed?

_____
_____
_____
_____
_____

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 oral retinoids 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 oral retinoid study, the Danish Dermatology Society (https://dds.nu/) will be contacted to recruit dermatologists. The same procedure as in valproate study will be used, i.e. first contacting an administration office by e-mail and phone to introduce the study and identify a contact person, and then sharing a link to a specialist/GP questionnaire via e-mail list of the society members. Additionally, an administrator of the Facebook group Psoriasis association (https://www.psoriasis.dk/) will be contacted with the information about the study asking him/her to post invitation and the link to the specialist/GP questionnaire on the group's website.

- The Danish Society for General Practitioners https://www.dsam.dk/flx/english/hippokrates/denmark/) will be contacted to recruit general

practitioners, and the Danish Pharmacy Association (https://www.apotekerforeningen.dk/) will be contacted to recruit pharmacists. The e-mail lists of the societies' members will be used to distribute the relevant questionnaires concerning both valproate and oral retinoids.

- To recruit patients, similar to the valproate study, the administrators of the relevant Facebook groups (i.e. Psoriasis association (https://www.psoriasis.dk/), Isotretinoin danish/swedish/norwegian (https://www.facebook.com/groups/isotretinoindanish/)) will be introduced to the study and asked to post the link to the patients' questionnaire on the groups' website.

GREECE

Recruitment of General Practitioners and Specialists

- Physicians will be approached (phone or e-mail) through professional societies (dermatologists, 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 dermatologists, 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 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 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
- 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 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 oral retinoids 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, dermatologists and midwives

- GPs, dermatologists 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
- Dermatologists will be recruited through their professional societies.

PORTUGAL

Recruiting GPs and specialists:

- Invitation through Portuguese physicians' societies (*Colégios de especialidade*), namely: dermatology, 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). (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 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
- 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 (dermatology, 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 personal networks

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 oral retinoids 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, dermatologists and midwives

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