RetinoidRiskAware

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

EU PE&PV research network

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Section 2: Summary

RetinoidRiskAware - Impact of EU label changes and pregnancy prevention programme for medicinal products containing oral retinoids: risk awareness and adherence

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Keywords

Teratogenicity; retinoids; risk minimization; risk awareness; pregnancy prevention programme; European Union; online survey; interviews; patients; pharmacists; prescribers

Rationale and background

Oral retinoids (acitretin, isotretinoin, alitretinoin and tretinoin) are licensed as medicinal products for dermatological conditions, including (severe) acne, eczema and psoriasis. Other oral retinoids are used to treat skin manifestations of T-cell lymphoma (bexarotene) and acute promyelocytic leukaemia (tretinoin). The teratogenic risk, congenital malformations and neurodevelopmental disorders associated with the use of retinoids by pregnant women are well established.

A pregnancy prevention programme (PPP) launched in 2003 for isotretinoin has since been extended to other oral retinoids treating dermatological conditions: acitretin and alitretinoin.. The effectiveness of the PPP 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 with the PPP.
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 an update of measures for pregnancy prevention was needed. In 2018, the PRAC established a new pregnancy prevention programme (PPP) to ensure that patients are made fully aware of the risks and the need to avoid pregnancy and revised the educational materials. These include a patient reminder card, a physician checklist and risk acknowledgement form, and a pharmacist checklist.

Research question and objectives

The research question of the study presented in this report was:
"To what extent are patients and healthcare professionals in the European Union aware of the risk of teratogenic effects of oral retinoids and of the PPP for oral retinoid containing medicinal products?"

The main objectives of the research were:

1. To assess the influence of the PPP on patients', prescribers', pharmacists' and midwives' awareness about the teratogenic risks of oral retinoids use during pregnancy, and on their knowledge, attitudes and practices.
2. To evaluate health care professionals' (prescribers, pharmacists, midwives) knowledge and adherence to the PPP and risk minimisation measures in relation to the use of medicinal products containing oral retinoids and their influence on retinoid exposure during pregnancy.

3. To assess patient knowledge and adherence to the PPP and risk minimisation measures.

Study design

The study was of mixed nature and involved collection and analysis of both quantitative and qualitative components. A cross sectional, web-based survey was developed and conducted among physicians, pharmacists and patients across eight European Union member states to provide insight into the key determinants of awareness and use of pregnancy prevention measures among patients and healthcare professionals.

Semi-structured telephone interviews with patients using oral retinoids shed light on the rationale for decision-making regarding treatment by healthcare professionals and patients.

Setting

The multi-country study was conducted in eight member states of the European Union: Belgium (only Flanders), Denmark, Greece, Latvia, Portugal, the Netherlands, Slovenia and Spain. We conducted telephone interviews with patients in Portugal and the Netherlands.

Subjects and study size

For the web-based survey, the patients included (n=298) were all women of childbearing age (aged 15-50) who were using or had used oral retinoids. The pharmacists included (n=660) had previously provided advice or dispensed oral retinoids to at least one woman in the childbearing age. The prescribers included(n=560) were either general practitioners or specialists, who previously consulted or prescribed oral retinoids to at least one woman in the childbearing age. In Spain and in the Netherlands, midwives have consulting functions. In these two member states, midwives, who had a consultation with at least one woman in childbearing age treated with oral retinoids, were included (n= 57).

Recruiting patients for the semi-structured telephone interviews during the COVID-19 crisis revealed to be a difficult mission. We aimed to hold telephone interviews with 6-8 patients from a convenience sample, both in Portugal and the Netherlands. In Portugal, six women agreed to be interviewed. In the Netherlands, only one patient could be interviewed.

Variables and data sources

In the web-based survey, patients were asked about:

- Characteristics (gender, age, type of retinoid used and education level)
- Awareness of risks of oral retinoids
- Source of information that created awareness
- Familiarity with the educational materials (patient brochure; patient reminder card; risk acknowledgement form; warning symbol; Patient Information Leaflet; QR code)
- Discussion on contraceptive measures with healthcare professionals
- Change of medication because of pregnancy
- Pregnancy testing before, after and during treatment with oral retinoids
- Pregnancies and treatment when using oral retinoids, before and after 2018
- Contraception methods and perceptions
- Change in retinoid use after 2018

Pharmacists were asked about:

- Characteristics (gender, age, type of pharmacist, work experience, frequency of dispensing oral retinoids, ever seen or suspected malformations caused by retinoids, perception of 'women in fertile age')
- Knowledge about the teratogenicity of oral retinoids and the sources of this knowledge
- Procedure at most recent dispensing of an oral retinoid
    - Current use of educational materials and likely future use
    - Counselling of female patients about contraception and treatment during pregnancy
    - Counselling of female patients at repeat prescriptions
    - Behaviour change since 2018
    - Awareness about/Use of measures from the prevention programme and influence on daily practice

Prescribers were asked about:

- Characteristics (gender, age, type of prescriber, work experience, counselling frequency, ever seen malformations caused by oral retinoids, perception of 'women in fertile age')
- Knowledge about the teratogenicity of oral retinoids and the sources of this knowledge
- Procedure at most recent prescribing of an oral retinoid
    - Current use of educational materials and likely future use
    - Prescribing habits
    - Monthly appointments
    - Pregnancy test implementation
    - Discussing effective contraception
    - Behaviour change since 2018
    - Awareness about/Use of measures from the prevention programme and influence on daily clinical practice

The midwives in Spain and the Netherlands were asked about:

- Characteristics (gender, age, work experience, attending frequency, counselling frequency, ever seen malformations caused by oral retinoids, perception of 'women in fertile age')
- Knowledge about the teratogenicity of oral retinoids and the sources of this knowledge
- Procedure at most recent consultation with a woman of childbearing age taking an oral retinoid
    - Current use of educational materials and likely future use
    - Counselling of women, also at repeat prescriptions
    - Behaviour change since 2018
    - Measures from the prevention programme influencing their daily clinical practice
    - Change in provided information
    - Difficulties in implementation and or use of prevention measures established in 2018

Results

The results of the web-based surveys show that there is a very high awareness of the teratogenic risks of oral retinoids among patients and healthcare professionals. However, although there seems to be medium awareness about the measures established by the EMA in 2018, both the implementation of and the adherence to these measures vary across member states. Despite being aware of the teratogenic risks, women do not always adhere to recommendations regarding the use of contraceptives and pregnancy testing. This could be related to their relatively young age. Less than

half (48%) of women discussed the use of contraceptives with a health care provider and 53% applied contraceptive measures. A minority of women performed pregnancy testing either before (27%), during (22%) and after (5%) the use of oral retinoids.

Patients had to a very limited extent come across information materials, including the patient brochure, the reminder card and the risk acknowledgement form as their sources of information about teratogenic risks. The awareness was mainly raised through verbal communication from health care professionals (mainly prescribers) as well as from the internet. Patients also indicated both on the survey and during interviews that the information they received from their prescriber was very important.

The warning symbol on the package was noticed by almost half of the patients (49%). The risk acknowledgement form was the other most frequently recognized material by patients among the dedicated information materials introduced by EMA in 2018. Approximately one out of five patients (21%) had signed the risk acknowledgement form. The reminder card, the patient brochure and the QR-code were only familiar to a limited number of patients respectively 4%, 7% and 6%. On the other hand, an overwhelming majority (95%) of the patients had read the patient information leaflet (PIL).

The pharmacists considered the warning symbol on the package to be very helpful both currently and towards the future, when informing patients about risks and as a reminder to verbally alert to the risks around pregnancy and medication use. They also indicated that patients are reluctant to repeatedly listen to the same information.

Healthcare professionals participating in this study had, to a large extent, gained their knowledge and awareness about the teratogenicity of retinoids during their academic training or post graduate education, rather than through the Pregnancy Prevention Programmes.

Prescribers considered the patient brochure and the risk acknowledgement form to be the most valuable risk management measures. Yet other tools such as educational materials from other sources, were also frequently reported as useful in their daily clinical practice.

Only a small proportion of health care providers and patients adhered to all aspects of the pregnancy prevention program.

Discussion

This study has shown that there is very high awareness of the teratogenic risks of oral retinoids among patients, prescribers and pharmacists. In Spain and the Netherlands, where midwifes hold consulting functions, their awareness was substantially lower than that of pharmacists and prescribers. Thus efforts to increase awareness among midwives are urgently needed as they may play an important role in periconception advice.

The awareness about the risk minimization measures and educational materials was moderate. However, their implementation, i.e. translation of evidence into healthcare practice, is a very challenging process and often not as straight forward as expected. Risk minimization measures that require significant time from healthcare professionals in clinical practice, such as the review and signature of the risk acknowledgement form, are less likely to be implemented. Furthermore, implementation of measures depends heavily on the healthcare system in each member state. Nevertheless, the measures contribute somewhat to the repetition of the teratogenic risk message,

which is considered essential by patients when trying to prevent exposure to oral retinoids during pregnancy. While adherence to individual measures was far from ideal, women's awareness of the teratogenic risks of retinoids was very high.

Visual measures, such as the warning symbol were perceived as helpful by patients and pharmacists as reminders to pay attention to treatment risks. The PIL remains an important information source for patients. Almost all patients reported to have read it.

Healthcare professionals had gained their knowledge and awareness about the teratogenicity of oral retinoids during their academic training or post graduate education. Most health care providers reported to be aware of the teratogenic risks of retinoids for longer than 5 years. Additional postgraduate training in communication about teratogenic risks may help to further optimise the PPPs. Specific issues, such as the use of the educational materials, the interpretation of the fertile age, the tasks of different healthcare providers when counselling patients and inter-disciplinary cooperation are topics to be further discussed and explored. Furthermore, professionals should have easy access to educational materials. Embedment of information from regulatory sources into the prescribing and dispensing systems would facilitate the uptake of all information and measures.

Conclusion

Despite a strikingly high awareness about the teratogenic risks of oral retinoids among patients and healthcare professionals, the use of risk minimization measures and educational materials remained low across the participating countries. Use of oral retinoids during pregnancy seems to still occur, although there is a high awareness about its risks. Since a baseline measurement is lacking, we cannot ascertain the extent to which an eventual use during pregnancy has been affected since the implementation of the 2018 measures.

Patients and pharmacists consider the repetition of the message about teratogenic risks to be essential and recognize visual measures such as the use of the warning symbol in the outer packaging as a helpful reminder. Ongoing patient counselling would be highly facilitated if the educational materials and information were easily accessible in prescribing and dispensing software systems.

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Section 3: Investigators

The **Coordinating Team** (CT) is composed by:

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This section provides an overview of all the teams involved, both in the coordination and per country involved, including their background and expertise, as well as contact details.

Country: Belgium

Description of institution (including location): The Pharmaceutical Care Unit is a research group at the Faculty of Pharmaceutical Science of Ghent University in Belgium with main research focus on the optimization of rational pharmacotherapy by preventing, detecting and managing drug-related problems, mainly in primary health care settings. More detailed information on the past and current research activities can be found on our webpage:
https://www.ugent.be/fw/bioanalysis/en/research/pharmaceutical-care/research.htm

Description of the research team/researcher(s) involved as to their background, competences and interests: Prof. Koen Boussery is associate professor in pharmaceutical care and pharmacokinetics at the Faculty of Pharmaceutical Sciences, and currently heads the Pharmaceutical Care Unit at Ghent University. The main aim of his research group is the optimization of the quality, appropriateness and safety of drug use in primary health care. His research group has specific expertise in the development, evaluation and implementation of interventions that focus on the timely detection, management and prevention of (potential) drug-related problems in community pharmacy practice and in primary health care, with a special focus on chronic conditions, older people, and self-treatment with medication. Prof. Lies Lahousse is a tenure track professor in pharmacoepidemiology and evidence-based use of medicines. Her research activities within the Pharmaceutical Care Unit combine clinical pharmacology with epidemiology to promote rational drug use in the society. The impact of drugs on public health is evaluated in terms of use, (cost)effectiveness and safety. Focused areas are therapy adherence, precision medicine, and multimorbidity.

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Country: Denmark

Description of the institution (including location): Social and Clinical Pharmacy (SCP) is a research group under the Department of Pharmacy, Faculty of Health and Medical Sciences, at the University of Copenhagen. SCP's research is mainly within three broad topic areas of Medicines Use, Clinical Pharmacy, and Pharmaceutical Policy. Research within each focus area can be situated on one or more of the levels of the user, organization and society.

Description of the research team/researcher(s) involved as to their background, competences and interests: Anna Birna Almarsdóttir is Professor in Social and Clinical Pharmacy. She has more than 25 years of experience with social and clinical pharmacy research, which have included areas such as health services research, pharmacoepidemiology, and drug utilisation research. Her main focus is currently on developing clinical pharmacy services (in the primary, secondary and tertiary health care sectors), and pharmaceutical policy analysis using both qualitative and quantitative research methods. Her methods interests are mainly questionnaire construction, scale development, and triangulation of qualitative and quantitative research methods. She graduated as PharmD from the University of Iceland in 1988 and received a PhD degree in Health Policy Analysis in 1994 from the University of North Carolina at Chapel Hill, USA. Her work experience includes Assistant and Associate Professorships in Clinical Pharmacy, at the Royal Danish School of Pharmacy and the University of Iceland, and Professorships at the University of Iceland and the University of Southern Denmark. In addition, she held a position as Senior Pharmacoepidemiologist at DeCode Genetics Inc and consulted with the pharmaceutical industry in Iceland. Anna Birna involved researchers from the SCP group in the work, Ramune Jacobsen and Johanne Mølby Hansen. Ramune Jacobsen is an Assistant Professor in Clinical pharmacy; she has more than 15 years of experience with social pharmacy and public health research, including implementation and evaluation research in health services for chronic disease management, epidemiological research in disease prevention, researching early origins of diseases, and survey-based research for health promotion. She graduated with a Master's degree in Medical Biology in Moscow (Russia) in 1994, and as a Master of Public Health in Kuopio (Finland) in 2003, and earned her PhD in Social Pharmacy in 2010 in Copenhagen (Demark). Johanne Mølby Hansen is a research assistant at the Social and Clinical Pharmacy group. She has 3 years of research experience with a variety of research interests such as pharmacy education, emergency contraception and wrote her master thesis on pharmacogenetics in primary care. Johanne Mølby Hansen graduated as a Master in Pharmacy from University of Copenhagen in august 2019.

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Description of the institution (including location): Our Laboratory of Hygiene and Environmental Protection belongs to the Department of Medicine, Democritus University of Thrace, Alexandroupolis, Greece. It presents a very strong background on epidemiological studies and preliminary experience on pharmacoepidemiological analysis and data analysis.

Description of the research team/researcher(s) involved as to their background, competences and interests: Christos Kontogiorgis, Assistant Professor has experience in pharmacoepidemiological studies. Theodoros Constantinides, Professor is an expert in epidemiological studies and statistical analysis. Evangelia Nena, Assistant Professor, expert on epidemiological studies and statistical analysis. Georgios Poulentzas, Pharmacist, Master's Degree Student with expertise in pharmacoepidemiological analysis and drug utilization studies. Panagiotis-Nikolaos Lalagkas, Pharmacist, Master's Degree Student with expertise in pharmacoepidemiological analysis and drug utilization studies. Panagiota Mantelou, Pharmacist, Master's Degree Student with expertise in pharmacoepidemiological analysis and drug utilization studies.

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Country: Latvia

Description of the institution (including location): The Institute of Public Health of Riga Stradins University is located in Riga, the capital of Latvia. The objective of the RSU Institute of Public Health is to carry out research, undertake academic training and promote the acquisition and improvement of scientific qualifications in the area of public health and healthcare organisation. The institute has research expertise in areas such as sexual and reproductive health, HIV, diabetes, nutrition, pharmaceutical policy, health systems, economics and many others.

Description of the research team/researcher(s) involved as to their background, competences and interests: Elita Poplavska, PhD is an assistant professor at the Faculty of Pharmacy and senior researcher at the Institute of Public Health. She holds a PharmD from Riga Stradins University and a PhD in Social and Administrative Pharmacy, University of Minnesota. Her research activities are related to pharmaceutical policy, medicines use research and pharmaceutical promotion involving qualitative and quantitative research methods. Mirdza Kursite, MD, MS is a lecturer at the Faculty of Public Health and Social Welfare. She holds an MD and Master's degree of Health Sciences in Health care from Riga Stradins University. Her research activities are related to patient - physician communication, adherence to therapy and health beliefs involving qualitative and quantitative research methods.

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Description of the institution (including location): Porto Pharmacovigilance Centre (PPC) is a Portuguese regional pharmacovigilance centre, part of the National Pharmacovigilance Centre which coordinated by Infarmed (National Authority of Medicines and health Products, I.P.). PPC is based on the Department of Community Medicine, Information and Health Decision Sciences of the Faculty of Medicine of the University of Porto, since its creation in 2000. The PPC covers a region with 1.8 million inhabitants and 24000 healthcare professionals and works closely with healthcare institutions, namely hospitals, primary health care units and community pharmacies.

Description of the research team/researcher(s) involved as to their background, competences and interests: Inês Ribeiro Vaz has a Doctorate degree in Clinical Research and Health Services, awarded by the Faculty of Medicine, University of Porto in 2016 with the thesis: "Using Information Systems in Pharmacovigilance. She has a Master on Public Health awarded by the Faculty of Medicine, University of Porto in 2009. Has a degree in Pharmaceutical Sciences awarded by the Faculty of Pharmacy, University of Porto in 1999. Performs duties as technical and scientific coordination of the Porto Pharmacovigilance Centre since 2003 and, over the last 15 years, has published several papers, both as author and as co-author, in the area of pharmacoepidemiology, pharmacovigilance and drug safety.

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Country: Slovenia

Description of institution (including location): Faculty of Pharmacy (FFA), University of Ljubljana (UL) is the only university organization in the Republic of Slovenia for the study of pharmacy and laboratory biomedicine. The Faculty of Pharmacy follows the concept of scientific pharmacy and clinical biochemistry and considers research and study as two inseparable parts. By European standards FFA is a medium-sized faculty. Yearly it admits 150 students of Uniform master's study program Pharmacy, 40 students of University study program Laboratory Biomedicine, 40 students of University study program Cosmetology, 40 students of Master's study program Laboratory Biomedicine, 25 students of Master's study program Industrial Pharmacy, and about 30 students of 3rd cycle of Bologna study program Biomedicine. Established in 1997 the Chair of social pharmacy focuses on the development of academic and experimental grounds for education and research in the broader area of social pharmacy. The area of interest are the influences of drugs as material, biomedical, ethical and proprietary category on the modern individual and society. Research includes pharmacoepidemiology, pharmacoeconomics and outcomes research. The Chair is devoted to the study of properties and development of information technology in acquisition and transfer of knowledge about medicines. It studies the role of pharmaceutical profession in the modern societies, and the methods of communications between pharmacists and other health professionals, and with lay public. Central concepts of interest are also patient counselling and pharmaceutical care.

Description of the research team/researcher(s) involved as to their background, competences and interests: Assoc. prof. Mitja Kos, M Pharm: Mitja Kos is the Head of the Chair of Social Pharmacy and an associate professor for social pharmacy at the University of Ljubljana, Faculty of Pharmacy, Slovenia. He graduated as a pharmacist in 1999 and defended his doctoral thesis on the topic of off-label prescribing in 2005. He has developed expertise in several different fields including pharmacoeconomics and outcomes research, pharmacoepidemiology, medicine pricing and regulation and pharmaceutical care practice. The focus of his scientific and professional activities are health technology assessment, comparative effectiveness and optimization of drug use. At the Faculty of pharmacy, University of Ljubljana he has built a nationally recognised reference centre for pharmacoeconomics and evidence based pharmacy practice. Recently, he has served as a member of the Health Council at the Ministry of Health of the Republic Slovenia and as a member of two expert commissions at the Agency for Medicinal Products and Medical Devices of the Republic Slovenia: one focusing on the evaluation of clinical trials and the other on drug prices.

Assoc. prof. Igor Locatelli, M Pharm: Igor Locatelli graduated in 2002 at the Faculty of Pharmacy, University of Ljubljana, where he has been employed since 2003. He concluded the postgraduate study of Biomedicine at University of Ljubljana in 2008, when he defended his doctoral thesis in clinical pharmacokinetics. Between 2002 and 2010 he worked as a researcher within the Chair of Biopharmaceutics and Pharmacokinetics, where he was involved in evaluation of pharmacokinetic and statistical models for analysing the data from preclinical studies and clinical trials. In 2010, he joined the Chair of Social Pharmacy, since then his research work embraces studies in pharmacoepidemiology and pharmacoeconomics with an emphasis on meta-analysis of clinical trials

Assist. Nanča Čebron Lipovec, M Pharm, PhD: Nanča Čebron Lipovec graduated in 2010 at the Faculty of Pharmacy, University of Ljubljana and started her career as a hospital and clinical pharmacist at the University Clinic of Respiratory and Allergic Diseases Golnik. In 2012, she became a research fellow at the same institution and started her doctoral studies in the field of Social medicine. In 2016 she

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Assist. Nejc Horvat, M Pharm, PhD: Nejc Horvat graduated in 2007 under the supervision of prof. dr. Aleš Mrhar and assist. dr. Mitja Kos. The theme title was: Development of a questionnaire measuring patient satisfaction with pharmacy services. In 2014 he defended his doctoral thesis titled: Evaluation of pharmacy services from the patient and expert perspective. Currently, he is a member of different research teams within the Chair of Social Pharmacy. His research focus is primarily the outcomes research, particularly evaluation of pharmacy services, health literacy and drug related problems. Other chair members: Assist. Nika Marđetko, M Pharm, PhD; Teaching assistant and researcher in the field of pharmacoeconomics and pharmaceutical marketing. Assist. Ana Janežič, M Pharm; Teaching assistant and PhD candidate in the field of patient related outcomes focusing on compliance, adherence and concordance in medicine taking. Assist. Janja Jazbar, M Pharm; Teaching assistant and PhD candidate in the field of pharmacoepidemiology. Assist. Špela Žerovnik, M Pharm, research fellow.

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Description of your institution (including location): The Navarre Health Service (NHS) is the provincial branch of the National Health Service in Spain. The Innovation and Organization Unit of the NHS carries out clinical research work in Navarre Province (some 650,000 inhabitants). This Unit hosts the Navarre Cochrane Associate Centre and has a long-standing experience on pharmacoepidemiology research work, critical appraisal of medical literature, systematic reviews, and knowledge translation.

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Country: Netherlands, quantitative research team

Description of the institution (including location): UPPER is the Utrecht Pharmacy Panel for Education and Research affiliated with the Division of Pharmacoepidemiology & Clinical Pharmacology at the Department of Pharmaceutical Sciences of Utrecht University. The network includes 600 pharmacies that provide internships for masters students of the School of Pharmacy and participate in pharmacy practice research. UPPER is very experienced in designing, executing and reporting studies in daily pharmaceutical practice applying both quantitative and qualitative methods.

Description of the research team/researcher(s) involved as to their background, competences and interests: Dr. Marcel L Bouvy PhD PharmD, professor of pharmaceutical care at the Department of Pharmacoepidemiology and Clinical Pharmacology at Utrecht university. In this function he is chair of UPPER. Marcel has been an active community pharmacist since 1992 and works at SIR institute for Pharmacy Practice and Policy in Leiden which closely cooperates with Utrecht University. Since 2016 he is member of the Dutch Medicines Evaluation Board. Marcel is active in several national and international committees and platforms aiming to improve the safe and effective use of medicines. He is past president of the research committee of ESCP, past president of the Scientific Section of Dutch Community Pharmacists (WSO), founding member of the European Society for Patient Adherence, Compliance and Persistence (ESPACOMP) and member of the editorial board of the International Journal for Pharmacy Practice. Marcel's research activities focus on patient adherence, medication safety and include both observational work and evaluation of innovative pharmacy interventions. Marcel is (co-)author of >300 papers in peer reviewed and national pharmacy journals, both professional and consumer-oriented book (chapters) on medicines and research reports.

Dr E.R. (Rob) Heerdink PhD is an associate professor of Clinical Pharmacoepidemiology at the Utrecht Institute for Pharmaceutical Sciences, Utrecht University and professor of Innovation of Pharmaceutical Care at the University of Applied Sciences Utrecht. He is principal investigator and managing director of the Centre for Clinical Therapeutics. His research is driven by questions from clinical practice and spans from traditional pharmaco-epidemiological methods to systems pharmacy research into context related aspects of pharmacotherapy. He has published over 200 peer-reviewed articles on topics including (psychiatric) pharmacotherapy, drug exposure patterns, adherence and the relation between pharmaceutical care and clinical outcomes and has served as co-promotor for over 25 PhD students. Dr Rob Heerdink is a founding and honorary member of the European Society for Patient Compliance and Persistence (Espacomp).

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Description of the institution (including location): The RIVM is the National Institute for Public Health and the Environment of the Netherlands and has been promoting public health and safeguarding environmental quality for over 100 years. The RIVM has expanded to become a knowledge institute at the centre of Dutch society, advising on health and environment. In our role as trusted advisor, we provide the government with impartial advice on infectious diseases, vaccination, population screening, lifestyle, nutrition, pharmaceuticals, environment, sustainability and safety. We carry out studies, provide advice and recommendations, and direct and implement prevention and control responses. Our work is primarily commissioned by Dutch ministries and inspectorates and projects are also undertaken within international frameworks, such as the European Union and United Nations. We have many national and international partners, and are continuing to build new networks in multidisciplinary cooperation. We are committed to supporting government and society in improving health and the environment.

Description of the research team/researcher(s) involved as to their background, competences and interests: Teresa Leonardo Alves is currently working as a Researcher for the Health Protection Unit of the National Institute for Public Health and the Environment (RIVM) in Bilthoven, the Netherlands. She holds a Pharm D in Pharmaceutical Sciences from Porto University in Portugal, a Master in Public Health from the Netherlands Institute of Health Sciences (Erasmus University, Rotterdam) and a PhD in Pharmaceutical Policy, Utrecht University, Netherlands. She has more than fifteen years' experience in the coordination and public relations of not-for-profit organizations in the field of pharmaceutical policy, having worked for the *International Pharmaceutical Federation*, *Health Action International* and the independent bulletin *Prescrire* in a variety of positions covering project management, communications and policy advocacy. She has developed invaluable knowledge of key stakeholders in European pharmaceutical policy as well as evidence-based advocacy skills. This has required expertise in identifying and maintaining contacts with NGO networks, policy-makers, academia and health authorities. She has also gained extensive experience as a fundraiser, public speaker, event organizer and editor.

Ingrid Hegger has worked at the National Institute for Public Health and the Environment since 1988. In doing so, she became an expert on the regulation of medicinal products, with special interest in biologicals. From 1990 to 1999 she was the Project Manager for the Control Authority Batch Release of immunological medicinal products and plasma derived products. She also acted as Scientific Assessor of biologicals and was member of the Biological Working Part of the European Medicines Agency from 1995 to 1999. She was also a member of the group of experts Sera and Vaccines of the European Pharmacopoeia, Council of Europe, from 1999 to 2007. Between 2001 and 2006, she was a Project leader for the batch release of investigational medicinal products for clinical trials. From 1999 onwards, her focus shifted towards "close-to-policy" projects in the field of health products, pharmaceutical care and health policy. Between 2003 and 2006, she was a member of the National working party for the implementation of EU directive 2001/20 on clinical trials. She has been involved in many projects covering a wide variety of topics, among which: existing barriers in the regulation of medicinal products, pharmaco-economics, orphan diseases, advanced medicinal products, clinical trials, eHealth, pharmacogenomics, pharmaceutical crime and risk-based supervision. In addition, her Ph.D. focused on the utilization of knowledge within public health policy and healthcare supervision.

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Section 4: Introduction: rationale and background

Retinoids are 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 extended to other oral retinoids: acitretin and alitretinoin. The effectiveness of the PPP 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 with the PPP in clinical practice. In addition, periodic safety update reports showed inconsistencies regarding the extent of the warnings and the risk minimization measures for pregnancy prevention in place between products with the same active substance, between oral and topical retinoids and between European Union (EU) Member States. 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 an update of measures for pregnancy prevention was 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 enhance 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 were recommended. In addition, several other measures were endorsed: the patient signature on the physician checklist/risk acknowledgement form; the dissemination of the patient reminder card; the dissemination of the pharmacist checklist; the inclusion of an appointment table in the patient reminder card and a pictogram/symbol with the boxed warning to be included on the outer package to warn patients about the harm to the unborn baby and to the need for effective contraception while on treatment.
The EMA required a study to investigate risk awareness and adherence to risk minimization measures amongst prescribers, pharmacists and users of oral retinoid containing medicinal products authorized in the EU following the implementation of the 2018 revised PPP in relation to teratogenic effects.

Section 5: Research objectives

Primary objective: To determine the extent of awareness among patients and healthcare professionals about the risk of teratogenic effects in women of childbearing potential exposed to medicinal products containing oral retinoids and about the PPP, with focus on:

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

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

1. 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);
2. Use of effective contraception throughout treatment in line with sections 4.4 and 4.6 of the Summary of Product Characteristics, including use of non-prescription or non-reimbursed contraceptives;
3. 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;
4. Obtaining patient signature for prescriber checklist and acknowledgment form where implemented in Member States;
5. Implementation of scheduled 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.

Section 6: Research Methods

Our study is of mixed nature and involves collection and analysis of both quantitative and qualitative components.

A cross sectional, web-based survey was developed and conducted among physicians, pharmacists and patients across eight European countries to provide insight into the key determinants of awareness and use of pregnancy prevention measures among patients and healthcare professionals. A set of structured interviews with patients using oral retinoids shed light on the rationale for decision-making regarding treatment by healthcare professionals and patients.

6.1. Study design: Cross-sectional survey

We conducted a web-based questionnaire among users and former users of oral retinoids, and among health care professionals: prescribers (general practitioners, dermatologists, other prescribers), midwives and pharmacists (community). All products containing oral retinoids included in this study are listed in ANNEX 1. Estimates of use of oral retinoids are listed in ANNEX 2.

A convenience sample of patients, prescribers and pharmacists (as well as midwives, where relevant) were planned to be included in each country. Regardless of the size of the country, we aimed that each country would complete and deliver for each study at least 50 completed patient questionnaires and 150 healthcare professional questionnaires.

Relevant patients and health care professionals were recruited in each country. They were invited to fill in the web-based questionnaire (see *questionnaires*). Data from the questionnaires were collected in a central database and subject to descriptive statistics.

6.1.2 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.

Respondents from Belgium were only recruited from the Flemish-speaking region, Flanders.

The implementation of the pregnancy prevention materials and measures varied across the countries included in our study, as is shown on table 1.

Table 1. Pregnancy prevention materials and measures implemented per country (as per EMA communication of 27 May 2019) and national team feedback

Pregnancy Prevention Programme Materials before 2018								
For patients	Patient Brochure, Contraception advice Brochure							
For pharmacists	Pharmacist brochure							
For physicians	Physician guide, Physician checklist and Acknowledgement form							
Pregnancy Prevention Programme Materials after 2018 review	BE	DK	GR	LV	NL	PT	SI	ES
Risk acknowledgment form with prescriber/carer checklist	Yes	Yes	Yes	Yes	Ongoing	Yes	Yes	Yes
Updated patient information leaflet, included boxed warning	Yes[1]	Yes	Yes[1]	Yes[1]	Partly	Yes[1]	Yes	Yes
QR code on patient information leaflet	Yes[1]	Yes	No	Yes[1]	Partly	Yes[1]	Yes[1]	Yes

Patient reminder card	Yes [2]	Yes	Yes	Yes	Ongoing	Yes	Yes	Yes
DHCP letter	Yes	Yes	Yes	Yes	Ongoing	Yes	Yes	Yes
Materials to be implemented as deemed fit at national level								
Prescription validity of 7 days	No	Rec [3]	No	Yes	No	No	Yes	No
Patient signature on Risk Acknowledgment Form	Yes				yes		Yes	Yes
Pharmacist Checklist/Guide	No	Yes	No	Yes	Ongoing	Yes	Yes	No
Visual reminder (warning) on outer packaging	Yes [1]	Yes	Yes[1]	Delayed	Partly	Yes[1]	Yes	Yes
Additional measures/activities adopted by some Member States								
Subject to special prescription				Yes				
One prescription for 4-week treatment				Yes		Yes		
Outreach to professional organisations	Yes				Yes		Yes	No
Press release					Yes	Yes		

1- with delay for some products
2 - available as a separate card
3- recommended

6.1.3 Subjects: eligibility criteria

Patients: Women in childbearing age (aged 15-50) who are using or have used oral retinoids in each country were invited to complete the web-based questionnaire (see *questionnaires*).

Prescribers: General practitioners and specialists were included if they had consulted or prescribed at least 1 woman in the childbearing age with oral retinoids.

Pharmacists were included if they had provided advice or dispensed medication to at least 1 woman in the childbearing age with oral retinoids.

Midwives were included in Spain and in the Netherlands, countries where they have consulting functions. They were included if they had reported to have had a consultation with at least one woman treated with oral retinoids products over the past year.

Healthcare professionals were 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 healthcare professionals that are in place in the participating countries;
- through advertising on (professional) websites, social media and newsletters aimed at the given healthcare professionals;
- through closed professional Facebook groups and other social media;
- through email or direct telephone contact established at their practices or institutions, or through the health service professional database;
- through leaflet distribution at their practices containing web links;

- through social networks of pharmacovigilance centres and of the drug regulatory agency;
- through personal contacts;
- through available university email listings of healthcare professionals.

Patient recruitment strategies included:

- asking pharmacists to select current and past users from pharmacy information systems, to contact patients pursuing and request them to fill in the web-based questionnaire;
- asking pharmacists to distribute leaflets and stickers with web links to patients purchasing oral retinoids ;
- asking physicians to select current and past users from prescriber dossiers, to contact patients and request them to fill in the web-based questionnaire;
- asking doctors and nurses to contact patients meeting inclusion criteria previously identified through the Health Service Information System;
- distribution of leaflets by doctors to their patients at hospital wards;
- approaching potential participants through patient organisations;
- advertising on online patient forums, social media and social networks;
- through university email listings.

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

6.1.4 Questionnaire development

After consulting the literature [1], an electronic survey assessing knowledge, attitudes and practices of healthcare professionals about the teratogenic and neurodevelopment effects oral retinoids was developed including questions on the influence of regulatory recommendations on this knowledge in practice. The survey was prepared to include questions to ascertain: awareness of the regulatory recommendations; whether physicians had prescribed such products; whether pharmacists had dispensed these products; how health professionals understood the regulatory message; and why it was being used. If respondents were aware and understood, they were asked whether it had influenced their prescribing or dispensing behaviour (e.g., has it affected their pharmacotherapeutic choices) and asked about their information provision to patients. If they were unaware, respondents were invited to foresee how this new knowledge would likely impact on their future prescribing/dispensing and information provision behaviours.

Topics included in the healthcare professionals' questionnaire covered:

(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 the pregnancy prevention programme and risk minimisation measures when prescribing these products, such as provision of patient brochures, use of healthcare professional guides, implementation of annual risk acknowledgement forms, seeking informed consent from patients using oral retinoids

1

(5) Whether medically supervised pregnancy testing is performed prior to treatment initiation, repeated testing during treatment and one month after stopping, including pregnancy test results where available in Member States

(6) Whether patient signatures 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 was of major interest. In addition, the pharmacists' questionnaire included questions on adherence by pharmacists to the provision of the patient card and to advising patients in case of planned or suspected pregnancy at each dispensing.
Topics included in the patient questionnaire covered:

(1) Awareness of a regulatory recommendation regarding the use of oral retinoids in women of childbearing age

(2) Effect of recommendation on use of medicine

(3) Provision of patient brochure by prescriber, or patient card by pharmacist

For patients currently using oral retinoids:

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

(5) Effective contraception use

(6) Provision of informed consent (signature) to the prescriber enabling data collection on oral retinoids and related products' use.

The National Team based in Copenhagen developed the first draft of the healthcare and patient questionnaires in English. These were subsequently reviewed by the Coordinating Team and the National Teams. The Danish team pilot tested the questionnaires by interviewing patients, medical specialists and pharmacists who had experience taking, prescribing or dispensing oral retinoids. The piloting of the questionnaires with general practitioners took place in the Netherlands. This step, which was scheduled from July 2019 onwards was only completed by October 2019, resulting in delay of the final version for the prescribers' questionnaire.

For more information about the questionnaires, please consult the English versions of the various questionnaires.

ANNEX 3 – Questionnaire for medical specialists and GPs

ANNEX 4 – Questionnaire for pharmacists

ANNEX 5 – Questionnaire for patients

Eventually, once the final questionnaires in English were agreed upon between September and October 2019, all national teams were invited to adapt them to their national settings and to translate them. A specific protocol was developed for the translation of the questionnaires and is available as ANNEX 6 – Protocol for translation of questionnaires.

We faced delays during the translation of the questionnaires which were required in native language by some local ethical committees. The translation proved to be an iterative process which resulted in several corrections to the surveys. The following step included seeking Ethical Approval. The approval and review also delayed the process, as some Committees also recommended minor adjustments to the questionnaires. These changes were implemented and contemplated mostly clarifications to the introductory text.
By early December 2019, seven countries had completed their translations for all questionnaires. The remaining country, the Netherlands delivered the translated questionnaires by mid-February 2020.

The first ethical approval was granted in Latvia at the end of October 2019 and the last Ethical waiver was granted in the Netherlands in May 2020 (postponed by the Ethical Review Board as study did not start due to COVID-19).

The surveys in various languages were uploaded into LimeSurvey, an online survey system (LimeSurvey GmBH, Hamburg, Germany). Questionnaire respondents were invited to follow a link to complete the survey online.

All National Research Teams were invited to start preparing for recruiting respondents from January onwards, as this was the most limiting factor for a successful implementation. Recruitment of participants and implementation of the survey overlapped for several months.

6.1.5 Survey implementation: relevant milestones

By mid-March 2020, the five countries who had already started surveying (Denmark, Latvia, Portugal, Belgium and Slovenia) experienced stagnation in the responses, due to the COVID-19 crisis. The public health scenario had great implications to the availability and willingness of healthcare professionals to participate in our surveys. The research teams considered it was unethical to overburden physicians and pharmacists with the survey at such a critical moment and opted not to send further reminders. Countries who at that point were about to start surveying chose their best approach taking into consideration their national situation. Some preferred to postpone the start for 2.5 months such as Spain, others such as Belgium and Greece intensified recruiting some of the target groups, such as specialists and patients.

The circumstances were particularly challenging for the research teams. Researchers working in academia in six countries were working to meet the needs to adapt curricula to distance learning, some researchers who belonged to high risk groups were in lockdown and unable to actively canvas respondents. Colleagues working at primary care services were overwhelmed with other tasks.

The last country to initiate recruitment was the Netherlands, which only started surveying pharmacists in June, and prescribers and patients in July 2020.

Reaching out to patients through pharmacies became difficult, as in many countries access to pharmacies was restricted or further strained. Many teams opted to use social media and to post links to the questionnaires in closed Facebook groups.

The subsequent delays in recruitment also meant that more time was needed to try and obtain the target response rates. According to the initial timeline all the surveys would have been completed by end May but this was extended to end September.

Table 2. Study milestones

	BE	*DK*	*GR*	*LV*	*NL*	*PT*	*SI*	*ES*

Questionnaire translated	2/11/2019	12/12/2019	6/12/2019	16/12/2019	13/12/2020	17/12/2019	17/12/2019	10/12/2019
Ethical approval or waiver received	9/03/2020	2/12/2020	17/03/2020	31/10/19	4/05/2020	19/12/2019	23/12/2019	26/02/2020
Planned start date for recruitment	02/2020	02/2020	02/2020	02/2020	02/2020	02/2020	02/2020	02/2020
Actual start date for recruitment	03/2020	03/2020	03/2020	03/2020	06/2020	03/2020	03/2020	15/05/2020
Planned end of Recruitment	30/05/2020	30/05/2020	30/05/2020	30/05/2020	30/05/2020	30/05/2020	30/05/2020	30/05/2020
Actual end of recruitment	09/2020	09/2020	08/2020	09/2020	09/2020	09/2020	09/2020	09/2020
Data translation of responses to open questions completed	25/09/2020	24/9/2020	3/09/2020	27/9/2020	7/10/2020	21/9/2020	15/09/2020	14/9/2020

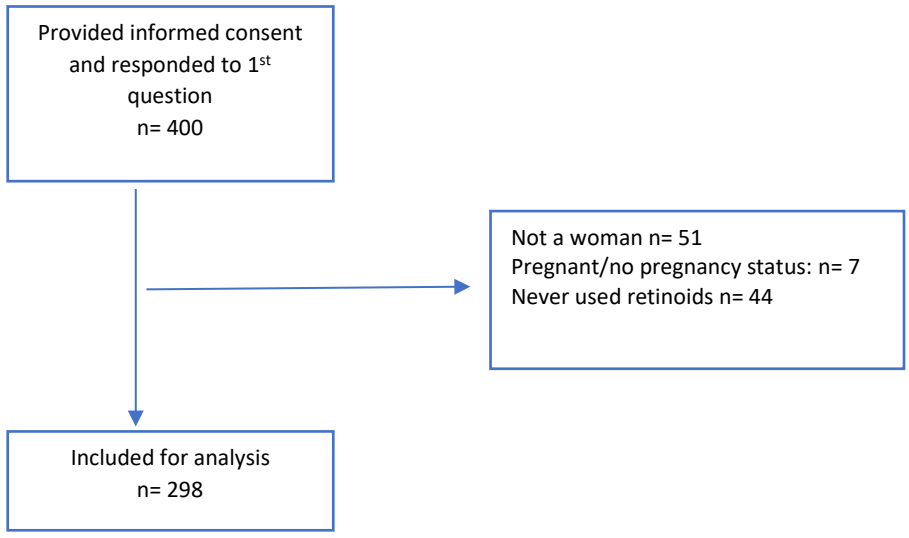
6.1.6 Study sample

6.1.6.1 Patients

A total of 400 respondents filled in the survey. The responses of all patients who did not identify as female or who did not provide information about their gender were excluded from the analysis, as well as any responses from women who were or might be pregnant, or who had never used oral retinoids, or who were not in childbearing age. Finally, the responses of 298 female patients using or having used oral retinoids were included in our study sample.

We considered that it was unethical to ask women who were/could be pregnant to fill a survey which assessed awareness about teratogenic harms arising from a medicine they were taking. There was an inherent risk that the survey could be their first source of risk awareness, therefore we opted to exclude them from answering questions and refereed them promptly to prescribers so that they could be further informed.

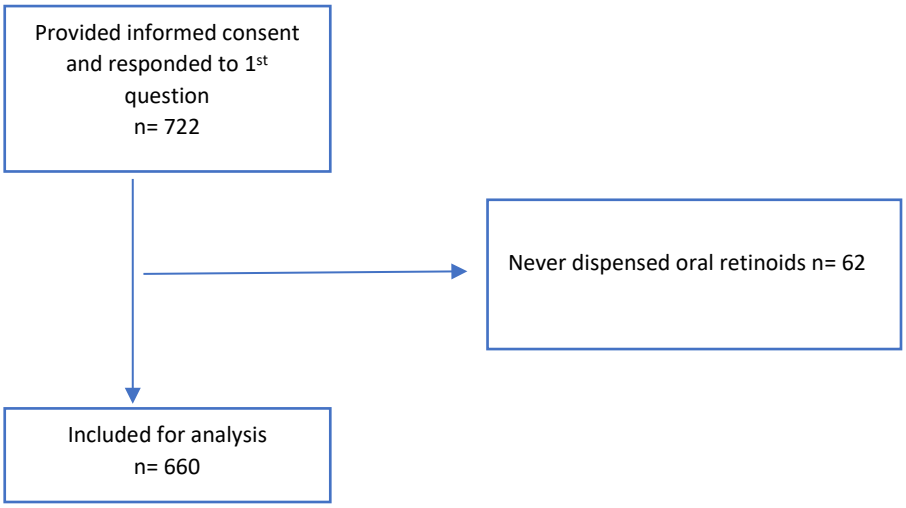
Figure 1 Flowchart of response patients



6.1.6.2 Pharmacists

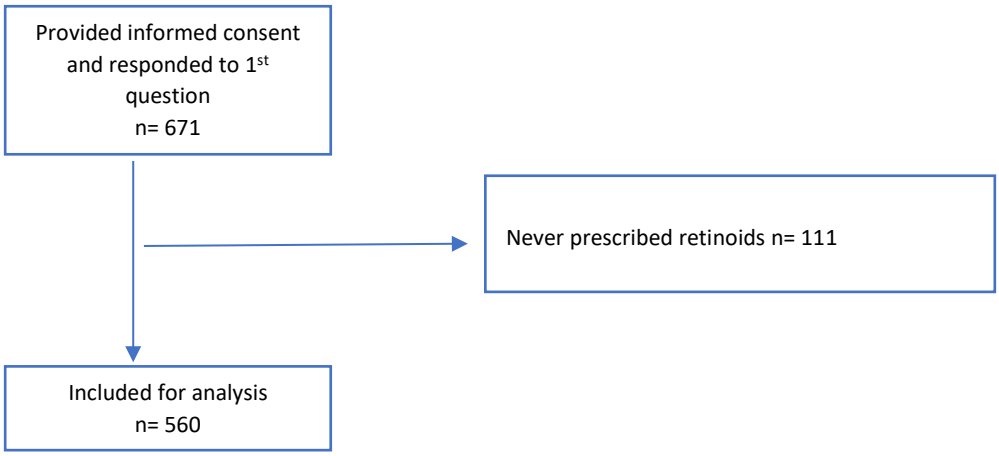
A total of 722 pharmacists responded to our survey. 62 pharmacists had never dispensed oral retinoids and were therefore excluded. The remaining responses from 660 pharmacists were included for analysis.

Figure 2 Flowchart of response pharmacists


Provided informed consent and responded to 1st question
n= 722
Never dispensed oral retinoids n= 62
Included for analysis
n= 660

6.1.6.3 Prescribers

The survey for prescribers was filled in by 671 respondents. The responses from 111 physicians who had never prescribed nor consulted a patient about oral retinoids were excluded from the analysis. The remaining responses for 560 respondents prescribing oral retinoids were included for analysis.

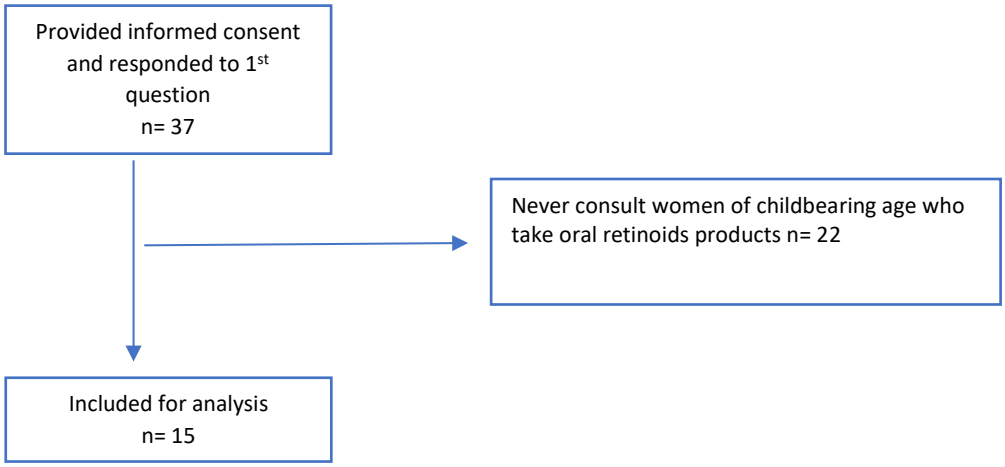


6.1.6.4 Midwives

As the questionnaires for midwives were prepared independently by the national teams in Spain and in the Netherlands, their results are also presented separately.

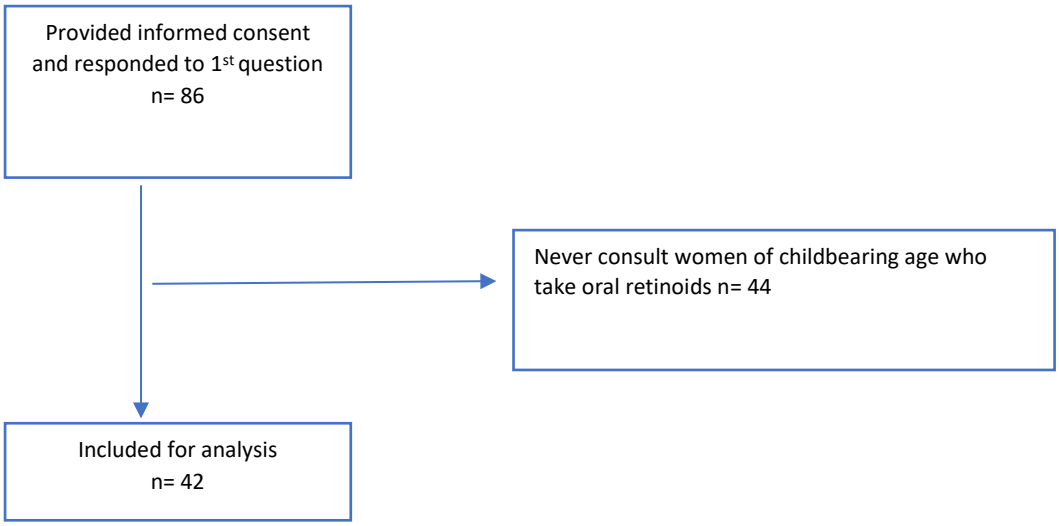
6.1.6.5 Spain

The survey for midwives was filled in by 37 respondents in Spain. The responses from 22 midwives who had never consulted women who took oral retinoids were excluded from the analysis. The remaining responses for 15 respondents were included for analysis.



6.1.6.6 The Netherlands

The survey for midwives was filled in by 86 respondents in the Netherlands. The responses from 44 midwives who had never consulted women who took oral retinoids were excluded from the analysis. The remaining responses for 42 respondents were included for analysis.



6.1.7 Quality Control

Efforts to improve the study quality were both implemented during the design of the study and during the analysis of the data.

The development of the questionnaires and pre-testing was done in iterative cycles by two national teams. Translations of the questionnaires were done in an iterative process with feedback to the study coordinators.

For the closed questions, the online questionnaire system included algorithms that automatically excluded responders who did not fulfil inclusion criteria (e.g., male patients in the patient questionnaire, doctors who did not prescribe, pharmacists who did not dispense).

For the open questions, national teams analysed responses carefully, in order to correct typos or words/expressions that could result in misunderstandings. The translations of the responses to the free-text questions were cross-checked by another member of the national team.

6.1.8 Analysis

Data analyses were descriptive in nature. Continuous variables were described using count, mean, standard deviation, median, and range. Categorical variables were described as counts and percentages. Free text answers were first translated into English by native speakers. Then they were coded by other 2 researchers through mind-mapping of key components. Subsequently, they were grouped into themes and listed, then checked by a third researcher. Following that, each national team checked again the coding and listing for the answers, selecting those relevant and most frequent to their country. All quantitative data were analysed using the statistical programme R.

6.2 Study design: Semi-structured interviews

In two countries (The Netherlands and Portugal) we aimed to hold telephone interviews with 6-8 patients (per country) from a convenience sample, with a range in age and varied educational background; including, when possible, both individuals who had used oral retinoids during pregnancy, and women who discontinued its use before getting pregnant.

The patients to be included in the interviews were identified from pharmacy databases and the first contact was established by their community pharmacist. When patients agreed to the interview, they were contacted by experienced researchers in participating countries.

The interviews were semi-structured based on similar topics and themes as the questionnaires, but seeking to obtain more insight about how the information about teratogenicity had been provided, when and how frequently. We also sought to elicit suggestions for the dissemination of such information to women of childbearing age, as well as collecting experiences from oral retinoid patients about their recollection and use of pregnancy prevention measures. Audio recordings from the interviews were transcribed verbatim and any personal data was anonymized.

In Portugal, a total of 3 pharmacies were contacted, 5 women were identified from the pharmacies. Two additional women were identified through personal contacts. From the seven women contacted, six agreed to be interviewed.

In the Netherlands, 3 pharmacies were invited to identify female users of oral retinoids in the fertile age and who had received at least one prescription over the past 12 months. 21 users were identified, mean age 20 years-old, age range 17 to 24 years-old. From these, nine women invited by email, six by email and telephone, another six only by telephone. From these, five did not respond, other 14 mentioned not to have time or not to be interested in participating. Although they agreed to the importance of preventing pregnancy when taking oral retinoids, the later claimed to have received sufficient information on retinoid risks and to being drained from all the form-filling completed during treatment. The remaining two agreed to be interviewed, but eventually only one accepted the researchers' request and responded to our questions.

For more details about the interview script, please consult ANNEX 7.

Table 3. Interview study milestones

	NL	*PT*
Interview script completed, English version	09/2020	09/2020
Script translated	10/2020	05/10
Planned start date for recruitment	07/2020	1/07/2020
Actual start date for recruitment	1/10/2020	5/10/2020
Planned end of Recruitment	11/10/2020	11/10/2020
Actual end of recruitment	11/2020	5/11/2020
Planned start of data transcription	N.A.	5/10/2020
Actual start of data transcription	N.A.	10/10/2020
Planned start of data translation and coding	N.A.	01/09/2020
Actual start of data translation and coding	N.A.	4/11/2020
Planned start of data analysis	N.A.	10/2020
Actual start of data analysis	N.A.	10/11/2020
Planned end of data analysis	N.A.	10/2020
Actual end of data analysis	N.A.	26/11/2020

6.2.1 Analysis

For the interview data, the analysis involved an inductive content analysis based on a close line-by-line reading of the responses and a conceptual coding scheme developed based on the major themes in the interview guides. Transcripts were categorized individually by two coders in Portugal and in the

Netherlands, in native language. Coders from all countries met prior to the analysis to predefined categories and codes to be used. They met again to evaluate the categories identified and to write up the results using illustrative quotes.

6.2.2 Information storage and management

All anonymized surveys and data from the interviews will be hosted in a server of the University of Utrecht, The Netherlands, and will be kept for 10 years. The interview recordings were destroyed once the data had been transcribed.

Section 7: Results

7.1. Main Results: surveys included per country

Table 4. Overview response per country

Total responders (n)			BE	DK	GR	LV	NL	PT	*SI*	ES
Patients	298		48	51	63	17	21	26	30	42
Pharmacists	660		71	96	62	51	88	133	60	99
Prescribers	560		48	63	98	48	114	104	35	50
Midwives	57		n.a.	n.a.	n.a.	n.a.	42	n.a.	n.a.	15

The patient response was rather low in Latvia (N=17) and in the Netherlands (N=21) and high in Greece (N=63). For the remaining countries, responses ranged from 26 to 51 patients. In most countries, more pharmacists responded than prescribers, except for Greece and the Netherlands. Annex 8 gives an overview of the representativeness of the respondents to the surveys per country.

7.1.1 Patients

Table 5. Characteristics of responding patients

	Overall		*BE*	*DK*	*GR*	*LV*	*NL*	*PT*	*SI*	*ES*
***Total** (N)*	298		48	51	63	17	21	26	30	42
Avg age Age (range)	26 (16-51)		25 (17-50)	26 (16-46)	24 (17-49)	28 (20-36)	27 (17-51)	30 (18-51)	27 (16-51)	26 (17-43)
***Current or former users of** (n (%)):*										
Isotretinoin	284(95%)		47 (98%)	50 (98%)	63 (100%)	17 (100%)	21 (100%)	23 (88%)	23 (77%)	40 (95%)
Acitretin	12(4%)		1 (2%)	1 (2%)	0	0	0	3 (12%)	6 (20%)	1 (2%)
Alitretinoin	2 (0,5%)		0	0	0	0	0	0	1 (3%)	1 (2%)
***Highest achieved education** (n (%)):*										
Primary	13 (4%)		0	5	1 (1%)	0	1 (5%)	0	6 (20%)	0
Secondary	70 (23%)		1 (2%)	14 (27%)	25 (40%)	3 (18%)	8 (23%)	9 (35%)	7 (23%)	3 (7%)
Professional	55 (18%)		23 (48%)	9 (18%)	3 (5%)	2 (12%)	6 (29%)	0	3 (10%)	9 (21%)
Undergraduate	111 (37%)		24 (50%)	19 (37%)	24 (38%)	9 (53%)	0	10 (38%)	12 (40%)	13 (31%)
Postgraduate	42 (14%)		0	2 (4%)	7(11%)	3 (18%)	6 (29%)	7 (27%)	1 (3%)	16 (38%)
Other	7(2%)		0	2 (4%)	3(5%)	0	0	0	1 (3%)	1 (2%)

The mean age of female users of retinoids across all countries was 26 and users in most countries have a comparable average age and range. Most patients (95%) were using or had used isotretinoin. The use of acitretin was relatively high in Slovenia (20%) and Portugal (12%) when compared to other countries. Alitretinoin and tretinoin were used by a small number of patients, only in Greece, Slovenia and Spain. The patients' educational levels varied across countries, with all educational levels being present in our sample but not within all countries.

Table 6. Awareness about risks and sources of information

	Overall		*BE*	*DK*	*GR*	*LV*	*NL*	*PT*	*SI*	*ES*
***Total** (N)*	298		48	51	63	17	21	26	30	42
***Aware of risks** (n (%)):*										
No	7(2%)		2 (4%)	1 (2%)	2 (3%)	0	0	0	2 (7%)	0
Yes	285(96%)		46 (96%)	49 (98%)	61 (97%)	17 (100%)	21 (100%)	25 (96%)	25 (83%)	41 (98%)
missing	6(2%)		0	1	0	0	0	1	3	1
If YES, source of information* [2]										
GP	56 (20%)		5	23	4	1	8	4	2	9
Dermatologist	225 (79%)		38	34	46	16	17	13	23	38
Pharmacist	90 (31%)		22	19	5	4	18	5	12	5
Internet	77 (27%)		12	21	10	9	10	2	10	3
Patient Information leaflet	150 (52%)		21	32	23	16	18	10	16	14
Packaging	66 (23%)		14	15	7	6	8	3	9	4
Patient brochure	25 (9%)		7	0	2	2	13	0	1	0
Reminder card	8 (3%)		0	5	0	0	1	0	1	1
Risk Acknowledgment form	47 (16%)		4	3	3	8	12	0	10	7
Other	17 (6%)		5	1	2	0	0	6	0	3

***Multiple choices possible**

Most patients were aware about the risks associated with the use of oral retinoids during pregnancy. Patients indicated that they had become beware about the risks from information provided by their dermatologist, followed by the information included in the Patient Information Leaflet. Pharmacists also played an important role, particularly in Belgium, Denmark and the Netherlands. GPs seemed to have a minor role in informing the patient about the risks in most countries, except in Denmark.

About one fourth (23%) of the patients mentioned to have noticed the warnings on the outer packaging. The patient brochure and the risk acknowledgement form were mentioned less frequently as sources of information. Nevertheless, in the Netherlands most patients recalled these educational materials. The reminder card was seldom mentioned across all countries.

The most frequently cited alternative source of information was academic knowledge (GR) (PT) (BE). Other sources named were the media, through news or dedicated TV programmes, or social networks. Some patients also mentioned not to remember where they had obtained the information.

[2] ***Multiple choices possible**

Table 7. Educational materials received and their sources

	Overall		BE	DK	GR	LV	NL	PT	SI	ES
Total (N)	298		48	51	63	17	21	26	30	42
Received patient brochure*	21 (7%)		7	n/a	n/a	n/a	10	0	4	n/a
from GP	1 (5%)		1	n/a	n/a	n/a	0	0	0	n/a
from Dermatologist	18(86%)		7	n/a	n/a	n/a	7	0	4	n/a
from Pharmacy	4(19%)		1	n/a	n/a	n/a	3	0	0	n/a
from Other	0		0	n/a	n/a	n/a	0	0	0	n/a
Received reminder card*	13 (4%)		1	3	2	2	1	0	3	1
from GP	0		0	0	0	0	0	0	0	0
from Dermatologist	13 (100%)		1	3	2	2	1	0	3	1
from Pharmacy	0		0	0	0	0	0	0	0	0
from Other	0		0	0	0	0	0	0	0	0
Reviewed risk Acknowledgement form*	59 (20%)		4	5	6	12	12	n/a	7	13
with GP	5(8%)		0	2	0	0	1	n/a	0	2
with Dermatologist	51(86%)		4	2	6	12	9	n/a	7	11
with Other	3 (5%)		0	1	0	0	2	n/a	0	0
Signed a risk acknowledgement form*	64 (21%)		6	4	2	11	14	n/a	10	17
with GP	5(8%)		0	1	0	0	4	n/a	0	0
with Dermatologist	59(92%)		6	3	2	11	10	n/a	10	17
with Other	0		0	0	0	0	0	n/a	0	0
Warning symbol	145 (49%)		30(63%)	25(49%)	22(35%)	12(71%)	13(62%)	14(54%)	15(50%)	14(33%)
Read Patient Information Leaflet	**222(74%)**		**33(69%)**	**45(88%)**	**43(68%)**	**17(100%)**	**17(81%)**	**22(85%)**	**18(60%)**	**27(64%)**
If so, did you read about use during pregnancy?										
Yes	211 (95%)		31(94%)	44(98%)	41(95%)	17(100%)	17(100%)	19(86%)	18(100%)	24(89%)
No	2(1%)		0	0	1(2%)	0	0	1(4%)	0	0
Not sure	9 (4%)		2(6%)	1(2%)	1(2%)	0	0	2(9%)	0	3(11%)
Did you notice a QR code?	13(6%)		0	2(4%)	2(5%)	3(18%)	1(6%)	n/a	2(11%)	3(11%)
Discussed contraceptive measures*	144 (48%)		16	36	19	12	12	12	12	25
If so, with whom?										
with GP	32 (22%)		3	18	3	0	2	2	0	4
with Dermatologist	116 (81%)		15	24	15	11	10	9	9	23
with Pharmacy	17 (12%)		1	3	5	0	4	2	1	1
with Other	17 (12%)		0	5	4	4	0	1	2	1
Changed medication because of pregnancy	1		0	1	0	0	0	0	0	0
No	21(7%)		4	3	7	0	0	2	3	2
missing	12(4%)		2	1	0	0	0	1	5	3

A few patients in Belgium, the Netherlands, Portugal and Slovenia reported to have received a Patient Brochure, mostly from their dermatologist and/or their pharmacist. About 20% of the patients had reviewed and/or signed the Risk Acknowledgement Form at their dermatologist. Interestingly, patients recruited in the Netherlands indicated that they have also reviewed and/or signed the Risk Acknowledgment Form at the pharmacy.

Almost all patients recalled having read the patient information leaflet (PIL) but they were mostly unaware of the QR code. Only very few (13 in total, 4% of the respondents) had received the reminder card from their dermatologist.

Half of the patients indicated that they had discussed contraceptive measures in relation to their retinoid use, 81% with their dermatologist and 22 % with their GP. In some cases, contraceptive measures had been discussed with the pharmacist (12%) or someone else (12%). In this case, patients mentioned to have it discussed with their gynaecologist (GR)(PT)(SI) or their endocrinologist.

21 patients (7% of the total responding patients) indicated that they had not changed their medication when they were planning to become or had become pregnant.

Table 8. Pregnancy testing before, during and after treatment

	Overall		BE	DK	GR	LV	NL	PT	SI	ES
Total (N)	298		48	51	63	17	21	26	30	42
Pregnancy testing before initiating treatment										
yes	81 (27%)		8(17%)	23(45%)	5(8%)	8(47%)	12(57%)	3(12%)	2(7%)	20(48%)
no	142(48%)		26(54%)	16(31%)	35(56%)	6(35%)	6(29%)	18(69%)	18(60%)	17(40%)
don't know	5 (2%)		0	1(2%)	0	1(6%)	0	1(4%)	1(3%)	1(2%)
not relevant	46 (15%)		11(23%)	9(18%)	17(27%)	2(12%)	3(14%)	3(12%)	1(3%)	0
missing	24(8%)		3(6%)	2(4%)	6(10%)	0	0	1(4%)	8(27%)	4(10%)
Pregnancy testing during treatment										
yes	64 (22%)		4(8%)	24(47%)	2(3%)	9(53%)	12(57%)	1(4%)	2(7%)	10(24%)
no	159(53%)		31(65%)	14(27%)	40(63%)	6(35%)	6(29%)	20(77%)	17(57%)	25(60%)
don't know	7(2%)		1(2%)	1(2%)	0	0	0	1(4%)	1(3%)	3(7%)
not relevant	44(15%)		9(19%)	10(20%)	15(24%)	2(12%)	3(14%)	3(12%)	2(7%)	0
missing	24(8%)		3(6%)	2(4%)	6(10%)	0	0	1(4%)	8(27%)	4(10%)
If yes, how often?										
At least every month	41 (64%)		3	20	1	7	7	0	1	2
Less than once a month	23 (36%)		1	4	1	2	5	1	1	8
Pregnancy testing after stopping treatment										
yes	15 (5%)		4(8%)	2(4%)	0	3(18%)	3(14%)	0	1(3%)	2(5%)
no	184 (62%)		28(58%)	26(51%)	42(67%)	8(47%)	12(57%)	19(73%)	18(60%)	31(74%)
don't know	13 (4%)		2(4%)	2(4%)	1(2%)	1(6%)	0	2(8%)	0	5(12%)
not relevant	62(21%)		11(23%)	19(37%)	14(22%)	5(29%)	6(29%)	4(15%)	3(10%)	0
missing	24 (8%)		3(6%)	2(4%)	6(10%)	0	0	1(4%)	8(27%)	4(10%)
If yes, how often?										
At least every month	4 (27%)		0	1	0	3	0	0	0	0
Less than once a month	11 (73%)		4	1	0	0	3	0	1	2

Asking about pregnancy testing in relation to treatment with retinoids resulted in a diverse picture. The number of patients tested for pregnancy at the start of the retinoid treatment was 27% on average, however, variation exists across countries rendering the above percentage unfit to describe the actual status of each country. In Belgium (17%), Greece (8%), Portugal (12%) and Slovenia (7%),

less than 20% of the patients reported to have been tested at the start of treatment, whereas this percentage was greater than 45% in other countries, such as Denmark (45%), Latvia (47%), the Netherlands (57%) and Spain (48%). Pregnancy testing while on treatment showed a comparable variation between countries, with Denmark exhibiting a percentage of 47%, while the same percentage is much lower in some other countries such as Belgium (8%), Greece (3%), Portugal (4%) and Slovenia (7%). When patients were tested during treatment, this was mostly reported to occur monthly for 64%. After stopping their treatment, only 15% of the patients had had a test, whereas the majority of 62% did not. For those who did test after stopping treatment, 73% reported doing it less than once a month. A substantial number of patients answered that pregnancy testing was not relevant. Many women referred not being sexually active as the reason to consider irrelevant any pregnancy testing before starting treatment (DK) (GR) (PT) (SI) (BE) (LV), during treatment (GR) (PT) (SI) (BE) (LV), after stopping treatment (BE) (LV). Additional reasons were:

- Unwillingness to become pregnant (BE)
- Unlikely or impossible to become pregnant
- Hysterectomy (DK)
- Menopause (PT)
- Contraceptive choice excluded need for testing (GR)
- The fact that they were still on treatment (DK) (GR) (PT) (BE).

Table 9. Pregnancies and treatment

	Overall		*BE*	*DK*	*GR*	*LV*	*NL*	*PT*	*SI*	*ES*
Total (N)	298		48	51	63	17	21	26	30	42
Pregnant in 2017 or earlier	32(11%)		5	10	2	2	4	2	3	4
If yes, used retinoids	1(3%)		0	0	0	0	0	0	1	0
Pregnant in 2018-2019	10(3%)		1	4	0	0	0	5	0	0
If yes, used retinoids	2(20%)		0	2	0	0	0	0	0	0

A total of 42 out of the 298 respondents (15%) got pregnant either before or after 2018. Despite the small sample, we ran an additional analysis to ascertain the awareness of women who became pregnant while on treatment. In total, 3 patients (7% of total pregnant patients) reported having used retinoids while being pregnant, 1 in Slovenia before 2018 and 2 in Denmark after 2018. All three women reported to be aware about the teratogenic risks of oral retinoids.

Table 10. Contraception methods and perceptions

	Overall		*BE*	*DK*	*GR*	*LV*	*NL*	*PT*	*SI*	*ES*
Total (N)	298		48	51	63	17	21	26	30	42
Using contraception										
Yes *No* *No need*	158(53%) 80(27%) 32(11%)		34(71%) 5(10%) 5(10%)	30(59%) 8(16%) 11(22%)	24(38%) 24(38%) 9(14%)	13(76%) 3(18%) 1(6%)	15(71%) 4(19%) 2(10%)	17(65%) 6(23%) 1(4%)	8(27%) 11(37%) 3(10%)	17(40%) 19(45%) 0
missing	28(9%)		4	2	6	0	0	2	8	6
Type of contraception*										
Oral contraceptive pill	93 (58%)		24	20	6	7	11	12	2	11
Contraceptive patch	0		0	0	0	0	0	0	0	0
IUD	24 (15%)		8	8	0	1	4	1	0	2
Diaphragm	1 (0,6%)		0	0	0	0	0	0	1	0

Condom	57 (36%)		8	5	21	7	2	4	5	5
Injected contraceptive	1 (0,6%)		0	0	0	0	0	1	0	0
Sterilisation	0		0	0	0	0	0	0	0	0
Sterilisation partner	0		0	0	0	0	0	0	0	0
Morning after pill	1 (0,6%)		1	0	0	0	0	0	0	0
Temperature/rhythm	2 (1%)		0	0	0	1	0	0	1	0
Interrupted intercourse	8 (5%)		1	1	3	1	0	0	2	0
Other	2 (1%)		0	2	0	0	0	0	0	0
For women that use contraception: Are you careful to use contraception when using retinoids										
Agree *Disagree* *Neutral*	124 (79%) 12 (7%) 22 (14%)		25(74%) 3(9%) 6(17%)	22(73%) 3(10%) 5(17%)	17(71%) 1(4%) 6(25%)	12(92%) 0 1(8%)	12(80%) 2(13%) 1(7%)	13(76%) 2(12%) 2(12%)	8(100%) 0 0	15(88%) 1(6%) 1(6%)

***Multiple choices possible**

The percentage of patients who declared to use contraception was 53%, whereas 27% of the patients indicated that they did not use contraceptive measures and another 11% that they did not need contraception. In most countries the percentage of contraception users was fairly above 50%. However, in Greece (38%), Slovenia (27%) and Spain (40%), patients who reported using contraception were a minority.

The most frequently used methods were oral contraceptive pills (58%), condoms (36%) and IUD (15%). Many patients (79%) agreed that they were careful to use contraception when using retinoids. However, in Denmark (43%), Greece (27%), Slovenia (27%) and Spain (38%) the percentages of patients who agreed with this statement where under 50%. Given the small samples at national level, we should be careful to impute any further interpretation.

Some women referred not being sexually active (GR) (BE) (LV) as the reason to consider irrelevant any information about contraception use. Others also mentioned to already be on the contraceptive pill to cope with menstrual pain, or that their current use of the pill was not related to their prior use of oral retinoids.

Table 11. Change in retinoid use after 2018

	Overall		*BE*	*DK*	*GR*	*LV*	*NL*	*PT*	*SI*	*ES*
Total (N)	298		48	51	63	17	21	26	30	42
Medication changed										
not at all	110 (37%)		29(60%)	18(35%)	15(24%)	5(29%)	14(67%)	8(31%)	3(10%)	18(43%)
not sure	61(21%)		3(6%)	16(31%)	14(22%)	7(41%)	1(5%)	3(12%)	10(33%)	7(17%)
certainly yes	24(8%)		4(8%)	9(18%)	2(3%)	3(18%)	1(5%)	2(8%)	3(10%)	0
stopped more than 2 years ago	70 (23%)		8(17%)	4(8%)	26(41%)	2(12%)	5(24%)	9(35%)	4(13%)	12(29%)
missing	33(11%)		4(8%)	4(8%)	6(10%)	0	0	4(15%)	10(33%)	5(12%)

Only 8% of the patients indicated that their medication had certainly been changed after 2018 whereas 37% reported no changes. A substantial number of patients was unsure about this (21%) or had stopped using the medication longer than two years ago (23%).

Patients reported the following changes to their medication use after 2018:

1. Stopping treatment:

- no more use of retinoids after 2018, (GR)
- no more use due to pregnancy: abortion took place; IUD displaced resulting in unplanned pregnancy (DK)

2. Adjusting treatment either by reducing dosage or frequency of use. (BE) (PT)
3. Affecting contraception choices:
   - Using IUD to prevent pregnancy
   - Being more careful to avoid pregnancy (DK)(GR)(PT)(BE)(LV)
   - Using the contraceptive pill (BE)
   - Concomitant use of oral contraceptive pill and condom (BE)
   - Unwilling to use hormonal contraception, opting to have frequent pregnancy tests.

We were interested in assessing whether there were differences in contraception use across different age strata.

Table 12. Contraception use across age strata in patients using oral retinoids

	Overall		*BE*	*DK*	*GR*	*LV*	*NL*	*PT*	*SI*	*ES*
***Total** (N)*	298		48	51	63	17	21	26	30	42
<24 years old	130		26	20	29	3	12	9	13	18
24-40 years old	145		20	27	32	14	7	11	13	21
>40 years old	23		2	4	2	0	2	6	4	3
No users of contraception	**80(27%)**		**5(10%)**	**8(16%)**	**24(38%)**	**3(18%)**	**4(19%)**	**6(23%)**	**11(37%)**	**19(45%)**
<24 years old	34 (42%)		4	1	10	0	0	4	5	10
24-40 years old	38 (48%)		1	5	12	3	2	1	5	9
>40 years old	8 (10%)		0	2	2	0	2	1	1	0
Current contraception use	**158(53%)**		**34(71%)**	**30(59%)**	**24(38%)**	**13(76%)**	**15(71%)**	**17(65%)**	**8(27%)**	**17(40%)**
Effective Contraception[1]	***119(75%)***		***32(94%)***	***28(93%)***	***5(21%)***	***8(62%)***	***15(100%)***	***16(94%)***	***3(37%)***	***12(71%)***
<24 years old	54 (45%)		16	9	5	2	11	4	1	6
24-40 years old	60 (50%)		15	19	0	6	4	10	2	4
>40 years old	5 (5%)		1	0	0	0	0	2	0	2
Less Effective Contraception[2]	***39(25%)***		***2(6%)***	***2(7%)***	***19(79%)***	***5(38%)***	***0***	***1(6%)***	***5(62%)***	***5(29%)***
<24 years old	10 (26%)		0	1	6	1	0	1	1	0
24-40 years old	28 (72%)		2	1	13	4	0	0	3	5
>40 years old	1 (2%)		0	0	0	0	0	0	1	0

[1] This includes one of the following options: oral contraceptive pill, contraceptive Patch, intrauterine device, diaphragm, Injected Contraceptive, Sterilisation, Sterilisation of partner
[2] This includes one of the following options: condom, morning after pill, temperature/rhythm, interrupted Intercourse, other.

Almost a third of women who responded to our survey (27%) did not use any form of contraception, with Spain holding the highest percentage (45%), followed by Greece (38%) and Slovenia (37%). Of the 158 women that used contraception, 119 (75%) used an effective form (oral contraceptive, contraceptive patch, intrauterine device, injected contraceptive, sterilisation or partner sterilisation), while 39 (25%) used a less effective form of contraception, such as condoms. Overall, 119 (40%%) of all women either used no contraception or a less effective method of contraception. No significant differences in the use of contraception between age groups were observed.

7.1.2 Pharmacists

Table 13. Pharmacists' characteristics

	Overall		BE	DK	GR	LV	NL	PT	SI	ES
Total	660		71	96	62	51	88	133	60	99
Age (avg)	39		34	38	39	31	42	38	40	43
Age (range)	21-69		23-67	25-68	24-65	24-53	25-64	21-66	25-69	25-69
Gender										
Female	517 (78%)		56(79%)	72(75%)	43(69%)	45(88%)	56(64%)	114(86%)	51(85%)	80(81%)
Male	140 (21%)		15(21%)	24(25%)	19(31%)	6(12%)	32(36%)	8(13%)	8(13%)	18(18%)
No gender statement	3(1%)		0	0	0	0	0	18(13%) 1 (1%)	1(2%)	1(1%)
Type of pharmacist										
Community-based	645(98%)		71(100%)	96(100%)	60(96%)	49(96%)	83(94%)	127(95%)	60(100%)	99(100%)
Hospital-based	7(1%)		0	0	1(2%)	2(4%)	0	4(3%)	0	0
Other	8 (1%)		0	0	1(2%)	0	5(6%)	2(2%)	0	0
Work experience										
0-5 years	222(34%)		31(44%)	49(51%)	19(31%)	24(47%)	20(23%)	38(28%)	18(30%)	23(23%)
6-10 years	128 (19%)		16(23%)	14(15%)	12(19%)	19(37%)	18(20%)	24(18%)	6(10%)	19(19%)
11-20 years	181(27%)		16(23%)	21(22%)	20(32%)	5(10%)	18(20%)	46(35%)	23(38%)	32(32%)
21-30 years	88 (13%)		4(6%)	6(6%)	5(8%)	3(6%)	25(28%)	20(15%)	8(13%)	17(17%)
> 31 years	41 (6%)		4(6%)	6(6%)	6(10%)	0	7(8%)	5(4%)	5(8%)	8(8%)
Frequency of dispensing retinoids										
At least once a week	71 (11%)		5(7%)	23(24%)	5(8%)	3(6%)	18(20%)	10(8%)	3(5%)	4(4%)
Multiple times/month	233 (35%)		29(41%)	52(54%)	20(32%)	9(18%)	47(54%)	46(34%)	18(30%)	12(12%)
Monthly or less	356 (54%)		37(52%)	21(22%)	37(60%)	39(76%)	23(26%)	77(58%)	39(65%)	83(84%)
Did you ever see/suspected a malformation with any medication	10 (2%)		**4**	0	0	1	2	3	0	0
Were those suspected malformations caused by retinoids?										
Yes	3		1	0	0	0	0	2	0	0
No	5		2	0	0	0	2	1	0	0
Don't know	2		1	0	0	1	0	0	0	0
Are these women in fertile age*										
15-17	415 (63%)		53	68	27	33	75	78	38	43
18-44	594 (90%)		68	83	59	48	83	114	56	83
45-50	269 (41%)		27	38	10	16	66	49	34	29
51-55	89 (13%)		9	6	1	1	26	21	17	8
Other	30 (5%)		0	4	3	1	7	4	2	9
missing	41 (6%)		3	9	0	2	2	16	3	6

***Multiple choices possible**

Nearly all responding pharmacists (98%) worked in a community based setting. The gender ratios reflect the situation in most European countries where female pharmacists are the majority. The variation in age and work experience shows patterns comparable across the countries included in our study and further stresses that all categories were represented in our sample. In some countries, the group of pharmacists had longer work experience (Netherlands , Spain), whereas pharmacists in other countries were younger and thus had shorter work experience (Denmark; Latvia).

Most pharmacists dispensed retinoids on a monthly (54%) or weekly basis (35%). Dispensing frequency was highest in Denmark and the Netherlands and lowest in Latvia and Spain.

Three pharmacists indicated to have seen or suspected malformations in the offspring of their patients caused by retinoid use. Their perception of the range of fertile age for women was rather divergent.

A substantial part of the pharmacists did not consider teenagers under 18 years (37%) and women above 45 years (54%) to be of fertile age.

Table 14. Knowledge of pharmacists about the teratogenicity of retinoids

	Overall		BE	DK	GR	LV	NL	PT	SI	ES
Total	660		71	96	62	51	88	133	60	99
Familiar with teratogenicity										
Yes	648 (98%)		71(100%)	96(100%)	62(100%)	51(100%)	88(100%)	127(96%)	60(100%)	93(94%)
No	5 (1%)		0	0	0	0	0	3(2%)	0	2(2%)
Missing	7 (1%)		0	0	0	0	0	3(2%)	0	4(4%)
Since when familiar										
<2 years	66(10%)		4(6%)	18(19%)	3(5%)	11(22%)	3(3%)	17(13%)	3(5%)	7(7%)
2-5 years	112 (17%)		17(24%)	18(19%)	11(18%)	21(41%)	9(10%)	14(11%)	11(18%)	11(12%)
>5 years	470 (73%)		50(70%)	60(62%)	48(77%)	19(37%)	76(86%)	96(76%)	46(77%)	75(81%)
missing	7 (1%)		0	0	0	0	0	3(2%)	0	4(4%)
How did you become familiar*										
Health authorities	144 (22%)		7	26	1	18	31	17	11	33
Regulatory Agencies	182 (28%)		22	33	4	18	29	37	19	20
Professional Associations	114 (18%)		3	11	1	3	38	26	12	20
Colleagues	132 (20%)		7	23	4	24	30	23	14	7
Professional Journals	121 (19%)		7	6	6	14	47	15	14	12
Pharmaceutical Companies	204 (31%)		13	36	16	11	45	34	32	17
Internet	77 (12%)		4	17	6	16	13	11	8	2
Seminars	50 (8%)		1	0	5	2	3	17	16	6
Academic Knowledge	457 (71%)		66	56	52	40	64	86	28	65
Professional Training	184 (28%)		23	1	18	7	32	52	23	28
Other	31 (5%)		3	8	1	0	7	5	2	5

***Multiple choices possible**

Almost all pharmacists reported to be familiar with the teratogenicity of retinoids. Most pharmacists (73%) were familiar with it for more than five years. In Latvia, most pharmacists (63%) became more recently familiar. Most pharmacists (71%) learned about retinoids' teratogenic potential during academic education. Other important information sources, although to a significantly lesser extent, were the Regulatory Agencies (28%), Pharmaceutical Companies (31%) and Professional Trainings (28%). Health authorities, professional associations and professional journals were considered important in about 20% cases.

In some countries (DK)(PT)(BE), pharmacists stated that they knew about the teratogenicity of retinoids due to personal experience. In the Netherlands pharmacists also indicated the pharmacy information software and the certification bureau as information sources regarding retinoid teratogenicity. One Dutch pharmacist reported a media/broadcast intervention as source of the awareness about oral retinoid teratogenicity in which a local celebrity attributed some of his child's severe health problems to his isotretinoin use.

Table 15. Procedure at most recent dispensing of retinoids

	Overall		BE	DK	GR	LV	NL	PT	SI	ES
Total	660		71	96	62	51	88	133	60	99
Any use of educational material										
Use of:										
Healthcare professional guide	36 (5%)		3(4%)	8(8%)	n/a	n/a	25(28%)	n/a	n/a	n/a
Pharmacist Checklist	102(15%)		3(4%)	5(5%)	n/a	8(16%)	40(45%)	36(27%)	10(17%)	n/a
Warning symbol	451(68%)		54(76%)	43(45%)	48 (77%)	30(59%)	81(92%)	86(65%)	47(78%)	62(63%)
Patient reminder card	91 (14%)		5(7%)	1(1%)	0	8(16%)	23(26%)	32(24%)	4(7%)	18(18%)
DHCP letter	137 (21%)		2(3%)	11(11%)	6(10%)	12(24%)	6(7%)	48(36%)	19(32%)	34(34%)
missing	41 (6%)		3(4%)	9(9%)	0	2(4%)	2(2%)	15(11%)	3(5%)	7(7%)
If not used now, will probably/very probably use in future:										
Healthcare professional guide	53 (26%)		18(28%)	16(20%)	n/a	n/a	19(31%)	n/a	n/a	n/a
Pharmacist Checklist	187 (52%)		19(29%)	27(33%)	n/a	9(22%)	25(54%)	74(90%)	33(70%)	n/a
Warning symbol	139 (83%)		11(79%)	31(70%)	12(86%)	17(89%)	4(80%)	29(91%)	7(70%)	28(93%)
Patient reminder card	267 (51%)		23(37%)	17(20%)	29(47%)	21(51%)	16(25%)	69(83%)	37(70%)	55(74%)
DHCP letter	230 (48%)		11(17%)	19(25%)	37(66%)	15(41%)	16(20%)	62(91%)	26(68%)	44(76%)
Do you counsel women about:										
Effective contraception	508 (77%)		56(79%)	63(66%)	43(69%)	44(86%)	84(95%)	99(74%)	52(87%)	67(68%)
Stop treatment when pregnant	382 (58%)		38(53%)	46(74%)	35(58%)					
Refer to prescriber	475 (72%)		50(70%)	47(49%)	52(84%)	16(31%)	65(74%)	84(63%)	44(73%)	51(51%)
Importance of taking pregnancy test	327 (50%)		20(28%)	59(61%)	22(35%)	39(76%)	69(78%)	96(72%)	39(65%)	66(67%)
all of the above	255 (39%)		14(20%)	55(57%)	19(31%)	23(45%)	69(78%)	58(44%)	27(45%)	41(41%)
				39(41%)		12(24%)	58(66%)	54(41%)		32(32%)
missing	74(11%)		7(10%)	16(17%)	0	5(10%)	3(3%)	24(18%)	5(8%)	14(14%)
Do you counsel different at first VS repeat prescriptions?										
Yes	334 (51%)		39(55%)	52(54%)	27(44%)	18(35%)	72(82%)	47(35%)	28(47%)	51(52%)
No	251 (38%)		25(35%)	28(29%)	35(56%)	28(55%)	13(15%)	61(46%)	27(45%)	34(34%)
missing	75(11%)		7(10%)	16(17%)	0	5(10%)	3(3%)	25(18%)	5(8%)	14(14%)
Did your behavior change since 2018										
Yes	168 (25%)		3(4%)	14(15%)	7(11%)	5(10%)	44(50%)	49(37%)	16(27%)	30(30%)
No	418 (63%)		61(86%)	66(69%)	55(89%)	41(80%)	41(47%)	60(45%)	39(65%)	55(56%)
missing	74(11%)		7(10%)	16(17%)	0	5(10%)	3(3%)	24(18%)	5(8%)	14(14%)
If your behaviour changed since 2018, which measures from prevention program influenced your daily clinical practice*										
Healthcare professional guide	35 (21%)		1(33%)	4(29%)	n/a	n/a	30(68%)	n/a	n/a	n/a
Pharmacist Checklist	59 (35%)		1(33%)	2(14%)	n/a	1(20%)	29(66%)	23(47%)	3(19%)	n/a
Warning symbol	113 (67%)		3(100%)	9(64%)	6(86%)	5(100%)	19(43%)	41(84%)	9(56%)	21(70%)
Patient reminder card	69 (41%)		1(33%)	1(7%)	0	2(40%)	15(34%)	27(55%)	4(25%)	19(63%)
DHCP letter	73 (43%)		0	6(43%)	2(29%)	3(60%)	3(7%)	31(63%)	14(87%)	14(47%)

Prescription Validity Yes No Not sure missing			n/a	n/a	n/a	44 1 0 6	n/a	44 38 16 35	53 2 0 5	n/a

***Multiple choices possible**

From the preventive measures, the majority of pharmacists (68%) used the warning symbol. However, there were notable differences between countries; in Denmark it was a significantly lower percentage (45%) whereas it was significantly higher in the Netherlands (92%). On average, the next frequently used measure was the DHCP letter (21%), followed by the Pharmacist Checklist (15%) and the Patient reminder card (14%). Again, a large variation between countries existed. The ranking of most influential measures from the prevention program for daily clinical practice was nearly the same as for the ranking of their use: the most influential was the warning symbol, followed by the DHCP letter and Patient Reminder Card. However, in several countries, pharmacists hardly use the patient reminder card whereas in Portugal and Spain, the patient reminder card has been used to a rather high extent (24% and 18% respectively) and influenced daily practice to a higher extent than in other countries. Only 255 (39%) pharmacists counselled women on all aspects of pregnancy prevention (effective contraception, stopping when pregnant, referring to prescriber when pregnant, highlighting the importance of pregnancy testing). Only 65 (10%) pharmacists adhered to all these pregnancy prevention counselling aspects and delivered a patient reminder card.

Compared to average, the use of the DHCP letter was low in Belgium (3%) and the Netherlands (7%). The Pharmacist Checklist had mostly been used in the Netherlands and Portugal. In the other countries, the use of the Pharmacist Checklist was either very low or not applicable.

Pharmacists not using the educational materials linked it to patients having already discussed risks with their physician (LV) and also to the fact that the pharmacy environment was not suitable in terms of privacy to make the patient comfortable to discuss such issues.

More specifically, when asked the same question about the healthcare professional guide, the most common answers given for not using it were due to lack of awareness (BE) or availability (DK)(BE), as well as the fact that it was unfit for use during the dispensing procedure (BE), due to it being impractical and time-consuming. Furthermore, some mentioned that there was no need for it, as there was already sufficient knowledge on the subject (DK), guidelines were integrated into the pharmacy information software (NL), that the patient needed to sign a statement before dispensing of the product (NL) and that document was useless (BE).

Similarly, for the Pharmacist Checklist, main reasons for not using it were lack of awareness (DK)(BE)(LV) and availability/accessibility (DK)(BE)(LV). Some pharmacists also considered it unfit for the dispensing procedure, as it is not practical (DK) and time consuming (BE). Others thought of it as unnecessary, because there is already enough knowledge available (DK)(LV), patients are already warned by the prescribers (DK), the checklist is already known so they have made their own protocol for retinoid dispensing (NL) and a surveillance signal is implemented to pop up in the pharmacy information software (NL).

Reasons for not using the patient reminder card do not significantly differ from the above. First of all, pharmacists responded that it happens due to lack of awareness (DK)(GR)(BE)(LV) and lack of availability in the pharmacy (DK)(GR)(BE)(LV). Pharmacists also stated that they prefer to warn and advise their patients through verbal communication methods, unless the medication is not collected

by the patients themselves (DK)GR). On the other hand, some thought additional warnings were unnecessary, as it is highly unlikely that patients are insufficiently informed about this issue for which there are many protocols. Lastly, some pharmacists stated that the patient reminder card was unfit for use during the dispensing procedure, since it is often forgotten (NL), it is not practical (DK)(BE) and it is time-consuming (BE).

Last but not least, primary reasons for not using the DHPC were again lack of awareness (GR)(BE) and lack of availability/accessibility (DK)(GR)(BE)(LV), since content was not known (BE) and due to language barriers (BE). Some pharmacists also mentioned that the DHCP is to be read once, so they are not systematically using it (DK)(LV). Others considered it unfit for use during the dispensing procedure, since it is not practical (DK)(BE), it is time consuming (DK)(BE)(LV) and it is only used as a means of legalization of the dispensing procedure. Lastly, some deemed its use unnecessary, since there is enough knowledge available (PT)(BE)(LV), an extensive checklist is already used in the pharmacy for every retinoid dispensing (NL) and information is obtained through the pharmacy information software and any updates to the guidelines would be integrated into the IT system (NL).

For all measures, a substantial part of the pharmacists indicated they would intend to use them in the future. The patient reminder card was indicated as the most likely measure to be used.

The mean percentage of pharmacists who counselled women about effective contraception during the first prescription for an oral retinoid was 77%, with a percentage higher than 65% for every country. A comparable situation was found for referral to the prescriber for further counselling on risks during pregnancy. On average, 72% of pharmacists referred patients to the prescriber. For each country, the percentage was higher than 60%. More than 50% of pharmacists recommended stopping treatment if the patient was pregnant, except in Denmark (49 %) and in Latvia (31 %). Half (50%) of pharmacists also advised about pregnancy testing, again with differences between countries.

About half (51%) of the pharmacists reported to counsel their patients differently at a first dispensing. The approach depends on the level of awareness of the patients (DK)(PT)(BE), whether the prescriber has already informed the patient about the risks and necessity of contraception use and pregnancy tests during treatment (LV), and whether the patient is accompanied by her parents or not (GR)(PT).

During the dispensing of the patient's first retinoid prescription, pharmacists:

- Check where all instructions have been provided by the prescriber and support the advice already given (ES)(GR)(PT)(LV)
- Check whether consent form has been signed by both prescriber and patient (NL)
- Explain the risks and the pregnancy prevention measures (DK)(ES)(GR)(PT)(SL)(LV) including advice to the patient (ES)(GR)(SL)(BE) and guidelines for proper use (SL)(BE).
- Highlight the importance of oral contraception and pregnancy prevention (DK)(PT)(SL)(BE)(LV)
- Go through the checklist (NL) and the pharmacy information leaflet (NL)
- Ask the patient to sign informed consent at the pharmacy (NL)

At the second or subsequent prescriptions, pharmacists:

- Monitor whether instructions are being remembered and followed by the patients (DK)(GR)(PT)(SL)(BE)(LV)
- While some provide basic advice as a reminder (ES)(GR)(PT)(SL)(BE)(LV), others believe that patients are already familiar with the risks and precautions and provide no further information (DK)(GR)(PT)(SL)(BE)(LV). The latter belief might have to do with the fact that patients are not willing to receive the same advice multiple times (DK)(ES)(GR)(PT)(BE)

- Focus on likelihood of pregnancy and contraception use (GR)
- Dispense medicines differently based on what the patient has experienced, with a focus on potential side-effects (DK)
- For patients who receive retinoids for more than a month, explain again safety and teratogenicity (NL)
- Ask the patient to sign informed consent form at the pharmacy (NL)

Since 2018, part of the pharmacists (25%) changed their behaviour when dispensing oral retinoid prescriptions. In Belgium, hardly any pharmacist (4%) indicated to have changed behaviour, whereas this percentage was significantly higher in the Netherlands (50%), Portugal (37%), Slovenia (27%) and Spain (30%).

When reporting changes to practice pharmacists mentioned the list below. Please note that the most frequent responses are in bold font:

- Changes to the **Advice provided, namely:**
    - Advise frequent communication with prescriber (SI)
    - Insist on informing them even though they say they know (ES) (PT)
    - **Improvement in the quality/amount of information provided** (GR) (PT) (SI)(LV)
    - Do not trust only the prescribers to advise/inform patients (GR)
    - **Highlight teratogenicity and risks while taken during pregnancy** (SI)(LV)
    - More aware and careful when dispensing (ES) (PT) (SI)
    - Explain the risks and the need for effective contraception
        - Insist/check the implementation on oral contraception/avoiding pregnancy (GR) (PT) (SI)
        - Recommend the performance of regular pregnancy tests (ES)
    - Use software applications to obtain scientific and administration information about the product (BE)
    - Inform/guide the patients not only during first dispensing but also thereafter (ES) (NL)

- **Changes regarding own/team education, namely:**
    - Gain knowledge by (reading) internet/articles (GR)
    - Increase the awareness/knowledge of the staff (ES) (PT)
    - Created in-house protocol for their pharmacy/organization (NL)

- **Changes regarding the use of materials, namely:**

    - **Provision of materials**
        - Positive change due to the use of the patient reminder card and the pharmacist checklist (PT)
        - Warning symbol helps to recall instructions when dispensing (DK) (ES) (PT)
        - Pharmaceutical companies provide more educational materials (PT)
        - Providing patients with the patient reminder card (ES)
        - Completing the care protocol (Pharmacom) (NL)
        - Reading DHCP Letters (ES)

- **Better communication**
  - Warning symbol provides better communication and improves awareness overall (DK) (GR) (PT)
  - Educational materials promote better communication and provide advice about risks and pregnancy prevention (ES) (PT)
- **Greater awareness**
  - Follow the 7-day prescription validity (ES)
  - Advise follow-up appointments with prescribers
  - Written information enhances verbal communication and increases patients' knowledge and awareness (PT)
  - Strict adherence to dispensing protocols and pregnancy prevention programme (NL)
  - Keep record of each dispensing episode occurred in the pharmacy (NL)
  - Follow the guidelines of local providers of pharmacy information systems (NL)

Pharmacists mentioned the following concerns and barriers to the implementation of the PPP measures (the most frequent responses are in bold font):

1. **Lack of time** (ES) (GR) (BE)

- Patients are in a rush (PT) (LV)
- Long queues at the pharmacy (SI) (LV)
- Short time for attending, also due to COVID measures (PT)

2. **Lack of awareness by pharmacists** (PT) (LV)

- About educational materials/measures
  - **Unaware of patient reminder card** (ES) (GR) (SI) (BE)
  - Unaware of patient reminder card and DHCP (ES) (SI) (BE)
  - **Unaware of the pharmacy checklist** (SI) (BE)
  - Unaware about established measures, only the warning symbol is noticeable (GR) (BE)
- Insufficient information provided by pharmacists to patients (GR)
- Insufficient information provided to healthcare professionals (ES) (GR)
- Insufficient information provided by prescribers to patients (GR)
- Insufficient information from regulatory bodies (GR) (SI)
- Insufficient information from pharmaceutical companies (GR)
- If your manager does not see the benefit of the measures, it is difficult for an employee to do it. (BE)

3. **Lack of resources**

- **Information technology**
  - Low accessibility to these materials through the electronic software of the pharmacy (ES) (BE)
  - Insufficient integration of these materials/tolls into the normal workflow and the software of the pharmacy (ES) (GR) (BE)
  - No standardized handling is possible in the pharmacy information system (NL) (BE)
- **Setting**

- **Lack of intimacy/privacy in pharmacy when dispensing - Topic (pregnancy, sexual life) is delicate to be discussed** (ES) (PT) (SI)

4. Measures are insufficient or inadequate

- Materials are many and not practical (DK) (BE)
- Education materials are not handy (DK) (SI) (BE)
- One form should include all the information (BE)
- All information should be included in the package
- Materials are useless if verbal information is provided (BE)
- If I have A-docs automatically printed from the system, all sorts of unwanted documents are also printed (NL)
- **Lack of accessibility to educational materials during dispensing procedure** (PT)
  - Packages without warning are still on the market
  - **Lack of availability of patient reminder card** (DK) (ES) (GR) (SI) (BE)(LV)
  - Lack of written material for the patient (BE)
  - **Lack of availability of patient reminder card and pharmacy checklist at the pharmacy** (SI)(LV)

5. Patient-related hindrances

- **Unwillingness to listen to advice provided** (GR) (PT) (SI) (BE)
- Patients do not realize the severity of the risks (GR) (PT)
- Unknown customers – patients are not regular customers (GR)
- Patients have already been previously informed at the pharmacy or by physician (SI)(LV)
- Product is not being picked up by the patient, but by someone else (DK) (PT) (BE)
- Concomitant use of oral retinoids and contraceptives is difficult
- Educational level of patients
  - Information is complex for the patients (BE)
  - Insufficient patient's knowledge (PT)
- Patients trust more the Internet (GR)
- Lack of adherence of the patients to the treatment (GR) (PT)
- Difficulty in communicating with young patients, who are usually accompanied by their parents, and to discuss avoiding pregnancy and effective contraceptive use (ES) (GR) (PT) (BE)
- Cultural, religious and economic barriers (PT)

6. Prescriber-related hindrances

- Prescribers should warn more the patients (GR) (PT)

- Lack of cooperation/communication between prescribers and pharmacists (ES)(GR) (PT)
- Public and private clinics differ in the information that is provided to patients (ES)
- Dermatologist should care/ensure that pregnancy tests are conducted (NL)
- Lack of adherence to prescription guidelines (NL)
- Lack of adherence to prescription validity and need for scheduling follow-up appointments (NL)
- Do not insist on use of effective contraception (NL)

7. Conditions of pharmacy practice

- Lack of enforcement of prescription-only status: "Product is dispensed without prescriber's prescription" (GR)
- General irresponsibility of pharmacists

We also asked pharmacists for additional suggestions and comments on how adherence to pregnancy prevention measures could be improved in their country. The suggestions received can be classified into different categories relating to resources, education and information, adherence to the PPP, education materials, patient-related suggestions and recommendations for prescribers. They are described in the list below (the most frequent responses are in bold font):

1.Resources

- **Resources – Better support through information technology:**
    - Stricter measures in the computer dispensing software (GR)
    - Increase the accessibility to these materials through the software of the pharmacy (BE)
    - Integrate these materials into the pharmacy software (DK) (PT) (BE)
    - **Warnings/alerts in the electronic pharmacy software** (DK) (ES) (GR) (SI) (BE)

2.Education/Information

- Campaigns to be held in social media to repeat the information to patients and healthcare professionals (prescribers and pharmacists) (ES) (GR)
- Webinar about the teratogenicity of oral retinoids and the existing educational materials (BE)
    - Conferences to be held to repeat the information to pharmacists (LV)
- **Increase the knowledge/awareness of pharmacists** (GR) (PT)(LV)
    - Clearer guidelines for the pharmacists regarding effective contraception for patients
- Increase the knowledge/awareness of the patients (GR) (PT)
    - Increase the knowledge of young patients regarding menstrual cycle, pregnancy, sexual activity and use of contraceptives (DK)
    - Improve health literacy (PT)
- **Increase the knowledge/awareness of the prescribers/dermatologists** (GR) (PT)(LV)
- I was unaware/not information about the measures implemented in 2018 (PT) (BE).

3.**Adherence to the PPP**

- Side-effects: Liver-related problems should also be taken into account (BE)
- Mandatory double contraception should be ensured
- Always warn about the incompatibility of oral retinoid treatment and pregnancy
- Restrict use of products to cases of severe acne (GR)
- Mandatory medically supervised pregnancy tests along with liver function and cholesterol level tests (GR)
- Overall monitoring of such prescriptions is good
- Adherence to 7-day dispensing validity after the prescription is issued
- Pharmacists should receive a proof that they asked the patient about birth control each time (NL)

4. Pregnancy Prevention Programme Educational Materials

- Include all the education materials in one form (BE)
- Increase the availability of materials at the pharmacy (LV)
    - **No patient reminder cards available** (ES) (SI)
    - DHCP is very helpful (SI)
    - Card should be attached to the outer package (DK) (SI)
    - More information on the package and the leaflet
    - Pictograms and warnings on the outer package are the most practical
    - Language barriers
    - Materials should be available through email (PT)

5. Patient-related

- Patients should pick up their own medicines and participate in a medicine-based discussion with the pharmacist (DK)
- Parents who collect the information for young patients should provide the information to their children (PT)
- These topics are delicate to be discussed in the pharmacy (SI)
- If a woman is not sexually active, she is unwilling to discuss it
- It is the patient's main responsibility to avoid a pregnancy (GR)

6.Prescriber-related

- Prescribers should consult more (ES)(LV)
- Prescription limited 30 days of treatment is not followed by prescribers (PT) (SI)
- Dermatologists should follow PPP strictly (NL)
- Promote better communication and cooperation between prescribers and pharmacists (NL) (SI)
- Prescribers should allow pharmacists to interfere with the PPP Implementation (NL)
- Transparency about the information/instructions provided by prescribers (NL)

7.1.3 Prescribers

Table 16. Prescribers' characteristics

	Overall		BE	DK	GR	LV	NL	PT	SI	ES
Total	560		48	63	98	48	114	104	35	50
Age (avg)	45		40	50	49	45	44	41	42	47
Age (range)	25-72		25-76	30-71	26-72	27-92	21-69	25-71	21-66	26-61
Gender										
Female	382(68%)		38(79%)	33(52%)	59(60%)	38(79%)	80(70%)	79(76%)	26(74%)	29(58%)
Male	173(31%)		9(19%)	28(44%)	39(40%)	10(21%)	34(30%)	24(23%)	8(23%)	21(42%)
No gender statement	5(1%)		1(2%)	2(4%)	0	0	0	1(1%)	1(3%)	0
Type of prescriber										
GP	164(29%)		25(52%)	26(41%)	21(21%)	11(23%)	4(3%)	54(52%)	3(9%)	20(40%)
Dermatologist	347(62%)		20(42%)	33(52%)	63(64%)	32(67%)	109(96%)	35(34%)	25(71%)	30(60%)
Other	49(9%)		3(6%)	4(7%)	14(15%)	5(10%)	1(1%)	15(14%)	7(20%)	0
Work experience										
0-5 years	135 (24%)		14(29%)	19(30%)	11(11%)	17(35%)	25(22%)	32(31%)	9(26%)	8 (16%)
6-10 years	112 (20%)		12(25%)	10(16%)	20(20%)	6(12%)	27(24%)	24(23%)	7(20%)	6 (12%)
11-20 years	149 (27%)		13(27%)	19(30%)	38(39%)	3(6%)	31(27%)	24(23%)	11(31%)	10 (20%)
21-30 years	111(20%)		5(10%)	10(16%)	20(20%)	13(27%)	22(19%)	13(12%)	7(20%)	21 (42%)
> 31 years	53(9%)		4(8%)	5(8%)	9(9%)	9(19%)	9(8%)	11(11%)	1(3%)	5 (10%)
Counselling frequency										
At least once a week	215(38%)		11(23%)	34(54%)	33(34%)	7(15%)	84(74%)	15(14%)	9(26%)	22(44%)
Multiple times/month	95(17%)		4(9%)	6(10%)	25(26%)	11(23%)	20(17%)	11(11%)	10(29%)	8 (16%)
Monthly or less	250 (45%)		33(68%)	23(36%)	40(41%)	30(62%)	10(9%)	78(75%)	16(45%)	20(40%)
Did you ever see/suspected a malformation with any medication	28 (5%)		3	1	2	0	1	12	3	6
Was that suspected malformations caused by retinoids?										
Yes	9		1	0	1	0	0	5	0	2
No	12		2	1	0	0	1	4	2	2
Don't know	7		0	0	1	0	0	3	1	2
Are these women in fertile age*										
15-17	360 (64%)		34	44	52	30	87	60	26	27
18-44	460 (82%)		40	49	92	41	94	73	31	40
45-50	297 (53%)		27	34	34	25	78	54	22	23
51-55	122 (22%)		11	10	11	10	39	20	11	10
Other	69(12%)		4	10	6	2	21	16	2	8
From 15-50 years old	176(31%)		17(35%)	25(40%)	23(23%)	15(31%)	38(33%)	34(33%)	11(31%)	13(26%)
Not recognizing 15-17 as fertile age	104(19%)		6(12%)	6(10%)	40(41%)	12(25%)	7(6%)	14(13%)	6(17%)	13(26%)

***Multiple choices possible**

Overall, the responding prescribers were predominantly dermatologists (62%) and GPs (29%), with quite different ratios for the individual countries. For example, in the Netherlands, the included prescribers were almost all dermatologists (96%) whereas in Portugal the percentage of GPs was 52%. In all countries, female prescribers were in the majority. The mean age and the age range for prescribers were higher than those of responding pharmacists. The variation in age and work experience shows patterns comparable across the countries included in our study and further stresses that all categories were represented in our sample.

Whereas a considerable part of the prescribers (38%) counselled a patient on the use of retinoids at least once a week, another part (45%) consulted patients monthly. Of all prescribers, nine explicitly indicated to have seen or suspected malformations in the offspring of their patients caused by retinoid use. In Portugal, the absolute number was 5, which is a relatively high number when compared to the

other countries. It should be noted that 95% of physicians did not answered this question, as they had previously indicated never to had seen or suspected drug-induced teratogenicity.

Most prescribers considered teenagers under 18 years to be fertile as well as women aged between 45-50 years (64% and 53% respectively). Women above 51 years were considered to be in fertile age by 22% of the prescribers.

Table 17. Knowledge of prescribers about the teratogenicity of retinoids

	Overall		*BE*	*DK*	*GR*	*LV*	*NL*	*PT*	*SI*	*ES*
Total	560		48	63	98	48	114	104	35	50
Familiar with teratogenicity										
Yes	545(97%)		47(98%)	60(96%)	96(98%)	47(98%)	113(99%)	99(96%)	33(94%)	50(100%)
Since when familiar										
<2 years	21(4%)		3(6%)	6(10%)	3(3%)	4(8%)	2(2%)	2(2%)	0	1(2%)
2-5 years	42(8%)		4(9%)	3(5%)	5(5%)	3(6%)	9(8%)	9(9%)	4(12%)	5(10%)
>5 years	482(88%)		40(85%)	51(81%)	88(90%)	40(84%)	102(90%)	88(85%)	29(82%)	44(88%)
missing	4(1%)		1(2%)	0	0	1(2%)	1(1%)	1(1%)	0	0
How did you become familiar*										
Health authorities	76(14%)		5	18	6	15	4	10	4	14
Regulatory Agencies	114 (21%)		17	20	20	10	13	16	3	15
Professional Associations	125(23%)		3	25	5	22	37	6	7	20
Colleagues	164(30%)		7	29	15	12	38	34	14	15
Professional Journals	125(23%)		6	11	22	17	25	23	10	11
Pharmaceutical Companies	157(29%)		4	20	36	24	18	20	19	16
Internet	68(12%)		4	12	17	10	14	5	6	0
Seminars	137(25%)		4	10	39	17	18	23	14	12
Academic Knowledge	409(75%)		45	35	70	27	104	80	12	36
Professional Training	189(35%)		7	23	36	21	18	40	18	26
Other	12(2%)		1	4	1	0	5	1	0	0

***Multiple choices possible**

Almost all prescribers (97% overall) reported to be aware about the teratogenicity of retinoids, with most prescribers (88%) being aware for longer than five years. The familiarity with teratogenicity was acquired during academic education. Other important information sources were professional training (35%), colleagues (30%) and pharmaceutical companies (29%).

Additional sources of information included:

- Pharmacotherapeutic compass (NL)
- Social network
- Cases among social network
- Package information (NL)
- Physician assistant to a specialist (NL)

Table 18. Procedure at most recent prescribing of retinoids

	Overall		BE	DK	GR	LV	NL	PT	SI	ES
Total	560		48	63	98	48	114	104	35	50
Any use of preventive measure										
Use of:										
Healthcare professional guide	58 (10%)		7(15%)	12(19%)	n/a	n/a	29(25%)	10(10%)	n/a	n/a
Patient guide	147 (26%)		19(40%)	27(43%)	n/a	n/a	93(82%)	8(8%)	n/a	n/a
Review the Risk Acknowledgment form	224(40%)		14(29%)		44(45%)	31(65%)	73(64%)	8(8%)	21(60%)	27(54%)
Sign the Risk Acknowledgment form	189(34%)		9(19%)		17(17%)		78(68%)	8(8%)	22(63%)	26(52%)
Patient reminder card	86(15%)		3(6%)	6(10%)	20(20%)	29(60%)	22(19%)	6(6%)	13(37%)	9(18%)
DHCP letter	68(12%)		2(4%)	2(3%)	17(17%)		2(2%)	n/a	7(20%)	10(20%)
missing	50(9%)		6(13%)	9(14%)	0	10(21%)	7(6%)	14(14%)	1(3%)	4(8%)
				9(14%)						
				7((11%)		7(15%)		19(18%)		
						6(13%)				
If not used now, will probably/very probably use in future:										
Healthcare professional guide	84(37%)		9(26%)	11(27%)	n/a	n/a	16(20%)	48(65%)	n/a	n/a
Patient guide	75(54%)		11(50%)		n/a	n/a	7(50%)		n/a	n/a
Review the Risk Acknowledgment form	135(48%)		8(26%)	9(34%)	32(60%)	10(91%)	12(35%)	48(62%)	8(67%)	14(74%)
Sign the Risk Acknowledgment form	155(49%)		10(31%)	4(8%)	54(66%)		11(38%)		7(63%)	10(53%)
Patient reminder card	136(40%)		13(33%)	3(6%)	47(60%)	11(84%)	20(24%)	47(62%)	12(57%)	18(50%)
DHCP letter	172(39%)		8(20%)	10(23%)	47(58%)		16(15%)		13(50%)	19(53%)
				8(17%)		16(50%)		49(63%)		
						21(63%)				
								n/a		
								40(56%)		
Prescribing procedure habits										
No prescription to women of this age	97(17%)		9(19%)	16(25%)	16(16%)	5(10%)	2(2%)	31(30%)	7(20%)	11(22%)
Careful when prescribing to these women	302(54%)		23(48%)		82(84%)	30(62%)	23(20%)		26(74%)	27(54%)
Stop treatment in case of a pregnancy	444(79%)		36(75%)	33(52%)	95(97%)	30(62%)	100(88%)	58(56%)	26(74%)	38(76%)
Refer to a specialist	261(47%)		16(33%)	48(76%)	71(72%)	27(56%)	16(14%)	71(68%)	18(51%)	26(52%)
				26(41%)				61(59%)		
missing	92(16%)		10(21%)	10(16%)	0	12(25%)	13(11%)	31(30%)	5(14%)	11(22%)
Do you schedule monthly appointments										
Agree	280(50%)		16(33%)	29(46%)	81(83%)	25(52%)	67(59%)	26(25%)	24(69%)	12(24%)
Disagree	140(25%)		18(37%)	9(14%)	9(9%)	8(17%)	32(28%)	37(36%)	3(9%)	24(48%)
Irrelevant	49(9%)		4(8%)	15(24%)	8(8%)	4(8%)	2(2%)	10(10%)	3(9%)	3(6%)
missing	91(16%)		10(21%)	10(16%)	0	11(23%)	13(11%)	31(30%)	5(14%)	11(22%)
Pregnancy tests implementation										
Before	375(67%)		22(46%)	39(62%)	84(86%)	30(62%)	95(83%)	52(50%)	19(54%)	34(68%)
Monthly	232(41%)		10(21%)		45(46%)		78(68%)		16(46%)	15(30%)
After	201(36%)		7(15%)	35(56%)	40(41%)	18(37%)	52(46%)	16(15%)	13(37%)	15(30%)
Discuss the results	331(59%)		22(46%)		71(72%)		87(76%)		18(51%)	33(66%)
				33(52%)		19(40%)		22(21%)		
				33(52%)		25(52%)		42(40%)		
missing	91(16%)		10(21%)	10(16%)	0	11(23%)	13(11%)	31(30%)	5(14%)	11(22%)
Effective contraception										
Discuss	432 (77%)		36(75%)	36(57%)	96(98%)	34(71%)	100(88%)	66(63%)	28(80%)	36(72%)
Prescribe	305(54%)		36(75%)		46(47%)		52(46%)		18(51%)	33(66%)
Refer to a specialist	345(62%)		14(29%)	27(43%)	88(90%)	24(50%)	82(72%)	69(66%)	25(71%)	25(50%)
missing	92(16%)		10(21%)		0		13(11%)		5(14%)	12(24%)
				32(51%)		32(67%)		47(45%)		
				10(16%)		11(23%)		31(30%)		
Adherence to PPP										
Stopping treatment when pregnant, pregnancy testing and discuss effective contraception	163 (29%)		5(10%)	32(51%)	31(32%)	11(23%)	47(41%)	14(13%)	11(31%)	12(24%)

+reviewing and signing Risk Assessment Form and delivering Patient Reminder Card	36 (6%)		1 (2%)	1 (2%)	5(5%)	3(6%)	17(15%)	2 (2%)	4(11%)	3(6%)
Did your behaviour change since 2018										
Yes *No* *missing*	80(14%) 406(74% 64(11%)		3(6%) 36(75%) 9(19%)	3(5%) 51(81%) 9(14)	28(28%) 70(71%) 0	8(17%) 33(69%) 7(15%)	15(13%) 92(81%) 7(6%)	10(10%) 69(66%) 25(24%)	7(20%) 27(77%) 1(3%)	6(12%) 38(76%) 6(12%)
*Which measures from prevention program influenced your daily clinical practice**										
Healthcare professional guide	16(20%)		2(67%)	0	n/a	n/a	9(60%)	5(50%)	n/a	n/a
Patient brochure	6(8%)		n/a	2(67%)	n/a	n/a	n/a	4(40%)	n/a	n/a
Review the Risk Acknowledgment form	37(46%)		1(33%)	1(33%)	19(68%)	5(62%)	n/a	2(20%)	5(71%)	4(67%)
Sign the Risk Acknowledgment form	28(35%)		n/a	1(33%)	10(36%)	6(75%)	n/a	4(40%)	5(71%)	2(33%)
Patient reminder card	21(26%)		1(33%)	0	9(32%)	0	6(40%)	n/a	3(43%)	2(33%)
DHCP letter	26(33%)		3(100%)	0	10(36%)	3(37%)	2(13%)	7(70%)	1(14%)	0

***Multiple choices possible**

Table 19. Awareness and use of measures by specialists and GPs prescribing oral retinoids across countries

	Overall			BE		DK		GR		LV		NL		PT		SI		ES	
	Both	Specialist	GP	Specialist	GP	Specialist	GP	Specialist	GP	Specialist	GP	Specialist	GP	Specialist	GP	Specialist	GP	Specialist	GP
Total	560	396	164	23	25	37	26	77	21	37	11	110	4	50	54	32	3	30	20
Healthcare professional guide	58(10%)	40(10%)	18(11%)	1(4%)	6(24%)	7(19%)	5(19%)	n/a	n/a	n/a	n/a	28(25%)	1(25%)	4(8%)	6(11%)	n/a	n/a	n/a	n/a
Patient Brochure	147(26%)	129(33%)	18(11%)	13(57%)	6(24%)	23(62%)	4(15%)	n/a	n/a	n/a	n/a	92(84%)	1(25%)	1(2%)	7(13%)	n/a	n/a	n/a	n/a
Review the Risk Acknowledgment form	224(40%)	187(47%)	37(23%)	9(39%)	5(20%)	4(11%)	2(8%)	31(40%)	13(62%)	28(76%)	3(27%)	72(65%)	1(25%)	2(4%)	6(11%)	20(63%)	1(33%)	21(70%)	6(30%)
Sign the Risk Acknowledgment form	189(34%)	171(43%)	18(11%)	8(35%)	1(4%)	1(3%)	1(4%)	11(14%)	6(29%)	26(70%)	3(27%)	77(70%)	1(25%)	3(6%)	3(6%)	21(66%)	1(33%)	24(80%)	2(10%)
Patient reminder card	86(15%)	74(19%)	12(7%)	1(4%)	2(8%)	6(16%)	3(12%)	16(21%)	4(19%)	9(24%)	1(9%)	22(20%)	0	n/a	n/a	13(41%)	0	7(23%)	2(10%)
DHCP letter	68(12%)	37(9%)	31(19%)	0	2(8%)	5(14%)	4(15%)	11(14%)	6(29%)	5(14%)	2(18%)	2(2%)	0	5(10%)	9(17%)	5(16%)	2(67%)	4(13%)	6(30%)

In general specialists were more aware and made more use of the various measures available (Table 19). Especially patient brochures and risk acknowledgement forms were far more often used by specialists compared to GPs. Some differences appeared between the countries, but numbers were quite low, especially for the GPs, to assess meaningful conclusions.

General remarks provided on why prescribers were unlikely/very unlikely to use information materials included:

- **Lack of time** (PT) (BE)
- Lack of availability
    - Lack of availability of these materials (BE)
- **Prescribers' responsibility** (GR) (PT)
    - Specialist's responsibility to prescribe so as a GP only prescribe oral retinoids as a follow-up prescription (DK) (BE)
    - As a Gynecologist only give advice about pregnancy and contraception (BE)

Not consulting the Healthcare Professional guide was due to:

- **No need for it**
    - Useless/**not necessary** (PT) (SI) (BE), oral information is provided
    - I have thorough knowledge regarding the risk/regulations and no need to read it (DK) (PT) (BE)
- **Lack of awareness**
    - Not aware of the health professional guide
- **Unfit for purpose**
    - Discard the health professional guide after been read/useless (BE)
    - Read it again only in case of an update/changes in the guidelines (NL)
- **Lack of availability** of healthcare professional guide

Not delivering the Patient Brochure was due to:

- **Lack of interest**
    - Many of patients do not read the Patient Brochure
    - Unwillingness of the patients to receive and consult the patient brochure
- **Lack of availability** of Patient Brochure
- **No need for it**
    - Patients already aware about the risks (BE)
    - Patient brochure useless/not necessary (PT) (BE)
    - I have thorough knowledge regarding the risk/regulations (BE)
    - Information is communicated verbally regarding the risks & effective contraception (DK) (PT) (BE)

Not reviewing/requesting signature of the “Risk acknowledgement form/checklist” was due to:

- **Lack of awareness**
    - Not aware of the Risk Acknowledgment Form (GR) (PT) (BE)
- **Lack of availability**
    - Risk Acknowledgment Form not available (BE)
- **No need for the Risk Acknowledgment form**
    - **Verbal communication about the risk of pregnancy & effective contraception is preferred** (LV) (DK) (GR) (PT) (BE)
    - I have thorough knowledge regarding the risk/regulations and no need to read the RAF (DK) (BE)
- **Redundancy**
    - Specialists are responsible for asking for the RAF to be signed (BE)

    - No need for reading/signing the RAF if the patient has already given consent to the treatment (DK)
- **Unfit for purpose**
    - Extra bureaucracy (LV)
    - Signing the RAF does not provide proof about pregnancy prevention & effective contraception/not legally valid (DK) (NL)
    - Used in the past/seemed useless (NL)
    - Requesting patients' signature is defensive (DK) (NL) (BE)

Not delivering the "Patient reminder card was due to:

- **Lack of availability**
    - Unavailable (DK) (SI) (BE)(LV)
- **Unfit for purpose**
    - Patient reminder card is not practical (SI)
- **Lack of awareness**
    - Unaware (GR) (BE)**,** unfamiliar with it (BE)
- **No need for it**
    - Verbal communication about pregnancy risks & effective contraception is preferred (GR) (SI) (BE)(LV)
    - Patient does not follow card (GR)
    - Patients aware of need to avoid pregnancy (GR) (BE)
    - Patient also has its responsibility in remembering (NL)
    - Patients already receive the information/instructions in a folder (DK) (NL)
    - Regular consultations:
        - Prescriptions are valid only for one month/afterward they recall their appointments (DK) (NL)
        - Appointments are already well-planned (DK) (NL)
        - They are called monthly (NL)
    - Different surveillance system (NL)

Not reading the "Direct to Healthcare Professional Communication letter" was due to:

- **No need**
    - **Information included in letter is already known** (DK) (GR) (PT) (SI) (BE)(LV)
    - I have thorough knowledge regarding the risk/regulations and no need to read the DHCP (GR) (PT) (BE)
    - Prefer to use the national guidelines (NL)
- **Lack of awareness**
    - Unaware about DHPC (GR) (BE)
- **Unfit for purpose:** usually discard the health professional guide after been read/useless (BE)

Overall, reviewing and signing the risk acknowledgement form was the most frequently used educational material (40% and 34% respectively). However, significant differences between countries can be observed. In Denmark and Portugal, prescribers using the risk acknowledgement form were a small minority of 10% or less, whereas this part of the prescribers was 60% or higher in the Netherlands and Slovenia.

Use of a healthcare professional guide and patient brochure was not applicable to four countries (Greece, Latvia, Slovenia and Spain). In these countries, use of the risk acknowledgement form was relatively high. For the remaining four countries, the overall use of the patient brochure was 26%.

However, its use shows a wide range of 8% use in Portugal to 82% in the Netherlands and in between about 40% use in Belgium and Denmark. The use of the healthcare professional guide was overall 10% with a significantly lower range between countries.

On average, the patient reminder card and DHCP letter were used by 15 % and 12 % of the prescribers respectively.

For all measures, a significant part of the prescribers indicated that they were likely to use them in future. Again, a wide variation between countries can be observed. For example, in Latvia the vast majority of the prescribers intended to use the risk acknowledgement form in future compared to a very small part of the Danish doctors.

The majority of doctors reported to be careful in treating women in fertile age with retinoids, whereas only few indicated that they do not prescribe retinoids to women in fertile age at all. In case of pregnancy, most prescribers advised stopping treatment, again with some variation. In the Netherlands, 100% would stop treatment, whereas in Latvia, 62% indicated to stop. Monthly appointments for monitoring the patient are used in 28% of the cases, although the percentage differs largely between countries (48% in Greece, 11% in Denmark).

About half of the prescribers made monthly appointments with their patients. In Greece, the percentage was 83%, whereas in other countries that percentage was lower.

67% of the prescribers would conduct pregnancy testing before starting the treatment with retinoids. Again, differences between countries should be noted. In Belgium, this percentage was 46%, whereas it was 86% in Greece. Pregnancy testing during and after treatment was conducted to a lower extent than at the start.

The vast majority of prescribers discussed contraceptive measures with their patients and/or prescribed contraception and/or referred to a specialist regarding this issue.

Only 14% of all prescribers reported to have changed their daily clinical practice since the implementation of the measures in 2018.

The most-frequently reported changes regarded the advice provided and changes around prescribing were, namely:

- **Advice provided:**
    - Contraception advice
        - Insist on the use of double contraception (GR)
        - Recommendation to use one or two contraceptive methods and perform pregnancy tests before starting and during treatment (GR)
    - More attention to contraceptive counselling (GR) (SI) (BE)(LV)
        - Inform about the risks, recommend use of effective contraception & make referral to gynaecologist
        - Increase in the amount of the advice provided /information about the risks & effective contraception (GR) (BE)
    - Increase in the amount of the advice/information provided to patients about the risks (ES) (GR) (SI)(LV)
    - Explanation of PPP to the patients (LV)

    - Information provided along with scheduled follow-up appointments and pregnancy tests before treatment starts
    - Provide written information/instructions to patients (GR) (BE)

- **Prescription procedure**
    - Request patient's signature before prescribing (GR) (SI)
    - Use more supportive documents during prescription procedures (LV)
    - Prescription issued only after patient written consent is provided, regarding awareness of risks and adherence to use of effective contraception (GR)
    - Recommendation for scheduling follow-up appointments (GR)
    - Request of monthly follow-up blood and β-human chorionic gonadotropin tests, apart from informing about the risks (GR)
    - Perform pregnancy test before prescribing/ monthly (GR) (NL)
    - Always use a written informed consent/signed by the patients (NL)
    - Checklist is not required to be signed (NL)

- **Awareness as prescriber**
    - More careful/alert/aware when it is time to prescribe (GR) (PT)
    - More careful explanation of the risks associated to the treatment (GR) (PT)(LV)
    - Consult the DHCP letter (GR)
    - Provide information in collaboration with the dermatologists (GR)
    - Do not issue these prescriptions due to type of specialization (GR)
    - Pharmacists do not dispense more than for 1month (NL)
    - Reducing prescription rates:
        - Inform patients regarding the risks and reduce the prescription rates of oral retinoids (GR)(LV)
        - No prescription implemented after 2018 (GR)

The most influential measure was the Risk Acknowledgement Form. Again, very different outcomes per country can be observed. In some countries, the Healthcare professional guide and DHCP-letter were indicated as being influential on daily clinical practice.

In what concerns barriers to the implementation of use of the PPP measures, prescribers mentioned:

1.Patients' related hindrances

- Lack of patient's adherence to the measures (GR) (PT)
- Patients unaware of severity of risks (GR)(LV)
- **Fear of using the medication/not trusting the medication** (GR) (SI) (BE)
- **Fear/stress from signing forms** (GR)
- Unwillingness of the patients to listen to the prescribers (LV)
- Patients are overwhelmed with all this written information/these instructions (LV)
- **Socioeconomical & cultural barriers** (GR) (BE)
    - Patients' educational level
- Patients' age (GR)
- Patients' lifestyle: smoking (GR)
- Use of contraception
    - Parents' rejection of contraception use (GR) (PT)
    - Unwillingness to use contraceptives

- Insufficient adherence to effective contraception (ES)
    - Sole use of condoms as a contraceptive method
    - Unwillingness to use double contraception (GR) (NL)
- Follow-up appointment cannot be planned beforehand (GR)

2. Lack of time (ES) (GR) (PT)

- **Lack of time & verbal communication is preferred** (GR) (PT) (BE)(LV)
- Lack of time & bureaucracy (DK) (GR) (BE)(LV)

3.Lack of awareness

- **Unfamiliar with the measures** (DK) (PT) (SI) (BE)(LV)
- **Unaware of all these measures** (GR) (SI) (BE)(LV)
- Insufficient awareness/knowledge from prescribers (BE)

4.Lack of availability

- Lack of easy access to these education materials (DK) (PT) (BE)(LV)
- Difficulty in finding these measures (BE)

5.Measures insufficient or inadequate

- No need for these measures (PT) (SI) (BE)
    - Patients are already being adequately informed (DK)
- **Bureaucracy** (DK) (GR) (PT) (SI)
- Written consent forms are but a way to legally disclaim prescribers (BE)
- Unfit for purpose
    - Not applicable to all women
        - The checklist states that if one of the questions is answered with 'no', the drug may in principle not be withdrawn. There are many children under the age of 16 who are not yet sexually active and are thus actually forced to use AOCs, which also entail risks (NL)
    - Measures are not practical (DK) (PT) (SI) (BE)
    - Not sufficient information is displayed on the package regarding the risks
    - Language barriers (NL)
    - Verbal communication is preferred over massive written formats (DK) (PT) (SI) (BE)
    - Patients may forget to read the Risk Acknowledgment Form (GR)
    - Patients may not pay enough attention to printed educational materials (GR)
    - Risk Acknowledgment Form provokes stress in patients
    - Developed and use own (prescribers') documents/printed instructions for the patients (PT) (LV)
    - Signing forms is not a proper way to ensure safety & pregnancy prevention (NL)
- Not part of a routine/forget to apply them on a daily basis (GR)
- (Difficulty in) ensuring the performance of monthly pregnancy tests (SI)

6.Conditions of prescribers' practices

- No point in using measures as the specific professionals (dermatologists) have the responsibility to do so/ I just do follow-up prescriptions (ES) (PT)

        - Only dermatologists can prescribe them (DK)(LV)
        - Gynaecologist only provides advice regarding contraception use
    - Depends on the willingness of the physician to communicate with patients (GR)
        - Personal relationships between prescribers and patients
    - Lack of adherence to follow-up appointments due to huge waiting lists in the patient care
    - Patient's sexual life is a delicate topic to be discussed
    - Lack of IT support
        - Guidelines on prescription are not updated
        - Lack of uniformity of the prescription system at a national level

7.Information overload: Prescribers & patients are overloaded with information (BE)

8.Not enough attention paid to the issue (GR)

9.Role of the pharmacists

- Pharmacists are now stricter
- Should not interfere in discussions about pregnancy prevention & contraception (NL)

We also asked prescribers for additional suggestions and comments on how adherence to pregnancy prevention measures could be improved in their country. The suggestions received can be classified into different categories relating to resources, education and information, prescription-related concerns, adherence to the PPP materials, as well as and the role of pharmacists. They are highlighted in the list below:

1. Education/Information

- Always informed about the risks/no problems have occurred yet (GR)
- Increase the awareness and knowledge of the doctors and specialists (e.g. dermatologists) responsible for starting these treatments (LV)
    - Increase the knowledge about effective contraception
- **Patient-related**
    - Promote sexual health education to the younger patients
    - Improve the patient's adherence
        - Lack of patient adherence to contraception
        - Difficulty in co-administration of oral retinoids and contraceptives
            - Some patients refuse to take contraceptives – they should sign a form accepting their personal responsibility to have an abortion in case of pregnancy (GR)
            - Young girls refuse to use contraception/not sexually active (NL)
    - Increase patient's awareness and knowledge about teratogenic risks (GR)
    - Increase alertness about contraception or abortion in case of unplanned pregnancy (GR)

2.Prescription-related suggestions

- Avoid prescription when patient plans to become pregnant (GR)
- Reluctant to prescribe acitretin (NL)
- The prescription procedure is time consuming (GR)

- Prescriptions should be valid for more than one month/patients' responsibility not to get pregnant (NL) (SI)
- Adherence to contraception for 2 years after stopping acitretin treatment is difficult
- Adherence to guidelines/monitoring
    - Scheduling follow-up appointments
    - Contraception use/Pregnancy testing
        - Gynaecologists should also intervene before treatment with oral retinoids takes place (GR) (PT)
        - No prescription until effective contraception has been established
        - Prescribing OAC & Nuva ring (NL)
        - Ensure double contraception use (GR)
        - No prescription without effective contraception & pregnancy tests before, every month and after the end of the treatment (DK)
        - Ask for HCG tests monthly
        - Lab tests once every 3 months and concomitant performance of pregnancy tests at home (NL)
        - Guidelines regarding contraception & monthly pregnancy tests may not be followed when patients are not active sexually (NL)
        - Call patients monthly to ask if there is a chance of a pregnancy (NL)
        - Monthly pregnancy tests are an exaggeration (NL)
        - Pregnancy tests do not really prevent a pregnancy/ in case of a pregnancy abortion is the solution (NL)
    - Use the 2018 program only if the patient objects to abortion should unplanned pregnancy take place (NL)

3.Pregnancy Prevention Programme Materials

- Adherence
    - PPP is strictly followed
    - Risk Acknowledgment form and information provided play key role in the safe prescription of the drug (GR)
    - Bureaucratic procedure (GR)
- Materials
    - There is not sufficient information on the package information leaflet regarding long-term adverse effects of the medication
    - Lack of availability of educational materials for oral retinoids other than isotretinoin (NL)
    - Checklist's language is difficult and not understandable by the patients (NL)
    - Educational materials are patronizing the prescription procedures/no personalized medicine (NL)
    - Educational materials should be different for each oral retinoid (e.g. isotretinoin, acitretin) (NL)
    - An informed consent form and a folder issued by the public health service would be useful to use in practice (BE)
    - Insufficient knowledge about the materials (ES)

1. Role of prescribers

- These drugs are mainly prescribed by a dermatologist/I do a follow up prescription (SI)
    - Mainly dermatologists’ responsibility

- Better communication between prescribers & patients (GR)

7.1.4. Midwives

In two countries (ES and NL) the role of midwives in monitoring safety of and advising about oral retinoid products was investigated.

7.1.4.1 Spain

Tables 21 and 22 show the results from Spain. A third of the midwives in Spain were unfamiliar with the teratogenicity of oral retinoids, reporting to only have become aware when filling our questionnaire. Most midwives in Spain report that they do not provide advice before conception, but rather mostly consult women that are already pregnant. If there is an issue with oral retinoids, they refer the woman to the prescriber. Overall, midwives in Spain seem largely unaware of specific measures to lower the risk of teratogenicity in users of oral retinoids.

Table 21. Knowledge of midwifes regarding teratogenicity of retinoid

	ES
Total	15
Since when familiar with teratogenicity	
At this moment	5 (33%)
<2 years	3 (20%)
2-5 years	1 (7%)
>5 years	5 (33%)
Missing	1 (7%)
How did you get familiar*	
Health authorities	4
Pharmaceutical Regulatory Agencies	2
Professional Associations	1
Colleagues	2
Professional Journals	0
Pharmaceutical Companies	0
Internet	2
Seminars	0
Academic Knowledge	5
Professional Training	4
Other	1
If other, specify (free answer)	"I learned of this in the context of attending a birth of a woman who had taken isotretinoin without knowing she was pregnant. I informed myself of the possibility of teratogenicity through internet. The baby was born with auditory pavilion agenesis"

*multiple answers possible

Table 22. Procedure at most recent consultation with a woman of childbearing age taking retinoids

	ES
Total	15
Pregnancy preventive measure	
Use of:	
Patient reminder card	1 (7%)
DHCP letter	0
Probably/very probably will use these in future of:	7 (47%)
Patient reminder card	10 (67%)
DHCP letter	"I don't know how to access it"
Reason (free answer)	"I work in the delivery room, I don't follow up on pregnancies"
	"I control few pregnancies"
	"I don´t have the patient reminder card"
Do you counsel women on [1]:	
Effective contraception	10 (67%)
Stop treatment when pregnant	10 (67%)
Refer to prescriber	10 (67%)
Take pregnancy test	10 (67%)

Do you counsel different at first or repeat prescriptions?	
Yes	2 (13%)
No	9 (60%)
Missing	4 (27%)
Reason (free answer)	"I make sure that the contraception fits her profile and I prefer long term methods where the woman's will does not come into play, forgetfulness, misuse etc." "I find out now"
Did your behavior change since 2018 [2]	
Probably or certainly yes	1 (7%)
Not sure	4 (27%)
Probably no or no	6 (40%)
Missing	4 (27%)
Which measures from prevention program influenced your daily clinical practice*	0
Patient reminder card	1 (7%)
DHCP letter	
How the provided information/advice has changed (free answer)	"The information has been new to me, so the advice has changed radically, however, I have not known any case of pregnancy and retinoid treatment"
Difficulties for the implementation and/or use of prevention measures stablished in 2018 (free answer)	"The hypermobility of some patients who take these treatments. It is difficult to follow up on them. There is no access to their health records in other Spanish Autonomous Regions" "I didn't know those cards. I took retinoids myself and don't know them either" "None" "Printed materials are scarce"
Additional points/suggestions/concerns (free answer)	"I think the dermatologists explain it correctly, do pregnancy tests at each visit and explain risks and need for contraception if sexually active. They also explain that voluntary termination of pregnancy is required if you become pregnant during treatment" "None" "In the only case I have of a pregnant woman with isotretinoin, the SITE (Telephone Information System for Pregnant Women) phone was called from the doctor´s office and had her doubts answered"

*multiple answers possible

1- Included: "always", "frequently", "few times"

2- included: "probably yes", "certainly yes"

7.1.4.2 Netherlands

In The Netherlands, 42 midwives answered a questionnaire about their practice in relation to use of oral retinoids as well as valproate by women of childbearing age. The oral retinoid results are presented here. Also, in The Netherlands only a few (7%) of the midwives had seen or suspected having seen a malformation associated with any medication use. A large proportion of midwives was unaware of the risks associated with oral retinoids, with 38% reporting they had learned about it during the completion of the questionnaire. Midwives in the Netherlands are almost exclusively involved in care for pregnant women. Almost all report to check all medication use at consultations, and consult with or refer to the prescriber when a safety issue is suspected. They do report very little experience with oral retinoids, and suggest their knowledge should be improved.

Table 22 Characteristics midwifes

	NL
Total	42
Age (avg)	42
Age (range)	24-63
Gender	
Female	39 (93%)
Male	3 (7%)
Work experience	
0-5 years	7 (17%)
6-10 years	7 (17%)
11-20 years	13 (31%)
21-30 years	7 (17%)
> 31 years	8 (9%)
Counselling frequency	
Weekly	0
Twice a month	0
Monthly	42 (100%)
Ever seen malformations suspected to be caused by medication use?	
Yes	3 (7%)
No	34 (81%)
Not sure	5 (12%)
If yes, was this related to use of oral retinoids or valproate?	0
Yes	2
No	3
Not sure	
Are these women in fertile age*	29 (69%)
15-17	40 (95%)
18-44	19 (45%)
45-50	3 (7%)
51-55	2 (5%)
Other	-from first menstruation to menopause
If other, specify (free answer):	- even younger than 15

*multiple answers possible

Table 23 Knowledge of midwifes regarding teratogenicity

	NL
Total	42
Since when familiar with teratogenicity of oral retinoids	16 (38%)
Only at this moment	5 (12%)
<2 years	10 (24%)
2-5 years	10 (24%)
>5 years	1 (2%)
Missing	
How did you get familiar*	
Health authorities	2
Pharmaceutical Regulatory Agencies	4
Professional Associations	0
Colleagues	2
Professional Journals	3
Pharmaceutical Companies	3
Internet	9
Seminars	0
Academic Knowledge	9
Professional Training	3
Other	3
If other, specify (free answer)	"National pharmacovigilance centre" "Used oral retinoids myself" "From use of oral retinoids by an acquaintance"

*multiple answers possible

Table 24 Procedure during consultation

	NL
Total	42
Do you ask about use of oral retinoids or valproate when consulting with a woman who wants to get pregnant?	
yes	35 (83%)
no	5 (12%)
missing	2 (5%)
Do you ask about use of oral retinoids or valproate when consulting a woman who is pregnant?	
yes	37 (88%)
no	2 (5%)
missing	3 (7%)
Measures taken when women are using valproate or oral retinoids*	
Consult with prescriber *Consult or refer to gynaecologist* *Consult with pharmacist* *Consult with pharmacovigilance centre* *Stop medication* *Prescribe folic acid*	35 (83%) 10 (24%) 4 (10%) 7 (17%) 3 (7%) 2 (5%)
Did your behaviour change since 2018 [1]	
Probably or certainly yes *Not sure* *Probably no or no* *Missing*	3 (7%) 14 (33%) 24 (57%) 1 (2%)
How the provided information/advice has changed	"We look up all medication used" "We systematically check all medication with the woman"
Additional points/suggestions/concerns	"In 30 years we have never seen use of oral retinoids. We always ask about medication use and if needed we have contact with the gynaecologist" "As midwives we do not see many women that want to get pregnant, so we do not do a lot of education." "Prescribers of the medication should be informed about the teratogenic risk" "We do not do a lot preconception counselling, so prevention is more of a task for doctors" "I did not know these risks, so it is good to do a study on this" "Women that use valproate often do not visit a midwife, because of their indication and are monitored and counselled by a gynaecologist' "The pharmacy should provide preventive education and monitoring of women of childbearing age" "we always ask about medication use but not specifically about use of retinoids. I did not know about the specific risks and have never had any information about this in the past years." "I did not know about the retinoids and would have liked to have more information on this. Also could not find the info at the pharmacovigilance centre" "I always refer to the prescriber when a woman uses medication and check with the pharmacovigilance centre" "there is more specific knowledge now, but it is still a rare situation in primary midwife care"

*multiple answers possible
1- included: “probably yes”, “certainly yes”

7.2 Main results: Interviews

General characteristics of the respondents

In the study, 7 female patients using or having used retinoids were interviewed: 1 patient from the Netherlands and 6 patients from Portugal. The Portuguese patients were respectively 19, 20, 26, 29, 33 and 39 years-old. One Portuguese patient lived in a rural area, whereas all others lived in an urban setting. The Portuguese patient who was 39-years old had one healthy child; other respondents did not have children. The patient from the Netherlands was 17 years-old, lived in an urban area and was completing the final year of secondary school.

Use of oral retinoids before and after 2018

All patients were using or had used isotretinoin to treat acne. In all cases, the medicine was prescribed by their dermatologist. For three patients, the first treatment with isotretinoin took place after 2018, whereas other 4 patients reported to have followed treatment (also) before 2018. The isotretinoin treatments lasted between several months to up to 1 or 2 years. Patients were treated for acne at several occasions, with a time-interval between treatments.

Use of oral retinoids and pregnancy

Patients did not report any pregnancy during their isotretinoin treatments. The patient who is a mother to a healthy child only became pregnant three years after stopping her treatment with isotretinoin. After giving birth to her child, she restarted isotretinoin use at a lower dose.

Familiarity with teratogenicity

Six out of the seven patients were aware of the teratogenic properties of isotretinoin. Nevertheless, the patient, living in a rural area in Portugal only became aware about it during the actual interview.

> *"I don't recall receiving any information about avoiding pregnancy. I really don't, seriously."*

Information about risks of isotretinoin and their sources

The six patients who were aware about the teratogenicity of isotretinoin prior to the interview were first informed by their dermatologist.

> *" The doctor said I could not get pregnant, that I needed to be very careful because it caused malformations to the fetus...so she explained."*

The dermatologists provided the information during the first consultation of a treatment cycle. When patients resumed treatment after having been treated with isotretinoin in the past, this information was repeated.

After the first consultation, only three Portuguese patients were reminded by the dermatologist at consecutive consultations. The patient from the Netherlands had a monthly consultation at the start of the treatment; within some months the frequency was slowly decreased.

Most Portuguese patients did not obtain information about the risks associated with isotretinoin at the pharmacy. The exception was one patient who was informed by the pharmacist at each dispensing.

"The only thing they mentioned at the pharmacy was since we were in spring, and the warm weather was starting, the pharmacist told me to watch out, that while on treatment I should not be too exposed to sunlight. That was the only thing I was told."

The patient from the Netherlands was informed at the pharmacy. She also proactively researched sources on the internet.

Three Portuguese patients and the Dutch patient felt well-informed about the risks of isotretinoin use. Despite all the information received and although they felt clarified, three interviewees, among which the Dutch patient, indicated not to have felt involved in the choice to use isotretinoin to treat their acne. Two patients felt it was their own decision.

Two Portuguese patients reported being aware that they should not become pregnant while using isotretinoin, but not being told exactly why that warning was necessary.

Contraception use and pregnancy testing

In five cases, the dermatologist discussed the need for contraception with the patient. Two patients reported not to have discussed it during consultations. Patients mentioned often that they were already using contraception prior to starting isotretinoin treatment.

The Dutch patient had pregnancy tests conducted before and during the isotretinoin treatment in 2019. Three Portuguese patients started treatment before 2018: one was enquired whether she would like to be tested; one was never tested; the third patient was never warned about the risks nor tested for pregnancy. From the three patients using isotretinoin in 2020, two patients were tested and another was not.

(Preferred) role of healthcare providers

Patients considered that their dermatologist should be primarily responsible for informing patients about the risks of retinoids. However, they also mentioned that their pharmacist should also provide information about these risks and recognized there was room for improvement here.

Pregnancy Prevention Programme materials

The Risk acknowledgement form was only signed by the patient from the Netherlands. The Portuguese patients were not aware that this form existed. Likewise, only the Dutch patient was familiar with the Patient Brochure.

None of the patients had ever seen the Patient card nor the QR code. On the other hand, all patients had noticed the Package warning. Most patients had seen and read the package leaflet, except one who indicated that she had not read it.

The need to fill the prescription within 7-days was only familiar to the patient from the Netherlands, where that measure is implemented.

The Dutch patient considered the implementation of the measures to be well-organized.

Suggestions on how to disseminate information about treatment risks

All the interviewed women were in childbearing age. Most patients, considered the information they had received to be sufficient. They stressed that the combination of oral and written information was crucial and that written reminders were also very important.

As to the provision of information, patients held the opinion that the prescribing doctor is to have the most prominent role, sharing information orally. However, the pharmacist should take up an additional role in reminding/reinforcing risk information.

The respondents suggested that teenagers should be orally informed by their GP and/or dermatologist. In addition, they alerted that additional clarifications by a female healthcare professional could be valuable, as sexual activity is a delicate subject. Given that pharmacists are often female they could play an important role in the provision of information to teenage users.

Additional remarks

While all patients mentioned that informing users about risks was very important, a few considered that the measures caused fear.

The patients reported isotretinoin to be very effective against acne with a long-lasting effect. As to side-effects, most mentioned dry lips, hair and skin. Furthermore, a few referred to hot flushes and changes in mood and sleepiness.

Section 8: Discussion

8.1 Key results

The results of our surveys show that there is a very high awareness of the teratogenic risks of retinoids among both patients and healthcare professionals. However, there is only medium adherence to the measures recommended in the Pregnancy Prevention Programme (PPP). While it seems that most healthcare professionals adhere partially the programme, only a few comply fully with all aspects. Women report to be adequately informed about the teratogenic risks, but pregnancy prevention measures do not seem to be thoroughly implemented nor monitored during and after treatment with retinoids. To which extent this last observation actually leads to exposure of pregnant women to retinoids, will be further ascertained once the outcomes of an ongoing study by the consortium using drug utilization databases are known[I].

It should be noted that the implementation of a programme, i.e. the translation of evidence into healthcare practice, is a very challenging process and often not as straight forward as expected[II,III]. The current measures to reinforce the message through communication about the teratogenic risk appear to be working. From the patient survey results and the limited number of interviews, the high awareness about the risks during pregnancy and the appreciation for the careful design of the PPP have emerged. Some healthcare professionals and patients also suggested that the paperwork and frequent reminders about the PPP were sometimes cumbersome. In the Netherlands, women referred to it as a reason for refusing to participate in the interviews. This could be partially due to the young age of retinoid users. Pregnancy is not a priority and some countries have a high baseline use of contraceptives. Concurrently, healthcare professionals may struggle to discuss pregnancy prevention with young women who clearly have no pregnancy wish. The reluctance of healthcare providers was also apparent from the low adherence to pregnancy testing during and after treatment with oral retinoids. On the other hand, it does seem very important to keep reminding also these younger women about pregnancy risks as unintended pregnancies do occur more frequently in this particular age group. The same goes for older women with completed families. Unintended pregnancies may still occur and will pose additional dilemmas when exposure to retinoids has taken place.
In this context it is important to note an additional finding from our study. Not all healthcare professionals identified women under 18 and over 44 to be in a fertile age, whereas they undoubtedly are so from a biological perspective. This was particularly evident in Southern and Eastern countries included in our study. This may have relevant implications for the information being provided to these women and a pertinent question to be explored in future research.

The majority of the patients could recall reviewing the risk acknowledgement form and reading the patient information leaflet. Less patients reported to remember the warning signal on the package, the patient brochure, the reminder card and the QR code. This low recognition of the latter educational materials may have several reasons. Most likely, it can be due to unawareness of health care providers about these materials, unavailability of the materials (some pharmacists mentioned to still dispense older packaging with older inserts without QR codes as no updated packages had been received) or due to the lack of motivation of the healthcare provider. Patients' recall bias may also play a role. Patients' awareness was probably also raised through verbal communication from health care professionals as well as from the internet. When looking specifically into the type of health care provider involved in the risk communication, specialists i.e. dermatologists seem to play a more

prominent role in informing patients when compared to general practitioners. This may partly due to the fact that in some countries retinoids are mainly prescribed by dermatologists, and in some GPs are not allowed to prescribe oral retinoids. The involvement of pharmacists in risk communication also varied across countries. Differences observed across countries may reflect the speed of implementation of changes to national packages of oral retinoids.

The usefulness of the PPP educational materials is open for discussion. On one hand, they certainly seem to be used and may thus contribute to risk awareness. On the other hand, they do not always seem to reach patients and may be too cumbersome. For pharmacists, it may be complex to distribute materials which are kept separately from the outer packages. The patient reminder card should preferably be attached to the medication boxes as an extra warning, but it may also be seen as an interim solution until the new packaging reaches the patients. It should be noted that the layout of most pharmacies in Europe usually does not allow for enough privacy to discuss delicate matters such as pregnancy prevention. This hampers the effective delivery of the information included in the PPPs in pharmacies. Box warnings may, however, still facilitate counselling by pharmacists. Health care information systems could remind both physicians and pharmacists about the PPP and facilitate the delivery of materials in an appropriate manner to women. Sometimes such electronic reminders are already in place.

A majority of the patients had read the patient information leaflet (PIL) and found this an important source of information. However, an updated PIL might not always be easily recognized by patients. This is a challenge when new information has to be communicated in a timely manner. It is also known that PILs are not optimal as information sources for patients due to their length, complexity and technical language used[IV].

The vast majority of healthcare professionals in this study had acquired their knowledge about the teratogenicity of retinoids during their academic training. This is not surprising as the teratogenic effects of vitamin A derivatives have already been known for more than 30 years. In most countries included in our study, midwives did not seem to play an important role in the care of women in childbearing age. Yet in Spain and the Netherlands they do have a consulting role. Our study shows that the knowledge of midwives as to teratogenicity in general and to oral retinoids in particular can be improved. This is not surprising as midwives are not generally targeted by the PPP measures.

Prescribers considered the patient brochure and the risk acknowledgment form to be the most influential risk management measures, whereas the warning symbol was defined as the most important by pharmacists. Given that all materials need to be accompanied by appropriate counselling, there seems to be an opportunity for more cooperation between health care providers on how to effectively delivery information to patients. Some patients do not consider repetition redundant. Here pharmacists could play an important role as the last station, to ensure that patients have been sufficiently informed before they start treatment.

As observed from the responses of prescribers and pharmacists, there is a need to embed the information from regulatory sources into the prescribing and dispensing systems. The use of printed materials may hamper implementation when many other prescribing and dispensing processes are usually dealt within the electronic system. It is important for systems to be able to alert about the need to counsel the patient on pregnancy prevention. Yet, this may lead to alert fatigue, whereby prescribers and pharmacist might be inclined to disregard relevant information due to too many alerts. Our results also indicate that prescribers complain about lack of time to implement the PPP and of increasing bureaucracy related to the measures. Some GPs point out that specialists who start prescribing the oral retinoids should be the ones to provide counselling to patients. This is a contentious point and it is important for joint responsibility to be delegated, both to GPs and

pharmacists.

8.2 Interpretation

We observed some variability across countries as to the adherence to the measures of the PPP. This may reflect several aspects. Firstly, the variability in the timing of the implementation of the measures by member states. Even when countries had implemented measures at the level of the regulatory bodies materials may still not have reached health care providers and patients as, old packaging may still be available at wholesalers or in pharmacies at the time of our surveys. Therefore, this could partially explain the low implementation of some measures, as they have not yet permeated physicians/pharmacists daily practices. Secondly, there are also differences in the structure of health care systems, of medical and pharmacy settings, the degree of automation in health care and the presence of alerts in these health care information systems and of cultures of patient counselling and patients' expectations. The division of labour can vary between medical specialties, so as the remuneration for consultations and their length. that the contact with patients varies across pharmacies, and pharmacists take up the role to further inform patients, while others may not. Also the extent of collaboration between health care providers, especially between prescribers and pharmacists, also differs greatly across countries. In addition, there are also variations in the health literacy of the population in each country, even though those might not be sufficiently large across the 8 countries to account for the differences identified [v].

8.3 Limitations of study

As for the majority of survey studies, selection or non-response bias must be considered when looking closely into our results. As we were unable to select respondents randomly from established sampling frames, it is important to consider selection bias. It is well known that participants (in this particular case, the survey respondents) may be somewhat different from non-participants in that respondents may be more motivated to participate, either because of bad or good experiences or a general sense of commitment to the improvement of healthcare.

Patients who responded are likely to be more health literate than non-responders, and as such also more likely to be able to look for information and to recall having used it. They are also more likely to respond to surveys about health. This affects the generalizability of our results and thus the low uptake of the PPP may then be more pronounced than that reflected in our data. One should note that even if we had been able to do random sampling from a population sampling frame, the likelihood that responders would be more health literate would still apply.

This selection bias is also likely to have taken place regarding pharmacists, prescribers and midwives recruitment, i.e. the most interested professionals are more likely to be willing to respond to the survey, also more likely to be more aware which would then have boosted their awareness about teratogenicity and the recognition of the implemented PPPs in each country.

The non-response rate cannot be calculated, as the sample was obtained by disseminating emails and electronic messages through various channels. Many questionnaires were sent with electronic links in e-mails or electronic newsletters and at least part of these e-mails will have been identified as spam by respondents' e-mail programs. As in many other survey studies, the reasons for non-response remain unknown. However, we expect that non-response is largely caused by random effects. The patient recruitment method led to the selection of a convenience sample of women who were current or former users of valproate products. Therefore, the conclusions of the study cannot be generalized with certainty. Nevertheless, we have taken stock on the representativeness of patient respondents in the participating countries (see Annex 8), by comparing the available data from national statistics

or other studies (such as age distribution of valproate users, or proportions of different contraceptives used by women of reproductive age) with analogical data from the study. In most countries, the patient respondent sample was younger and had a higher education level than those reported in national data.

The Covid-19 pandemic also did make it harder to recruit health professionals, as the crisis imposed other pressing priorities than responding to surveys, and made it difficult to contact those who could distribute the links to the surveys. In some countries we were dependent on health care providers to contact users of retinoids. Sometimes health care providers were reluctant to contribute to the identification of patients because of the COVID-19 priorities. For the patient recruitment we have relied on social media more than anticipated, which may have lead to inclusion of women of younger age and of higher socioeconomic status and education.

The results from the qualitative interviews are not to be evaluated from the standpoint of generalizability. The aim of the interviews was to provide deeper understanding of what women who use or have used oral retinoids know and think about the PPPs. The main limitation here is that it was not possible to do a cross-country comparison of the understanding of patients, i.e., whether the themes that came up during the interviews would be similar. Results from the qualitative interviews must be interpreted with caution as these were primarily from one country (Portugal). In the Netherlands it proved difficult to motivate women to participate in interviews. Only one woman accepted. Women who were contacted were not interested, and did not see the point in granting an interview as they had already received so much information about oral retinoids' risks.

8.4 Recommendations

To ensure the effective delivery of the PPP all health care providers should be aware of their joint responsibility. Repetition of information is valuable. There could be some reluctance or even fear of overstating something that is already well-known, but this concern should be further discussed and awareness could be raised among healthcare professionals about all medicines with teratogenic potential, taking into account that legal responsibilities might differ per country.

As there is some reluctance about the use of risk acknowledgement forms both from prescribers and patients, reinforcing the importance of such forms is key. Concurrently, we would recommend finding ways to decrease the perceived 'paper-work'. Further research on how the measures and the educational materials fit current professional practice could be needed, i.e., on how the information should be framed to be culturally acceptable to patients and professionals. The use of paper materials may be perceived as old-fashioned both for patients and professionals, particularly among younger age groups.

Surprisingly, only a limited number of women mentioned to recall identifying the warning symbol included in the outer packaging. We recommended to further investigate why that occurs as a lack of comprehension could play a role. Subsequently, an improvement of the visibility of the warning symbol might be needed or further training of pharmacists and pharmacist technicians to alert patients about the warning symbol during dispensing and counselling.

The integration of clinical decision support systems in health care provider information systems can remind prescribers and pharmacists to appropriately inform patients. Such systems have shown impact in other fields (e.g., avoidance of drug-drug interactions), but should be used carefully and targeted towards patient groups. Also, the delivery of information materials may be improved with such systems, e.g., by either printing materials in the pharmacy or prescribers' office or by direction of patients to electronic sources that can be accessed both on personal computers and mobile devices.

Section 9: Conclusions

This study into the awareness and uptake of new risk minimisation measures on the teratogenic risks of using retinoids by women of childbearing potential has shown that the awareness about the risks associated with exposure to retinoids during pregnancy was high among patients, prescribers and pharmacists. The pregnancy prevention materials, however, that are offered do not seem to be yet fully incorporated in daily clinical practice and adherence to recommendations regarding the use of contraceptives and pregnancy testing is low. Several barriers to the implementation of the pregnancy prevention programme measures exist and suggestions for improvement have been made.

Prescribers considered the patient guide and the risk acknowledgment form to be the most influential risk management measures, whereas the warning symbol was defined as the most important by pharmacists. Given that all materials need to be accompanied by appropriate counselling, there seems to be an opportunity for more cooperation between healthcare providers on how to deliver effectively information to patients. Efforts should be undertaken to make pregnancy prevention a joint responsibility of all health care providers involved but to prevent unnecessary repetition of counselling and too much bureaucracy.

Health care providers complain about lack of time to implement the PPP and of increasing bureaucracy related to the measures. Educational materials do not always reach patients. Materials should preferably be linked to the drug-packaging or be integrated in health care information systems.

Finally it is important to note an additional finding from our study. Not all health care professionals identified women under 18 and over 44 to be in a fertile age, whereas they undoubtedly are so from a biological perspective. This was particularly evident in Southern and Eastern countries included in our study. This may have relevant implications for the information being provided to these women.

The findings of this study should be integrated with the findings of epidemiological work into the occurrence of pregnancies with retinoid exposure in the different European countries. Additional qualitative work may be needed to get more insight in the barriers and facilitators of the pregnancy prevention program. Health care providers and patients should be involved in redesigning these programs if further changes to the program seems needed.

Section 10: References

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ANNEX 1 - INVENTORY OF ORAL RETINOIDS 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® TEVA	hard capsules 25 mg
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

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.

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

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|

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

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.
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

Age Group	INN	Number of packages dispensed to women	Number of packages dispensed to men	Total Amount of packages dispensed
	Acitretin	12	15	27

10 - 14 years	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
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
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 (♀ chronic users, adherent to therapy)***
acitretin	D05BB02	10mg cap (33%); 25mg cap (67%)	Acitretina IFC / Neotigason	23142,24	*92*
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*

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

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

ANNEX 3 - Questionnaire for GPs and medical specialists

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 oral retinoids 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.

e

ANNEX 4 - Questionnaire for pharmacists

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;

ANNEX 5- Questionnaire for patients

(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 - Protocol for translation of questionnaires on impact of EU pregnancy prevention measures program from English into local languages

From the UCPH team: Anna Birna Almarsdóttir, Johanne Mølby Hansen, and Ramune Jacobsen

Step 1:
Two native speaking researchers (or translators) translate the questionnaires in pairs (valproate and retinoid). I.e. they translate the two patient questionnaires, the two GP questionnaires, the two specialist questionnaires, and two pharmacist questionnaires in tandem. This process results in individually translated versions of the 8 questionnaires from the two translators.

Step 2:
The two translators then meet, compare and discuss the wording of each question in their individual versions for each of the four pairs of questionnaires (valproate and retinoid).

In this process they focus on:

- The target group for the questionnaires and their use of words and specific terms
- How patients as lay persons use words and terms about medicines and health
- Consistency of wording throughout all the questionnaires, although the patient questionnaires will sometimes use different words from those in the questionnaires for professionals
- Keeping the wording as simple as possible

This process results in the one agreed-upon version for each of the 8 translated questionnaires.

Step 3:
Then a third native speaking researcher (or validator), who has not seen the questionnaires before, reads the agreed-upon version of the translated questionnaires raising questions and noting any lack of clarity, which then are clarified during a meeting with the two translators.

This process results in the validated versions of the 8 translated questionnaires.

Step 4:
The validated versions of the 8 translated questionnaires are then compared to their corresponding English versions and any remaining inconsistencies are resolved by consensus between the two translators and the validator.

This process results in the final versions of the 8 translated questionnaires.

ANNEX 7 - SCRIPT FOR TELEPHONE INTERVIEWS – ORAL RETINOIDS

Introduction

Good morning/good afternoon. My name is X and I'm a researcher from Y.

First of all, we would like to thank you for your willingness to participate in this interview. Your collaboration will helps us to better understand the information that has been provided about the use of certain medicines.

As mentioned in the email we have sent previously, this interview will be recorded to allow accurate analysis, however, no personal information will be published in the course of this research. The recording will be destroyed once the notes are completed.

We expect that this interview will take approximately 20 minutes.

Can we proceed or do you have any questions that you would like to ask now?

We are going to talk about your experience of taking one of the specific medicines our research focusses on, to be more specific: oral retinoids

Sociodemographics (questions that intend to characterize the participant's profile)
1. **What is your year of birth?** 2. **What is the highest level of education that you completed?** 3. **Is the region where you live urban or rural?**
Therapy profile (questions that intend to characterize the participant's pharmacological profile)
4. **What is the name of the medicines you are using / have used?** **I would like to focus on medicine X and ask you some questions.** 5. **Are you currently undergoing treatment with medicine X or did you in the past?** 6. **If "in the past" - do you remember when? (was it before or after 2018)?** 7. **For which indication are you / were you taking medicine X?** 8. **Who prescribed this medication?**
Knowledge about the risks of therapy (questions that intend to characterize the level of knowledge of the participant, timing and sources of information about the medication risks)
9. **Are you aware that this medicine X can cause serious problems when used during pregnancy?** 10. **HOW were you informed?** 11. **WHO informed you?**

12. **WHEN were you informed? How often have you been informed?**

    a. **During the first consultation**
    b. **At consultations thereafter**
    c. **At the pharmacy, when being dispensed the first prescription**
    d. **At the pharmacy, being dispensed refill prescription**
    e. **When I mentioned I wanted to become pregnant to my healthcare professional**
    f. **When I became pregnant**

13. **At the end of that explanation were you fully informed?**
14. **Did you feel free to ask any questions to the person providing you the information?**
15. **Did you feel involved in the decisions about your treatment?**

Knowledge of the necessary measures and educational materials

(questions that aim to characterize the level of knowledge of the participant, timing and sources of information on the necessary measures and their educational materials, as well as heir suitability)

16. **Has the need for effective contraception and pregnancy tests been discussed with you?**
17. **WHO did it and WHEN? Once or on several occasions? Reminders?**
18. **We would like to know if you have seen or received about any of the materials or measures that I will list, and WHO provided them and WHEN.**

ORAL RETINOIDS (brief explanation of materials)

- **Patient guide with patient card**
- **Packaging warning notice**
- **Information leaflet**
- **Prescription valid for only 7 days**
- **Prescription for only 1 month of therapy**

19. **Regarding the materials mentioned above, do you consider them suitable?**
    - **Are they useful materials?**
    - **Are they the most effective way to communicate?**
    - **Is the message clear and objective?**

20. Regarding the health professionals involved (family doctor, specialist doctor, pharmacist, midwives), what is your opinion on their role as information providers ?
Suggestions for more effective communication in the future
Finally, we would like you to brainstorm about what would be the best way to convey this information (give some options: orally, through an app, with the delivery of a card, etc. Allow to speak freely)
Is there any other aspect that you would like to share on this subject and that has not been addressed?

ANNEX 8 Representativeness of respondents per country

Belgium

In Belgium, oral retinoids are licenced for the treatment of severe, refractory acne (isotretinoin), severe psoriasis (acitretin), severe keratinisation disorders (acitretin) and mainly prescribed by dermatologists (76.1%).

Retinoids are mainly used by young females. In Belgian respondents, the mean age of retinoid users was 25 (range 17 to 50 years) and nearly all (98%) were current or former users ef isotretinoin. This is in line with the prescription figures which indicate that young females were the main users or oral retinoids (National prescriptions database 2014).e

Among the Belgian patient respondents, 71% indicated to use contraception. This figure of fertile women using contraception is within the 84% threshold reported in 2018 by the National Health Survey (Charafeddine et al., 2018), and the 54% reported from national prescription figures (Algemeen Pharmaceutische Bond (APB), 2018). The most frequently used contraception method by Belgian patients were oral contraceptive pills (50%) followed by IUDs (17%) and condoms (17%). This is in line with results from the National Health Survey which have shown that the pill was most popular among women aged 14 to 29 (64%) and then substantially decreasing in the age groups 30-39 years (35.7%) and 40-49 years (34.1%), in favour of the hormonal IUD (Charafeddine et al., 2018).

Among the prescribers who responded to the oral retinoids survey, 42% were dermatologists. According to our National prescriptions database, dermatologists are responsible for 76% of all isotretinoin prescriptions. 79% of responding pharmacists were female, which is in line with the national figure of 71%.

Denmark

Only ***0.6%*** of all women **patients** of reproductive age using retinoids responded to the survey: 51 in the survey vs. 8383 women aged 18 to 44 years old purchased available oral retinoids in primary care in DK over 2019 (medstat.dk).

The oral retinoids used by our patients overlap greatly with those reported in national prescription statistics, namely isotreinoin - 98% use in the study vs. 99% nationally; and for acitretin - 2% in the study vs. 1 % nationally.

The percentage of women in childbearing age in our sample who used hormonal contraception (oral contraceptive pills or IUD) was considerably higher (by appr. 30%) than that reported at national level : 54,9% in our study vs. 23,5%, respectively (statistikbanken.dk, medstat.dk). Possibly, women in our sample had been using or were still using oral retinoids, and thus more likely to use contraception to avoid pregnancy women in the age group 18-44 generally.

The response rate for **pharmacists** was reasonable **- *16%.*** The proportion of pharmacists responding who were women was very close to the gender distribution in pharmacy studies: 74% vs. 75%, respectively. Thus, the gender distribution in the sample matched the gender distribution of all pharmacists in Denmark. However, we cannot ascertain whether it matches the gender distribution

of community pharmacists in the country, as not all graduated pharmacists work in community pharmacies.

The response rate for **general practitioners** was still under the 1% response rate for GPs, namely (***0.76%).*** When compared to the national statistics, our respondents were younger, there was a bit less people with over 30 y of experience or over 65 y of age (appr. 3% difference). Gender distribution was very similar to the national data: 51% in the national statistics vs. 52% of women in our sample,. However, it should be noted that the numbers in the sample include both GPs and dermatologists

We obtained a very good response rate –of***35,5 %*** for **dermatologists**, approximately one third of all the dermatologists in the country responded. Our sample seems younger than the national average (majority 25-30 y and 45-55 y in our sample vs. majority 55-65 y nationally). Gender distribution in our sample is more equitable than in national statistics, for neurologists: 52% female dermatologists in our sample vs. 41% of women dermatologists at national level. However, it should be noted that the numbers in the sample include both GPs and dermatologists

Greece

No response rate data could be estimated for **patients**. As to **pharmacists**, the latest estimate of the pharmacist population is of 11,368 professionals. Given that 62 responded to our survey, that is a response rate of 0.55%.

A total of 3,232 **general practitioners** were registered in Greece in 2019, 21 responded to our survey, which means a response rate of 0.65%.

As to specialists, 1384 **dermatologists** were registered in 2019. Given that 63 responded to our survey, our response rate is approximately 4.5%.

No further information could be obtained regarding the gender and age distribution of pharmacists nor physicians.

Latvia

Our **patient** sample was very small and included only 17 patients, aged between 20 and 36 years old, with a slightly older distribution that the national data. The majority held undergraduate education, which seems a lower degree that the national estimates. Patients in our sample were more likely to use contraception than the national average: 73% in sample vs. 57.2% nationally. National data indicate that the most prevalent method are male condoms. In our sample condoms and oral contraceptive pills were most frequently used.

There are 1680 **pharmacists** registered in Latvia, of whom we were able to survey 51, thus obtaining a response rate of app. 3%.

There are 1680 general practitioners of which we surveyed 11, , thus obtaining a response rate of app. 0,65%.

There are 128 dermatologists in Latvia, of which we surveyed 32, obtaining a response rate of 25%.

No further information could be obtained regarding the gender and age distribution of pharmacists nor physicians.

Netherlands

According to national drug utilisation data (http://www.gipdatabank.nl) there were 14.966 women aged 15-45 years in The Netherlands that received at least one prescription for an oral retinoid in 2019. 59% of use was in the agegroup 15-24, and 41% in the agegroup 25-44. Prescription over age 45 was very low. The participants in the Dutch sample that responded to the questionnaire (n=21) had an average age of 27, and a comparable age-distribution. All responders were current or former users of isotretinoin, which is in line with Dutch prescribing practices. Distribution of highest received education was somewhat skewed towards higher education in the Dutch sample compared to the whole population. About 59% of all Dutch women aged 15-49, use some form of anticonception. This was higher in our sample (71%), but that may be due to a lower average age. The oral contraceptive pill was the most frequently used method of contraception both in our sample as in the whole Dutch female population (contraception data from Statistics Netherlands http: https://www.cbs.nl). Response among pharmacists was 88, with an average age of 42 (25-64), and 64% women. Both the age range and the gender-distribution mirror the total Dutch pharmacist population in which about 60% are women. Most oral retinoids are dispensed in a community pharmacy setting, so the 94% community pharmacists is to be expected. A total of 114 Dutch prescribers filled in the questionnaires of which 96% were dermatologists. The Dutch general practitioners' acne guideline advices to refer patients to dermatologists for treatment with oral retinoid, so this number is to be expected. In the Netherlands there are 480 registered dermatologists of which 109 (23%) filled in the questionnaire. 70% of the dermatologists that filled in the questionnaire was female, which was higher than the 60% females in all Dutch dermatologists.

Portugal

In the Portuguese sample, women with higher education represents 27% of the Portuguese sample which is similar to the portguese reality. In fact, according to the information available on the National Statistics Database, for females aged 15 and over, only 22,2% had obtained the highest level of education.

Regarding contraception use, 65% of our sample reported using them, which is a lower percentage than the 94% use reported by sexuality active women between 15 and 49 years, in a Portuguese study from 2016 [Águas F, Bombas T, Pereira da Silva D. Evaluation on portuguese women contraceptive practice. Acta Obstet Ginecol Port 2016;10(3):184-192)]. On the other hand, the type of contraceptives used by our sample were similar to the results obtained by Águas et al., with oral contraceptives pills (hormonal pills) being the most preferred, followed by male condoms and in third place by intrauterine devices and injected contraceptive *ex aequo*.

According to INFARMED data (portuguese regulatory authority), the female age group most exposed to oral retinoids is the group of 15-19 years.

There are 14667 pharmacists registered in Portugal (data from the Pharmacists professional association), of whom we were able to survey 133, thus obtaining a response rate of app. 1%.

There are 55432 physicians in Portugal (data from Physicians professional association) of which we surveyed 104, thus obtaining a response rate of app. 0,71%.

No further information could be obtained regarding the gender and age distribution of pharmacists nor physicians.

Slovenia

The mean age of our patient sample (27 years) is comparable to the mean age of all female patients between 16 and 55 years receiving retinoids in 2019 (27,7 years, range 16 to 54 years, SD 11,5 years). According to the National Public Health Institute, the most frequently used form of contraception are hormonal pills (used by 95% of women using any type of contraception). One out of three women aged between 20 and 24 years of age uses hormonal contraception and every 5th woman in the age group 15 to 19 years and 25 to 29 years; after 30 years of age, the use of hormonal contraception drops. These data are comparable with the results from our sample, where 27% of women reported use of contraceptive methods.

In 2019, a total of 1182 pharmacists worked in community pharmacies in Slovenia. The responses to the questionnaire were obtained from 60 pharmacists, resulting in a 5% response rate.

In Slovenia we have 950 registered GPs and 315 GPs in training. Estimated from the national prescriptions database, 122 GPs have prescribed retinoids in 2019 (6% of all registered GPs and GPs in training). The responses to the questionnaire were obtained from 3 GPs, resulting in a 2,5% response rate. The extremely low response rate might be attributed to the Covid-19 pandemic as well as to the general low prescribing rate of retinoids by GPs.

Based on the estimates from the national prescriptions database, a total of 69 dermatologists prescribed retinoids to female patients in 2019. We have received responses from 25 dermatologists, which sums up to a 36% response rate.

Spain

Given the access to primary health data by the Spanish researchers based in Navarre, we were able to compare baseline data among the female population and our sample.

Comparison of age and sex:

Total number of women in Navarre between 15-49 years	**143,638**
Women Navarre 15-24 years	23.7%
Women Navarre 25-39 years	39.7%
Women Navarre 40-49 years	36.7%

Total number of women in Navarre TAKING ORAL RETINOIDS between 19-49 years	**697**
Women Navarre TAKING ORAL RETINOIDS 19-24 years	262 (37.6%)
Women Navarre TAKING ORAL RETINOIDS 25-40 years	353 (50.6%)
Women Navarre TAKING ORAL RETINOIDS 41-49 years	82 (11.8%)

Mean age of women in Navarre taking oral retinoids between 19-49 years: 28.4 (range: 19-50) years

During the study duration there were 697 women aged 19-49 years taking oral retinoids in Navarre, of which 673 were prescribed isotretinoin (96.6%) and the rest acitretin (3.4%). These data are similar to those obtained from our sample (95% of the patients responding the survey had received isotretinoin and 2% acitretin).
The mean age among patients age taking oral retinoids in Navarre was 28.4 (range: 19-49) years, slightly higher than the mean age in our sample [26 (range: 17-43) years).

Comparison of contraception use and methods:
A National Survey on Contraception was implemented in Spain in 2020 (Habits of the female population in relation to the use of contraceptive methods)[1]. The survey was carried out between July 31 and August 15. A total of 1,800 women aged between 15 and 49 years participated in the survey. A percentage of 70.3% of Spanish women of childbearing age currently use a contraception method, while 29.3% do not use any (this includes women who are not sexually active). The distribution of those using a contraceptive method by age range is as follows:

15-19 years: 62.9%; 20-24 years: 74.7%; 25-29 years: 80.4%; 30-34 years: 66.9%; 35-39 years: 66.8%; 40-44 years: 66.5%; 45-49 years: 66.9%.

The condom (31.3%) is the main contraceptive method used by women of childbearing age who are sexually active. The Second choice is oral contraceptive pills, which are mentioned by 18.5% of women. The copper intrauterine device (IUD), partner's sterilization and hormonal IUD are used in 4.0-4.3%. All other methods are uncommon (<2.5%). A percentage of 25.7% of the women declares to use two contraception methods simultaneously. Overall, the condom is the most widely used method of contraception for women across all age groups. Oral contraception is highest among women aged 20-24, and declines with age. The choice for contraception method is the responsibility of gynecologists, followed by own initiative and then by GPs.

In our sample, the percentage of women using contraception was significantly lower than the percentage obtained from the National survey (40% vs 70.3%). The most frequently used contraceptive method in our study was the contraceptive pill (64.7%), followed by condom (29.4%) and IUD (11.8%). This does not overlap fully with the results of the national survey.

Survey participants were first recruited from Navarre Health Service information systems, but later the surveys were also disseminated through patient organizations based in our region but also at national level, and through social media. Some participants might therefore reside in other regions of Spain. However, no differences are expected in terms of pregnancy prevention practices between women from our region and those in other regions.

Pharmacists: As of 2019, there were 1509 licensed pharmacists in Navarre, of which 1,134 (75.1%) were community-based pharmacists. Overall, 99 pharmacists participated in the survey, all of them community pharmacists, which represents a response rate of 8.7% for this group. As to gender, there are 1,154 females (76.5%) and 355 males (23.5%) registered, which is in line with the majority of female responders in our survey (81%). Average age of all licensed pharmacists in Navarre is approximately 45 years, which is again similar to the average age in survey responders (43 years).

Prescribers: There are 427 GPs in the Navarre Health Service, of which 32.3% are male, with a mean age of 53.3 years. A total of 20 dermatologists are registered in the Navarre Health Service, of which 15% are male, with a mean age of 45.0 years.

The distribution of GPs and dermatologists by years of profession is shown below:

Years of profession	GPs (no., %)	Dermatologists (no., %)
0-5	26 (6.1%)	2 (10.0%)
6-10	59 (13.8%)	4 (20.0%)
11-20	107 (25.1%)	7 (35.0%)
21-30	153 (35.8%)	5 (25.0%)
≥31	82 (19.2%)	2 (10.0%)

A total of 50 prescribers participated in our survey, of which 42% were male, with an average age of 47 years. Of those responding, 60% were dermatologists (n=30) and 40% GPs (n=20). Most of the responders had 21-30 years of experience (42%) followed by 11-20 years of experience (20%). These results overlap largely with the overall years of experience reported by most GPs in Navarre.

As described in the protocol, survey participants were first recruited from the Navarre Health Service through mailing lists but, later on, surveys were also disseminated to professionals based at other regional systems or organizations through advertising on (professional) networks, websites and media. Although most participants belonged to the Navarre Health Service, there were some participants based elsewhere. Nonetheless, no differences are expected in terms of medical practices among professionals from our organization and those based at other regional services.

Midwives: A total of 153 midwives are registered in the Navarre Health Service, of which 4.6% are male, with a mean age of 41.6 years. The distribution of the midwives in Navarre by years of professional practice is as follows: 24.2% 0-5 years, 20.3% 6-10 years, 27.5% 11-20 years, 11.1% 21-30 years and 17.0% ≥31 years.

Fifteen midwives participated in the survey. As described in the protocol, first midwives from Navarre Health Service were recruited through mailing lists but, later on, surveys were also disseminated to midwives from other regional systems and organizations through advertising on (professional) networks, websites and media. However, no differences are expected in terms of medical practices between professionals from our organization and those based at other regional services.

Bias

Limitations inherent to cross-sectional surveys such as social desirability and selection bias cannot be ruled out. Web-based surveys tend to promote social desirability bias. Our results may therefore be an overestimation of the awareness and compliance among patients and healthcare professionals about the risk management measures, and the reality may be more discouraging. Voluntary participation of targeted healthcare professionals may lead to non-response bias and in our surveys several questions were left incomplete.