PASS Study Information

Title	Study to Evaluate Physician Knowledge of Safety and Safe Use Information for Diane-35 and Its Generics in Europe: An Observational Post-Authorisation Safety Study
Version identifier of the final study report	Version 1.0
Date of last version of the final study report	31 May 2016
EU PAS register number	ENCEPP/SDPP/9312
Active substance	INN: cyproterone acetate 2 mg/ethinylestradiol 35 µg; ATC code: G03HB01
Medicinal product	Diane-35 and its generics (CPA/EE)
Product reference	Not applicable
Procedure number	Referral: EMEA/H/A-107i/1357
Marketing authorisation holder(s)	Bayer Pharma AG on behalf of a group of marketing authorisation holders
Joint PASS	Yes
Research question and objectives	The primary objective of this study was to measure physician knowledge and understanding of the key information included in the educational material for Diane-35 developed by Bayer. Specifically, the following objectives were addressed: ▪ Investigation of whether physicians have received any educational material related to CPA/EE ▪ Assessment of physicians' knowledge and understanding of key safety information pertaining to the patient information card ▪ Assessment of physicians' knowledge and understanding of key safety information included in the prescribers' checklist pertaining to the following areas: – Contraindications relevant to thromboembolism – Risk factors for thromboembolism – Signs and symptoms of thromboembolism
Country(-ies) of study	Austria, the Czech Republic, France, the Netherlands, and Spain
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Marketing authorisation holder(s)

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1. Abstract

Title: Study to Evaluate Physician Knowledge of Safety and Safe Use Information for Diane-35 and Its Generics in Europe: An Observational Post-Authorisation Safety Study

31 May 2016

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Keywords: Diane-35 and its generics; post-authorisation safety study; evaluation of risk minimisation measures; physician survey

Rationale and background: At the request of the European Medicines Agency (EMA), a Dear Healthcare Professional Communication, a patient information card, and a prescriber checklist were developed and distributed to increase awareness and understanding about risks associated with Diane-35 (cyproterone acetate 2 mg/ethinylestradiol 35 µg) and its generics (CPA/EE). In addition, the current study was conducted to address the EMA's request to evaluate the understanding and use of these materials, which were distributed in addition to the routine risk minimization measures (RMMs), (i.e., Summary of Product Characteristics [SmPC], Patient Information Leaflet [PIL]).

Research question and objectives: The primary objectives were to measure whether physicians received the Dear Healthcare Professional Communication, the Patient Card, and the Prescriber Checklist, respectively, and to evaluate their awareness and understanding of the key safety messages.

Study design: The study was a joint, observational, cross-sectional study among physicians with recent experiences with CPA/EE. Bayer was responsible for liaising with the generic companies and was requested by the PRAC to take the lead in the consortium that was formed. Physicians who had recently prescribed CPA/EE within the previous 6 months were considered eligible. Physician specialty was considered when selecting the sample in each country based on the CPA/EE prescribing patterns in each country. The study targeted recruitment of up to 25% dermatologists in each country. The following physician specialties were recruited in each country:

- Austria and the Czech Republic: gynaecologists and dermatologists
- The Netherlands: general practitioners and dermatologists
- France and Spain: general practitioners, gynaecologists, and dermatologists

Eligible physicians were invited to complete a web-based questionnaire regarding their knowledge of key safety information included in the educational materials.

Setting: Austria, the Czech Republic, France, the Netherlands, and Spain

Participants and study size, including dropouts: Physicians were eligible to participate if they had prescribed CPA/EE within the previous 6 months. Across the five countries, 11,102 physicians were invited to participate, of whom 1,347 responded. Of these, 363 were ineligible, 6 refused consent, 154 did not respond to the consent question, 55 were excluded because the study had achieved its target for their specialty, 10 did not fulfil the definition of a completed questionnaire, and 759 physicians completed the questionnaire.

Variables and data sources: Data were obtained through questionnaire responses.

Results: The percentage of physicians who reported receiving at least one of the three educational materials was 51.0%: 45.5% received the Dear Healthcare Provider Letter (DHPL), 16.2% received the Patient Card, and 16.9% received the Prescriber Checklist. Knowledge was highest (≥ 80% of physicians) for symptoms of possible deep vein thrombosis, pulmonary embolism, and cerebrovascular accident; most important risk factors for thrombosis; instructions of use in smokers; and approved indication for moderate to severe acne. A smaller percentage of physicians (69.2%) was aware of the approved indication for hirsutism. Knowledge was variable with 65.2%-98.9% of physicians reporting correct responses for risky time periods/special situations. The percentage of physicians who responded correctly was variable for contraindications (59.3%-98.8%), symptoms of possible myocardial infarction (42.8%-98.8%), other general risk factors for thrombosis (42.2%-96.8%), instructions related to immobilisation (47.0%-97.2%), and selected concomitant medical conditions (44.7%-95.5%). Approximately 48% of physicians responded correctly to the question regarding prescribing CPA/EE for acne only after failure of topical therapy or systemic antibiotics. For most questions, knowledge did not vary by physician specialty, receipt of educational materials, number of patients prescribed CPA/EE in the last 3 months, and number of years practicing medicine.

Discussion: Knowledge of thromboembolism risk was 80% or higher. Knowledge was variable for topics that were more complex or less frequently encountered in which physicians might consult additional references. The knowledge about prescribing CPA/EE after failure of other acne treatments was approximately 48%.

Marketing Authorisation Holder(s): Bayer Pharma AG

Names and affiliations of principal investigators: Elizabeth Andrews, MPH, PhD, RTI Health Solutions, Research Triangle Park, NC; Kim Davis, MS, BS, RTI Health Solutions, Research Triangle Park, NC

2. List of abbreviations

ATE	arterial thromboembolism
Bayer	Bayer Pharma AG
CI	confidence interval
CPA/EE	cyproterone acetate 2 mg/ethinylestradiol 35 µg
CRM	Customer Relationship Management
DHPC	Dear Healthcare Professional Communication
DHPL	Dear Healthcare Provider Letter
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GP	general practitioner
MAH	marketing authorisation holder
NCA	National Competent Authority
PASS	Post-Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PIL	Patient Information Leaflet
RMM	Risk Minimization Measures
RTI-HS	RTI Health Solutions
SmPC	Summary of Product Characteristics
VTE	venous thromboembolism

3. Investigators

Principal Investigator

Investigator	Country	Institutional Affiliation
Principal		
Elizabeth Andrews, MPH, PhD	United States	RTI Health Solutions, Research Triangle Park, North Carolina

4. Other responsible parties

This was a joint, observational post-authorisation safety study (PASS). RTI Health Solutions (RTI-HS), an independent non-profit research organisation, was responsible for the design, conduct, analysis, and reporting of the study. Bayer Pharma AG (Bayer) is the marketing authorisation holder (MAH) of Diane-35 and the sponsor of the study. Bayer collaborated with RTI-HS on the study design and also was responsible for fulfilling any obligations for reporting results to regulatory agencies. In addition, 17 market authorisation holders for generic versions of Diane-35 participated in the study. Bayer was responsible for liaising with the generic companies. Acumen Fieldwork, a market research field agency with proven expertise in all methods of qualitative, quantitative,

and medical research field management and recruitment, was responsible for cognitive pretesting of the questionnaire. FreelanceCRA Network (FCRA), an international network of Senior Clinical Research Associates, was responsible for coordinating the determination of local requirements for regulatory and/or ethics committee notifications and submissions, as needed. Lightspeed All Global, a specialist agency solely focused on the operational aspects of market research among health care providers was responsible for physician recruitment and data collection.

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5. Milestones

Milestone	Planned Date	Actual Date	Comments
Regulatory approval of original protocol		11 September 2014	
Regulatory approval of protocol and physician questionnaire	August 2014	6 May 2015	Requested update was submitted April 2015
Completion of cognitive pretesting of questionnaire	February 2015	24 February 2015	
Registration in the EU PAS register	April 2015	9 April 2015	
Submission for institutional review board (IRB) review and approval, ethics committee (EC) review and approval (if required), and Commission Nationale de l'Informatique et des Libertés (CNIL) review and approval	IRB review and approval: April 2015	13 April 2015	IRB approval for request of exemption
	EC reviews not required		
	CNIL acknowledgement: July 2015	24 December 2015	
Data collection	Start after IRB approval and CNIL acknowledgement (in France) and continued for 3 months		
Netherlands		26 June 2015 to	

Milestone	Planned Date	Actual Date	Comments
		9 September 2015	
Austria		26 June 2015 to 13 October 2015	
Czech Republic		30 June 2015 to 20 August 2015	
Spain		17 September 2015 to 16 October 2015	
France		11 January 2016 to 21 February 2016	
Database lock		22 February 2016	
Final report of study results	2 months from completion of data analysis (targeted 29 May 2016)	31 May 2016	

6. Rationale and background

Diane-35 (cyproterone acetate 2 mg/ethinylestradiol 35 µg [CPA/EE]) was first authorised in Germany 1985. CPA/EE has been approved via national procedures and is available under several different trade names in all EU Member States (European Medicines Agency [EMA], 2013e). The revised indication for CPA/EE is treatment of moderate to severe acne related to androgen sensitivity (with or without seborrhoea) and/or hirsutism in women of reproductive age (EMA, 2013a). For the treatment of acne, CPA/EE should be used only after topical therapy or systemic antibiotic treatments have failed (EMA, 2013a). CPA/EE should not be used in combination with other hormonal contraceptives (EMA, 2013a).

The revised indication resulted from a review of combination medications containing CPA/EE that was initiated in February 2013 at the request of France, under Article 107i of Directive 2001/83/EC, (EMA, 2013f). The review was conducted by the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). The PRAC reviewed data related to the risks of thromboembolic events based on results from clinical studies, pharmacoepidemiological studies, published literature, postmarketing experience on the safety of these medications, and submissions from stakeholders (EMA, 2013a). The review concluded that the risk of venous thromboembolism (VTE) with these medications is 1.5 to 2.0 times higher than for combined oral contraceptives containing levonorgestrel and may be similar to the risk associated with contraceptives containing gestodene, desogestrel, or drospirenone (EMA, 2013b). Information on the risks of arterial thromboembolism (ATE) associated with these medications is sparse but indicates that this risk is lower than the risk of VTE (EMA, 2013b). Based on the review, the Coordination Group for Mutual Recognition and Decentralised Procedures—Human (CMDh) endorsed the recommendation of the PRAC, which concluded that the benefits of CPA/EE outweigh the risks, provided that several measures were taken to minimise the risk of VTE and ATE (EMA, 2013c).

The PRAC endorsed a Direct Healthcare Professional Communication to the health care professionals to communicate the revised indication and to highlight the risk of the thromboembolic events and it's risk factors at the end of the referral (June 2013).

The PRAC recommended that educational material for health care providers should focus on thromboembolism and its risks factors, signs, and symptoms and contraindications relevant to thromboembolism. In addition, MAHs were required to evaluate the effectiveness of this risk-minimisation communication. As part of the risk management plan, Bayer developed educational material, the Patient Information Card and Prescriber Checklist, for prescribers with the aim to increase awareness and understanding among physicians who CPA/EE. The current study was conducted to address the requirement to evaluate these elements of the risk management plan.

The timing and distribution of the educational materials was the responsibility of each MAH and each country. After the outcome of the PRAC referral procedure and the finalization of the educational materials, the materials were provided to the local Bayer offices in each country. The implementation of the educational materials in each country was subsequently agreed with the National Competent Authorities (NCAs). Both the national translations of the core educational materials as well as the manner of distribution in the specific country and the target stakeholder groups of health care providers were agreed upon with authorities at the country level. The NCA approval timelines varied between member states; first approvals were gained in July 2014 in Austria and Czech Republic, whereas the approval in Spain was received in April 2015.

Educational materials were disseminated within a broad variety of channels, such as post-mailed hardcopies (in all five countries in scope), hand delivered by Bayer representatives (Austria), posted on Bayer country websites (Netherlands, Spain, Czech Republic), posted on the NCA website (Netherlands, Czech Republic), and faxed (France). The timing of dissemination varied by country based on regulatory approval of the local translations, starting from July 2014 in Czech Republic to April 2015 in Spain. Target stakeholder groups for distribution of educational materials, as agreed with the NCAs of the member states, were dermatologists (all five countries in scope), gynecologists (Netherlands, Czech Republic, Austria, France), general practitioners (GPs) (Netherlands and France), pharmacists (Netherlands and France), and endocrinologists (France, Czech Republic). The educational material was distributed only to dermatologists in Spain.

7. Research question and objective

The primary objective of this study was to measure physician knowledge and understanding of the key information outlined by the PRAC. Specifically, the following objectives were addressed:

- Investigation of whether physicians have received any educational material related to CPA/EE
- Assessment of physicians' knowledge and understanding of key safety information pertaining to the patient information card
- Assessment of physicians' knowledge and understanding of key safety information included in the prescribers' checklist pertaining to the following areas:
  - Contraindications relevant to thromboembolism

- Risk factors for thromboembolism
- Signs and symptoms of thromboembolism

As part of good research practices, the protocol and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) checklist were registered in the EU PAS Register (ENCePP, 2015a) prior to the start of data collection (9 April 2015). The study was designed and implemented in line with the International Society for Pharmacoepidemiology *Guidelines for Good Pharmacoepidemiology Practices* (ISPE, 2007); EMA *Guidelines on Good Pharmacovigilance Practices (GVP), Module VIII – Postauthorization Safety Studies* (EMA, 2013d); and ENCePP *Guide on Methodological Standards in Pharmacoepidemiology* (ENCePP, 2015b).

The contract between RTI-HS and Bayer includes independent publication rights.

The RTI-HS study team received approval for exemption from review by the RTI International institutional review board on 13 April 2015.

8. Amendments and updates

None.

9. Research methods

9.1 Study design

The study was an observational, cross-sectional study of knowledge, understanding, and self-reported behaviour among a sample of physicians with recent experience with CPA/EE in five European countries (Austria, the Czech Republic, France, the Netherlands, and Spain). Eligible physicians were invited to complete a brief questionnaire regarding their knowledge of key safety messages as outlined in the CPA/EE educational materials. A cross-sectional survey approach was selected for this study because the main information on knowledge and understanding of the educational material could be obtained only through interaction with physicians. Annex 2 presents the educational materials.

9.2 Setting

This cross-sectional study was conducted in five European countries: Austria, the Czech Republic, France, the Netherlands, and Spain. The five countries included were chosen to provide some diversity in practice patterns and to observe physician knowledge in different settings. In addition, prescribing levels in these countries were such that there was a sufficient number of eligible physicians who had experience with CPA/EE to participate in the study.

Data collection ran from 26 June 2015 to 21 February 2016.

9.3 Subjects

9.3.1 Physician selection and recruitment

The physician sampling frame was constructed primarily from a physician panel composed of convenience samples in each country and derived from multiple sources (e.g., hospital books, medical directories, yellow pages, peer referrals). In Austria and the Czech Republic, where the physician panel sizes were limited, physicians also were recruited via telephone. Physician contact information was identified via a proprietary database and some publicly available sources (e.g., physician and clinician websites). In France, Spain, and the Netherlands, physicians were recruited via e-mail using a random sample of physicians from an existing physician online panel with the aim of obtaining a sample generally representative of physicians who have prescribed CPA/EE. In Austria and the Czech Republic, the entire population of eligible physicians in the physician panels was invited to participate given the smaller size of the countries. In addition, to supplement the panels, physicians in Austria and the Czech Republic were identified and recruited via telephone from different cities and different types of health care settings (e.g., public vs. private). Target numbers or ranges of respondents by country and within country by specialty were established in advance. When the target ranges had been met, no further responses were allowed in that category.

Physician specialty was considered when selecting the sample in each country based on the Diane-35 prescribing patterns in each country, with up to 25% of the target within each country being dermatologists. Specialties considered for each country were as follows:

- Austria and the Czech Republic: gynaecologists and dermatologists
- The Netherlands: GPs and dermatologists
- France and Spain: GPs, gynaecologists, and dermatologists

9.3.2 Physician eligibility

To participate, physicians must have met the following eligibility criteria:

- Licensed and practicing dermatologist, gynaecologist, or GP
- Prescribed CPA/EE to at least one patient in the past 6 months

9.3.3 Physician survey

The physician assessment was initiated in each country after a period of time sufficient to allow prescribers to have received the prescriber educational materials and use the information in their practice. Physicians who were recruited by telephone in the Czech Republic and Austria were given the option to complete the survey via the Internet or a telephone interview. For survey completion via the Internet, invitations were sent via e-mail to the selected sample of physicians, inviting them to participate and providing a link to a web-based questionnaire. Interested physicians logged in to the study website

by entering a unique identification number and password. The questionnaire began with informed consent. After participants consented, they completed the self-administered questionnaire. A screening question was included at the beginning of the questionnaire to confirm that the physician had prescribed CPA/EE within the past 6 months.

The web-based format for completion of the consent form and self-administered questionnaire was chosen because of the efficiency and utility of the mode (e.g., question-branching logic and ability to stop participants from going back to previous questions to change answers). Most physicians have convenient access to complete a web-based questionnaire, so the use of this technology is not believed to have introduced a respondent bias; however, an option for a telephone interview was offered to physicians who were recruited via telephone.

9.4 Variables

The questionnaire contained only closed-ended, multiple-choice questions (e.g., true/false/I don't know, yes/no/I don't know) with no free-text response fields and elicited responses measuring physician knowledge and understanding of the key safety information included in the CPA/EE educational material. CPA/EE was described in the questionnaire as "Diane-35 and its generics." The physician questionnaire included items in the following content areas:

- The approved indication of CPA/EE
- Contraindications relevant to thromboembolism (i.e., current VTE, ATE, or cerebrovascular accident; history of VTE, ATE, or cerebrovascular accident; and selected comorbid conditions)
- Risk factors associated with thromboembolism (e.g., obesity, prolonged immobilisation, surgery, age, smoking, selected comorbid conditions)
- Signs and symptoms of a thrombus (e.g., unusual unilateral leg pain; sudden severe pain in the chest; sudden breathlessness; visual disturbances; weakness or numbness in face, arm, or leg)

The questionnaire included additional items to characterise the physicians and their practices (e.g., physician specialty, years in practice, patient volume) and to investigate physician receipt and use of any educational materials related to CPA/EE. Annex 3 provides the physician questionnaire.

9.5 Data sources and measurement

The source of information for the study was self-reported data collected from physicians using a standard questionnaire with closed-ended response choices.

The questionnaire was developed using best practices for instrument development. The questions were tailored to the study objectives and the information in the CPA/EE educational materials. Additional questions were included to obtain information needed to describe the study population and assess potential differences across subgroups.

To thoroughly evaluate the questionnaire before fielding the study, it was tested through cognitive interviews with physicians in each country. The pretest interviews helped to identify problems with questionnaire items, such as wording and response choices, and ensured that participants understood the questions. Likewise, the cognitive testing helped to identify cultural or translational issues with the draft questionnaires so that they could be modified to meet the individual needs of each country while maintaining comparability across the study.

Interviews with 9 physicians were conducted first in Austria using a German version of the questionnaire to identify issues and optimise wording. Based on feedback from physicians in Austria, the questionnaire was revised in English, and the questionnaire was then translated into Czech, Dutch, French, and Spanish. Interviews with 4 physicians per country (16 total) were then conducted to confirm wording and facilitate cultural adaptation to each country. Based on participant feedback during cognitive testing, several revisions were made to simplify the questionnaire to aid physicians in completion prior to the start of data collection.

9.6 Bias

In any observational study, researchers must address the potential for biases, particularly if there is a possibility that the respondents are not representative of the target population. Likewise, the potential for response error may present an additional source of bias. Efforts were made to both minimise and identify potential sources of bias in this study as described below.

9.6.1 Cognitive pretesting

The physician questionnaire was cognitively pretested prior to data collection to identify any problems with the questionnaire items, wording, and response choices as well as to ensure consistency across cultures and languages. This process helped to ensure that the questions measured the appropriate concepts consistently and accurately across all countries.

9.6.2 Sample selection

To minimise sampling bias, the sampling frame was stratified by specialty in an effort to recruit a sample that was generally representative of the distribution of prescribers in each country. From these strata, physicians in France, the Netherlands, and Spain were randomly selected from existing physician panels and invited to participate. For Austria and the Czech Republic, all potential prescribers included in the panels were invited to participate, and physicians also were recruited via telephone. Demographic (e.g., sex and age) and practice characteristics were collected and compared among the eligible physicians as well as physicians who were not eligible to participate in the survey based on the screening question (i.e., CPA/EE within the previous 6 months). In addition, the demographic and practice characteristics were compared with those characteristics

available for prescribing physicians from other external sources outside the survey data-collection efforts. Furthermore, the diversity of specialties included in the final sample gave some assurance that the target population was well represented.

However, despite efforts to ensure a generally representative sample, participants may have differed from non-participants on key characteristics measured in the survey (e.g., number of years practicing medicine, receipt of educational materials) and other types of characteristics. The direction and magnitude of such potential bias are not known.

9.6.3 Data-collection methods

The questionnaire was administered as an online questionnaire, and physicians who were recruited via telephone in Austria and the Czech Republic also were given the option to complete the questionnaire via telephone. Physicians were not able to go back and change answers to previous questions. This restriction minimised the likelihood of the respondent searching for answers via the Internet or other sources.

9.7 Study size

The study aimed to recruit 60 to 120 physicians per country in Austria, the Czech Republic, and the Netherlands and 100 to 200 physicians per country in France and Spain, for a total of at least 500 participating physicians. Assuming that the *total* sample of participants can be treated as a simple random sample and that the percentage of correct responses to a yes/no question is 85%, then the two-sided 95% confidence interval (CI) is 81.6% to 88.0% for a total sample size of 500. For the smaller countries, assuming that the sample of participants in each country can be treated as a simple random sample and that the percentage of correct responses to a yes/no question is 85%, then the two-sided 95% CI is 73.4% to 92.9% for a sample size of 60. For the larger countries, assuming that the percentage of correct responses to a yes/no question is 85%, then the two-sided 95% CI is 79.3% to 89.6% for a sample size of 200.

The widest CIs (i.e., those corresponding to a sample size of 60) for the physician survey were deemed acceptable to allow reasonable precision to describe physician knowledge of the key safety messages in the educational materials.

9.8 Data transformation

The following summary variables were derived to facilitate evaluation and interpretation of the study results. Derived variables were created for each of the 12 knowledge questions that had more than one correct "Yes" response to them (i.e., questions 8, 10-15, and 17-21); these variables indicated the number of correct responses selected. For example, question 17, which had six correct "Yes" responses, had the following six derived variables:

- **Q17_6 Correct**: 1 if all six of the correct "Yes" responses were ticked "Yes"; 0 otherwise

- **Q17_5 Correct**: 1 if at least five of the correct "Yes" responses were ticked "Yes"; 0 otherwise
- **Q17_4 Correct**: 1 if at least four of the correct "Yes" responses were ticked "Yes"; 0 otherwise
- **Q17_3 Correct**: 1 if at least three of the correct "Yes" responses were ticked "Yes"; 0 otherwise
- **Q17_2 Correct**: 1 if at least two of the correct "Yes" responses were ticked "Yes"; 0 otherwise
- **Q17_1 Correct**: 1 if at least one of the correct "Yes" responses was ticked "Yes"; 0 otherwise

9.9 Statistical methods

9.9.1 Main summary measures

The main summary measures consisted of the number and percentage of responses to each survey question and the number and percentage of responses for the derived variables to questions with more than one correct "Yes" response, in participants who were eligible for the study and provided informed consent.

Separate summary tables were generated to display the response distributions of all questions. The responses to the questions were divided into the following six categories:

- Physician prescribing and practice characteristics
- Receipt of educational materials for CPA/EE and ratings regarding usefulness
- Knowledge of the signs and symptoms of thromboembolism
- Knowledge of the risk factors for thromboembolism
- Knowledge of the prescribing guidelines, indications, and contraindications for CPA/EE
- Knowledge of the information for patients taking CPA/EE

The terminology used in the analysis tables reflects the wording used in the questionnaire. For example, the Dear HealthCare Professional Communication was more specifically referred to as the "Dear HealthCare Provider Letter" in the questionnaire, and CPA/EE products were referred to as "Diane-35 and its generics."

Table 1 presents the question numbers that correspond to each of these categories. The tables are provided in Annex 4. The correct-response (Yes*) and false-response options (No*) to the knowledge questions are indicated as such in the summary tables.

Table 1. Listing of Main Analysis Tables (Overall and by Country)

Table No.	Table Title	Question Number(s)
A-1	Physician Prescribing and Practice Characteristics of Participants and Non-Participants: All Countries	1-6, 24
A-1.1 to A-1.5	Physician Prescribing and Practice Characteristics of Participants and Non-Participants by Country	1-6, 24
A-1.9	Physician Prescribing and Practice Characteristics Among Eligible Physicians By Country and Overall	1-6, 24
A-2.1	Materials and Ratings About Diane-35 by Country and Overall	22, 23
A-3.1	Knowledge of the Signs and Symptoms of Thromboembolism by Country and Overall	18-21
A-4.1	Knowledge of the Risk Factors for Thromboembolism by Country and Overall	15, 17
A-5.1	Knowledge of the Prescribing Guidance, Indications, and Contraindications for Diane-35 by Country and Overall	8, 9, 14, 16
A-6.1	Knowledge of the Information for Patients When Taking Diane-35 by Country and Overall	10-13

9.9.1.1Stratification of Physician Results

In addition to the overall and by-country results, the knowledge questions have been stratified by the following variables to explore the association between each variable and physician knowledge levels:

- Physician specialty (based on response to question 1)
- Years in practice (based on response to question 2)
- Number of patients prescribed CPA/EE for the treatment of acne or hirsutism in the past 3 months (based on response to question 24)
- Whether the physician reported receipt of educational materials for CPA/EE (based on response to question 22)

Table 2 presents the table numbers that correspond to each variable that was stratified. Annex 4 presents these stratified results tables.

Table 2. Listing of Stratification Analysis Tables

Table No.	Table Title
A-2.2, A-3.2, A-4.2, A-5.2, A-6.2	Physician Specialty
A-2.3, A-3.3, A-4.3, A-5.3, A-6.3	Years Practicing Medicine
A-2.4, A-3.4, A-4.4, A-5.4, A-6.4	Number of Patients Prescribed Diane-35 or its generics in the Last 3 Months
A-2.5, A-3.5, A-4.5, A-5.5, A-6.5	Receipt of Educational Materials

9.9.2 Main statistical methods

Data analyses were descriptive and focused on summarising the questionnaire responses in eligible participants who provided informed consent. Summary tables consisting of frequencies with percentages were created for all questionnaire responses and the derived variables for questions with more than one correct "Yes" response. Percentages for individual questionnaire responses were based on the number of participants—that is, both those who answered the question and those who did not answer the question—and the number who did not answer the question was captured by the number and percentage "Missing" in the summary tables.

Descriptive tables summarising survey responses were generated for all countries combined and stratified by country, physician specialty, years practicing medicine, number of patients prescribed to in the last 3 months, and receipt of educational materials. No imputation of missing data was performed, and no formal hypothesis testing was conducted.

Exact 95% binomial CIs were calculated around the percentage of correct-response (Yes*) and false response options (No*) for the knowledge questions and for the derived variables to questions with more than one correct "Yes" response. For the 12 knowledge questions that had more than one correct answer, the results are reported in the corresponding sections below based on the percentage of physicians who correctly answered at least three-fourths of the correct "Yes" responses (i.e., selected 3 out of 4 correct "Yes" responses; 4 of 5; 5 of 6; 7 of 9; and 9 of 12).

Demographic (sex and age) and practice characteristics (physician specialty, type of practice, years practicing medicine, number of patients prescribed to in the last 3 months) were collected and compared among the eligible physicians (both for those who provided consent and for those who did not) and physicians who were not eligible to participate in the survey based on the screening question. In addition, available demographic and practice characteristics were summarised for prescribing physicians from other sources outside the survey data-collection efforts in Austria (Customer Relationship Management [CRM]-System, data on file, 2014), the Czech Republic (Institute of Health Information and Statistics of the Czech Republic, 2013; OneKey

[Cegedim Czech Republic] database, data on file, 2014), the Netherlands (OneKey [the Netherlands] database, data on file, 2014), Spain (IMS and Bayer CRM, data on file, 2014; Lightspeed All Global data on file, 2014), and France (Conseil de l'Ordre Medecins, data on file, 2014; Lightspeed All Global data on file, 2014).

All analyses were performed using SAS software version 9.4 (Cary, NC: SAS Institute, Inc.; 2002-2012). Programmes, logs, and output were independently reviewed for accuracy according to relevant standard operating procedures.

9.9.3 Missing values

Individuals who had the opportunity but did not answer a question were included in the count of respondents. These missing data counts and their respective percentages were summarised in the row labelled "Missing" under the question in the summary tables.

9.9.4 Sensitivity analyses

None.

9.9.5 Amendments to the statistical analysis plan

None.

9.10 Quality control

This project was conducted in accordance with the internal standard operating procedures of participating institutions.

All key study documents, such as the analysis plan and data-collection forms, underwent quality-control review, senior scientific review, and editorial review.

During data collection, the logic, range, and edit checks that were programmed in the electronic data capture system allowed for real-time resolution of data errors or data discrepancies. The data were monitored, and a respondent must have taken more than 6 minutes to complete the survey. In addition, each respondent must have had variation in their responses and provided a response to at least 12 of the 15 knowledge questions. False-response options were added for most of the knowledge questions to try to maximise the likelihood of the respondent paying attention to each response choice. The results for "false-response" options are presented in the summary tables; however, these results are not presented within the report, except where relevant (i.e., question 8 assessed knowledge of the approved indications for CPA/EE).

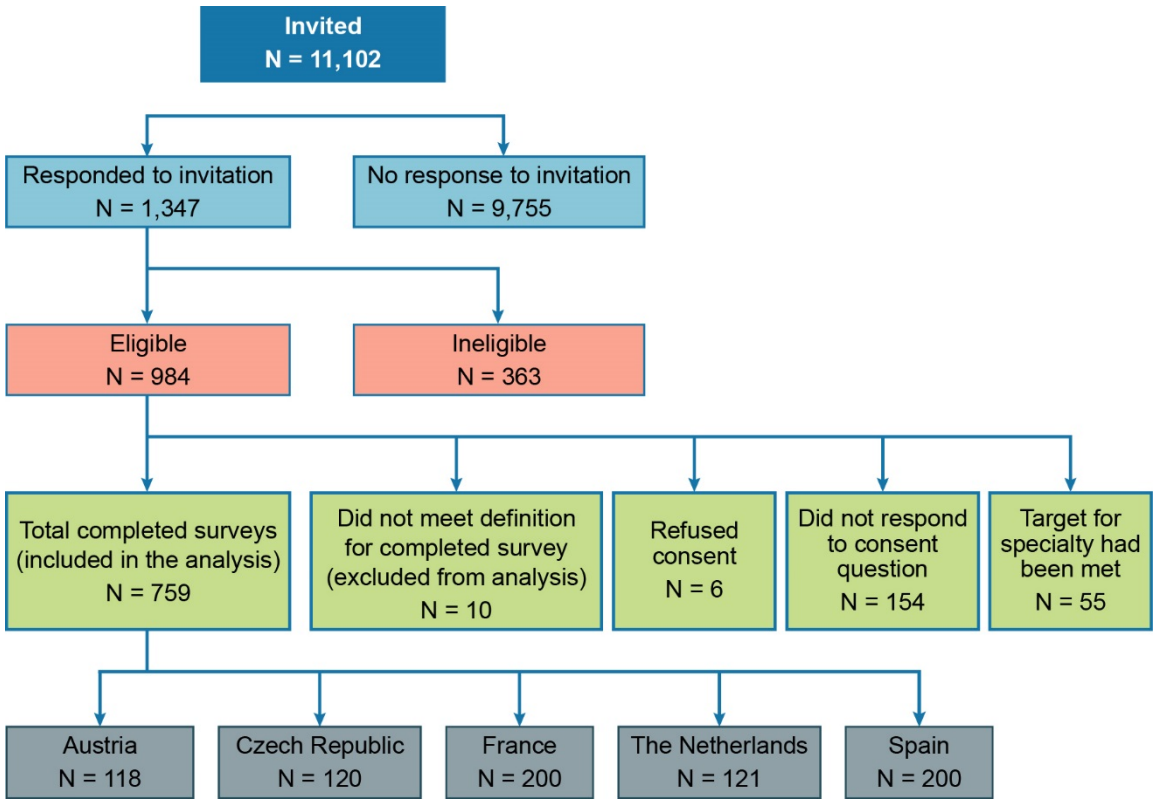
During the analysis, the principal programmer reviewed all programmes, logs, and output for accuracy according to relevant RTI-HS standard operating procedures. All analyses were confirmed through double independent programming.

10. Results

10.1 Participants

A total of 11,102 physicians were invited to participate in the survey. Of those, 1,347 responded to the invitation. Of the physicians who responded, 363 were ineligible, 6 refused consent, 154 did not respond to the consent question, 55 were excluded because the target for their specialty had been met, and 10 did not meet the definition for completion of the questionnaire (i.e., accessed the questionnaire link but did not complete the questionnaire, did not provide a response to at least 12 of the 14 knowledge questions, or completed the questionnaire in fewer than 6 minutes). The remaining 759 physicians completed the questionnaire resulting in a response rate of approximately 7% (759/11,102). Figure 1 presents the distribution of physicians invited to participate.

Figure 1. Distribution of Physicians



10.2 Descriptive data (Annex 4; Table A-1.9, Table A-2.1)

Table 3 describes the physician demographics and prescribing and practice characteristics.

Physicians were asked to specify their specialty as part of the questionnaire. Physician specialties included general medicine or family practice (42.0%) (GPs), dermatology (20.4%), obstetrics and gynaecology (OB/GYN) (37.0%), and internal medicine (0.5%) (Table 3). The study participants consisted of more males (62.6%) than females (37.4%). Overall, most participants (98.0%) were aged 30 to 69 years. Almost three-fourths of physicians (73.8%) reported that they practiced in a general setting, approximately one-third (37.5%) reported that they practiced at a hospital-based clinic, and 2.4% practiced in another type of setting.[1] Physicians' experience (as measured by years in practice) was categorised into 5-year increments up to 25 years. Approximately one-third of physicians (35.2%) had been in practice more than 25 years, with durations fairly evenly distributed across the increments fewer than 25 years.

Table 3. Physician Demographics and Prescribing and Practice Characteristics

	No. of Physicians (%)					
Question	Czech Republic (n = 120)	Netherlands (n = 121)	Spain (n = 200)	Austria (n = 118)	France (n = 200)	Overall (N = 759)
Physician specialty (question 1)						
General medicine or family practice	0	71 (58.7%)	117 (58.5%)	0	131 (65.5%)	319 (42.0%)
Dermatology	6 (5.0%)	50 (41.3%)	34 (17.0%)	31 (26.3%)	34 (17.0%)	155 (20.4%)
Obstetrics and gynaecology	114 (95.0%)	0	49 (24.5%)	87 (73.7%)	31 (15.5%)	281 (37.0%)
Internal medicine	0	0	0	0	4 (2.0%)	4 (0.5%)
Other	0	0	0	0	0	0
Missing	0	0	0	0	0	0
Sex (question 3)						
Male	71 (59.2%)	66 (54.5%)	127 (63.5%)	69 (58.5%)	142 (71.0%)	475 (62.6%)
Female	49 (40.8%)	55 (45.5%)	73 (36.5%)	49 (41.5%)	58 (29.0%)	284 (37.4%)
Missing	0	0	0	0	0	0
Physician age (question 4)						
18-29 years	0	1 (0.8%)	0	4 (3.4%)	0	5 (0.7%)
30-39 years	7 (5.8%)	32 (26.4%)	54 (27.0%)	30 (25.4%)	9 (4.5%)	132 (17.4%)

[1] This was a "tick all that apply" question; thus, the sum of the response percentages can be greater than 100%.

Question	No. of Physicians (%)					
	Czech Republic (n = 120)	Netherlands (n = 121)	Spain (n = 200)	Austria (n = 118)	France (n = 200)	Overall (N = 759)
40-49 years	34 (28.3%)	38 (31.4%)	56 (28.0%)	36 (30.5%)	46 (23.0%)	210 (27.7%)
50-59 years	43 (35.8%)	38 (31.4%)	76 (38.0%)	33 (28.0%)	94 (47.0%)	284 (37.4%)
60-69 years	33 (27.5%)	12 (9.9%)	13 (6.5%)	11 (9.3%)	49 (24.5%)	118 (15.5%)
≥ 70 years	2 (1.7%)	0	1 (0.5%)	3 (2.5%)	2 (1.0%)	8 (1.1%)
Missing	1 (0.8%)	0	0	1 (0.8%)	0	2 (0.3%)
Practice type[a] (question 5)						
General practice	113 (94.2%)	70 (57.9%)	117 (58.5%)	76 (64.4%)	184 (92.0%)	560 (73.8%)
Hospital-based clinic	33 (27.5%)	50 (41.3%)	91 (45.5%)	79 (66.9%)	32 (16.0%)	285 (37.5%)
Other	8 (6.7%)	1 (0.8%)	2 (1.0%)	3 (2.5%)	4 (2.0%)	18 (2.4%)
Missing	0	0	0	0	0	0
Years practicing medicine (question 2)						
0-15 years	**11 (9.2%)**	**55 (45.%)**	**80 (40.0%)**	**49 (41.5%)**	**35 (17.5%)**	**230 (30.3%)**
≤ 5 years	0	4 (3.3%)	1 (0.5%)	6 (5.1%)	0	11 (1.4%)
6-10 years	4 (3.3%)	23 (19.0%)	25 (12.5%)	23 (19.5%)	5 (2.5%)	80 (10.5%)
11-15 years	7 (5.8%)	28 (23.1%)	54 (27.0%)	20 (16.9%)	30 (15.0%)	139 (18.3%)
16-25 years	**45 (37.5%)**	**34 (28.1%)**	**71 (35.5%)**	**39 (33.1%)**	**72 (36.0%)**	**261 (34.4%)**
16-20 years	16 (13.3%)	19 (15.7%)	27 (13.5%)	20 (16.9%)	26 (13.0%)	108 (14.2%)
21-25 years	29 (24.2%)	15 (12.4%)	44 (22.0%)	19 (16.1%)	46 (23.0%)	153 (20.2%)
> 25 years	**64 (53.3%)**	**32 (26.4%)**	**49 (24.5%)**	**29 (24.6%)**	**93 (46.5%)**	**267 (35.2%)**
Missing	0	0	0	1 (0.8%)	0	1 (0.1%)

[a] This was a "tick all that apply" question; thus, the sum of the response percentages can be greater than 100%.

Source: Table A-1.9.

As described in Section 9.9.2, the knowledge questions were stratified by country and four additional variables to evaluate whether there were variations in knowledge among subgroups. Table 3 presents physician specialty and years practicing medicine, and Table 4 presents the distribution of responses overall and by country for the number of patients prescribed CPA/EE in the past 3 months and receipt of educational materials. Discussion of the results for these variables is included in the relevant results sections below.

Table 4. Stratification Variables

Question	Czech Republic (n = 120)	Netherlands (n = 121)	Spain (n = 200)	Austria (n = 118)	France (n = 200)	Overall (N = 759)
Total no. of patients prescribed Diane-35 and its generics for treatment of acne or hirsutism in the past 3 months (question 24)						
0-3 patients	67 (55.8%)	101 (83.5%)	63 (31.5%)	60 (50.8%)	111 (55.5%)	402 (53.0%)
None	2 (1.7%)	9 (7.4%)	6 (3.0%)	5 (4.2%)	14 (7.0%)	36 (4.7%)
1-3 patients	65 (54.2%)	92 (76.0%)	57 (28.5%)	55 (46.6%)	97 (48.5%)	366 (48.2%)
> 3 patients	50 (41.7%)	19 (15.7%)	128 (64.0%)	52 (44.1%)	87 (43.5%)	336 (44.3%)
4-6 patients	25 (20.8%)	12 (9.9%)	48 (24.0%)	29 (24.6%)	46 (23.0%)	160 (21.1%)
7-10 patients	17 (14.2%)	4 (3.3%)	37 (18.5%)	10 (8.5%)	23 (11.5%)	91 (12.0%)
11-15 patients	3 (2.5%)	2 (1.7%)	22 (11.0%)	7 (5.9%)	11 (5.5%)	45 (5.9%)
> 15 patients	5 (4.2%)	1 (0.8%)	21 (10.5%)	6 (5.1%)	7 (3.5%)	40 (5.3%)
I'm not sure	2 (1.7%)	1 (0.8%)	9 (4.5%)	6 (5.1%)	2 (1.0%)	20 (2.6%)
Missing	1 (0.8%)	0	0	0	0	1 (0.1%)
Which of the following material(s) have you received? (Tick all that apply) (question 22)						
Dear Healthcare Provider Letter	104 (86.7%)	32 (26.4%)	73 (36.5%)	21 (17.8%)	115 (57.5%)	345 (45.5%)
Patient Card	50 (41.7%)	9 (7.4%)	20 (10.0%)	27 (22.9%)	17 (8.5%)	123 (16.2%)
Prescriber Checklist	33 (27.5%)	15 (12.4%)	18 (9.0%)	32 (27.1%)	30 (15.0%)	128 (16.9%)
Other	9 (7.5%)	5 (4.1%)	11 (5.5%)	8 (6.8%)	6 (3.0%)	39 (5.1%)
None of the above	15 (12.5%)	79 (65.3%)	115 (57.5%)	67 (56.8%)	78 (39.0%)	354 (46.6%)
Missing	1 (0.8%)	0	0	0	0	1 (0.1%)

Source: Table A-1.9, Table A-2.1.

10.3 Outcome data

Not applicable.

10.4 Main results

Key results from physicians who completed the questionnaire are presented in the following sections. All physicians completed the survey via the Internet. The results are organised in the following categories, which also correspond to the analysis tables provided in Annex 4:

- Physician prescribing and practice characteristics
- Receipt of educational materials and ratings
- Knowledge of the signs and symptoms of thromboembolism
- Knowledge of the risk factors for thrombosis
- Knowledge of the prescribing guidance, indications, and contraindications for CPA/EE
- Knowledge of the information for patients when taking CPA/EE

First, we describe the results for the overall sample, then results stratified by country, physician specialty, years practicing medicine, number of patients prescribed to in the last 3 months, and whether the physician reported receiving the educational materials.

The text and figures highlight the results overall and stratified by country. The stratified results are reported within the text or figures where the stratifications resulted in a greater than 15% difference in the percentage of physicians who selected at least three-fourths of the correct responses. Knowledge did vary by physician specialty for three questions (i.e., 9, 13, and 14). Results are reported in Sections 10.4.5 and 10.4.6. Knowledge was higher for physicians who reported receipt of the educational materials for two questions (i.e., 13 and 14). Knowledge varied by number of patients prescribed CPA/EE in the last 3 months for question 9 and by years practicing medicine for question 13.

10.4.1 Physician Prescribing Practices (Annex 4, Table A-1.9; Question 24)

Physicians were asked to estimate the number of patients for whom they prescribed CPA/EE for treatment of acne or hirsutism in the past 3 months (see Table 4 for results). Approximately 5% had not prescribed CPA/EE to any patient in the past 3 months. Overall, almost half of physicians (48.2%) had prescribed to 1 to 3 patients, and results varied across the countries, ranging from 28.5% in Spain to 76.0% in the Netherlands.

Across all respondents, almost one-fourth (21.1%) had prescribed to 4 to 6 patients, and results varied across the countries, ranging from 9.9% in the Netherlands to 24.6% in Austria.

Across all respondents, approximately one-fourth of physicians (23.2%) reported prescribing to 7 or more patients, and results varied across the countries, ranging from 5.8% in the Netherlands to 40.0% in Spain.

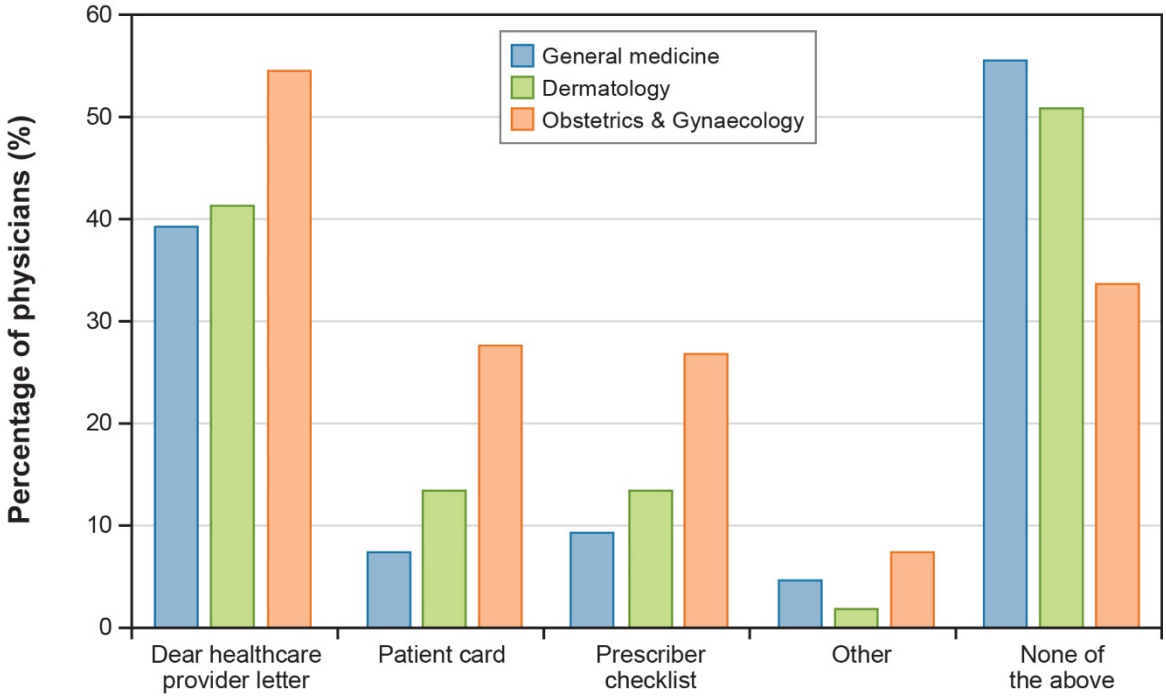
10.4.2 Receipt of Educational Materials and Ratings (Annex 4, Table A-2.1, Table A-2.2, Table A-2.3, Table A-2.4; Questions 22, 23)

Across all countries, the most frequently reported materials received by physicians were the Direct Healthcare Provider Letter (DHPL) (45.5%), the Patient Card (16.2%), and Prescriber Checklist (16.9%). The percentage of physicians who reported receiving at least one of the three educational materials was 51.0%. The receipt of each of these

materials varied by country and was highest for the Czech Republic. The reported receipt of the DHPL ranged from 17.8% in Austria to 86.7% in the Czech Republic. The reported receipt of the Patient Card ranged from 7.4% in the Netherlands to 41.7% in the Czech Republic. The reported receipt of the Prescriber Checklist ranged from 9.0% in Spain to 27.5% in the Czech Republic. In Spain, the educational materials were distributed only to dermatologists. Overall, almost half (46.6%) of the physicians reported that they did not receive any of the CPA/EE educational materials or any other materials; this ranged from 12.5% in the Czech Republic to 65.3% in the Netherlands.

A larger percentage of OB/GYNs reported receipt of any of the three CPA/EE educational materials (27.0%-54.8%) compared with dermatologists (13.5%-41.3%) and GPs (9.4%-39.2%) (Figure 2).

Figure 2. Responses to Question 22 Stratified by Physician Specialty: Which of the following material(s) have you received?



The percentage of physicians who reported receipt of each of the educational materials was similar and higher for physicians who had been practicing for more than 25 years (21.7%-55.1%) or 16 to 25 years (16.5%-49.0%) compared with physicians who had been practicing 0 to 15 years (11.7%-30.4%). A slightly higher percentage of physicians who had prescribed CPA/EE to more than 3 patients in the last 3 months reported receipt of each of the educational materials (21.4%-51.2%) compared with physicians who had prescribed to 0 to 3 patients (13.4%-41.8%).

Physicians were asked to rank how helpful the educational materials were in treating and educating patients (1 = not at all helpful to 4 = extremely helpful). Of the physicians who reported receiving the DHPL, 76.5% rated it as either a 3 or 4. Of the physicians who reported receiving the Patient Card, 80.5% rated it as either a 3 or a 4, and 73.4% of

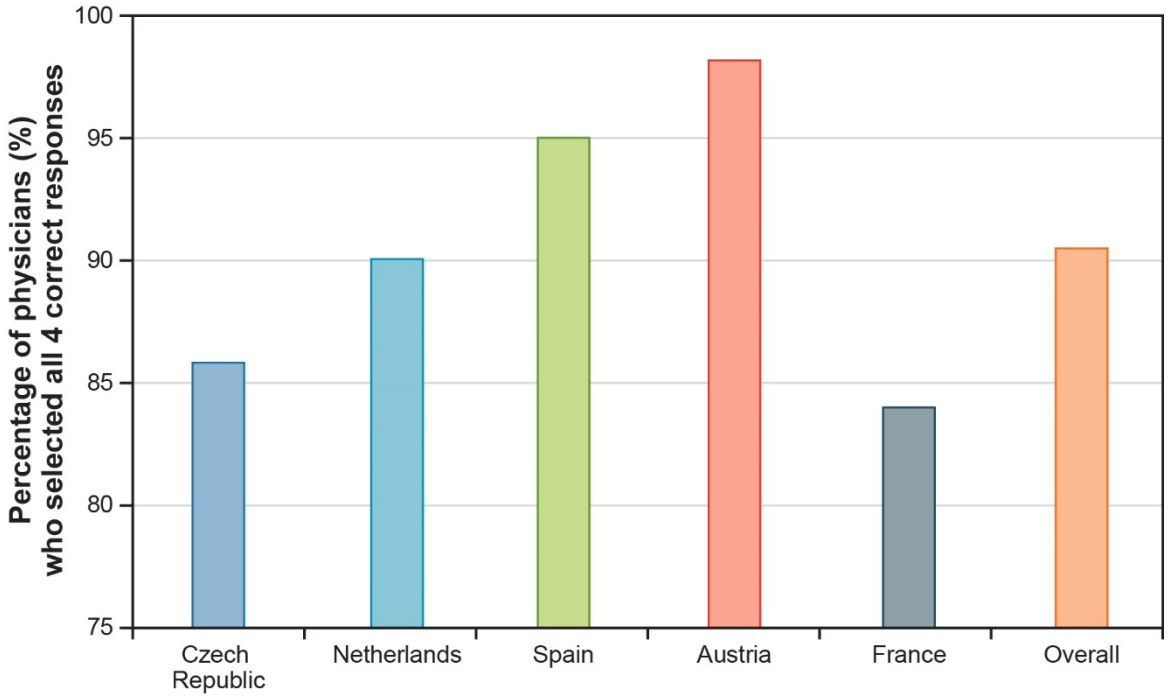
physicians who reported receiving the Prescriber Checklist indicated a 3 or 4 rating. These ratings were fairly consistent across countries and all other stratifications.

10.4.3 Knowledge of the Signs and Symptoms of Thromboembolism (Annex 4, Tables A-3.1-A-3.5; Questions 18-21)

Knowledge of Possible Deep Vein Thrombosis Symptoms (Question 18)

Physicians' knowledge of the symptoms of a possible deep vein thrombosis was high overall and consistently high across countries, with 90.4% of physicians selecting all four of the correct responses (i.e., severe pain in a leg, swelling in a leg, changes in skin colour in a leg, and feeling of tenderness or warmth in a leg). The percentage of physicians who selected all four correct responses ranged from 84.0% in France to 98.3% in Austria (Figure 3). Knowledge was consistently high across all stratifications.

Figure 3. Percentage of Physicians Who Selected All Four Correct Responses to Question 18: A patient should be advised to seek immediate medical attention for which of the following symptoms of a possible deep vein thrombosis?

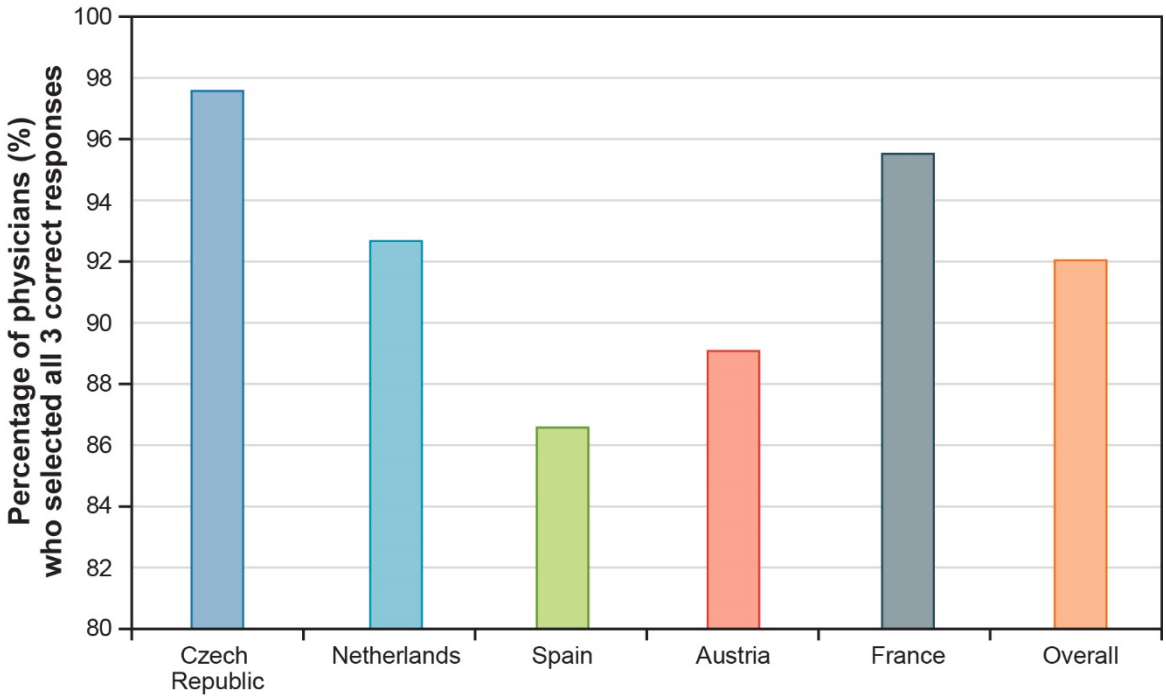


Knowledge of Possible Pulmonary Embolism Symptoms (Question 19)

Physicians' knowledge of the symptoms of a possible pulmonary embolism was high overall and consistently high across countries, with 92.0% of physicians selecting all three of the correct responses (i.e., sudden unexplained breathlessness or rapid breathing, severe pain in the chest that may increase with deep breathing, sudden cough without an obvious cause). The percentage of physicians who selected all three correct

responses ranged from 86.5% in Spain to 97.5% in the Czech Republic (Figure 4). Knowledge of possible pulmonary embolism symptoms was consistently high across all stratifications.

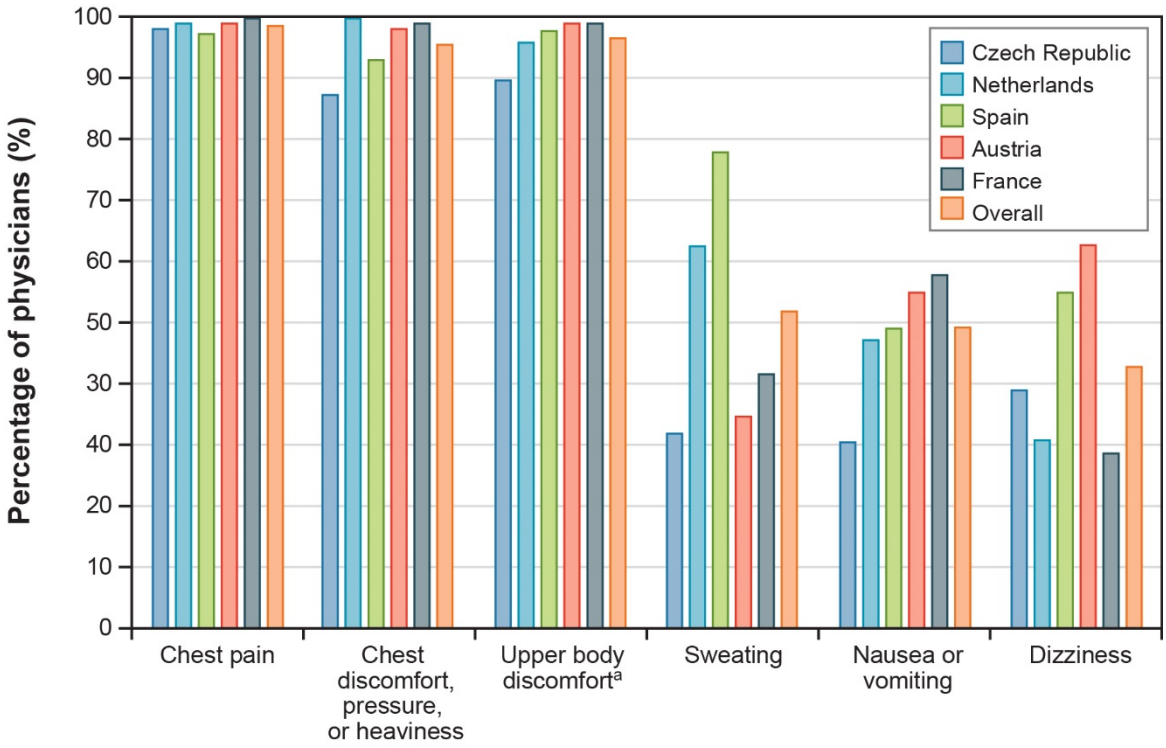
Figure 4. Percentage of Physicians Who Selected All Three Correct Responses to Question 19: A patient should be advised to seek immediate medical attention for which of the following symptoms of a possible pulmonary embolism?



Knowledge of Possible Myocardial Infarction(MI) Symptoms (Question 20)

Physicians were presented with a list of six correct responses to the following question: A patient should be advised to seek immediate medical attention for which of the following symptoms of myocardial infarction? Physicians' knowledge was high overall (95.7%-98.8%) on specific MI symptoms (i.e., chest pain; chest discomfort, pressure, or heaviness; upper body discomfort radiating to the back, jaw, throat, and arm together with a feeling of fullness associated with indigestion or choking), and ranged from 42.8%-51.9% for the three unspecific symptoms (i.e., sweating, nausea or vomiting, dizziness). Figure 5 presents correct responses by country and overall. Approximately 47% of physicians selected at least five out of six of the correct responses. Knowledge was similar across all other stratifications using the selection of five out of six correct responses as a basis for comparison.

Figure 5. Percentage of Physicians Reporting Correct Responses to Question 20: A patient should be advised to seek immediate medical attention for which of the following symptoms of a possible myocardial infarction?

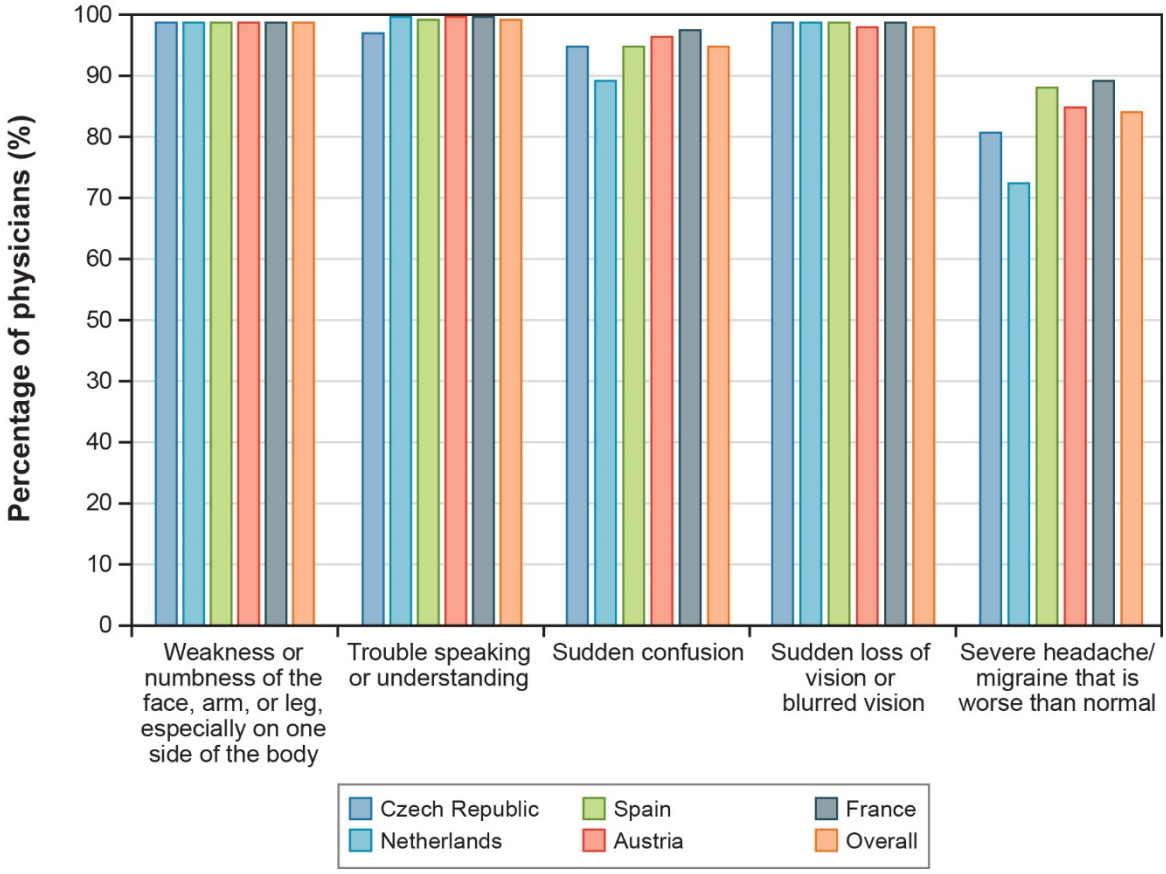


[a] Upper body discomfort described as radiating to the back, jaw, throat, and arm together with a feeling of fullness associated with indigestion or choking.

Knowledge of Possible Cerebrovascular Accident Symptoms (Question 21)

Physicians were presented with a list of five correct responses to the following question: A patient should be advised to seek immediate medical attention for which of the following symptoms of a possible cerebrovascular accident? Physicians' knowledge of the five symptoms of a possible cerebrovascular accident ranged from 84.7% to 99.5% for all symptoms and was 97.5% for physicians selecting at least four of the five correct responses (Figure 6). The percentage of physicians who selected four of the five correct responses ranged from 93.4% in the Netherlands to 99.0% in France. Knowledge levels were similar across all other stratifications.

Figure 6. Percentage of Physicians Reporting Correct Responses to Question 21: A patient should be advised to seek immediate medical attention for which of the following symptoms of a possible cerebrovascular accident?



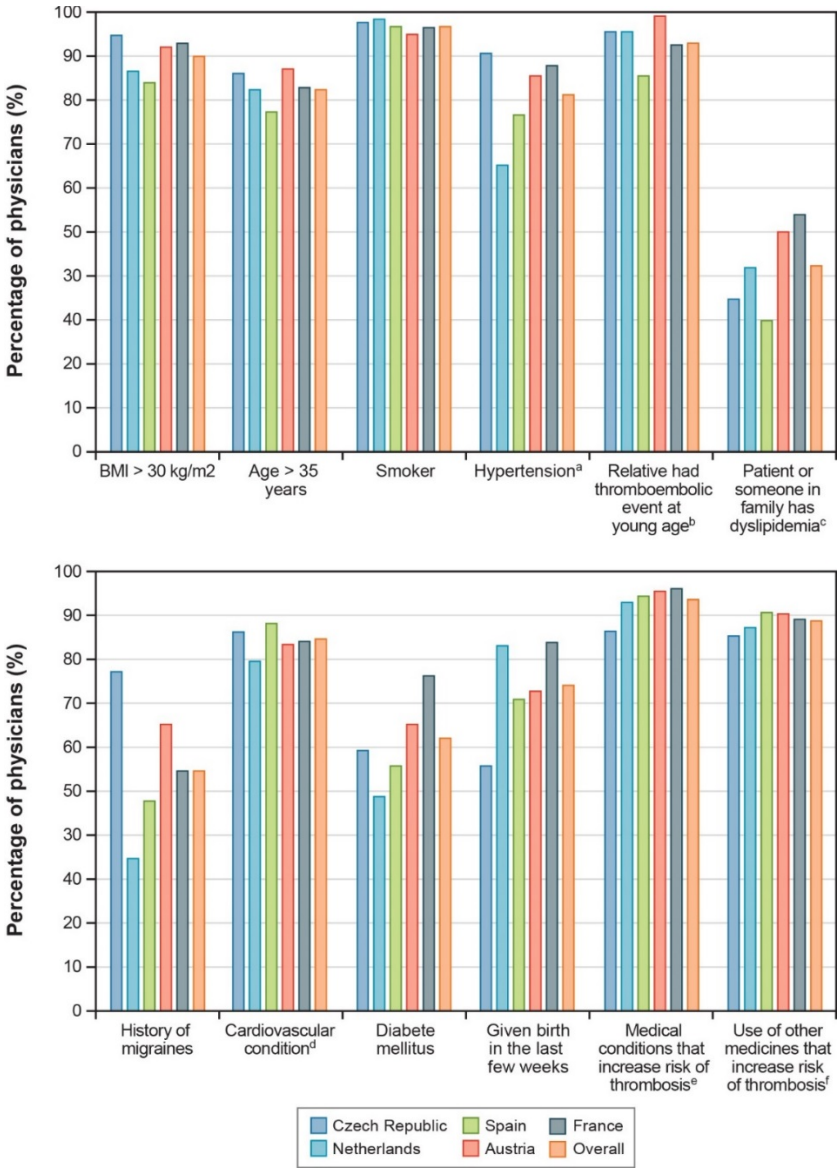
10.4.4 Knowledge of the Risk Factors for Thrombosis (Annex 4, Table A-4.1 to A-4.5; Questions 15, 17)

Knowledge of Risk Factors for Development of Thrombosis (Question 15)

Physicians' knowledge of the 12 risk factors associated with the potential development of thrombosis ranged from 81.4% to 96.8% on 8 of the possible risk factors. Physicians' knowledge on risk factors associated with diabetes mellitus was 62.2%, having given birth in the last few weeks (74.3%), patient or someone in her immediate family has dyslipidemia (42.2%), and history of migraines (54.9%). Figure 7 presents correct responses by country and overall.

Approximately three-fourths (71.0%) of physicians selected at least 9 of the 12 correct responses. Knowledge, using the percentage of physicians who selected 9 of the 12 correct responses as a basis, was similar across all other stratifications.

Figure 7. Percentage of Physicians Reporting Correct Responses to Question 15: Which of the following risk factors for the development of thrombosis should be considered prior to prescribing Diane-35 and its generics?



BMI = body mass index.

[a] Hypertension defined as systolic blood pressure of 140-159 mm Hg or diastolic blood pressure of 90-99 mm Hg.

[b] Answer choice was worded as "The patient has a close relative (e.g., parent or sibling) who has had a thromboembolic event at a young age (e.g., before 50)."

[c] Family was described as "immediate family."

[d] Cardiovascular conditions included atrial fibrillation, arrhythmia, coronary heart disease, and cardiac valve disease.

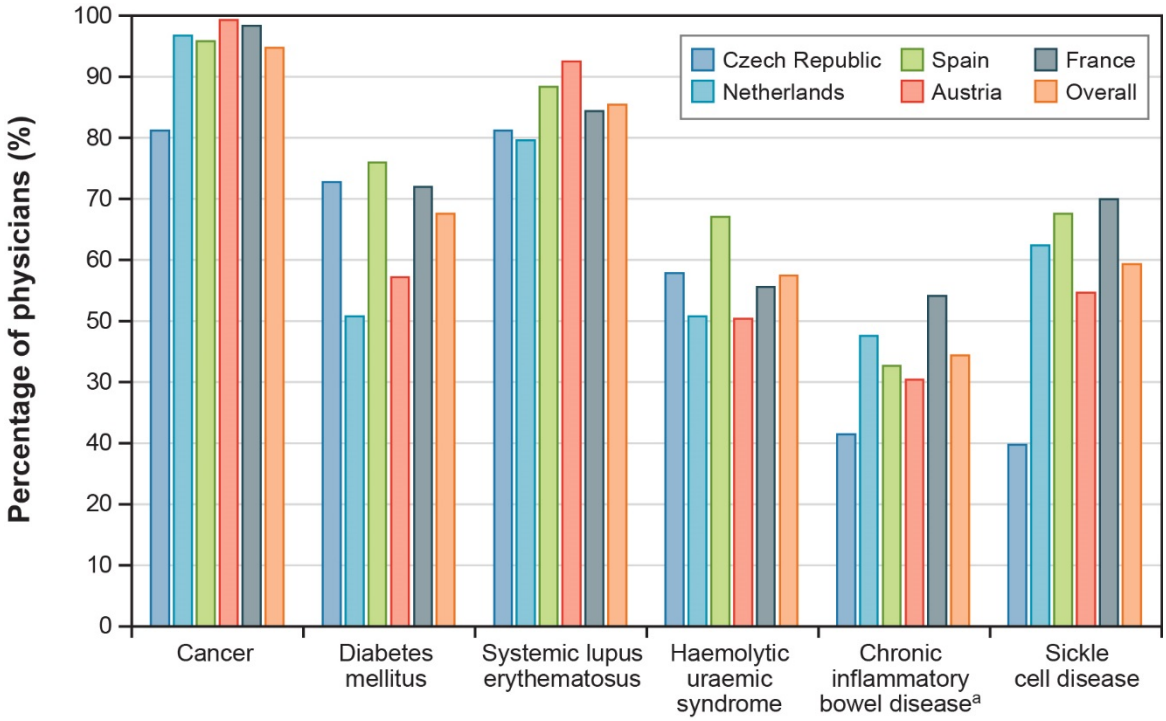
[e] Medical conditions included cancer, systemic lupus erythematosus, sickle cell disease, Crohn's disease, ulcerative colitis, and haemolytic uraemic syndrome.

[f] Medicines included corticosteroids, neuroleptics, antipsychotics, antidepressants, and chemotherapy.

Knowledge of Medical Conditions That Can Increase the Risk of Thrombosis (Question 17)

Physicians' knowledge of the six medical conditions that can increase the risk of thrombosis was highest for cancer (95.5%) and systemic lupus erythematosus (86.0%). Knowledge was 68.0% for diabetes mellitus and ranged from 44.7% to 59.8% for the other three medical conditions (i.e., haemolytic uraemic syndrome, chronic inflammatory bowel disease, sickle cell disease). The percentage of physicians who selected five of the six correct responses was 42.4% overall and ranged from 31.7% in the Czech Republic to 53.0% in Spain. Knowledge, using the percentage of physicians who selected five of the six correct responses as a basis, was similar across all other stratifications. Figure 8 presents correct responses by country and overall.

Figure 8. Percentage of Physicians Reporting Correct Responses to Question 17: Which medical conditions can increase the risk of thrombosis?



[a] Chronic inflammatory bowel diseases listed included Crohn's disease and ulcerative colitis.

10.4.5 Knowledge of the Prescribing Guidance, Indications, and Contraindications for CPA/EE (Annex 4, Table A-5.1 to A-5.5; Questions 8, 9, 14, 16)

Knowledge of the Indications for CPA/EE (Question 8)

Physicians' knowledge of the approved indication for the treatment of moderate to severe acne related to androgen sensitivity (with or without seborrhoea) in women of reproductive age was 92.0% overall and ranged from 88.0% in France to 95.0% in the Netherlands. Knowledge was similar across all other stratifications. Figure 9 presents correct responses by country and overall.

Physicians' knowledge of the approved indication for the treatment of hirsutism in women of reproductive age was 69.2%, ranging from 49.0% in France to 86.5% in Spain. Knowledge of this approved indication was similar across all other stratifications.

There were three false response options included in this question:

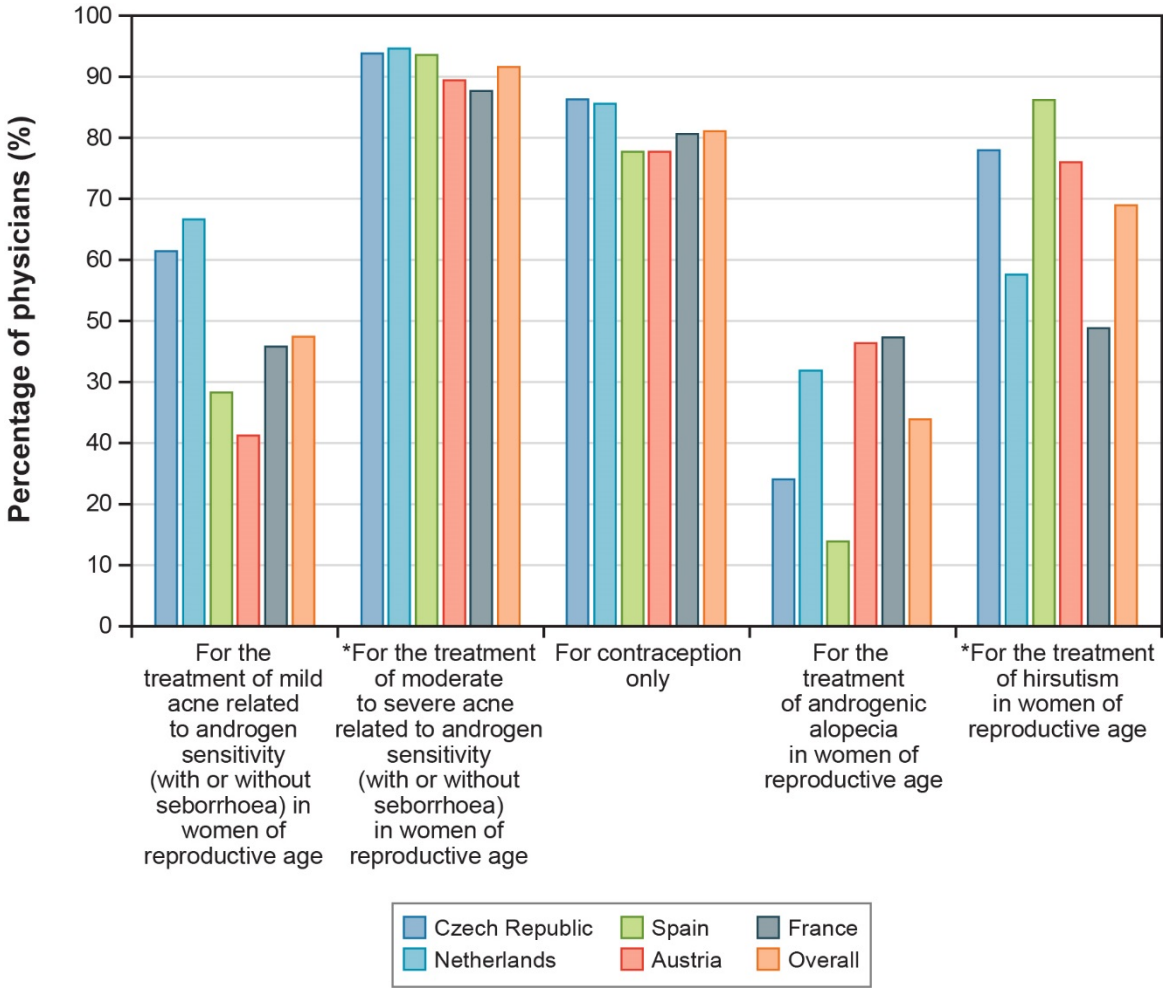
1. For the treatment of mild acne related to androgen sensitivity (with or without seborrhoea) in women of reproductive age
2. For contraception only
3. For the treatment of androgenic alopecia in women of reproductive age

Approximately half of the physicians (47.6%) correctly indicated that false option 1 was not an approved indication, with responses ranging from 31.4% in Austria to 66.9% in the Netherlands. A higher percentage of physicians who reported receipt of any of the CPA/EE materials correctly indicated that this was not an approved indication compared with physicians who received no educational materials. Knowledge was similar for all other stratifications.

Approximately 81% of physicians correctly indicated that false option 2 was not an approved indication, with responses ranging from 78.0% Spain and Austria to 86.7% in the Czech Republic. Knowledge was similar across all stratifications.

Approximately one-third of physicians (34.0%) correctly indicated that false option 3 was not an approved indication, with responses ranging from 14.0% in Spain to 47.5% in France. A higher percentage of physicians (41.0%) who had prescribed CPA/EE to 0 to 3 patients in the last 3 months compared with physicians who had prescribed to more than 3 patients in the last 3 months (25.6%) correctly reported this false response option. Knowledge was similar across all other stratifications.

Figure 9. Percentage of Physicians Reporting Correct Responses to Question 8: For which of the following purposes is Diane-35 and its generics indicated?

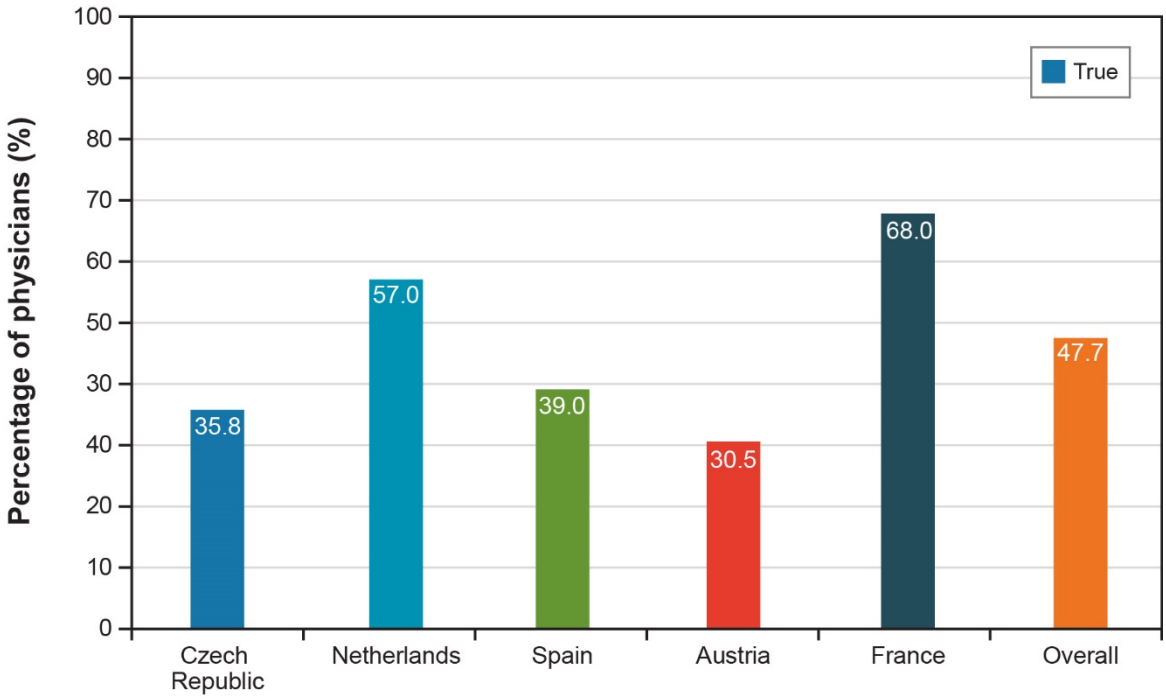


Asterisk "*"denotes correct response as "Yes"; other responses were false response options that were answered correctly.

Knowledge of the Use of CPA/EE for the Treatment of Acne (Question 9)

Physicians' knowledge of the approved indication to treat acne with CPA/EE only after topical therapy or systemic antibiotic treatments have failed was 47.7%. Results varied across the countries, ranging from 30.5% in Austria to 68.0% in France (Figure 10). Correct responses were highest among GPs (59.2%) and dermatologists (45.8%) compared with OB/GYNs (35.6%). A larger percentage of physicians who had prescribed CPA/EE to 0 to 3 patients in the last 3 months versus more than 3 patients reported correct responses (54.7% vs. 39.6%). Knowledge was similar for all other stratifications.

Figure 10. Percentage of Physicians Reporting Correct Responses to Question 9: For the treatment of acne, Diane-35 and its generics should be used only after topical therapy or systemic antibiotic treatments have failed



Knowledge of Contraindications in Patient Populations (Question 14)

Physicians' knowledge of the contraindications was high overall (92.2%-98.8%) on three of the nine contraindications (i.e., patients who have a current or history of a thromboembolic event, patients who have knowledge of a predisposition for a blood clotting disorder, patients who are experiencing or expected to experience a period of prolonged immobilisation).

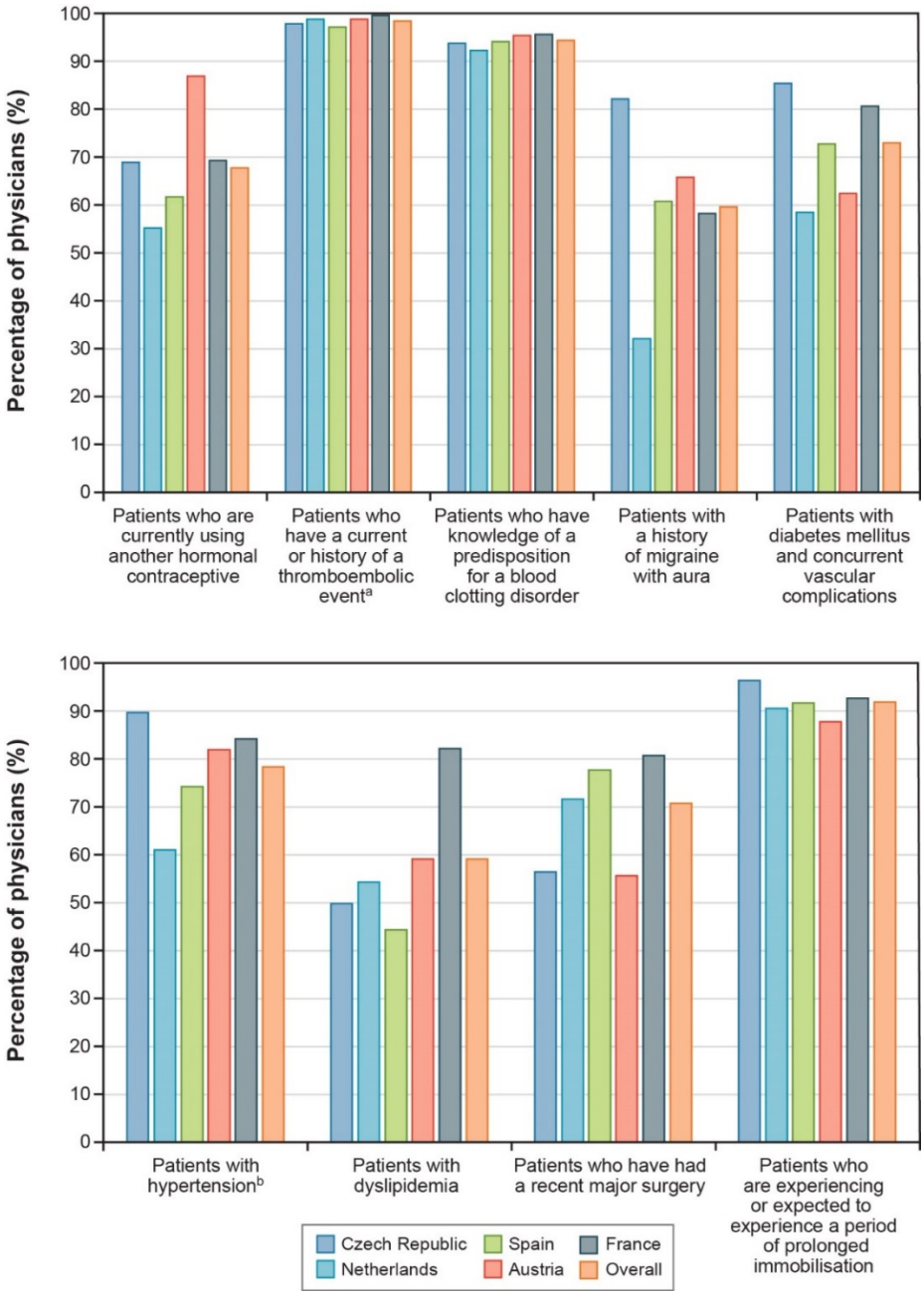
The percentage of physicians who responded correctly to four of the nine contraindications (i.e., patients who are currently using another hormonal contraceptive, patients with diabetes mellitus and concurrent vascular complications, patients with hypertension, patients who have had a recent major surgery) varied and ranged from 68.0% to 78.7%.

Physicians' knowledge regarding contraindications for patients with a history of migraine with aura was 59.9% and 59.3% for patients with dyslipidemia.

Among all respondents, the percentage of physicians who selected at least seven of the nine correct responses was 66.5% and ranged from 47.1% in the Netherlands to 78.5% in France. The percentage of physicians who selected at least seven of the nine correct responses was highest among OB/GYNs (76.5%) compared with GPs (64.3%) and dermatologists (52.9%). More physicians who reported receipt of any of the educational materials (74.0%-77.3%) selected at least seven of the nine correct responses compared

with physicians who had received other educational materials (59.0%) or no educational materials (60.5%). Knowledge was similar for all other stratifications. Figure 11 presents correct responses by country and overall.

Figure 11. Percentage of Physicians Reporting Correct Responses to Question 14: Diane-35 and its generics are <u>contraindicated</u> in which of the following patient populations?



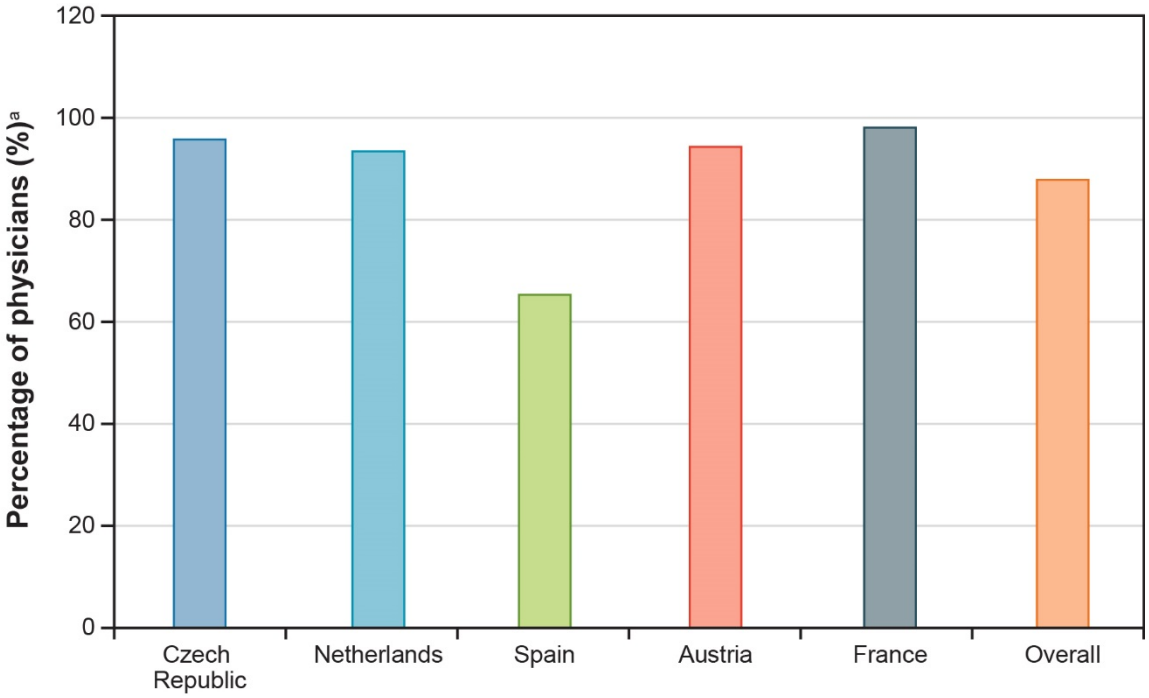
[a] Blood clotting disorders included deep vein thrombosis, pulmonary embolism, myocardial infarction, cerebrovascular accident, transient ischaemic attack, and angina pectoris.

[b] Hypertension is defined as systolic blood pressure of 160 mm Hg or diastolic blood pressure of 100 mm Hg.

Knowledge of Prescribing Guidance on the Use of CPA/EE in Smokers (Question 16)

Physicians' knowledge of the prescribing guidance of CPA/EE for women who smoke was high overall (87.7%), ranging from 65.5% in Spain to 98.0% in France (Figure 12). Knowledge was similar for all other stratifications.

Figure 12. Percentage of Physicians Reporting Correct Response to Question 16: What is the prescribing guidance on the use of Diane-35 or its generics for women who smoke?



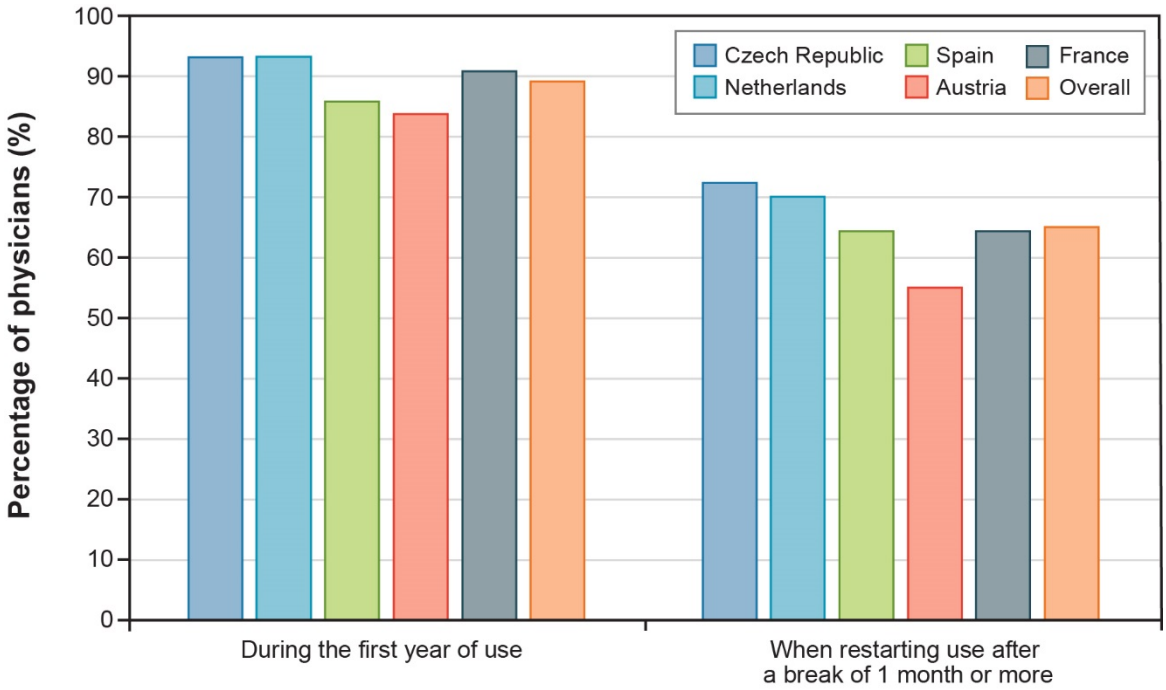
[a] The correct response was, "Women who are greater than 35 years of age should strongly be advised to stop smoking or use a nonhormonal treatment for her acne and/hirsutism."

10.4.6 Knowledge of the Information for Patients When Taking CPA/EE (Annex 4, Table A-6.1 to A-6.5; Questions 10-13)

Knowledge of Informing Patients About the Time Period(s) of Greatest Thrombosis Risk When Taking CPA/EE **(Question 10)**

Physicians' knowledge of the time period during the first year of use in which the risk of thrombosis is highest was high overall (89.3%), ranging from 83.9% in Austria to 93.4% in the Netherlands. Physicians' knowledge of the time period when restarting use after a break of 1 month or more was 65.2% and varied across countries, ranging from 55.1% in Austria to 72.5% in the Czech Republic. Knowledge of both of these time periods was similar across all stratifications. Figure 13 presents correct responses by country and overall.

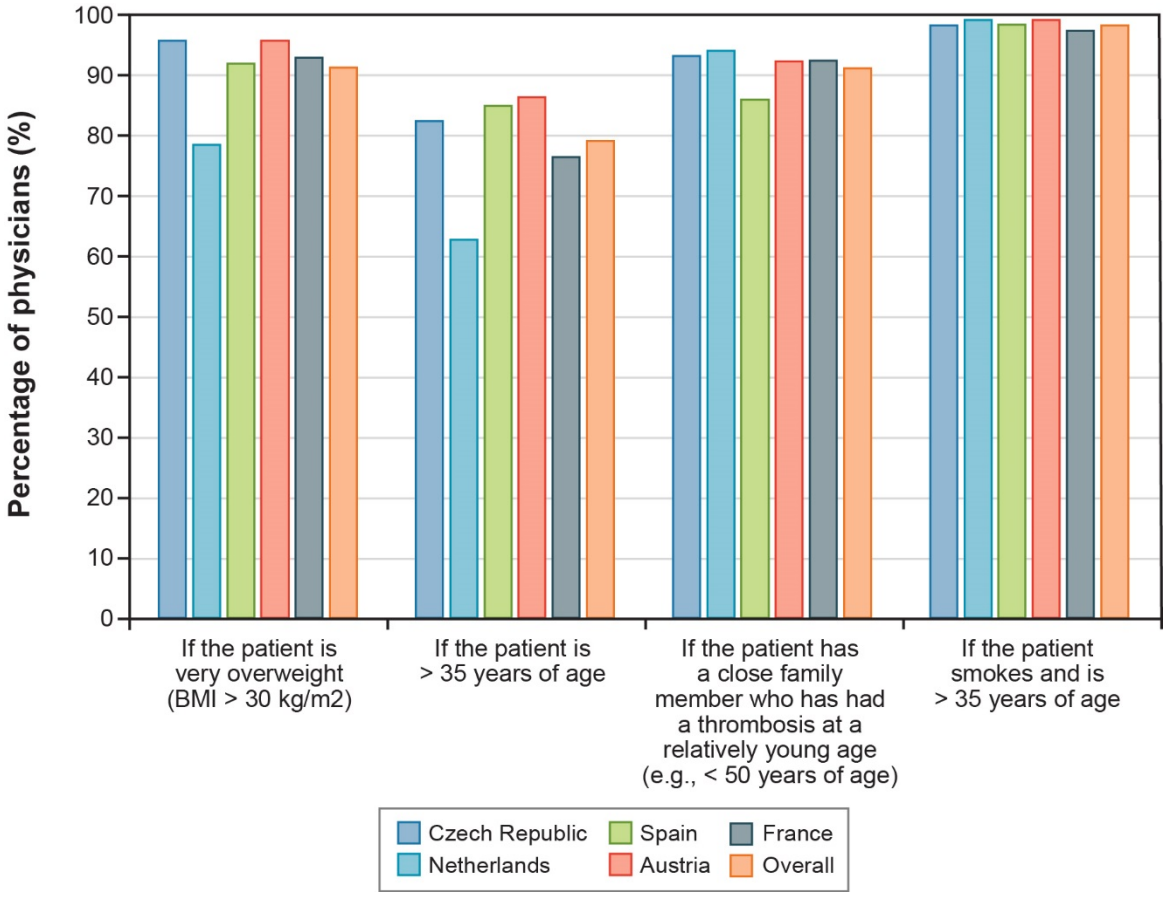
Figure 13. Percentage of Physicians Reporting Correct Responses to Question 10: Patients should be informed that when taking Diane-35 or its generics that the risk of thrombosis is highest during which time periods?



Knowledge of Thrombosis Risk Factors for CPA/EE (Question 11)

Physicians' knowledge of the highest risk factors for development of a thrombosis was high overall for all four risk factors (79.1%-98.4%). Correct responses were consistently high across countries with the exception of two of the risk factors (i.e., patient is very overweight and patient is older than 35 years of age); physician knowledge in the Netherlands was 78.5% for the risk factors of being overweight and 62.8% for age. The percentage of physicians who selected at least three of the four correct responses was 92.8% and was consistent across countries. Knowledge was similar for the selection of at least three of the four correct responses across all stratifications. Figure 14 presents correct responses by country and overall.

Figure 14. Percentage of Physicians Reporting Correct Responses to Question 11: When taking Diane-35 or its generics, the risk of a thrombosis is highest with which of the following risk factors?

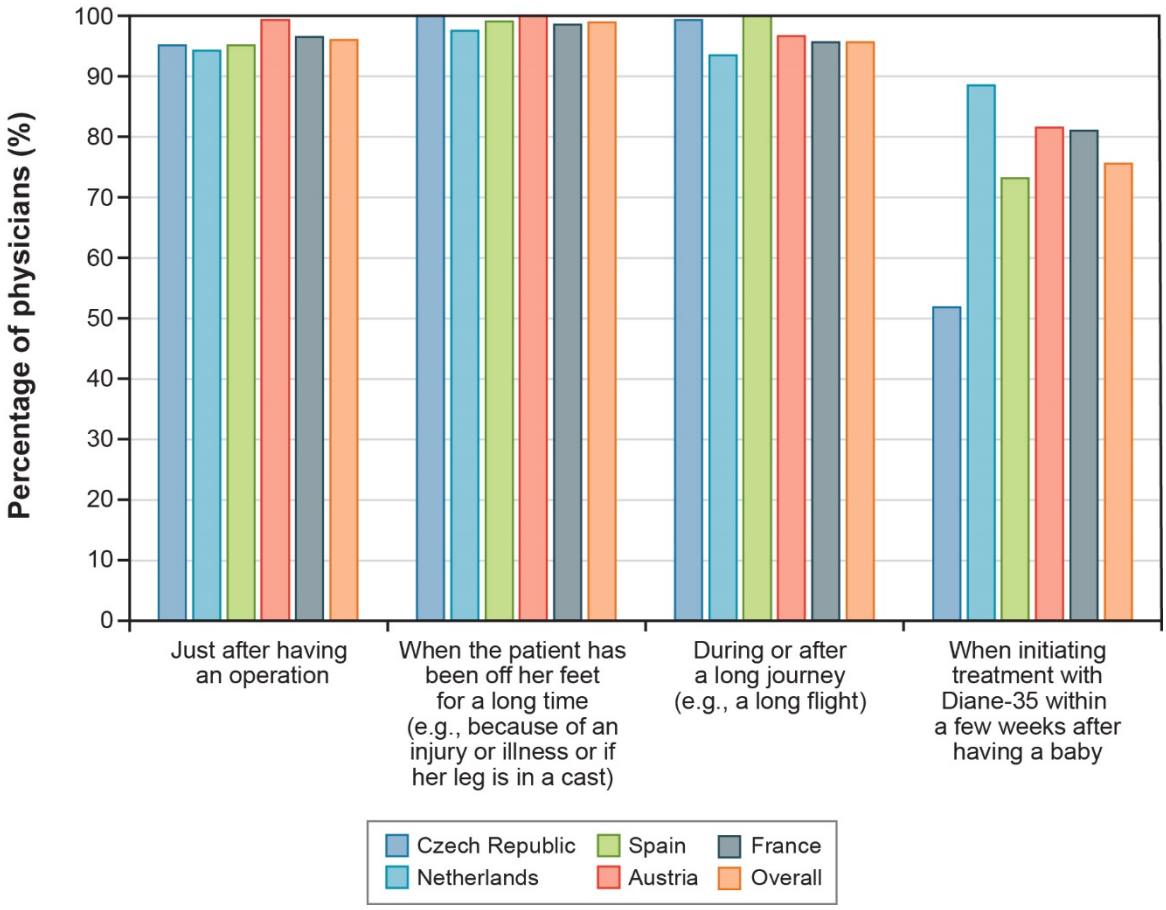


BMI = body mass index.

Knowledge of Thrombosis Symptoms (Question 12)

Physicians' knowledge of the situations when a patient may show symptoms of a thrombosis was high overall (95.5%-98.9%) for three of the four situations (i.e., just after having an operation, been off feet for a long time, during or after a long journey) and was consistently high across countries. Knowledge was 75.5% for one of the situations (i.e., when initiating treatment with CPA/EE within a few weeks after having a baby), and responses varied across countries, ranging from 51.7% in the Czech Republic to 88.4% in the Netherlands. The percentage of physicians who selected at least three of the four correct responses was 96.0% and consistent across countries and stratifications. Figure 15 presents correct responses by country and overall.

Figure 15. Percentage of Physicians Reporting Correct Responses to Question 12: Patients taking Diane-35 or its generics should watch out for symptoms of a thrombosis in which of the following situations?



Knowledge of Instructions for Patients (Question 13)

Physicians' knowledge of the four instructions that should be provided to patients when a patient might need major surgery or experience an injury or condition that may require a period of prolonged immobilisation varied. Knowledge was high overall (97.2%) and consistent across countries for informing the patient to tell their doctor, nurse, or surgeon that they are taking CPA/EE .

Physicians' knowledge was 67.1% for instructing patients to use a non-hormonal treatment for their skin condition and, if necessary, a non-hormonal method of contraception during this time. Correct responses for this instruction ranged from 44.6% in the Netherlands to 78.3% in the Czech Republic.

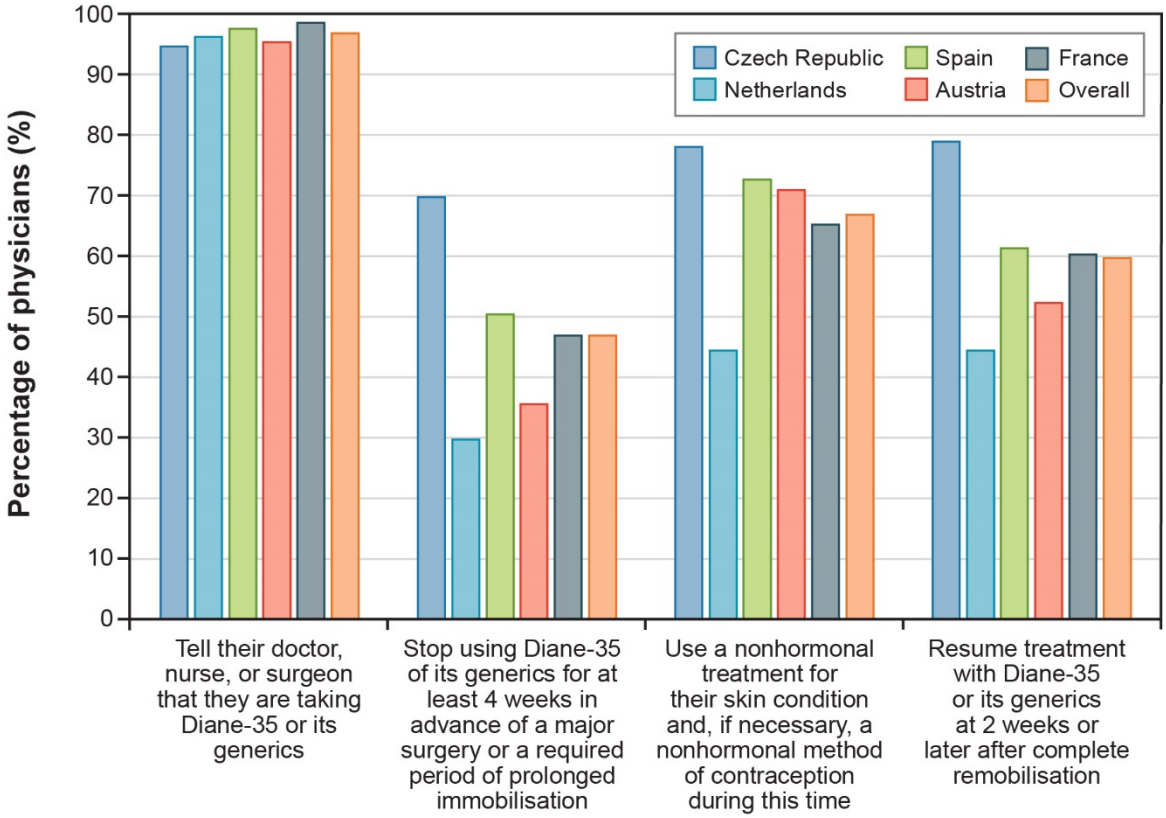
Physicians' knowledge for instructing a patient that she should stop using CPA/EE for at least 4 weeks in advance of a major surgery or a required period of prolonged immobilisation was 47%, and results varied across countries, ranging from 29.8% in the Netherlands to 70.0% in the Czech Republic. Physicians' knowledge was 59.9% for

instructing patients to resume treatment with CPA/EE at least 2 weeks or later after complete remobilisation, and results varied across countries, ranging from 44.6% in the Netherlands to 79.2% in the Czech Republic.

The overall percentage physicians who selected at least three of the four correct responses was 58.4%, and results varied across countries, ranging from 37.2% in the Netherlands to 81.7% in the Czech Republic. The percentage of physicians who selected at least three of the four correct responses was highest for OB/GYNs (70.8%) compared with GPs (53.0%) and dermatologists (47.1%). The percentage of physicians who selected at least three of the four correct responses was higher for physicians who had been practicing medicine longer (65.5% for physicians practicing > 25 years and 61.3% for 16-25 years vs. 47.0% for 0-15 years). The percentage of physicians who selected at least three of the four correct responses was 46.9% for physicians who reported no receipt of educational materials versus those who received any educational materials (64.1%-77.2%). Knowledge was similar based on number of patients prescribed the treatment in the last 3 months.

Figure 16 presents correct responses by country and overall.

Figure 16. Percentage of Physicians Reporting Correct Responses to Question 13: What instructions should patients taking Diane-35 or its generics receive regarding the potential need for a major surgery, or occurrence of an injury or condition that may also require a period of prolonged immobilisation?



10.5 Other Analyses (Annex 4, Table A-1)

10.5.1 Comparison of Participants and Non-Participants

Prior to the screening and consent questions, the questionnaire included questions about physician demographics (e.g., sex and age) and physician practice characteristics. These questions were included at the beginning of the questionnaire to facilitate physicians responding to them so that the characteristics of physicians who participated in the survey could be compared with those of physicians who did not participate (i.e., who started the questionnaire and were eligible but did not consent or complete it) and with those of physicians who were not eligible to participate in the survey based on their response to the screening question. In addition, available physician demographic and practice characteristics were summarised from other external sources outside the survey data-collection efforts. Obtaining such data can be challenging because its availability is quite variable across countries, making conclusive comparisons to the participating physicians somewhat difficult. The distribution of specialties among the participants was driven by prespecified sampling targets to achieve representation among each speciality type.

In the overall sample, there were 18 eligible non-participants (i.e., did not consent or complete the survey), and no comparisons were made because of the small sample size. In the overall sample, 363 physicians were not eligible and will be referenced as *noneligible participants*. The sample size of physicians and the availability of variables from external sources varied across countries.

In the Czech Republic, there were 120 eligible participants and 224 noneligible participants, and two external sources were identified for comparisons. These external sources included 3,598 physicians (Cegedim OneKey database, data on file, 2014) and 3,598 physicians (Institute of Health Information and Statistics of the Czech Republic, 2013). A comparison of the participants with noneligible participants revealed a similarity in age and years practicing medicine and a difference in the distribution of physician specialties and gender. A comparison of the participants with external sources revealed a similarity in age and gender and a difference in physician specialities. The distribution of participants was 95.0% OB/GYNs and 5.0% dermatologists, and the distribution from the external source (Cegedim OneKey database, data on file, 2014) was approximately three-fourths OB/GYNs and one-fourth dermatologists.

In the Netherlands, there were 121 eligible participants and 53 noneligible participants, and 11,482 physicians were identified from an external source. A comparison of the participants with noneligible participants revealed some similarity in years practicing medicine and a difference in the physician specialty, gender, and age. A comparison of the participants with the external source revealed a similarity in gender and a difference in physician specialties. The distribution of participants was 58.7% GPs and 41.3% dermatologists, and the distribution from the external source was 94.2% GPs and 5.8% dermatologists.

In Spain, there were 200 eligible participants and 24 noneligible participants, and two external sources were identified for comparisons. These external sources included 5,602 (IMS & Bayer CRM, data on file, 2014) and 1,533 physicians (Lightspeed All Global Workforce Counts for Spain, data on file, 2014). A comparison with the noneligible participants is limited because of sample size. A comparison of the participants with the external source revealed a similarity in physician specialty and somewhat similar age distribution.

In Austria, there were 118 eligible participants and 35 noneligible participants, and 2,606 physicians were identified from an external source. A comparison with the noneligible participants is limited because of sample size. A comparison of the participants with the external source revealed a similarity in physician specialty and gender.

In France, there were 200 eligible participants and 27 noneligible participants, and two external sources were identified for comparisons. These external sources included 97,080 physicians (Conseil de l'Ordre des Médecins, data on file, 2014) and 3,604 physicians (Lightspeed All Global Workforce Counts for France, data on file, 2014). A comparison with the noneligible participants is limited due to sample size. A comparison of the participants with the external sources revealed similarities in age and differences in physician specialty and gender. The distribution of participants was 65.5% GPs, 17.0% dermatologists, 15.5% OB/GYNs, and 2.0% internal medicine, and the distribution from the external sources was 93.4% GPs, 3.7% dermatologists, and 3.0% OB/GYNs. The distribution of gender for the overall sample was 71.0% males compared with 55.2% males based on the external source.

10.6 Adverse Events/Adverse Reactions

No adverse events were reported during the study in any country.

11. Discussion

11.1 Key results

More than half (51.0%) of physicians had received at least one of the three CPA/EE educational materials. Almost half (45.5%) of physicians reported receipt of DHPL. The reported receipt of the DHPL was highest in the Czech Republic and lower in the other countries. The reported receipt of the Prescriber Checklist (16.9%) and/or Patient Card (16.2%) was low across all countries. Most of the physicians (81.0%) who received at least one of the CPA/EE materials found it helpful or extremely helpful.

One of the most important factors in prescribing an estrogen/progestogen treatment is communication to all patients of the risks associated with the potential development of thromboembolism. The questions with the greatest percentage of correct responses (≥ 80%) included (1) symptoms of possible deep vein thrombosis, pulmonary embolism, and cerebrovascular accident; (2) most important risk factors for thrombosis; and (3)

instructions of use in smokers. Knowledge regarding the indicated use of CPA/EE for moderate to severe acne related to androgen sensitivity (with or without seborrhoea) was 92%, and knowledge about the avoidance of its use for contraception alone in women of reproductive age was 81.4%. A smaller percentage of physicians (69.2%) was aware of the indicated use of CPA/EE for hirsutism. Approximately one third of physicians (34.0%) were aware of the revised indication related to removal of the androgenic alopecia indication, and approximately half of physicians (47.7%) were aware of prescribing for acne only after failure of topical therapy or systemic antibiotics The percentage of physicians who responded correctly was variable for contraindications (59.3%-98.8%), symptoms of possible myocardial infarction (42.8%-98.8%), other general risk factors for thrombosis (42.2%-96.8%), instructions related to immobilisation (47.0%-97.2%), and selected concomitant medical conditions (44.7%-95.5%).

11.2 Strengths

Two key strengths of the study were the sample size achieved and the diversity of physicians. The targeted numbers of physician respondents in each country were achieved. The distribution of physicians by age, gender, specialty, practice type, and years prescribing medicine represented a broad diversity.

The physician survey was conducted after physicians had the opportunity to have received the CPA/EE educational materials and had a chance to use that information in their practice, allowing for evaluation of how well they understood the safety information provided in the educational materials and applied it to their practices.

Accuracy of responses among physicians was facilitated by the pretesting of the questionnaire through formal cognitive pretesting with physicians in each country. The wording of the questions and response choices should have been easily understood by the respondents.

11.3 Limitations

The study targeted recruitment of up to 25% dermatologists in each country. Special recruitment efforts were planned in each country to achieve this target. In the Netherlands, 41.3% of participants were dermatologists. In Austria, 26.3% of participants were dermatologists. In Spain and France, 17% of participants were dermatologists even after extending data collection and sending additional reminders to physicians to participate. Only 5.0% of participants in the Czech Republic were dermatologists despite extending data collection and additional recruitment efforts. We experienced a high number of screening failures in the Czech Republic (i.e., dermatologists had not prescribed CPA/EE in the past 6 months). These results are consistent with anecdotal reports received from Bayer that dermatologists in the Czech Republic do not typically prescribe CPA/EE.

As with all voluntary, cross-sectional surveys that depend on physicians agreeing to participate, some limitations are inherent. Although the study is designed to select a

diverse and generally representative sample of prescribers, there exists no exhaustive list of all prescribers of CPA/EE from which to draw a sample; hence, it was not possible to select a random sample of all prescribers. Therefore, although participants were diverse in characteristics, the study participants may not necessarily represent all relevant prescribers. In addition, as is true with most surveys, it was possible that respondents who completed the questionnaire differed from non-respondents in other characteristics that were not measured in the questionnaire. The direction and magnitude of any bias because of differences in responders and non-responders was not known. A meaningful comparison of participants and non-participants in the assessment of physician demographics and practice characteristics was not possible because very few physicians who did not wish to participate in the survey responded to the demographic and practice characteristic questions, and characteristics of the invited physicians were not otherwise available. We could not compare physician and practice characteristics of the physician participants to what is known about the overall prescribing population because that information was not available. As a compromise, available demographic and practice characteristics were summarised for physicians from other external sources outside the survey data-collection efforts alongside those from participants and non-participants.

In general, physician response rates for surveys have been somewhat low historically. Low response rates may result in higher likelihood that participating physicians are not representative of all prescribing physicians. Thus, the resulting estimates of physician understanding about CPA/EE may be biased. If participants discontinue the survey because they do not know how to answer the knowledge questions, then the frequency of substantial physician knowledge will be overestimated.

11.4 Interpretation

Little information is in the public domain to set thresholds for acceptable levels of knowledge and behaviour related to risk-minimisation measures. A recent publication (Knox et al., 2015) reported on *patient* understanding of medication guides from a review of 66 assessment reports submitted to the United States Food and Drug Administration. A total of 30% of reports achieved an 80% knowledge level (percentage correct) for the single most important risk communicated in the medication guide with a mean knowledge level of 63.8%. In our study, physician knowledge of thromboembolism risk was greater than 80%.

Knowledge and behaviour reflect many factors, including availability and access to information, literacy and numeracy, beliefs, and motivation as the DHPC was distributed in 2013 and the prescriber's checklist and patient information card were distributed from July 2014 in Austria and Czech Republic to April 2015 in Spain after approval from individual health authorities. The relatively low level of reported receipt of the physician education material may reflect poor recall, if the material had indeed been received, or various reasons for not receiving the educational material. Variability across countries could reflect inherent differences in physician behaviour or different intensity of the educational efforts. Little information is in the public domain to be able to compare the percentage of physicians who report receipt of educational materials based on results

from post-authorisation safety studies. A recent publication (Brody et al., 2016) reported the results of a multinational survey of 800 EU physicians that assessed the receipt of educational materials: for that study, physicians' reported receipt of the educational materials ranged from 16.0% to 69.0% across the participating countries. For the overall sample across countries in our study, the reporting receipt for each of the educational materials ranged from 16.2% for the Patient Card, to 16.9% for Prescriber Checklist, to 45.5% for the Dear Healthcare Provider Letter. More than half (51.0%) of physicians had received at least one of the three CPA/EE educational materials.

Knowledge varied across categories of information, with higher knowledge associated with the most important information (e.g., indicated use for acne, non-concomitant use with other hormonal contraceptive, symptoms of thromboembolism, most important risk factors for thromboembolism, and instructions of use in smokers). However, the knowledge regarding revised indications related to hirsutism and about prescribing after failure of other acne treatments was not as high. Knowledge regarding rare high risk medical conditions and instruction of treatment pause during major surgery or a required period of prolonged immobilisation might require physicians to refer to the Prescriber Checklist or other product information.

11.5 Generalisability

As noted in Section 11.2, the study achieved broad diversity in physician characteristics within the five countries, allowing for stratification of results by multiple characteristics. There was heterogeneity of some results by country; it is unknown how well these results would relate to other countries.

12. Other information

Not applicable.

13. Conclusion

The study met its objectives to evaluate whether physicians received the educational materials for CPA/EE and to assess physician knowledge and understanding of key safety information as well as use of the materials. The reported receipt of at least one of the educational materials was just over 50%.

In general, knowledge of most important topics was high. Knowledge varied for topics that were more complex or less frequently encountered. The knowledge of thromboembolism risk was high. The knowledge was high regarding the indicated use of CPA/EE for moderate to severe acne and avoidance of its use for contraception alone. However, knowledge about prescribing after failure of other acne treatments and about the removed indication for androgenic alopecia was not as high. In general, the observed patterns of knowledge among the physicians were as expected—with greatest knowledge on the indicated use and most important risks emphasised in the educational material and other product information and less knowledge on more complex aspects of safe use (e.g., unspecific symptoms of myocardial infarction, a few of the less well-known medical

conditions that might increase the risk of thromboembolism, and instructions of use during major surgery or a required period of prolonged immobilisation) for which we would assume that physicians would consult the label and/or prescriber checklist rather than rely on recall. Although almost half of the physicians did not report receiving the educational materials, the high level of knowledge among treating physicians suggests that the key safety information through other sources (e.g., product label, social media, seminars or symposia) is available to the treating physicians.

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15. Appendices

Annex 1. List of stand-alone documents

None.