Post-Authorisation Safety Study (PASS) Report - Study Information

Acronym/Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Report version and date	v 1.0, 05 MAY 2022
Study type/study phase	Observational, post-approval Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☒ YES ☐ NO
EU PAS Register number	EUPAS41194
Active substance	INN: Cyproterone; ATC code: G03HA01
Medicinal product	Androcur (cyproterone) and its generics
Product reference	BAY94-8367
Procedure number	EMEA/H/A-31/1488
Study Initiator and Funder	Bayer Pharma AG on behalf of a group of MAHs
Research question and objectives	The primary objective of this study is to measure physician awareness and level of knowledge of the key safety information included in the revised summary of product characteristics (SmPC) and the Direct Healthcare Professional Communication (DHPC) for CPA monotherapy regarding the risk of meningioma. Specifically, the following information will be collected: • Investigate whether physicians have received and reviewed the revised SmPC and DHPC • Assess physicians' knowledge and understanding of key safety information pertaining to the restrictions for the use of CPA due to the risk of meningioma
Countries of study	France, Germany, Poland, Spain, the Netherlands
Authors	PPD

	PPD PPD RTI Health Solutions

ATC = Anatomical Therapeutic Chemical Classification System; CPA = cyproterone acetate; DHPC = Direct Healthcare Professional Communication; EU PAS Register = The European Union electronic Register of Post-Authorisation Studies; MAH = Marketing Authorisation Holder; PASS = post-authorisation safety study; SmPC = summary of product characteristics.

Marketing authorisation holder

Marketing authorisation holder(s)	Bayer AG
MAH contact person	PPD Bayer AG Muellerstrasse 178 13353 Berlin, Germany

MAH = Marketing Authorisation Holder.

Table of contents

Tables

Figures

1. Abstract

Acronym/Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Report version and date **Author**	v 1.0, 05 MAY 2022 PPD PPD PPD
Keywords	Androcur (cyproterone); post-authorisation safety study; evaluation of risk-minimisation measures; physician survey
Rationale and background	As an outcome of an Article 31 referral for CPA monotherapy, Bayer and other MAHs have revised the SmPC and developed a DHPC to describe the risk of meningioma associated with the use of CPA. Bayer along with the other MAHs for CPA are conducting a joint observational cross-sectional survey to assess physicians' awareness and level of knowledge of the key safety information included in the revised SmPC and the DHPC regarding risk of meningioma.
Research question and objectives	The primary objective of this study is to measure physician awareness and level of knowledge of the key safety information included in the revised SmPC and the DHPC for CPA monotherapy regarding the risk of meningioma. Specifically, the following information will be collected: • Investigate whether physicians have received and reviewed the revised SmPC and DHPC • Assess physicians' knowledge and understanding of key safety information pertaining to the following restrictions for the use of CPA due to the risk of meningioma. Specifically: o The occurrence of meningiomas (single and multiple) in association with CPA monotherapy doses ≥ 25 mg/day o Restriction of use of CPA monotherapy 10 mg/50 mg in women when no results have been

	achieved at lower dose CPA-containing products or with other treatment options o Restriction of use of high-dose CPA in men with sexual deviations when other interventions are not appropriate o After clinical improvement with CPA monotherapy is achieved, treatment should be maintained with the lowest possible dose o The risk of meningioma increases with increasing cumulative doses of CPA o CPA is contraindicated in patients with a meningioma or a history of meningioma o If a patient treated with CPA monotherapy is diagnosed with meningioma, treatment with all cyproterone-containing products must be permanently stopped o Awareness of signs and symptoms of meningiomas
Study design	This is an observational, cross-sectional survey to assess knowledge and understanding among a diverse sample of physicians who have recently prescribed (e.g., within previous 12 months) CPA monotherapy in France, Germany, Poland, Spain, and the Netherlands. Physicians from a physician panel were invited to complete a brief web-based questionnaire regarding their knowledge of the revised SmPC and DHPC.
Setting	The study was conducted in France, Germany, Poland, Spain, and the Netherlands.
Subjects and study size, including dropouts	Physicians eligible to participate included dermatologists, endocrinologists, gynaecologists, general practitioners, urologists, oncologists (who treat prostate cancer), and psychiatrists involved in the treatment of hypersexuality/reduction of drive in sexual deviations who had prescribed CPA monotherapy in the past 12 months and worked in an office or hospital-based setting. The target sample size was a minimum of 600 participating physicians across the 5 countries. Specifically, the survey targeted a minimum of 200 physicians in France and a minimum of 100 physicians each in Germany, Poland, the Netherlands, and Spain. With a study size of 100 physician responses for a given question, the maximum width of an exact 95% confidence interval around the percentage who responded correctly is 20.3%, and 200 responses gives a maximum width of 10.3%.

Variables and data sources	The source of information for the study was self-reported data collected from physicians enrolled in panels from the target countries using a standard questionnaire. The questionnaire assessed physician knowledge of the key safety messages outlined in the revised SmPC and evaluated their receipt and understanding of the DHPC.
Results	Questionnaire responses from 613 participants were analysed using descriptive tables to characterise the level of knowledge, understanding, and practices among these physicians. Across all countries and specialties, 43% of participants correctly identified meningioma as a warning and precaution added to the prescribing label for CPA monotherapy among the response options. Physicians in France were most aware, with 63% selecting the correct response. By specialty, 62% of gynaecologists and 60% of endocrinologists had the highest awareness of the updated warning for meningioma. Overall, 66% of physicians correctly identified the clinical signs and symptoms of meningioma by providing all 7 correct responses. Knowledge of each of the signs and symptoms individually ranged from 72% to 92%. Overall, 75% of physicians correctly reported that the risk of meningioma increases with increasing cumulative doses of CPA monotherapy. Similarly, 73% of physicians correctly reported that treatment with CPA-containing products must be permanently stopped if a patient is diagnosed with meningioma. Most physicians knew that CPA monotherapy should be prescribed with the lowest effective dose, with 85% selecting the correct response. Most physicians (74%) also correctly indicated that patients using CPA monotherapy should be monitored for meningiomas in accordance with clinical practice. Regarding the use of CPA monotherapy in patients with a history of meningioma, overall, 39% of physicians correctly identified the statement, “CPA monotherapy may be used in patients with a history of meningioma under carefully controlled conditions” as false. When responses were stratified by physician specialty, correct responses ranged from 17% for oncologists up to 57% for gynaecologists. In total, 69% of physicians had written a prescription for CPA monotherapy within the past 3 months, with 25% indicating they had prescribed it within the past month. Physicians in Spain and Germany had the highest proportion of physicians reporting they had prescribed CPA within the past 3 months

	(75%); recent use was lowest among physicians in the Netherlands (61%). Prescription use within the past 3 months was highest among gynaecologists (75%), urologists (75%), oncologists (74%), and endocrinologists (73%) and lowest among psychiatrists (54%). In the past 12 months, 55% of physicians had prescribed CPA monotherapy for androgenisation in women (ranging from 46% in the Netherlands to 58% in Spain). Specialties most often indicating they had prescribed for androgenisation in women included gynaecologists (95%), dermatologists (90%), endocrinologists (87%), and general practitioners (63%). Among physicians who had prescribed CPA monotherapy for androgenisation in the past 12 months (n = 339), 73% correctly responded that CPA monotherapy at doses of 10 mg or 50 mg should be prescribed for androgenisation when no satisfactory results have been achieved with other treatment options. Among specialties that most often prescribed androgenisation in the past 12 months, the proportion of physicians selecting this correct response ranged from 73% among gynaecologists and general practitioners to 81% of endocrinologists. Among physicians who had prescribed CPA monotherapy for androgenisation in the past 12 months, 40% were aware that CPA should only be prescribed at doses of 10 mg or 50 mg when no satisfactory results have been achieved with lower dose CPA-containing products. Gynaecologists were most aware of this precaution, with 49% selecting this response. Among physicians who had prescribed CPA monotherapy for androgenisation in the past 12 months, 34% correctly identified as false the statement, “After using CPA monotherapy at a dose of 10 mg (Germany and Netherlands only) or 50 mg (France, Poland, and Spain only) and achieving clinical improvement of moderate to severe signs of androgenisation, the patient can continue using CPA monotherapy at this dose for as long as it is necessary.” Knowledge was highest among gynaecologists, with 41% selecting the correct response. Among physicians who indicated they had prescribed CPA monotherapy for sexual deviations in men in the past 12 months (18% of all physicians, 77% of psychiatrists), 56% correctly identified that CPA monotherapy should only be used when other interventions are considered inappropriate. The proportion of physicians selecting the correct response ranged from 43% in France to 63% in Poland. Knowledge was highest among endocrinologists (86%), followed by

	psychiatrists (63%) and urologists (60%). Overall, 45% of physicians indicated that in the past 12 months they had prescribed CPA monotherapy for antiandrogen treatment in inoperable carcinoma of the prostate, although 96% of oncologists, 89% of urologists, and 55% of general practitioners indicated they had prescribed for this indication. Among the physicians who had prescribed CPA monotherapy for this indication in the past 12 months, 75% of physicians indicated the use of CPA monotherapy for the treatment of inoperable prostate carcinoma and luteinising hormone-releasing hormone (LHRH) flare remains unchanged per the SmPC. The proportion of physicians selecting the correct response ranged from 68% in France to 90% in Poland and was highest among oncologists (78%), followed by urologists (74%) and general practitioners (71%). Regarding physician knowledge of the doses of CPA monotherapy for which the occurrence of meningiomas has been reported, 36% of physicians correctly reported 50 mg, 29% correctly reported 100 mg, and 24% correctly reported 300 mg. In France, 61% of physicians selected at least 1 correct response. The results of the question evaluating physician knowledge of the approved indications for CPA monotherapy showed that most physicians correctly identified the appropriate indication. The percentage of correct responses was higher among specialties that most often prescribed for the specific indication. For example, almost all endocrinologists (97%), dermatologists (93%), and gynaecologists (92%) correctly identified “severe signs of androgenisation” as an approved indication of CPA monotherapy 50 mg. Likewise, nearly all oncologists (93%) and urologists (92%) correctly identified “treatment of inoperable carcinoma of the prostate” as an approved indication for this dosage. Seventy-nine percent of psychiatrists correctly identified “reduction of drive in sexual deviations in men,” while the proportion of other physician specialties ranged from 33% to 60%. Physicians in France were asked questions specific to additional requirements around use of CPA monotherapy in France. In total, 43% of the French physicians correctly identified that a magnetic resonance imaging (MRI) should be performed on a patient at the initiation of treatment with CPA monotherapy. Psychiatrists (71%) and endocrinologists (67%) had the highest proportion of specialists correctly respond; urologists (20%) and oncologists (36%) had the lowest

	proportion of specialists selecting the correct response. Twenty-one percent of French physicians were aware of how often an MRI should be performed on a patient after the first MRI (after 5 years and then every 2 years thereafter). The most frequently selected response to the question was "every 2 years," which was selected by 42% of physicians. When combining the results for physicians selecting either response, more than 60% were at least correctly aware of the requirement that an MRI is required every 2 years. Endocrinologists (33%), gynaecologists (31%), and psychiatrists (29%) had the highest proportion of specialists select the correct response "after 5 years and then every 2 years thereafter." When combining these results with the more conservative response of "every 2 years," over 60% of endocrinologists (83%), gynaecologists (76%), and oncologists (60%) were aware of this requirement. In total, 67% of the physicians in France were aware that patients being treated with CPA monotherapy are required to sign a consent form. Endocrinologists (100%), gynaecologists (83%), and dermatologists (80%) had the highest proportion of specialists selecting the correct response. Urologists (16%) and oncologists (44%) had the lowest proportion of specialists selecting the correct response, with a large proportion of these specialists selecting "I don't know" (44% and 40%, respectively). Overall, 42% of physicians reported that they received the revised SmPC. Of those, 69% reported that they read the document. A similar percentage of physicians (40%) reported that they received the DHPC. Of those, 82% of physicians reviewed the DHPC.
Discussion	The study overall met its objective of evaluating whether physicians received and reviewed the revised SmPC and DHPC and assessing physicians' knowledge and understanding of key safety information pertaining to the restrictions for use of CPA. In general, the knowledge of the risk of meningioma associated with use of CPA monotherapy was high; however, only 43% of physicians indicated their awareness of the recent changes in the warning and precautions implemented in the label. In general, the observed patterns of knowledge among the physicians were as expected—with greatest knowledge on the indicated use of CPA monotherapy relevant to the per-specialty indication and most important risks of meningioma

	and less knowledge on more complex aspects of safe use, especially correct use in indications that were not in the area of specialty of the respective physician (e.g., questions specific to the dosage of CPA monotherapy). Of the 42% of physicians who confirmed receipt of the revised SmPC and the 40% who confirmed receipt of the DHPC, 69% and 82%, respectively, reported they had read each document. This is in line with other risk-minimisation surveys and could be because of recall bias, given that the survey was launched more than 6 months after distribution of the DHPC in most countries and more than 4 months after SmPC approval.
Marketing Authorisation Holder(s)	Bayer AG
Names and affiliations of principal investigators	PPD RTI-HS

CPA = cyproterone acetate; DHPC = Direct Healthcare Professional Communication; MAH = Marketing Authorisation Holder; RTI-HS = RTI Health Solutions; SmPC = Summary of Product Characteristics.

2. List of abbreviations

ATC	Anatomical Therapeutic Chemical Classification System
CNAM	French Health Insurance
COVID-19	coronavirus disease 2019
CPA	cyproterone acetate
DHPC	Direct Healthcare Professional Communication
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS Register	The European Union electronic Register of Post-Authorisation Studies
LHRH	luteinising hormone-releasing hormone
MAH	marketing authorisation holder
OQA	Office of Quality Assurance
OS	observational study
PAS	post-authorisation study
PASS	post-authorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
RTI-HS	RTI Health Solutions
SmPC	summary of product characteristics
SOP	standard operating procedure

3. Investigators

Principal Investigator	Country	Institutional Affiliation
PPD	United States	RTI Health Solutions, Research Triangle Park, North Carolina

4. Other responsible parties

Bayer AG is the marketing authorisation holder of Androcur (cyproterone acetate [CPA]) in the European Union (EU) and the study initiator and partial funder of the study. Other Marketing Authorisation Holders (MAHs) of CPA monotherapy products are also funding the study. Bayer is responsible for fulfilling any obligations for reporting results to regulatory agencies. Bayer collaborated with RTI Health Solutions (RTI-HS), an independent nonprofit research organisation. RTI-HS was responsible for the design, conduct, analysis, and reporting of the study. Kantar, a global research operations partner, was responsible for physician recruitment and data collection.

4.1 Study initiator and funder

Role: OS Conduct Responsible
Name: PPD
Email: PPD

Role: Qualified Person responsible for Pharmacovigilance (QPPV)
Name: PPD

Role: MAH contact person (Regulatory Affairs)
Name: PPD

Role: OS Safety Lead
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Role: OS Medical Expert
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Role: OS Statistician (Internal)
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Role: OS Statistician (External)
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Role: OS Epidemiologist (Internal)
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Role: OS Epidemiologist (External)
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Role: Regulatory Affairs responsible (External)
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MAH = marketing authorisation holder; OS = observational study.

4.2 Collaborators/Committees

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5. Milestones

Table 1: Milestones

Milestone	Planned date	Actual date	Comments
Registration in the EU PAS Register	Before the start of data collection	11 JUN 2021	
Ethical review (as required)	Before the start of data collection	Germany: 18 JUN 2021 France: 22 JUN 2021 Spain: 27 JUL 2021	Ethical review was not required in the Netherlands or Poland.

Start of data collection	Q3 2021	18 OCT 2021	The start of data collection was slightly delayed due to delays in finalising the contract with the global operations partner.
End of data collection	Q4 2021	16 DEC 2021	
Final report of study results	Q2 2022	05 MAY 2022	

EU PAS Register = The European Union electronic Register of Post-Authorisation Studies; Q2 = second quarter; Q3 = third quarter; Q4 = fourth quarter.

6. Rationale and background

Cyproterone acetate (CPA) is a synthetic progesterone derivative with antiandrogenic properties and is available as monotherapy in dosages of 10 mg, 50 mg, and 100 mg for oral administration and 300 mg/3 mL in depot formulation for intramuscular administration in multiple European countries. The CPA monotherapy 10 mg and 50 mg strengths authorised indications are for moderate and severe signs of androgenisation in women (e.g., hirsutism, androgenetic alopecia, acne, and seborrhoea), while the authorised indications for formulations of 50 mg and above and depot formulations are for reduction of sex drive in hypersexuality and sexual deviations in men and antiandrogen treatment in inoperable carcinoma of the prostate or palliative antiandrogenic treatment of prostate cancer. Approved indications for CPA monotherapy differ among the different strengths and among countries in which CPA monotherapy products are authorised.

A recent French pharmacoepidemiology study was conducted by Weill and colleagues[1] to estimate the number of cases of meningioma that are deemed attributable to prolonged exposure of CPA 50 mg and 100 mg in women between 2007 and 2015. A further overview was conducted by the French National Agency for Medicines and Health Products Safety to evaluate meningioma cases in which the use of CPA was reported. On 7 July 2019, the French National Agency for Medicines and Health Products Safety triggered a referral under Article 31 of Directive 2001/83/EC resulting from both of these resources, and requested that Pharmacovigilance Risk Assessment Committee (PRAC) assess the benefit-risk of CPA-containing products and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended, or revoked.[2] In addition, the PRAC reviewed data from epidemiological studies, including the French Health Insurance (CNAM) study, postmarketing case reports, and data submitted by MAHs.[2] The authors of the review concluded that while the absolute risk of meningioma in association with CPA use remains low, the risk increases with increasing cumulative doses. The PRAC noted that most cases occur after prolonged exposure to high doses of CPA (25 mg/day or higher), but cases of meningioma have also been identified after short-term exposure to high doses (cumulative dose > 12 g) of CPA.[2] The PRAC concluded that the benefit-risk balance of CPA-containing products remains favourable.

The PRAC recommended that for all indications except prostate carcinoma, treatment with CPA should be restricted to situations where alternative treatments are unavailable or considered inappropriate, and that the lowest possible effective dose should be used. The PRAC also noted that available data do not indicate an increased risk of meningioma in association with low-dose combination products containing 2 mg or less of CPA. The PRAC further recommended updates to the product information of CPA-containing products to reflect current knowledge on the risk of meningioma. In addition, PRAC recommended the sponsors conduct a joint observational cross-

sectional survey to assess physicians' awareness and level of knowledge of this risk. A risk-minimisation plan for CPA monotherapy was not required nor requested.

In response to the PRAC recommendation to reflect current knowledge on the risk of meningioma, Bayer Pharma AG (Bayer), along with the other MAHs for CPA monotherapies, developed a Direct Healthcare Professional Communication (DHPC) in line with the content proposed by the PRAC and has revised the summary of product characteristics (SmPC) to describe the risks associated with the use of CPA monotherapy. The DHPC and amendments to the relevant sections of the SmPC and package leaflet were adopted and distributed on a national level as summarised in Table 2.

Table 2: Dates of distribution of DHPC and approval of updated SmPC by country

Country	DHPC dissemination	SmPC approval
France	16 APR 2020	29 JUN 2020
Germany	16 APR 2020	21 AUG 2020
Poland	16 APR 2020	23 JUL 2020
Spain	12 NOV 2020[a]	1 JUL 2020
The Netherlands	20 APR 2020	23 JUN 2020

COVID-19 = coronavirus disease 2019; DHPC = Direct Healthcare Professional Communication; SmPC = summary of product characteristics.

[a] Dissemination of the DHPC in Spain was postponed due to the COVID-19 pandemic.

The study protocol and physician questionnaire were reviewed by European health authorities during a subsequent procedure (NL/H/xxxx/WS/495). The aforementioned work-sharing procedure was approved by the Reference Member State Netherlands on 29 April 2021. Based on the PRAC review of the post-authorisation safety study (PASS) protocol version 2.0 and in accordance with Article 107n(2)(a) of Directive 2001/83/EC, the PRAC considered that the study is non-interventional, and the PASS protocol for cyproterone acetate can be endorsed.

As part of good research practices, the protocol and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) checklist were registered in the European Union electronic Register of Post-Authorisation Studies (EU PAS)[3] on 11 June 2021 before the start of data collection on 18 October 2021. End of data collection was on 16 December 2021.

7. Research question and objectives

The primary objective of this study was to measure physician awareness and level of knowledge of the key safety information included in the revised SmPC and the DHPC for CPA monotherapy regarding the risk of meningioma. Specifically, the following information was collected:

- Investigate whether physicians received and reviewed the revised SmPC and DHPC
- Assess physicians' knowledge and understanding of key safety information pertaining to the following restrictions for the use of CPA due to the risk of meningioma. Specifically:
  - The occurrence of meningiomas (single and multiple) in association with CPA monotherapy doses ≥ 25 mg/day

- Restriction of use of CPA monotherapy 10 mg/50 mg in women when no results have been achieved at lower dose CPA-containing products or with other treatment options
- Restriction of use of high-dose CPA in men with sexual deviations when other interventions are not appropriate
- After clinical improvement with CPA monotherapy is achieved, treatment should be maintained with the lowest possible dose
- The risk of meningioma increases with increasing cumulative doses of CPA
- CPA is contraindicated in patients with a meningioma or a history of meningioma
- If a patient treated with CPA monotherapy is diagnosed with meningioma, treatment with all cyproterone-containing products must be permanently stopped
- Awareness of signs and symptoms of meningiomas

8. Amendments and updates

None.

9. Research methods

9.1 Study design

The study was an observational, cross-sectional survey to assess knowledge and understanding among a sample of physicians who had recently prescribed (e.g., within the previous 12 months) CPA monotherapy.

Physicians were recruited from a physician panel[1] with the aim of obtaining a sample generally representative of physicians who have prescribed CPA in the selected countries. The number of physicians in some of the specialties on the panel is relatively limited. Therefore, all of the panel physicians for each specialty in each country were invited to participate to achieve the target study sample.

In France, Germany, Poland, and Spain, physicians were invited to participate via an email, which included a link to the web-based questionnaire. Physicians in the Netherlands were contacted via telephone initially and, once it was confirmed they were interested in the study, they were sent an email with a link to the web-based questionnaire. Interested physicians logged in to the study website by entering a unique identification number and password. The physicians then completed informed consent and screening questions to confirm their specialty and that they had prescribed

[1] The panel of physicians is owned and maintained by Lightspeed Health, a web-based survey research company and division of Kantar. Lightspeed Health recruits physicians from all specialties for various research purposes. The panel is composed of physicians derived from multiple sources (e.g., hospital books and directories, medical directories, physician referrals). Each panel member is recruited by telephone and opts in to the panel twice. A stringent sampling procedure for panel member recruitment is in place to target a representative demographic cross section. A rigorous verification process is implemented to confirm potential panelists' practising status. The verification process includes checking physician background data against the medical directories in the EU (General Medicine Council in the United Kingdom). Panel membership is only finalised once live contact and verification is made with the physician at an office location. Physicians on the panel are routinely asked to participate in surveys. Recruitment and maintenance of the panel members are independent of the study. More details on the panel are provided in the study protocol.

CPA monotherapy to at least 1 patient within the past 12 months and worked in an office or hospital setting. Physicians who completed the consent and were deemed eligible could continue and complete the self-administered questionnaire. Physicians were not able to go back to previous questions, which kept them from changing their answers based on subsequent questions.

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 respondents 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.

Reminders were used in all countries to boost response. Additional efforts were made in some of the countries to reach the target study size for some specialties, including sending additional reminders and use of additional partner panels to recruit the sample of gynaecologists in France.

Data collection ran from 18 October 2021 to 16 December 2021.

Questionnaire responses were analysed using descriptive tables to characterise the level of knowledge, understanding, and reported safe use practices among these physicians, stratified by country and other relevant characteristics.

An attempt was made to obtain data for the general population of each specialty to assess the representativeness of participants. Such data could not be found, so a comparison of participants could not be made.

9.2 Setting

This cross-sectional study was conducted in France, Germany, Poland, Spain, and the Netherlands. Five countries were included to provide some diversity in practice patterns and to observe physician knowledge in different settings. In addition, it was anticipated that drug use in these countries would be such that there would be a sufficient number of eligible physicians who have experience with CPA monotherapy to participate in the study.

9.3 Subjects

This study was conducted with physicians who met the eligibility criteria in the target countries. To be eligible for the study, physicians met all the following eligibility criteria:

1. Licensed and practising dermatologist, endocrinologist, gynaecologist, general practitioner, urologist, oncologist (who treats prostate cancer), or psychiatrist involved in the treatment of hypersexuality/reduction of drive in sexual deviations
2. Prescribed CPA monotherapy to at least 1 patient in the past 12 months
3. Worked in an office or hospital-based setting
4. Electronic acknowledgement of informed consent

The study had the following predetermined recruitment targets for each country:

- Up to 30% general practitioners
- Up to 25% urologists or oncologists with a minimum of 5 of each type (e.g., 10% urologist, 15% oncologist)

- Minimum of 5 physicians each for dermatologists, psychiatrists, gynaecologists, and endocrinologists
  - In France, given the high prescribing pattern of CPA monotherapy by gynaecologists in France, up to 40% of total respondents in France could be gynaecologists.

9.4 Variables

The physician questionnaire was developed to elicit responses measuring physician knowledge and understanding of the key information included in the revised SmPC and DHPC for CPA monotherapy. This questionnaire contained mostly closed-ended questions (e.g., multiple choice, true/false) with a few free-text response fields (e.g., other, please specify), eliciting responses measuring physician knowledge and understanding of the key information in the revised SmPC and DHPC for CPA monotherapy. Questions related to the following concepts were included in the survey:

- Approved indications of CPA monotherapy
- Occurrence of meningiomas in association with CPA monotherapy
- Contraindications relevant to meningioma
- Signs and symptoms of meningioma
- Restriction of the indication to second-line treatment
- Approved dosing (i.e., treatment should be prescribed for the shortest possible time and with the lowest effective dose)
- Risk factors associated with meningioma (i.e., risk increases with increasing cumulative doses)

The questionnaire also included the following items to investigate physician receipt and use of the DHPC and revised SmPC:

- Receipt and review of the DHPC and SmPC
- Estimated time between the physicians' review of the DHPC and SmPC and completion of the survey

In addition, the physician questionnaire included queries on the following items to characterise the physicians and their practices:

- Physicians' practice setting
- Average number of CPA monotherapy prescriptions each month
- Years in practice
- Gender
- Age

The questionnaire was administered in the local language for each country. It was administered electronically and programmed so that respondents could not move backward in the survey to change their answers to previous questions.

9.5 Data sources and measurement

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

The questionnaire was developed and tested using best practices for instrument development.[4] The questions were tailored to the study aims and the information provided in the revised SmPC and DHPC.

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

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 intervention effects and/or response error may present additional sources of bias. Efforts were made to both minimise and identify potential sources of bias in this study as described below.

As summarised in Table 2 (see Section 6), the revised SmPC was approved between June 2020 and August 2020, and the DHPC was disseminated in France, Germany, Poland, and the Netherlands in April 2020 and in Spain in November 2020. Given the survey was not administered until October 2021 through December 2021, there is potential for recall bias for the information contained within the disseminated materials as well as recall of receiving the materials.

As noted above, the physician questionnaire was cognitively pretested prior to data collection to identify any problems with the questionnaire items, wording, and response choices, and to ensure consistency across cultures and languages. The questionnaire was modified based on feedback from the cognitive interviews with physicians. This process helped to ensure that the questions measured the appropriate concepts consistently and accurately across all countries and to minimise bias in responses.

The physician survey was administered as an online questionnaire. Physicians were not able to go back to previous questions. This kept them from changing their answers based on subsequent questions.

9.7 Study size

The target sample size for the physician survey was a minimum of 600 participating physicians across the 5 countries. Specifically, we targeted a minimum of 200 physicians in France and a minimum of 100 physicians each in Germany, Poland, the Netherlands, and Spain.

With a study size of 100 physician responses for a given question, the maximum width of an exact 95% confidence interval (CI) around the percentage who responded correctly is 20.3%, and 200 responses gives a maximum width of 10.3%.

9.8 Data transformation

Derived variables were created for each of the 6 knowledge questions (i.e., Questions 1a, 1b, 1d, 7, 8, and 10) that asked the respondent to "select all that apply" and had more than 1 correct response; these derived variables indicated the number of correct responses selected.

9.9 Statistical methods

All analyses were performed using SAS Release: 3.8 Enterprise Edition statistical software (Cary, NC: SAS Institute, Inc.; 2021). No formal hypothesis testing was conducted. Version 1.0 of the statistical analysis plan is provided as a stand-alone document referenced in Annex 1 of this report.

9.9.1 Main summary measures

Data analyses were descriptive in nature and focused primarily on summarising the questionnaire responses. Summary tables consisting of frequencies with percentages were created for all questionnaire responses. Response distribution percentages for a question were based on the total number of respondents who had an opportunity to answer the question. This total excluded those who were asked to skip the question because of an answer given in a previous question (skip pattern). The sum of respondents who were asked to skip the question was listed in a row labelled "Not applicable skip pattern" under the question, with no percentage calculated for that row. The counts of respondents who had an opportunity but did not answer were included in the row labelled "No answer" with a calculated percentage.

Exact 95% CIs were generated around the percentage of participants who answered each knowledge question correctly. These CIs were calculated for the overall results, results by country, and results by physician specialty, but not for the other stratified tables.

9.9.2 Main statistical methods

The analysis population consisted of respondents who were eligible for the study, provided informed consent, and completed at least 1 knowledge question in full.

Questionnaire items were divided into the following categories:

- Knowledge about indications and dosing
- Knowledge about meningioma
- Miscellaneous knowledge questions
- Physicians' experience regarding prescribing indications and patient volume
- Sources of information about CPA monotherapy, including receipt and use of the SmPC and DHPC for CPA monotherapy
- Physician and practice characteristics

Separate tables for each category were generated to display the response distributions of all questions, by country and overall.

Table 3 presents the question numbers that correspond to each of the categories.

Table 3: Listing of main analysis tables

Table number	Analytical table title	Question number
Table A-1	Knowledge: Indications and Dosing	1a, 1b, 1c, 1d
Table A-2	Knowledge: Meningioma	5, 7, 8
Table A-3	Knowledge: Meningioma [Continued]	9
Table A-4	Knowledge: Miscellaneous	9a, 9b, 9c, 10-13
Table A-5	Prescribing Indications and Volume	2-4
Table A-6	Discussing Risks With Patients and Sources of Information About CPA Monotherapy	6, 6a, 14, 14a, 14b, 15
Table A-7	Physician and Practice Characteristics	S1, S3, 16, 17

CPA = cyproterone acetate.

In addition, the knowledge questions were stratified to explore the association between each of the variables listed below and physician knowledge levels. The stratification variables were as follows:

- Physician specialty (Screening Question 1)
  - Dermatology
  - Endocrinology
  - General practice
  - Gynaecology
  - Oncology
  - Psychiatry
  - Urology
  - Other
- Practice setting (Screening Question 3)
  - Office-based practice
  - University/research-oriented/teaching hospital
  - Other hospital
- Time since last wrote a prescription for CPA monotherapy (Question 4)
  - Less than 1 month ago
  - 1 to 3 months ago
  - 4 to 6 months ago
  - > 6 months ago
  - I don’t know

- Time since last read sources of information about CPA monotherapy (Question 15)
  - Within the last week (including today)
  - Within the last 4 weeks
  - Within the last 3 months
  - Within the last 6 months
  - More than 6 months ago
  - I don't remember
- Number of years practising medicine (Question 16)
  - 5 years of less
  - 6 to 10 years
  - 11 to 15 years
  - 16 to 20 years
  - 21 to 25 years
  - > 25 years
- Gender (Question 17)
  - Male
  - Female
  - Decline

A formal set of analysis tables was created for the stratification variables. The survey included 19 knowledge questions that consisted of a total of 32 correct response options, as some questions had a single correct response whereas others had up to 5 correct response options. To quantify the knowledge across the various categories within each stratification variable, results focused on identifying when there was a difference at least 10% between each specific stratification compared with the highest correct response proportion. The value of 10% was chosen to represent a real difference in knowledge as opposed to just random chance resulting from sampling variability. A general summary of the results for each of the 6 stratification variables listed above is provided in Section 10.4.

9.9.3 Missing values

No imputation of missing values was performed.

9.9.4 Sensitivity analyses

Not applicable.

9.9.5 Amendments to the statistical analysis plan

Not applicable.

9.10 Quality control

This project was conducted in accordance with internal standard operating procedures (SOPs) of participating institutions. The RTI-HS Office of Quality Assurance (OQA), an independent unit that reports to the Executive Vice President of RTI-HS, oversaw quality assurance for this study.

RTI-HS followed our established quality management system to conduct this study including the following:

- Training of RTI-HS staff
- Ensuring data protection and integrity
- Collecting, analysing, and managing data
- Maintaining records
- Performing vendor qualification, quality control, and quality-review activities

RTI-HS SOPs were used to guide the conduct of the study. These procedures included rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

RTI-HS OQA qualified Kantar as an approved vendor (via on-site audit in 2019) before this study was initiated. Kantar has been a trusted partner and has been continuously qualified throughout the duration of this study without interruption.

In accordance with relevant RTI-HS SOPs, quality-control activities were performed throughout the project. This included the following activities:

- The initial programmer reviewed all program log files for errors and warning messages and retained electronic copies of all final log files in the project folder.
- The programmer accounted for the number of observations reported at each executed data step and noted in the program code when the number of observations increased or decreased. A second programmer independently wrote program code and confirmed the findings of the initial programmer.

10. Results

10.1 Participants

A total of 10,579 physicians were invited to participate in the survey. Of those, 1,242 physicians responded to the invitation. Of the physicians who responded, 272 were not eligible because they did not qualify, 4 did not provide informed consent, 24 were excluded because their specialty quota had been met, and 329 did not complete the screening questions. The remaining 613 physicians completed the questionnaire (200 surveys from France, 103 from Germany, 100 from Poland, 110 from Spain, and 100 from the Netherlands) and are included in this analysis. The overall response rate was 5.8% (613/10,579), though participation was capped once target sample size in each

country was reached.

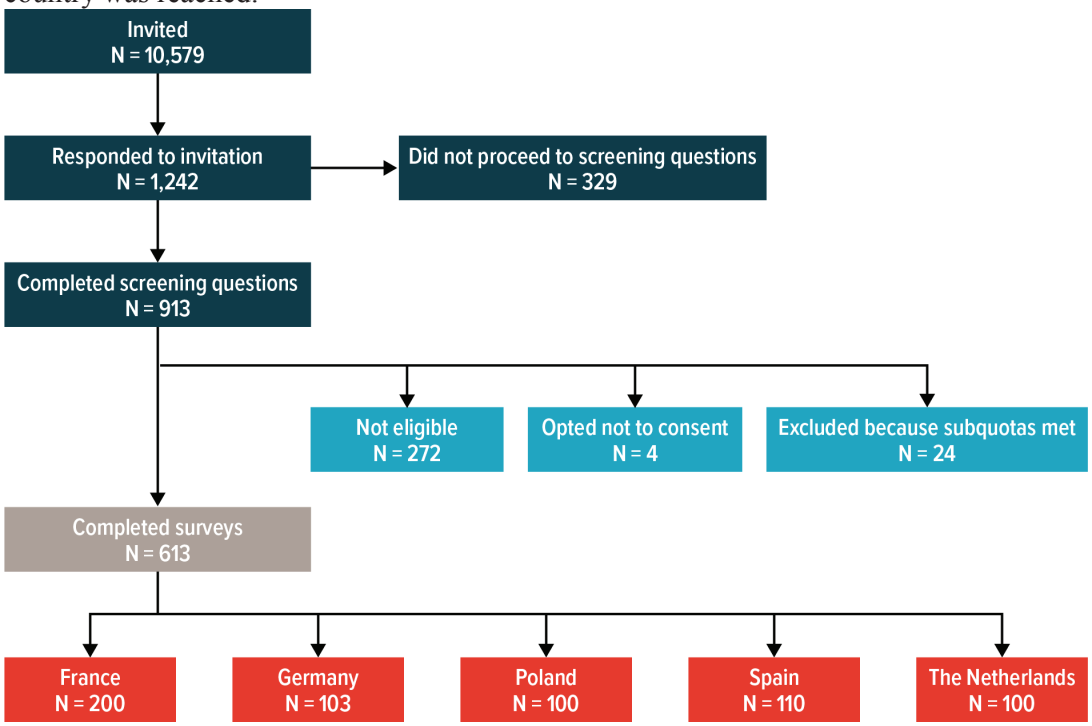
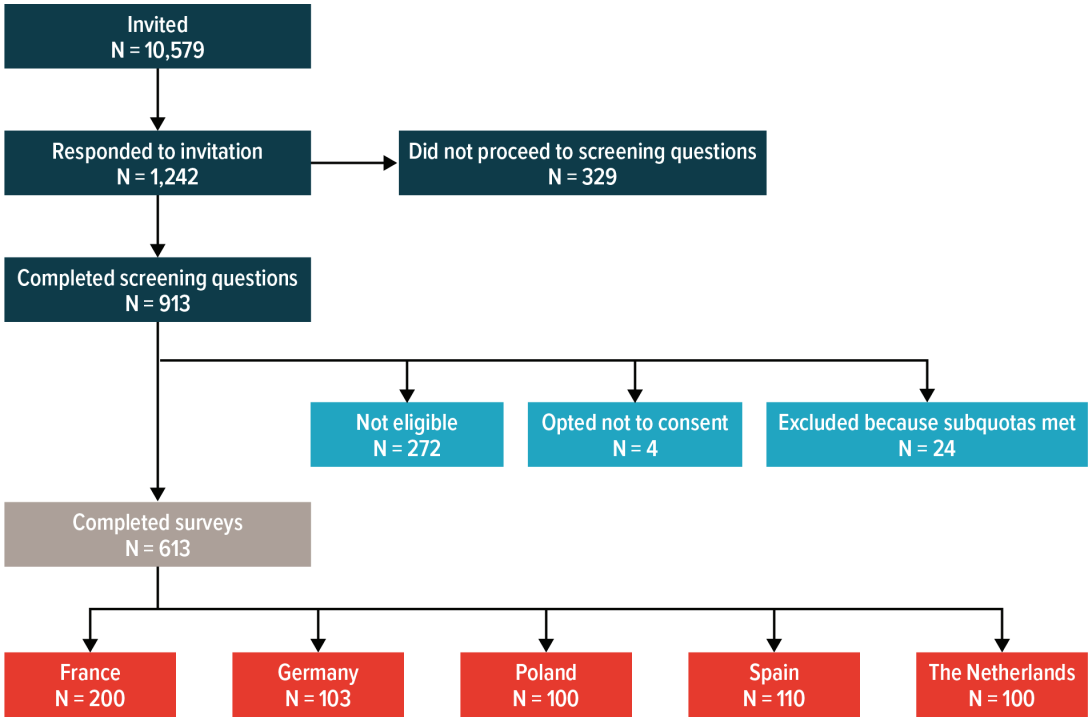


Figure 1 presents the disposition of physicians invited to participate.

Figure 1: Disposition of physicians invited to participate



10.2 Descriptive data

Of the 613 physicians who completed the survey, the distribution by specialty within medicine for all countries aligned with predefined minimum recruitment targets described in Section 9.3: general practice (30%), gynaecology (19%), urology (15%), oncology (11%), and dermatology (11%) and at least 5 endocrinologists and psychiatrists in each country. The majority of physicians characterised their practice as either office-based (46%) or a university/research-oriented/teaching hospital (33%) rather than other hospital (21%). Physicians most commonly reported having been practising medicine for 11 to 15 years (21%), 16 to 20 years (21%), or more than 25 years (21%), and only 4% reported that they had been practising for 5 years or less. Sixty-five percent of the physicians identified as male. Table 4 provides characteristics of the participating physicians.

Table 4: Physician and practice characteristics

Question	France (N = 200) n (%)	Germany (N = 103) n (%)	Poland (N = 100) n (%)	Spain (N = 110) n (%)	The Netherlands (N = 100) n (%)	Overall (N = 613) n (%)
Which of the following best describes your specialty? (S1)						
Dermatology	10 (5)	13 (13)	14 (14)	13 (12)	18 (18)	68 (11)
Endocrinology	6 (3)	5 (5)	6 (6)	6 (5)	7 (7)	30 (5)
General practice (i.e., family medicine or internal medicine or primary care physician)	60 (30)	31 (30)	30 (30)	32 (29)	30 (30)	183 (30)
Gynaecology	65 (33)	14 (14)	14 (14)	15 (14)	7 (7)	115 (19)
Oncology (treating prostate cancer)	25 (13)	11 (11)	11 (11)	15 (14)	8 (8)	70 (11)
Psychiatry	7 (4)	14 (14)	10 (10)	13 (12)	8 (8)	52 (8)
Urology	25 (13)	15 (15)	15 (15)	16 (15)	21 (21)	92 (15)
Other, please specify: _____	2 (1)	0 (0)	0 (0)	0 (0)	1 (1)	3 (0)
How would you characterise your practice? (S3)						
Office-based practice	98 (49)	76 (74)	58 (58)	11 (10)	41 (41)	284 (46)
University/research-oriented/teaching hospital	51 (26)	22 (21)	23 (23)	84 (76)	23 (23)	203 (33)
Other hospital	51 (26)	5 (5)	19 (19)	15 (14)	36 (36)	126 (21)
How many years have you been practising medicine? (Q16)						
5 years or less	3 (2)	3 (3)	13 (13)	4 (4)	1 (1)	24 (4)
6 to 10 years	20 (10)	5 (5)	36 (36)	15 (14)	16 (16)	92 (15)

11 to 15 years	34 (17)	23 (22)	23 (23)	23 (21)	27 (27)	130 (21)
16 to 20 years	41 (21)	19 (18)	15 (15)	24 (22)	28 (28)	127 (21)
21 to 25 years	43 (22)	29 (28)	6 (6)	14 (13)	17 (17)	109 (18)
More than 25 years	59 (30)	24 (23)	7 (7)	30 (27)	11 (11)	131 (21)
Do you identify as…? (Q17)						
Male	157 (79)	70 (68)	45 (45)	59 (54)	69 (69)	400 (65)
Female	38 (19)	29 (28)	51 (51)	49 (45)	31 (31)	198 (32)
Diverse	PPD					
Prefer not to answer						

10.3 Main results

In the following sections, we present key results from physicians who completed the questionnaire. The results are organised in the following categories:

- Knowledge of updated safety information for CPA monotherapy
- Knowledge of meningioma
- Physicians' experience prescribing CPA monotherapy
- Knowledge about approved indications and dosing of CPA monotherapy
- Additional knowledge questions asked in France only
- Sources of information about CPA monotherapy, including receipt and use of the SmPC and DHPC for CPA monotherapy

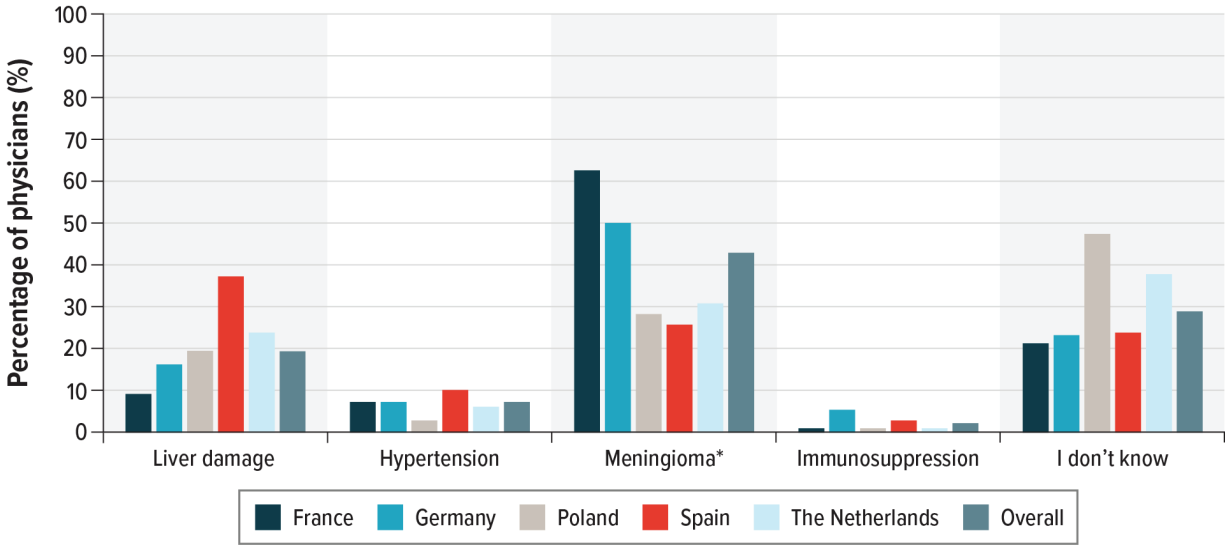
Knowledge of key safety information is described for the overall sample, then stratified by country and physician specialty.

Graphs highlight the stratification results in which the largest differences were seen or where the stratifications seem of most interest.

10.3.1 Knowledge of updated safety information for CPA monotherapy

Overall, 43% of physicians correctly identified that a special warning and precaution about meningioma was added in 2020 to the prescribing label for CPA monotherapy, as shown in Figure 2. Those in France (63%) and Germany (50%) were most aware of this addition (Annex 2, Table 2, Question 5).

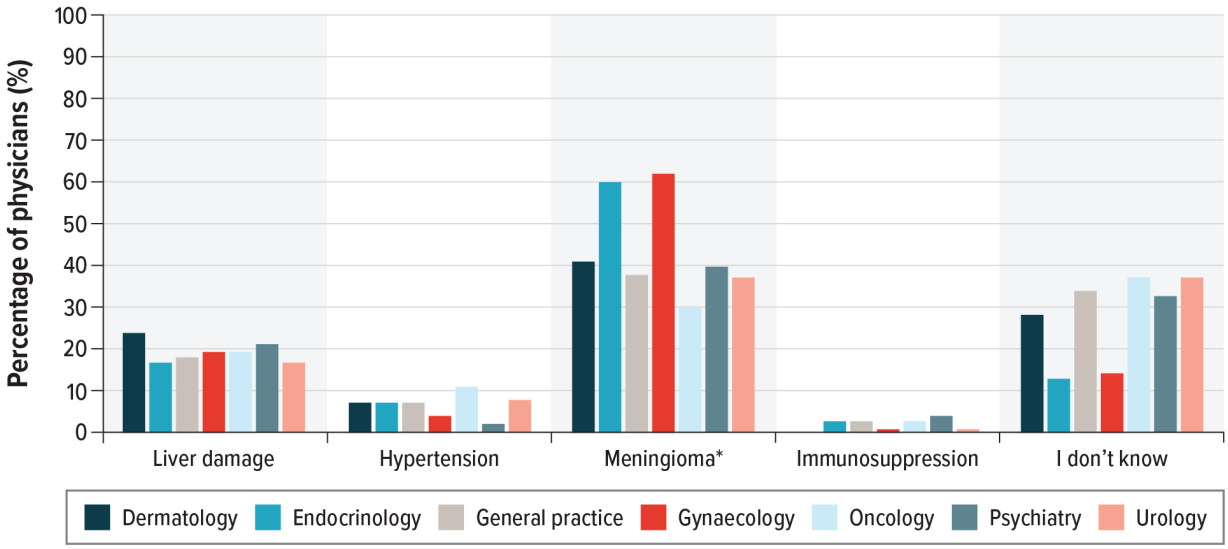
Figure 2: Responses to Question 5 by country: What special warning and precaution was recently added in 2020 to the prescribing label for CPA monotherapy? (N = 613)



* Correct response is marked with an asterisk.

As shown in Figure 3, physicians specialising in gynaecology (62%) and endocrinology (60%) were most aware of the warning about changes in the label regarding meningioma with use of CPA monotherapy; oncologists (30%) had the least awareness (Annex 3, Table 2, Question 5).

Figure 3: Responses to Question 5 by specialty: What special warning and precaution was recently added in 2020 to the prescribing label for CPA monotherapy? (N = 613)



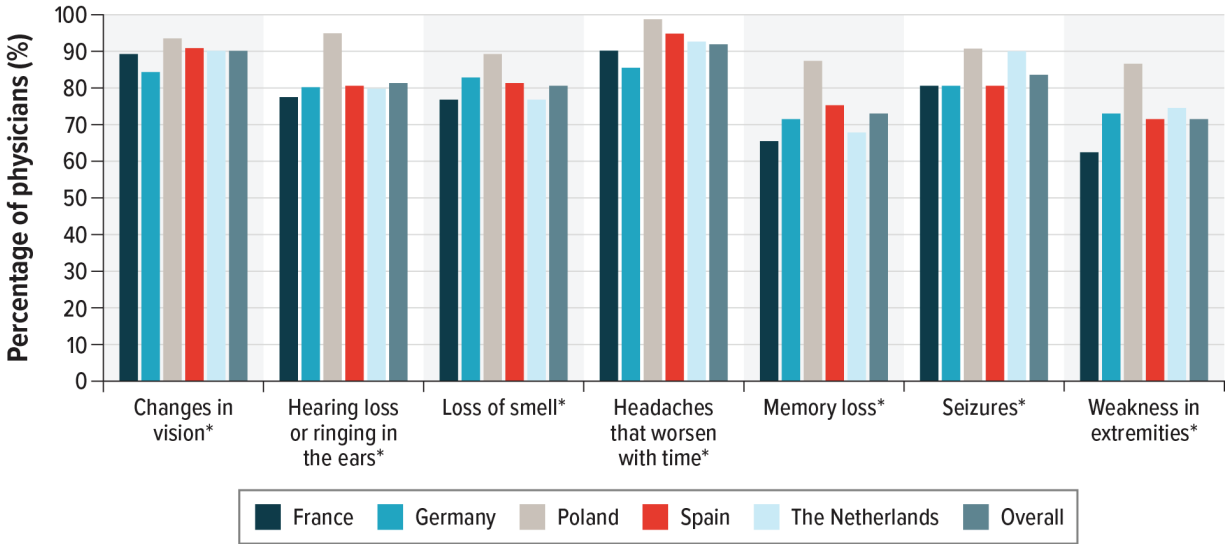
* Correct response is marked with an asterisk.

10.3.2 Knowledge of meningioma

Physicians were asked to identify clinical signs and symptoms of meningioma from a list of 7 signs and symptoms, all of which were correct. The list included the following, with the overall percentage of physicians selecting each in parentheses: headaches that worsen with time (92%), changes in vision (90%), seizures (84%), hearing loss or ringing in the ears (82%), loss of smell (81%), memory loss (73%), and weakness in extremities (72%). As shown in Figure 4, more physicians from Poland identified each of the individual signs and symptoms correctly (87% or higher for each sign or symptom) compared with other countries, although more than 60% of physicians from the other 4 countries correctly identified each of the symptoms individually (Figure 4).

Over 80% of physicians from Poland correctly identified all 7 signs and symptoms, whereas the proportion among the other countries who correctly identified all 7 ranged from 56% in France to 69% in Germany and Spain. Overall, 98% of physicians selected at least 1 correct response, ranging from 95% in Germany to 100% in Poland (Annex 2, Table 2, Question 8).

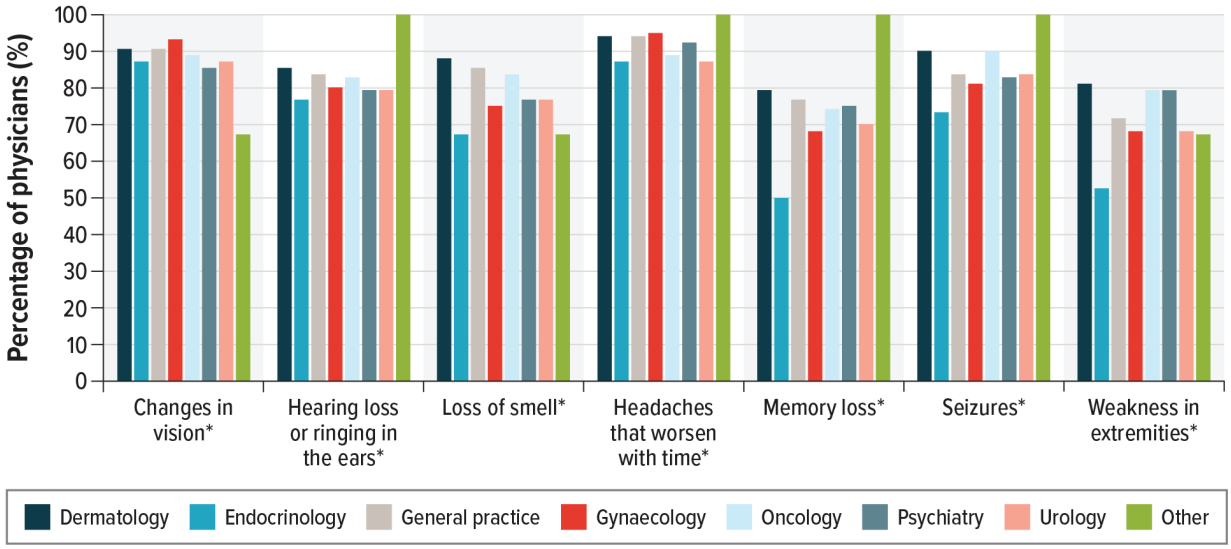
Figure 4: Responses to Question 8 by country: Which of the following may be clinical signs and symptoms of meningioma? (N = 613)



* Correct response is marked with an asterisk.

By physician specialty, dermatologists had the highest proportion who identified all 7 signs and symptoms (78%), followed by psychiatrists (73%), oncologists (71%), general practitioners (67%), gynaecologists (58%), and endocrinologists (50%). Figure 5 shows the percentage of physicians correctly selecting each sign and symptom by specialty (Annex 3, Table 2, Question 8).

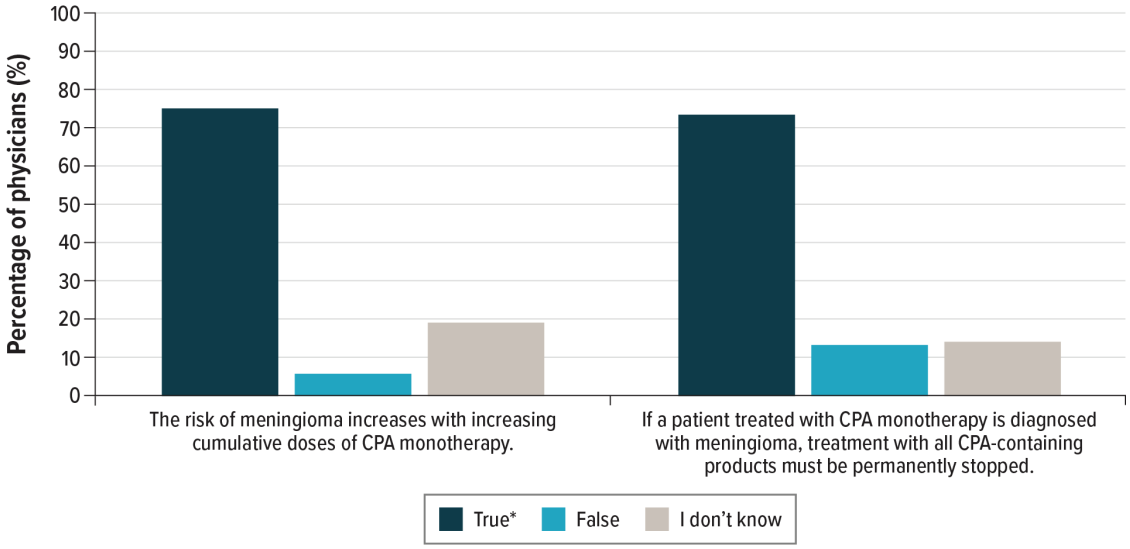
Figure 5: Responses to Question 8 by specialty: Which of the following may be clinical signs and symptoms of meningioma? (N = 613)



* Correct response is marked with an asterisk.

In a series of 5 true/false questions, physicians were further queried on their knowledge of meningioma and how it relates to CPA monotherapy. Overall, 75% of physicians correctly identified that the risk of meningioma increases with increasing cumulative doses of CPA monotherapy, and 73% correctly identified that if a patient treated with CPA monotherapy is diagnosed with meningioma, treatment with all CPA-containing products must be permanently stopped. As shown in Figure 6, correct responses to both questions were high across all countries (at least 64% for all) (Annex 2, Table 3, Question 9). There was somewhat more variability by physician specialty, but only oncologists had fewer than 60% of physicians correctly answer either of the questions (56% and 47%, respectively), and most other specialties had more than 70% correctly answer each of the 2 questions (Annex 3, Table 3, Question 9).

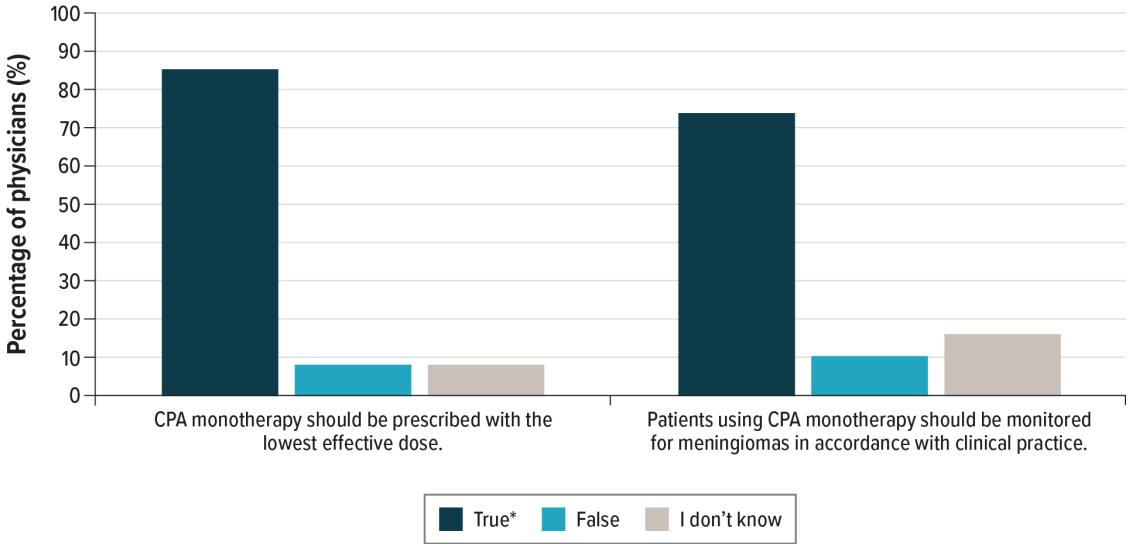
Figure 6: Responses to Question 9: Please indicate whether each of the following statements about CPA monotherapy is true or false. (N = 613)



* Correct response is marked with an asterisk.

Two of the other true/false questions had a similarly high proportion of correct responses, with 85% of physicians correctly indicating that CPA monotherapy should be prescribed with the lowest effective dose and 74% indicating that patients using CPA monotherapy should be monitored for meningiomas in accordance with clinical practice. As shown in Figure 7, results to both questions were similar among all 5 countries, with the exception of the Netherlands, where only 44% of physicians agreed that patients using CPA monotherapy should be monitored for meningiomas in accordance with clinical practice (Annex 2, Table 3, Question 9). As with the previous 2 true/false questions, oncologists had the lowest proportion selecting the correct response, with 66% and 54% on the 2 questions, respectively (Annex 3, Table 3, Question 9).

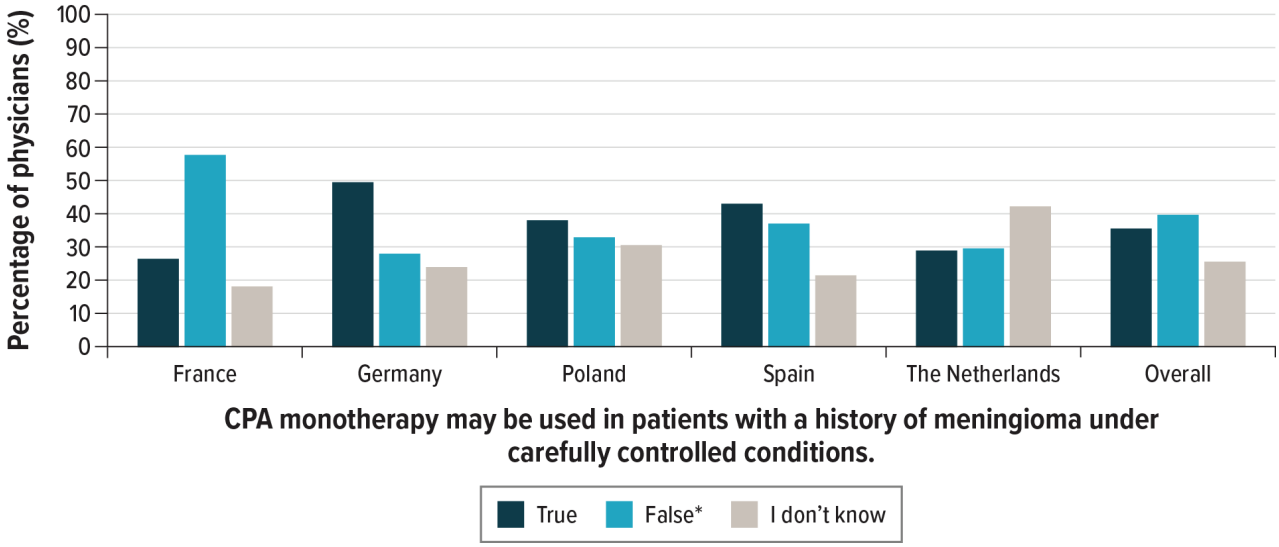
Figure 7: Responses to Question 9: Please indicate whether each of the following statements about CPA monotherapy is true or false. (N = 613)



CPA = cyproterone acetate.
* Correct response is marked with an asterisk.

Overall, the last true/false question had a lower proportion of physicians (39%) selecting the correct response that the statement "CPA monotherapy may be used in patients with a history of meningioma under carefully controlled conditions" was false, ranging from 27% in Germany to 57% in France, as shown in Figure 8 (Annex 2, Table 3, Question 9). However, when responses were stratified by physician specialty, correct responses ranged from 17% for oncologists up to 57% for gynaecologists (Annex 3, Table 3, Question 9).

Figure 8: Responses to Question 9 by country: Please indicate whether each of the following statements about CPA monotherapy is true or false. (N = 613)



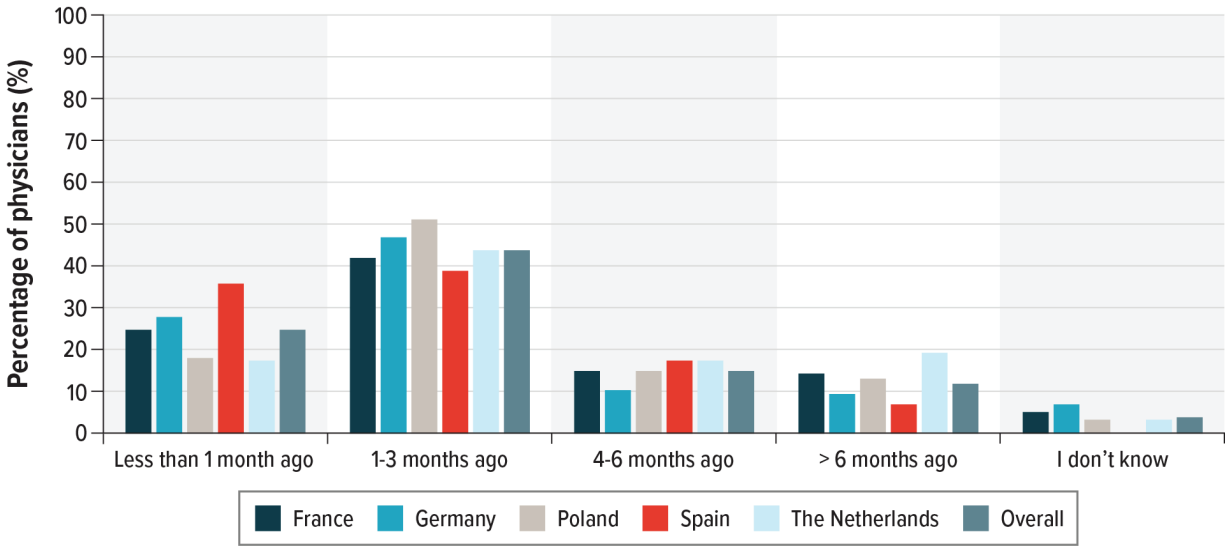
CPA = cyproterone acetate.
* Correct response is marked with an asterisk.

10.3.3 Physicians' experience prescribing CPA monotherapy

Physicians were asked when they had last prescribed CPA monotherapy for any indication. Overall, 69% of physicians had written a prescription for CPA monotherapy within the past 3 months, with 25% indicating they had prescribed it within the past month. As shown in

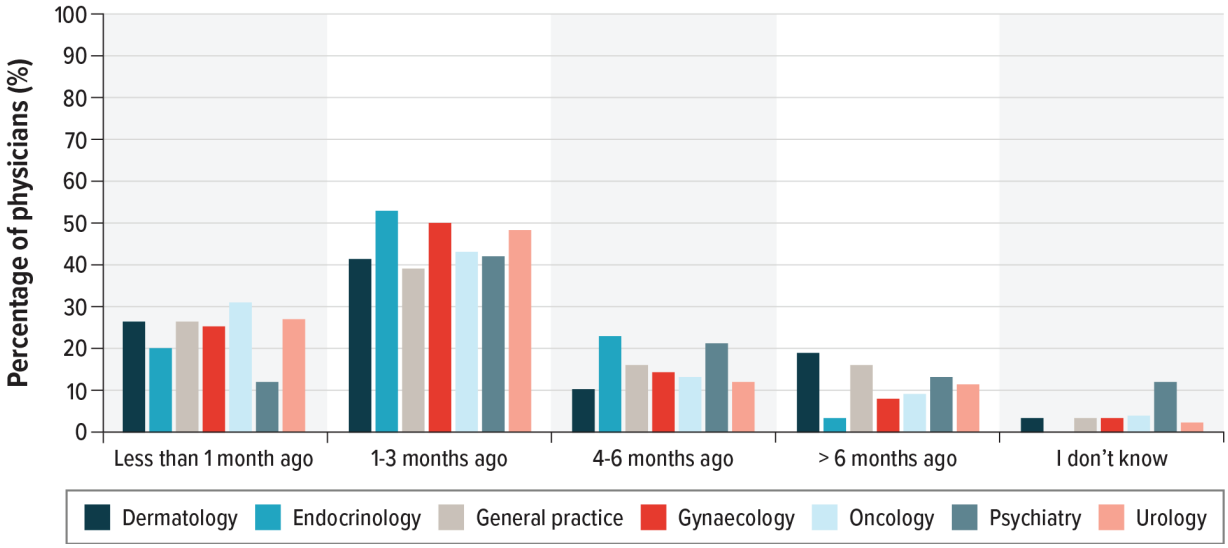
Figure 9, results were similar across countries with the Netherlands indicating less use within the past month (17%) and Spain showing greater use within in the past month (36%) (Annex 2, Table 5, Question 4).

Figure 9: Responses to Question 4 by country: When did you write your most recent prescription for CPA monotherapy for any indication? (N = 613)



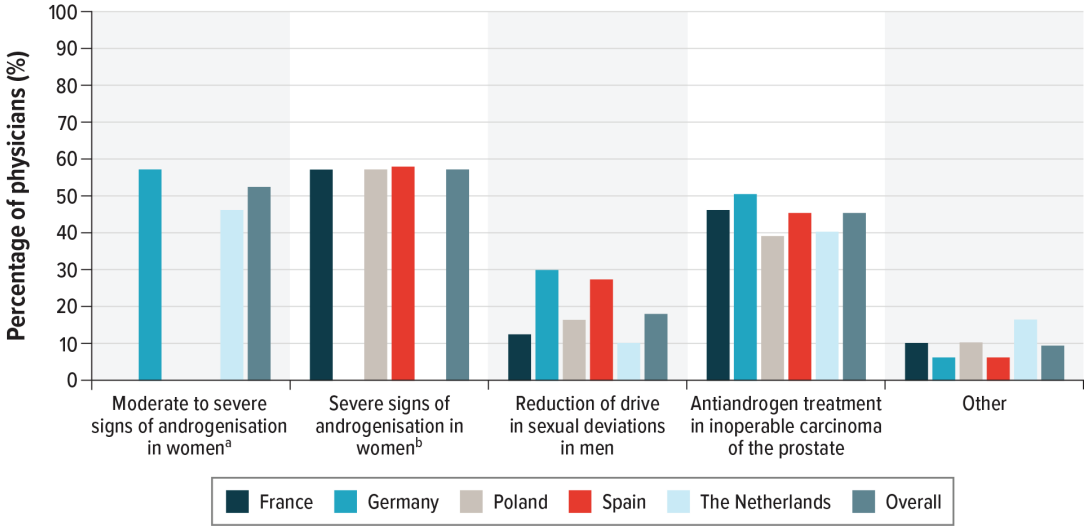
As shown in Figure 10, prescription use within the past 3 months was highest among gynaecologists (75%), urologists (75%), oncologists (74%), and endocrinologists (73%) and lowest among psychiatrists (54%) (Annex 3, Table 5, Question 4).

Figure 10: Responses to Question 4 by specialty: When did you write your most recent prescription for CPA monotherapy for any indication? (N = 613)



Physicians were asked for which indications they prescribe CPA monotherapy and were given up to 5 options of approved indications (based on country, some options were only available in a subset of the countries) from which to select. Physicians could select as many options as they wanted. Figure 11 shows a summary of indications selected by country. Results for each approved indication are summarised in the sections below.

Figure 11: Responses to Question 2 by country: In the past 12 months, for which indications have you prescribed CPA monotherapy? (N = 613)



[a] This response option was only displayed for Germany and The Netherlands.
[b] This response option was only displayed for France, Poland, and Spain.

10.3.3.1 Androgenisation in women

The indication option, "**moderate to severe** signs of androgenisation in women" was only available in Germany, selected by 57%, and the Netherlands, selected by 46%.

Among those who selected "**moderate to severe** signs of androgenisation in women" (n = 59 in Germany and n = 46 in the Netherlands), the majority in each country indicated that they had prescribed CPA monotherapy for this indication to 1 to 5 patients in the past 3 months (59% in Germany and 87% in the Netherlands); only 8% in Germany and 4% in the Netherlands indicated that they had not prescribed CPA monotherapy for this indication in the past 3 months (Annex 2, Table 5, Question 2).

The indication option, "**severe** signs of androgenisation in women" was only available in France, Poland, and Spain and was selected by 57%, 57%, and 58% of participating physicians from each country, respectively.

Among those who selected "**severe** signs of androgenisation in women" (n = 113 in France, n = 57 in Poland, and n = 64 in Spain), the majority in each country indicated that they had prescribed CPA monotherapy for this indication to 1 to 5 patients in the past 3 months (71% in France, 88% in Poland, and 66% in Spain); only 4% in France and Poland and 3% in Spain indicated that they had not prescribed CPA monotherapy for this indication in the past 3 months (Annex 2, Table 5, Question 2).

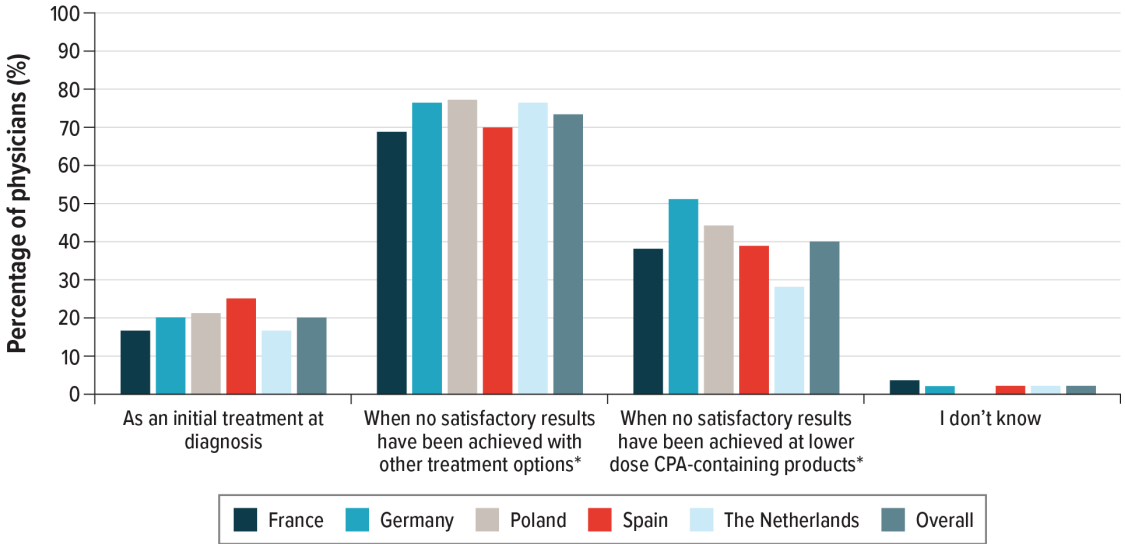
Specialties most often indicating they had prescribed for "moderate to severe or severe signs of androgenisation in women" in the past 12 months included: gynaecologists (95%), dermatologists (90%), endocrinologists (87%) and general practitioners (63%) (Annex 3, Table 5, Question 2).

10.3.3.1.1 Knowledge questions about use of CPA monotherapy to treat androgenisation in women

Two questions were asked of the subset of physicians who indicated that they had prescribed CPA monotherapy for moderate to severe signs or for severe signs of androgenisation in women in the past 12 months, as measured in Question 2 (n = 339).

Physicians from all countries were asked when CPA monotherapy at doses of 10 mg or 50 mg should be prescribed for moderate to severe signs of androgenisation in women. There were 2 correct choices among the response options: (1) "When no satisfactory results have been achieved with other treatment options," and (2) "When no satisfactory results have been achieved at lower dose CPA-containing products." Seventy-three percent of physicians selected the first correct response, whereas only 40% selected the second correct response. As shown in Figure 12, this pattern of approximately 70% or higher for the first response and approximately 50% or less on the second response was consistent across countries. Overall, 88% of participants selected at least 1 correct response to the question (Annex 2, Table 4, Question 10).

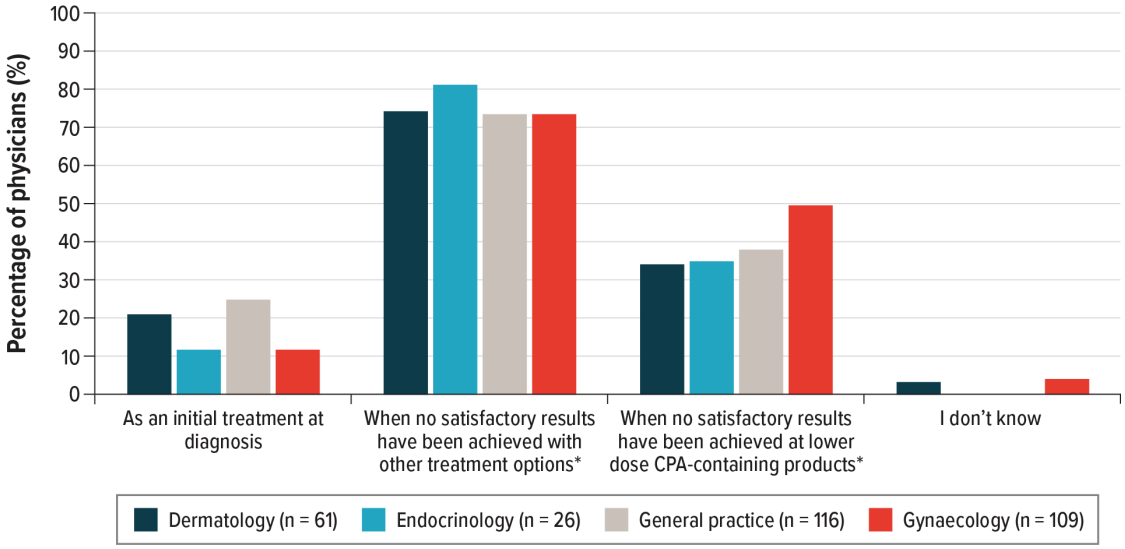
Figure 12: Responses to Question 10: When should CPA monotherapy at doses of 10 mg or 50 mg be prescribed for moderate to severe signs of androgenisation in women? (N = 339)



CPA = cyproterone acetate.
* Correct response is marked with an asterisk.

Figure 13 displays results to this question for the physician specialties where at least 10 specialists had prescribed CPA monotherapy for androgenisation in the past 12 months. Endocrinologists had the highest proportion of specialists selecting the first correct response, "when no satisfactory results have been achieved with other treatment options" (81%), and gynaecologists had the highest proportion of specialists selecting the second correct response, "when no satisfactory results have been achieved at lower dose CPA-containing products" (49%). Upon combining responses, the specialists selecting at least 1 correct response ranged from 92% of endocrinologists to 85% of dermatologists (Annex 3, Table 4, Question 10).

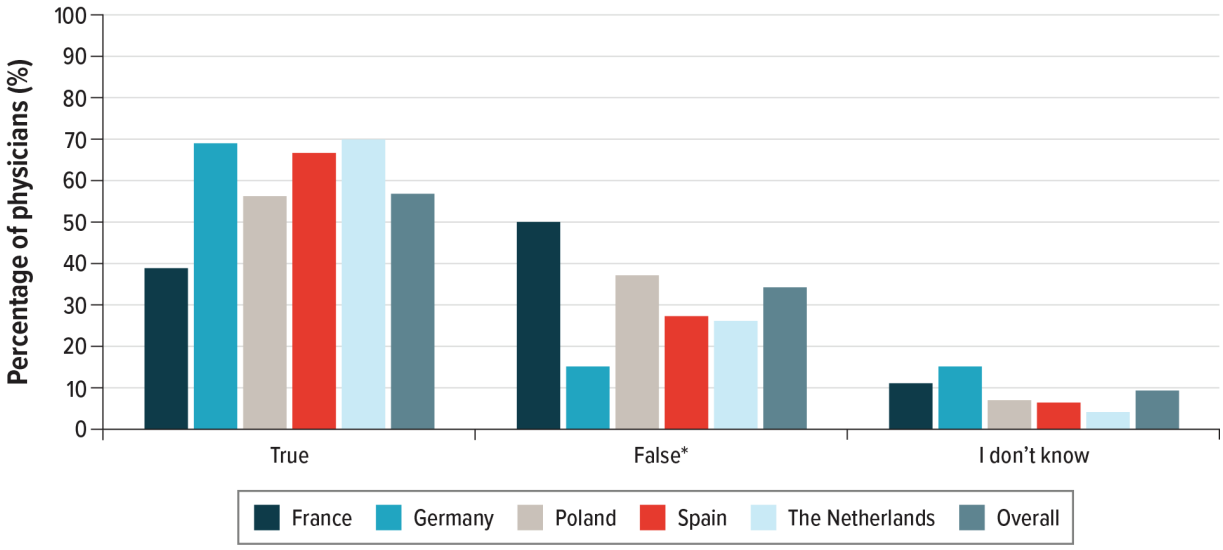
Figure 13: Responses to Question 10 by specialty: When should CPA monotherapy at doses of 10 mg or 50 mg be prescribed for moderate to severe signs of androgenisation in women? (N = 339)



CPA = cyproterone acetate.
* Correct response is marked with an asterisk.
Note: Results are shown where ≥ 10 specialists had prescribed CPA monotherapy for the indication in the past 12 months.

The second question asked among the subset of physicians who had prescribed CPA monotherapy in the past 12 months for moderate to severe signs or severe signs of androgenisation in women was "After using CPA monotherapy at a dose of 10 mg (in Germany and Netherlands only) or 50 mg (in France, Poland, and Spain only) and achieving clinical improvement of moderate to severe signs of androgenisation, the patient can continue using CPA monotherapy at this dose for as long as it is necessary." As shown in Figure 14, 34% of physicians correctly indicated that this was a false statement, ranging from 15% in Germany to 50% in France (Annex 2, Table 4, Question 11).

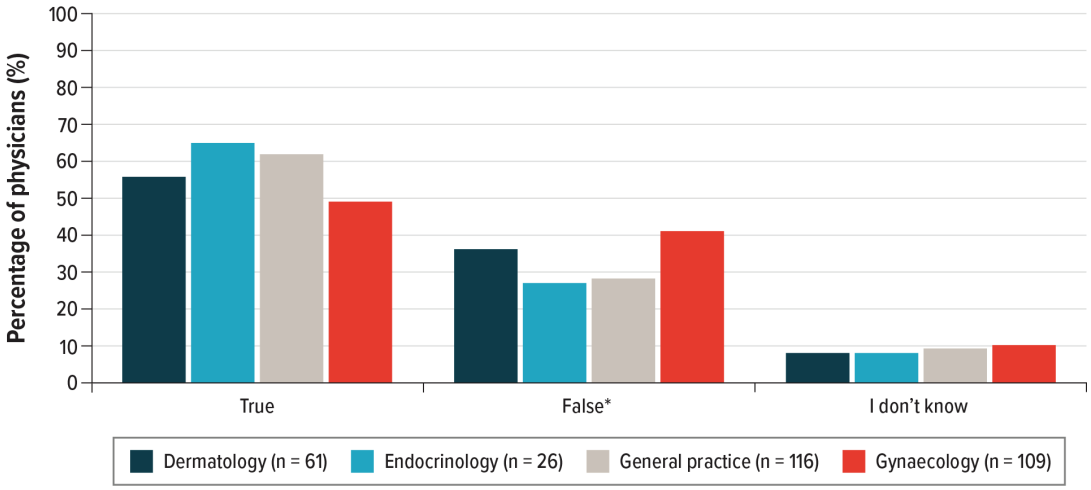
Figure 14: Responses to Question 11: After using CPA monotherapy at a dose of 10 mg (in Germany and Netherlands only) or 50 mg (in France, Poland, and Spain only) and achieving clinical improvement of moderate to severe (in Germany and Netherlands only) or severe (in France, Poland, and Spain only) signs of androgenisation, the patient can continue using CPA monotherapy at this dose for as long as it is necessary. (N = 339)



* Correct response is marked with an asterisk.

As shown in Figure 15, among the physician specialties where at least 10 specialists had prescribed CPA monotherapy for androgenisation in the past 12 months, gynaecologists had the highest proportion of specialists selecting the correct response (41%); endocrinologists had the lowest proportion selecting the correct response, with 27% selecting "false" (Annex 3, Table 4, Question 11).

Figure 15: Responses to Question 11 by specialty: After using CPA monotherapy at a dose of 10 mg (in Germany and Netherlands only) or 50 mg (in France, Poland, and Spain only) and achieving clinical improvement of moderate to severe (in Germany and Netherlands only) or severe (in France, Poland, and Spain only) signs of androgenisation, the patient can continue using CPA monotherapy at this dose for as long as it is necessary. (N = 339)



* Correct response is marked with an asterisk.
Note: Results are shown where ≥ 10 specialists had prescribed CPA monotherapy for the indication in the past 12 months.

10.3.3.2 Reduction of drive in sexual deviations in men

The indication option, "reduction of drive in sexual deviations in men" was selected by 18% of the physicians overall, ranging from 10% in the Netherlands to 30% in Germany. Among those who selected "reduction of drive in sexual deviations in men" (n = 110), 75% indicated that they had prescribed CPA monotherapy for this indication to 1 to 5 patients in the past 3 months, ranging from 65% in France to 100% in Poland. Seven of the 110 physicians (6%) indicated that they had not prescribed CPA monotherapy for this indication in the past 3 months (Annex 2, Table 5, Question 2).

Seventy-seven percent of psychiatrists had prescribed for this indication in the past 12 months, 93% of whom had prescribed to 1 to 5 patients in the past 3 months.

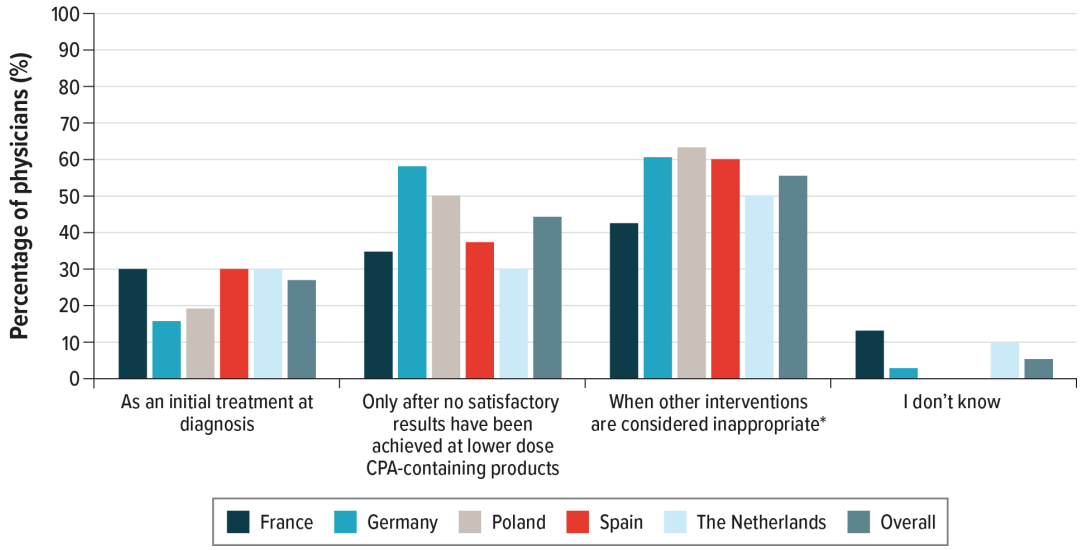
10.3.3.2.1 Knowledge question about use of CPA monotherapy to treat sexual deviations in men

One knowledge question was asked of the subset of physicians who indicated that they had prescribed CPA monotherapy for reduction of drive in sexual deviations in men, as measured in Question 2 (n = 110).

Physicians who had previously indicated that in the past 12 months they had prescribed CPA monotherapy for reduction of drive in sexual deviations in men were asked when CPA monotherapy should be prescribed for reduction of drive in sexual deviations in men. The question presented the approved dosage for each country: 50 mg, 100 mg, and 300 mg for Germany and the Netherlands, 50 mg and 100 mg for France and Poland, and 50 mg for Spain. As shown in Figure 16, 56% of physicians selected the correct response that this should be done "when other interventions are considered inappropriate." At least 60% of physicians in Germany, Poland, and Spain selected the

correct response. Knowledge was lower in France and the Netherlands, with only 43% and 50%, respectively, selecting the correct response (Annex 2, Table 4, Question 12).

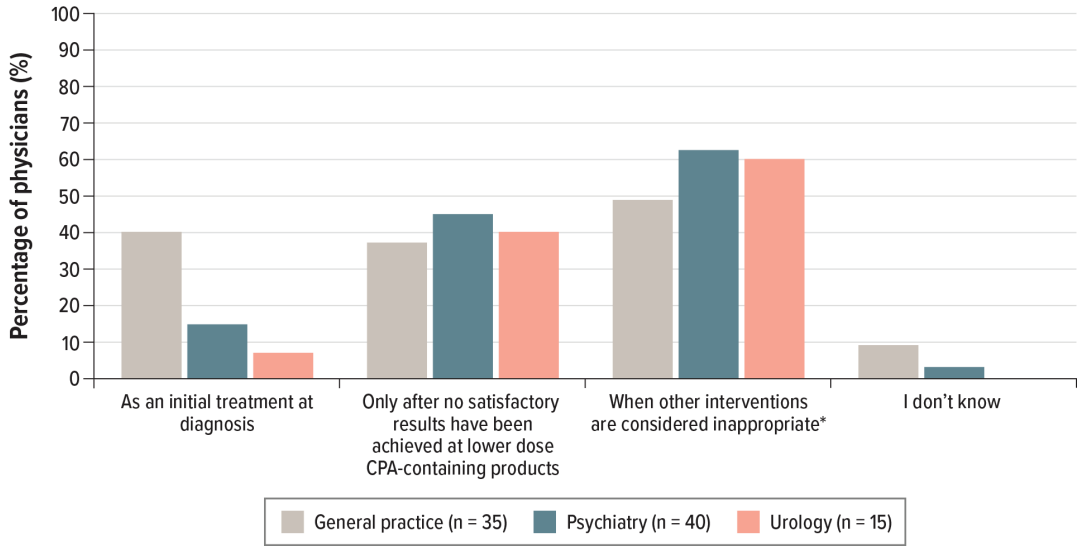
Figure 16: Responses to Question 12: When should CPA monotherapy at doses of 50 mg, 100 mg, or 300 mg/3 mL (in Germany and the Netherlands only), 50 mg or 100 mg (in France and Poland only), or 50 mg (in Spain only) be prescribed for reduction of drive in sexual deviations in men? (N = 110)



CPA = cyproterone acetate.
* Correct response is marked with an asterisk.

Sample sizes for this question are small when reviewing the results by specialty. As shown in Figure 17, for those specialties where at least 10 specialists had prescribed CPA monotherapy for reduction of drive in sexual deviations in men in the past 12 months, the proportion of physicians answering this question correctly was highest among psychiatrists (63%), followed by urologists (60%) and general practitioners (49%). (Annex 3, Table 4, Question 10).

Figure 17: Responses to Question 12 by specialty: When should CPA monotherapy at doses of 50 mg, 100 mg, or 300 mg/3 mL (in Germany and the Netherlands only), 50 mg or 100 mg (in France and Poland only), or 50 mg (in Spain only) be prescribed for reduction of drive in sexual deviations in men? (N = 110)



CPA = cyproterone acetate.
* Correct response is marked with an asterisk.
Note: Results are shown where ≥ 10 specialists had prescribed CPA monotherapy for the indication in the past 12 months.

10.3.3.3 Antiandrogen treatment in inoperable carcinoma of the prostate

The indication option, "antiandrogen treatment in inoperable carcinoma of the prostate" was selected by 45% of the physicians, ranging from 39% in Poland to 51% in Germany. Among those who selected "antiandrogen treatment in inoperable carcinoma of the prostate" (n = 274), 65% indicated that they had prescribed CPA monotherapy for this indication to 1 to 5 patients in the past 3 months. Fifteen of the 274 physicians (5%) indicated that they had not prescribed CPA monotherapy for this indication in the past 3 months (Annex 2, Table 5, Question 2).

Specialties most often prescribing for this indication included oncologists (96%), urologists (89%), and general practitioners (55%) (Annex 3, Table 5, Question 2).

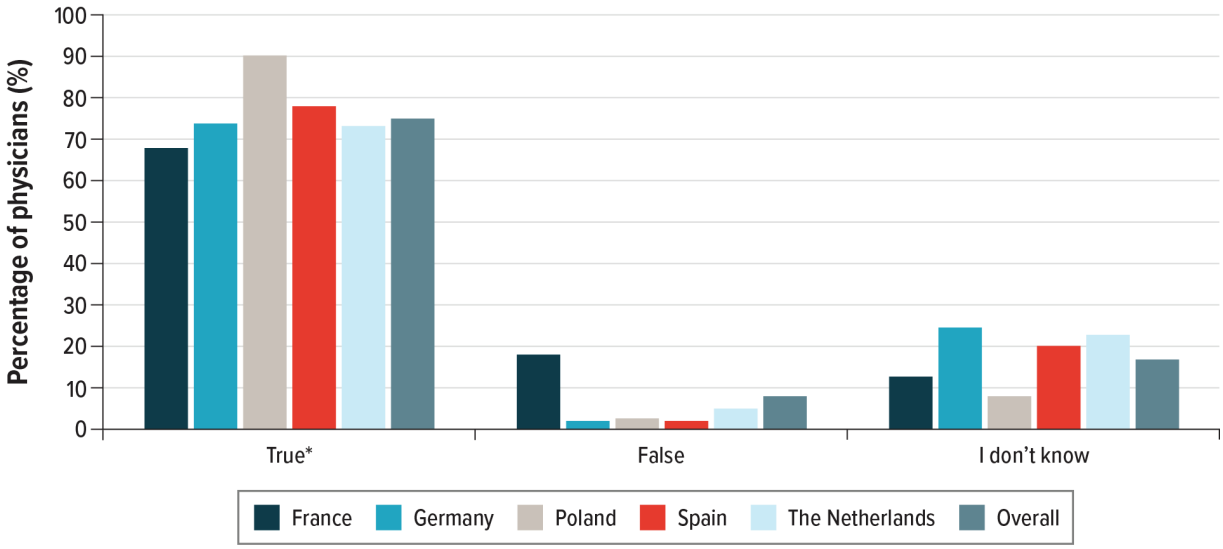
10.3.3.3.1 Knowledge question about use of CPA monotherapy to treat inoperable carcinoma of the prostate

One knowledge question was asked of the subset of physicians who indicated that they had prescribed CPA monotherapy for antiandrogen treatment in inoperable carcinoma of the prostate, as measured in Question 2 (n = 274).

Physicians who had previously indicated that in the past 12 months they had prescribed CPA monotherapy for antiandrogen treatment in inoperable carcinoma of the prostate were asked whether the statement "The use of CPA monotherapy for the treatment of inoperable prostate carcinoma and LHRH (luteinising hormone-releasing hormone) flare remains unchanged per the summary of product characteristics (SmPC)" was true. Seventy-five percent of physicians correctly indicated the

statement as true, ranging from 68% in France to 90% in Poland, as shown in Figure 18 (Annex 2, Table 4, Question 13).

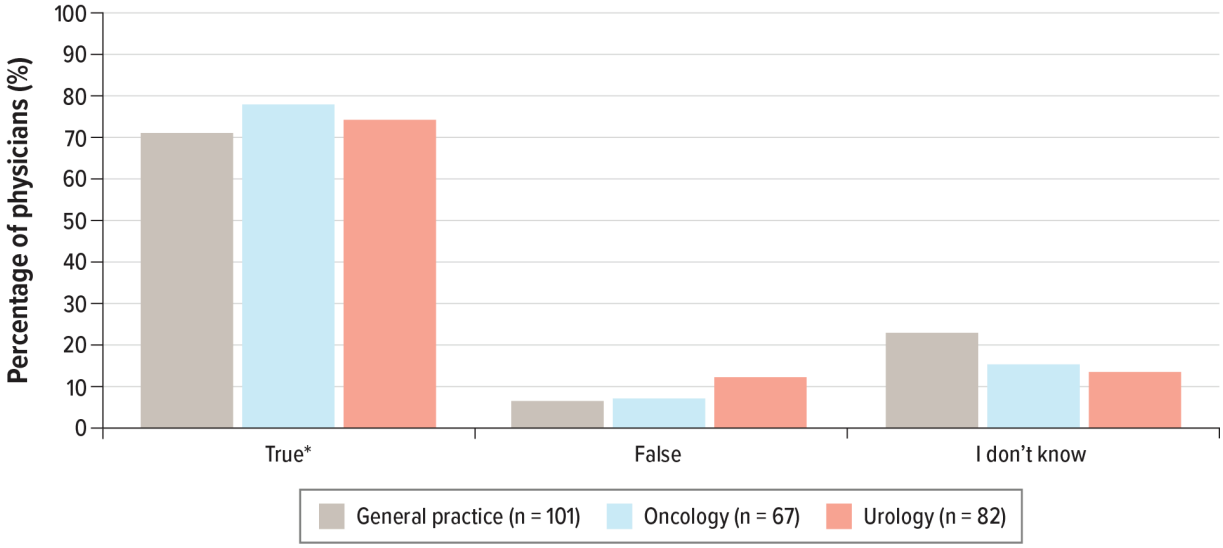
Figure 18: Responses to Question 13: The use of CPA monotherapy for the treatment of inoperable prostate carcinoma and LHRH (luteinising hormone-releasing hormone) flare remains unchanged per the Summary of Product Characteristics (SmPC). (N = 274)



* Correct response is marked with an asterisk.

For those specialties where there were at least 10 responses, the proportion of physicians answering this question correctly was highest among oncologists (78%), followed by urologists (74%) and general practitioners (71%), as shown in Figure 19 (Annex 3, Table 4, Question 13).

Figure 19: Responses to Question 13 by specialty: The use of CPA monotherapy for the treatment of inoperable prostate carcinoma and LHRH (luteinising hormone-releasing hormone) flare remains unchanged per the Summary of Product Characteristics (SmPC). (N = 274)



* Correct response is marked with an asterisk.
Note: Results are shown where ≥ 10 specialists had prescribed CPA monotherapy for the indication in the past 12 months.

10.3.3.4 Other

Physicians were also given the option of selecting "other" among the list of indications for which they had prescribed CPA monotherapy over the past 12 months. Very few physicians (9%, n = 58) selected this option. Among those who selected "other," 59% (n = 34) indicated that they had prescribed CPA monotherapy for an "other" indication to 1 to 5 patients in the past 3 months, while 19% (n = 11) indicated that they had not prescribed to any patients in the last 3 months (Annex 2, Table 5, Question 2).

10.3.4 Knowledge about approved indications and dosing of CPA monotherapy

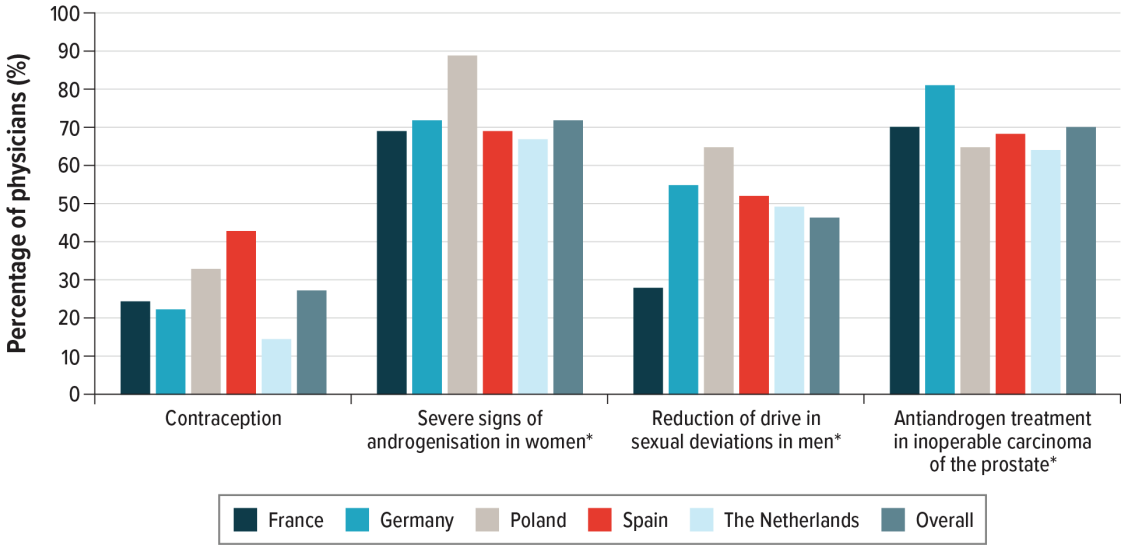
Physicians were asked to select the approved indication for CPA monotherapy for each approved dosage in their respective country. Physicians could select as many options as they wanted. Results for each dosage of CPA monotherapy are summarised in the sections below.

10.3.4.1 CPA monotherapy, 50 mg

CPA monotherapy is approved in 50 mg strength in all 5 countries. As shown in Figure 20, most physicians correctly identified "severe signs of androgenisation in women" and "antiandrogen treatment in inoperable carcinoma of the prostate" as approved indications of CPA monotherapy 50 mg (72% and 70%, respectively). Results were fairly consistent across all countries, with the exception of Poland where 89% of physicians correctly identified "severe signs of androgenisation in women" and Germany where 81% of physicians correctly identified "antiandrogen treatment in inoperable carcinoma of the prostate." Overall, 46% of physicians correctly identified "reduction of drive in sexual deviations in men" as an approved indication, ranging from 28% in France to 65% in Poland. Overall, 27% of physicians selected the incorrect response "contraception" (ranging from 14% in the Netherlands to 43% in Spain).

Overall, 33% of physicians selected all 3 approved indications correctly, 25% selected 2 correct responses, and 39% selected 1 correct approved indication. Poland had the highest proportion select all 3 correct responses (52%), and France had the lowest at 20%. Overall, 97% of physicians selected at least 1 correct response, and 58% selected at least 2 correct responses (Annex 2, Table 1, Question 1a).

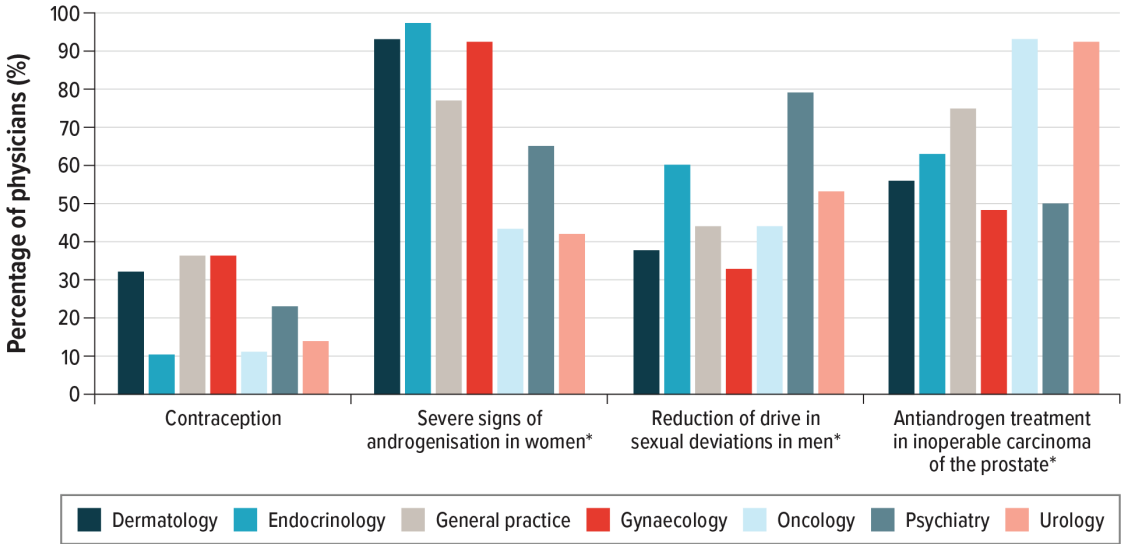
Figure 20: Responses to Question 1a by country: Which are the approved indications of CPA monotherapy 50 mg? (N = 613)



* Correct response is marked with an asterisk.

As shown in Figure 21, almost all endocrinologists (97%), dermatologists (93%), and gynaecologists (92%) correctly identified "severe signs of androgenisation" as an approved indication. Likewise, nearly all oncologists (93%) and urologists (92%) correctly identified "treatment of inoperable carcinoma of the prostate" as an approved indication for this dosage. Seventy-nine percent of psychiatrists correctly identified "reduction of drive in sexual deviations in men," while the proportion of other physician specialties ranged from 33% to 60% (Annex 3, Table 1, Question 1a).

Figure 21: Responses to Question 1a by specialty: Which are the approved indications of CPA monotherapy 50 mg? (N = 613)



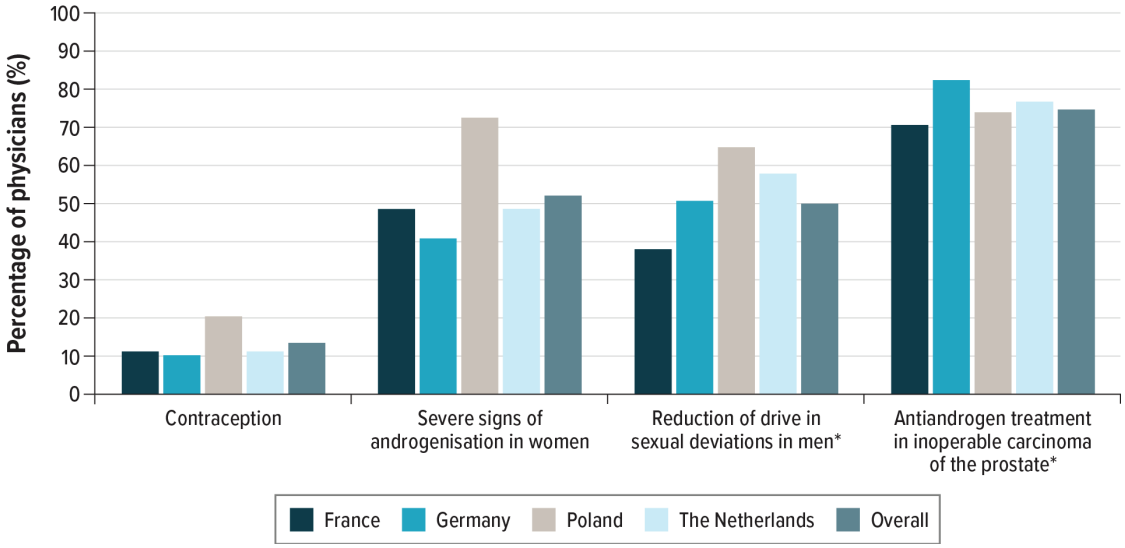
* Correct response is marked with an asterisk.

10.3.4.2 CPA monotherapy, 100 mg

Cyproterone acetate monotherapy is approved in 100 mg strength in all countries except Spain. As shown in Figure 22, most physicians (75%) identified "antiandrogen treatment in inoperable carcinoma of the prostate" as an approved indication of CPA monotherapy 100 mg, and this was consistent across all countries. Overall, 50% of physicians correctly identified "reduction of drive in sexual deviations in men" as an approved indication, ranging from 38% in France to 65% in Poland. Physicians incorrectly identifying "severe signs of androgenisation in women" as an approved indication ranged from 41% in Germany to 73% in Poland.

Overall, 40% of physicians selected the 2 approved indications correctly, and 46% of physicians selected 1 correct approved indication. Poland had the highest proportion of physicians select both correct responses (54%), and France had the lowest at 27%. Overall, 86% of physicians selected at least 1 correct indication (Annex 2, Table 1, Question 1b).

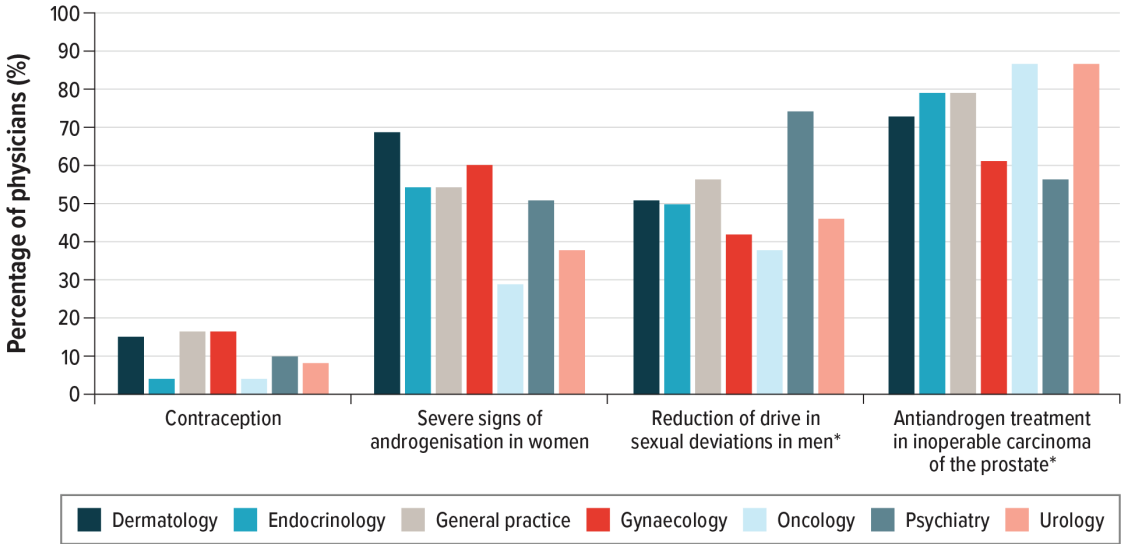
Figure 22: Responses to Question 1b by country: Which are the approved indications of CPA monotherapy 100 mg? (N = 503)



* Correct response is marked with an asterisk.

As shown in Figure 23, similar to the 50 mg dosage, most oncologists (87%) and urologists (87%) correctly identified "treatment of inoperable carcinoma of the prostate" as an approved indication for 100 mg. A large proportion of endocrinologists (79%), general practitioners (79%), and dermatologists (73%) also selected this indication as a correct response. Reduction of drive in sexual deviations was correctly selected by 74% of psychiatrists; the proportion of physicians selecting this correct response among the other specialties ranged from 38% to 56% (Annex 3, Table 1, Question 1b).

Figure 23: Responses to Question 1b by specialty: Which are the approved indications of CPA monotherapy 100 mg? (N = 503)

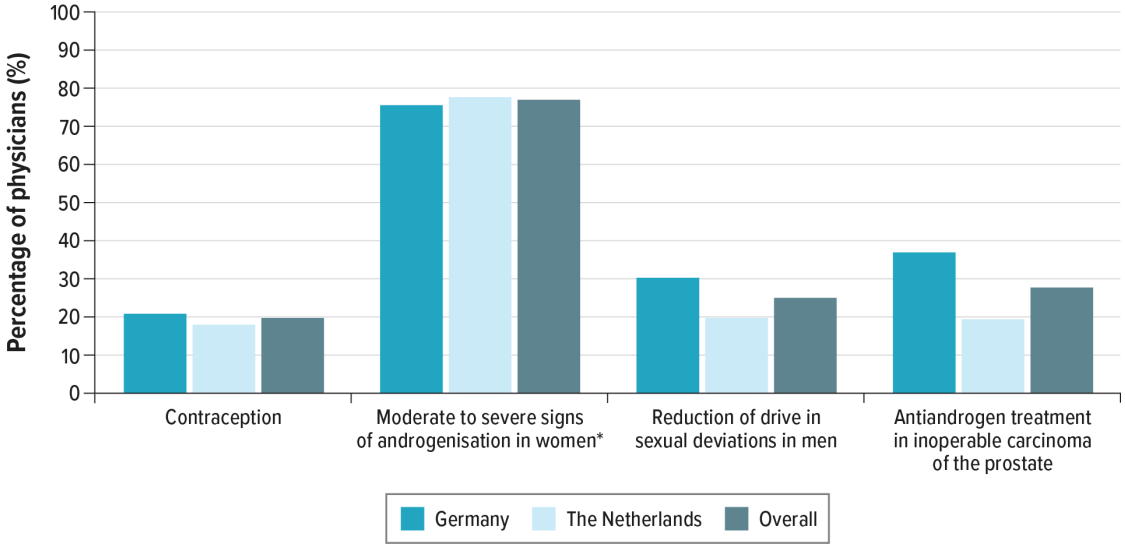


* Correct response is marked with an asterisk.

10.3.4.3 CPA monotherapy, 10 mg

CPA monotherapy is approved in 10 mg strength in Germany and the Netherlands only. As shown in Figure 24, most physicians (77%) correctly identified "moderate signs of androgenisation in women" as the approved indication of CPA monotherapy 10 mg. Results were similar between Germany and the Netherlands (Annex 2, Table 1, Question 1c).

Figure 24: Responses to Question 1c by country: Which are the approved indications of CPA monotherapy 10 mg? (N = 203)

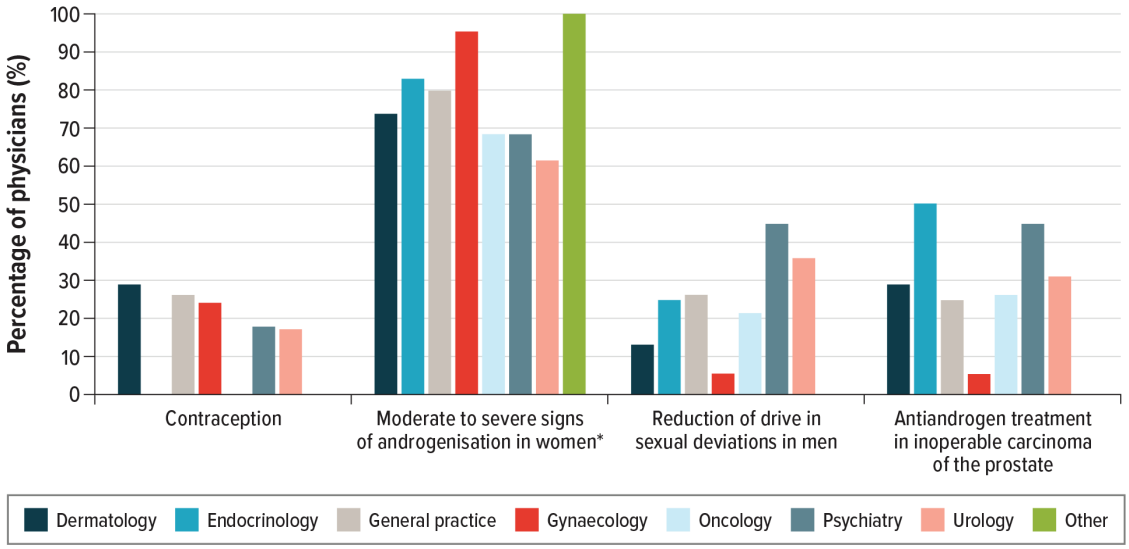


* Correct response is marked with an asterisk.

As shown in Figure 25, gynaecologists (95%), dermatologists (84%), endocrinologists (83%), and general practitioners (80%) correctly selected "moderate to severe signs of androgenisation in

women" as the correct indication for CPA monotherapy 10 mg. Knowledge of the correct indication was lower among oncologists (68%), psychiatrists (68%), and urologists (61%) (Annex 3, Table 1, Question 1c).

Figure 25: Responses to Question 1c by specialty: Which are the approved indications of CPA monotherapy 10 mg? (N = 203)



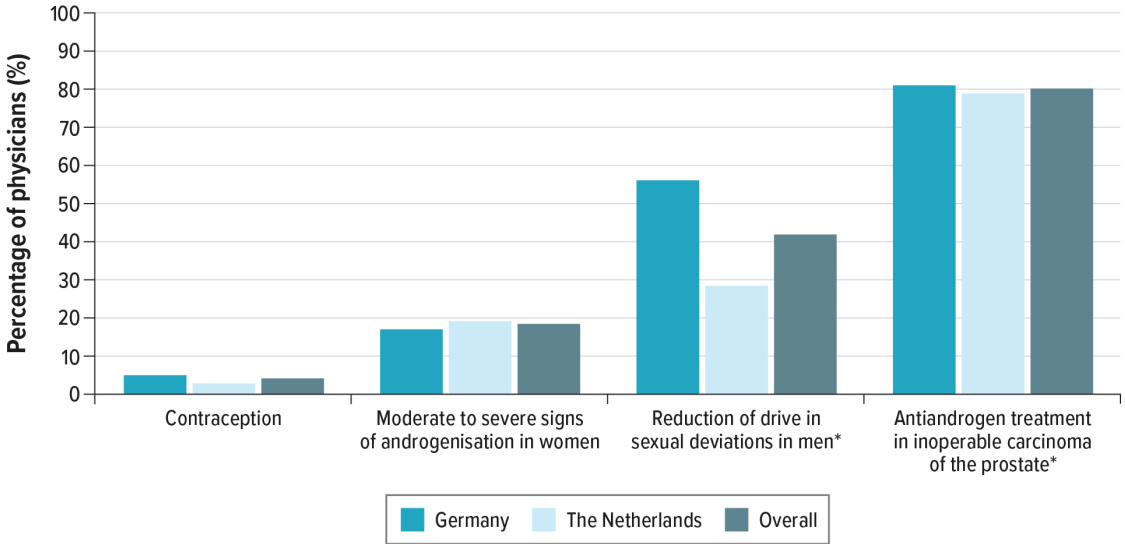
* Correct response is marked with an asterisk.

10.3.4.4 CPA monotherapy, 300 mg

CPA monotherapy is approved in 300 mg depot formulation in Germany and the Netherlands only. As shown in Figure 26, 80% of physicians identified "antiandrogen treatment in inoperable carcinoma of the prostate" as an approved indication of CPA monotherapy 300 mg. Overall, 42% of physicians correctly identified "reduction of drive in sexual deviations in men" as an approved indication (56% in Germany and 28% in the Netherlands).

A total of 30% of physicians selected the 2 approved indications correctly, and 63% of physicians selected 1 correct approved indication. Overall, 93% of physicians selected at least 1 approved indication (Annex 2, Table 1, Question 1d).

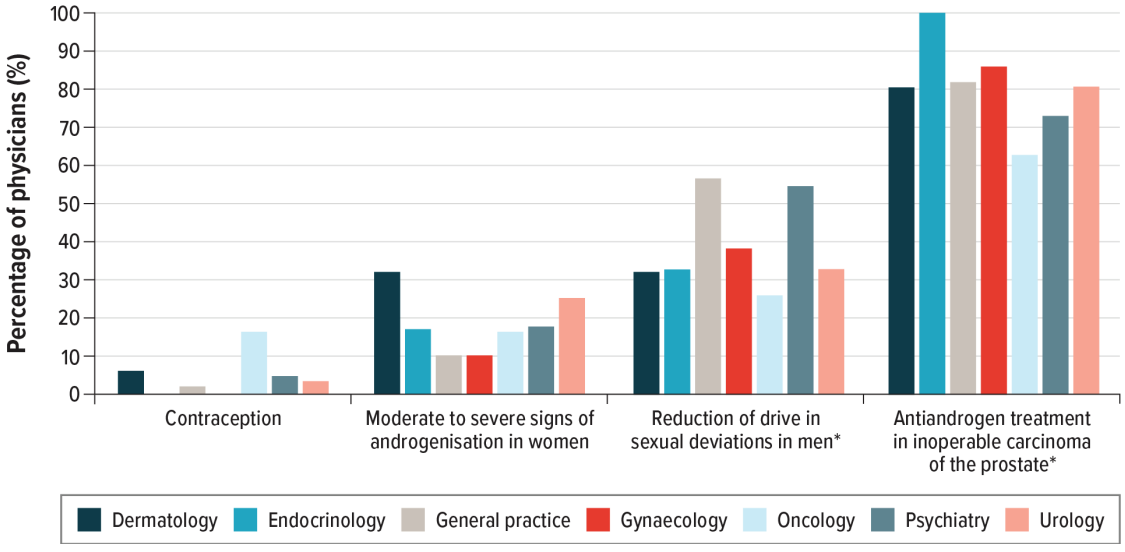
Figure 26: Responses to Question 1d by country: Which are the approved indications of CPA monotherapy 300 mg? (N = 203)



* Correct response is marked with an asterisk.

As shown in Figure 27, gynaecologists (86%), general practitioners (82%), dermatologists (81%), and urologists (81%) and all endocrinologists (100%) correctly selected "antiandrogen treatment in inoperable carcinoma of the prostate" as the correct indication for CPA monotherapy 300 mg. Knowledge of this correct indication was slightly lower among psychiatrists (73%) and oncologists (63%). Knowledge of the "reduction of drive in sexual deviations in men" as an approved indication ranged from 26% for oncologists to 57% for general practitioners (Annex 3, Table 1, Question 1d).

Figure 27: Responses to Question 1d by specialty: Which are the approved indications of CPA monotherapy 300 mg? (N = 203)

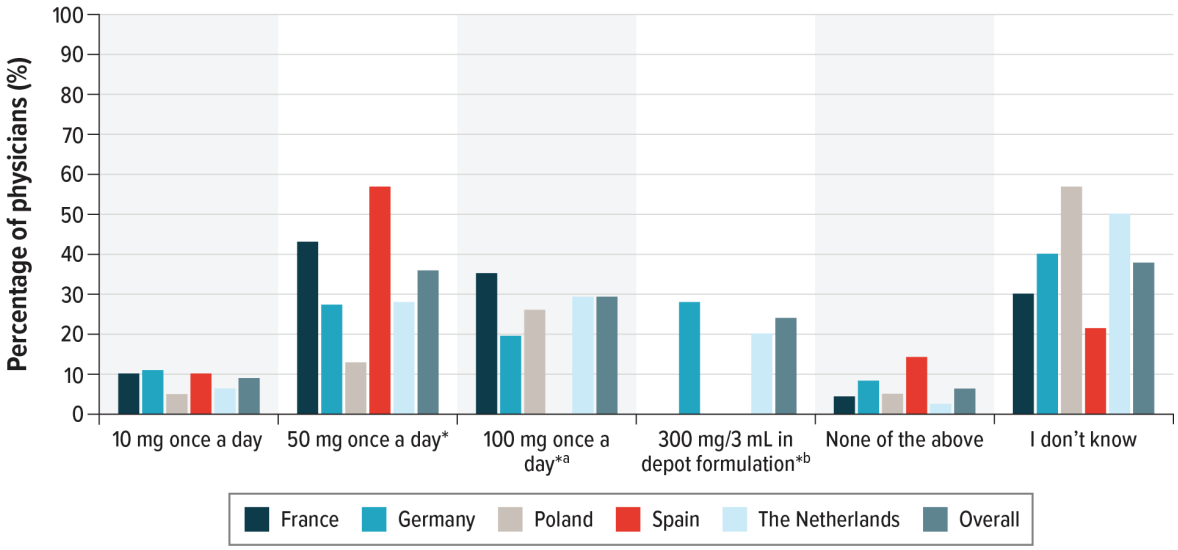


* Correct response is marked with an asterisk.

Physicians were asked for which dose(s) of CPA monotherapy had the occurrence of meningiomas been primarily reported, with the response options including 50 mg, 100 mg, and 300 mg, depending on country. Only participants in countries where the dose was available were given each specific dose as a response option; 50 mg was an option in all countries, 100 mg was an option in all countries except Spain, and 300 mg was only an option in Germany and the Netherlands. As a result, the number of physicians who faced each of the 3 response options was different. This was a "select all that apply" question, and all 3 doses were considered correct responses. As shown in Figure 28, 36% of physicians selected 50 mg, 29% of physicians who had the response option 100 mg selected it, and 24% of those who had the response option 300 mg selected it.

Among the physicians in Germany and the Netherlands, the only countries who had all 3 response options, 13% and 12%, respectively, selected all 3 of the correct responses. Across all countries, the number of physicians selecting at least 1 correct response was 33% in Poland, 43% in the Netherlands, 46% in Germany, 57% in Spain, 61% in France (Annex 2, Table 2, Question 7).

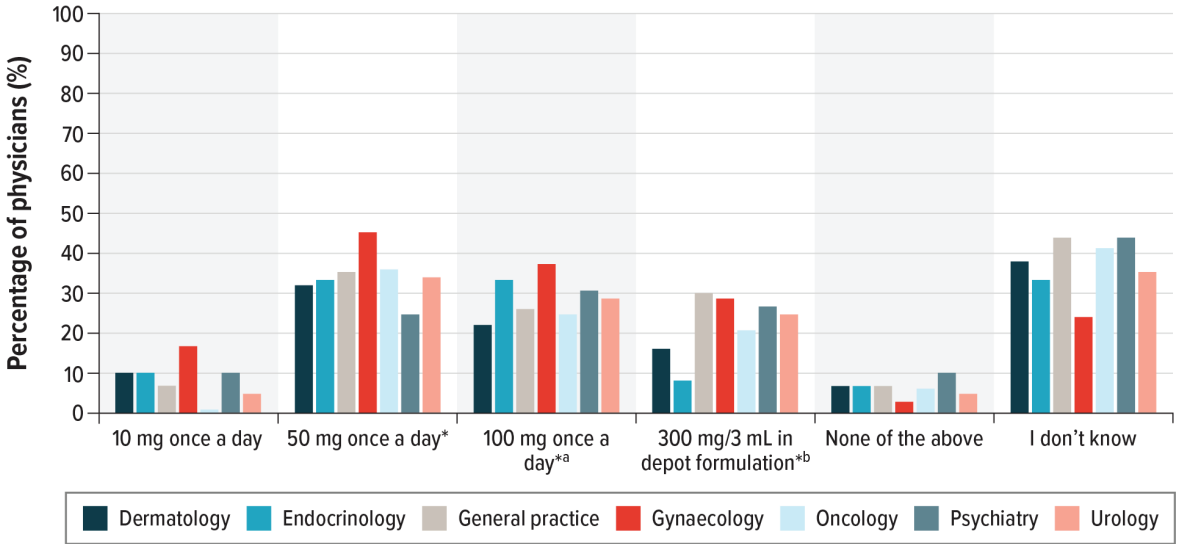
Figure 28: Responses to Question 7 by country: For which dose(s) of CPA monotherapy has the occurrence of meningiomas been primarily reported? (N = 613)



* Correct response is marked with an asterisk.
[a] Response excluded in Spain.
[b] Response excluded in France, Poland, and Spain.

As shown in Figure 29, gynaecologists had the highest proportion selecting the correct response than any other specialty, with 45%, 37%, and 29% correctly selecting doses 50 mg, 100 mg, and 300 mg, respectively (Annex 3, Table 2, Question 7).

Figure 29: Responses to Question 7 by specialty: For which dose(s) of CPA monotherapy has the occurrence of meningiomas been primarily reported? (N = 613)



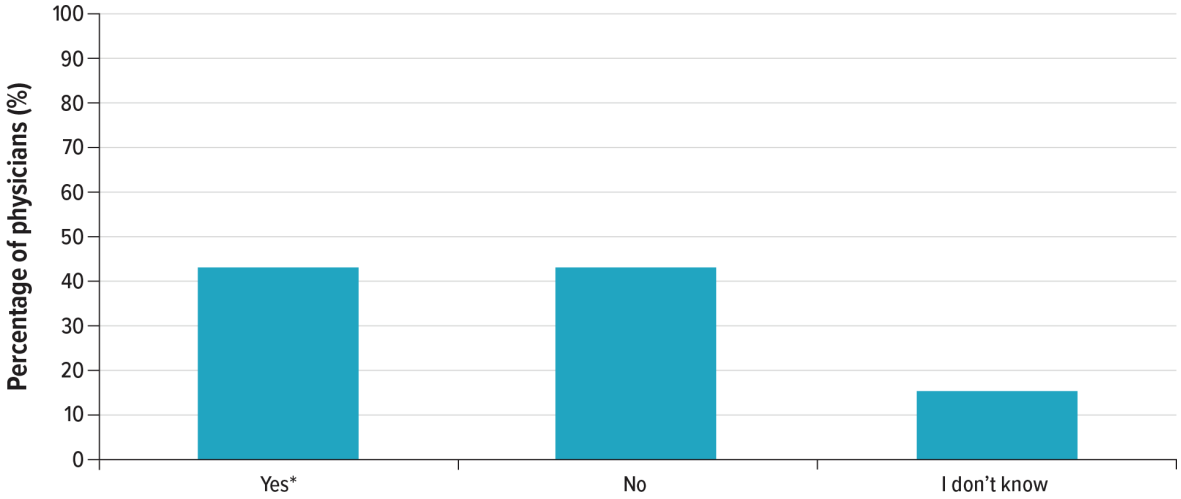
* Correct response is marked with an asterisk.
[a] Response excluded in Spain.
[b] Response excluded in France, Poland, and Spain.

10.3.5 Additional knowledge questions asked in France only

Three additional knowledge questions were asked to physicians in France only (N = 200). Results stratified by specialty should be interpreted with caution, as sample sizes among some of the specialties were small per the recruitment strategy for France.

As shown in Figure 30, 43% of the French physicians correctly responded "yes" to the question, "Should an MRI (magnetic resonance imaging) be performed on a patient at the initiation of treatment with CPA monotherapy?" (Annex 2, Table 4, Question 9a).

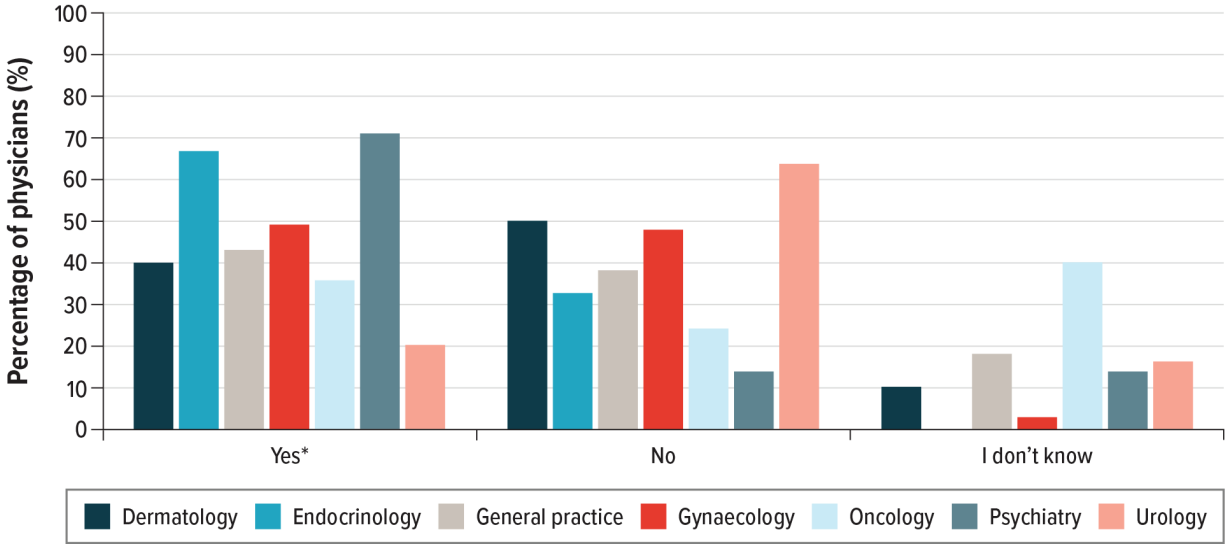
Figure 30: Responses to Question 9a. Should an MRI (magnetic resonance imaging) be performed on a patient at the initiation of treatment with CPA monotherapy? (N = 200)



* Correct response is marked with an asterisk.

As shown in Figure 31, psychiatrists (71%) and endocrinologists (67%) had the highest proportion of specialists correctly respond "yes" to the question, "Should an MRI (magnetic resonance imaging) be performed on a patient at the initiation of treatment with CPA monotherapy?" Urologists (20%) and oncologists (36%) had the lowest proportion of specialists selecting the correct response. Gynaecologists (49%), general practitioners (43%), and dermatologists (40%) were close to the overall average for all participants (43%) (Annex 3, Table 4, Question 9a).

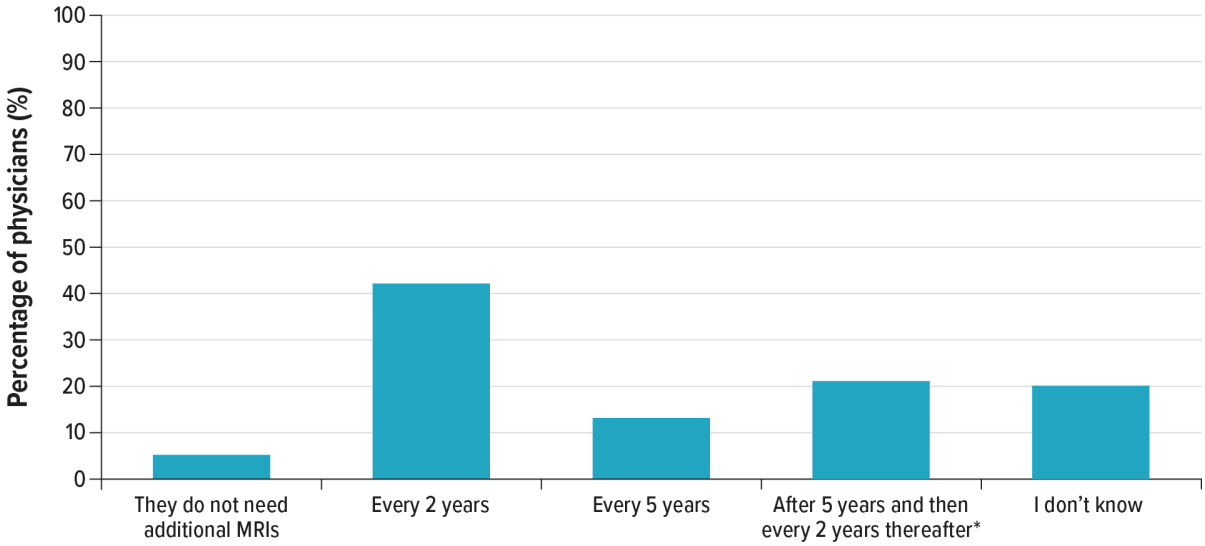
Figure 31: Responses to Question 9a by specialty. Should an MRI (magnetic resonance imaging) be performed on a patient at the initiation of treatment with CPA monotherapy? (N = 200)



* Correct response is marked with an asterisk.

For the question, "After the first MRI, how frequently should an MRI be performed on a patient being treated with CPA monotherapy?" 21% correctly indicated the correct response, "After 5 years and then every 2 years thereafter," as shown in Figure 32. The most frequently selected response to the question was "every 2 years," which was selected by 42% of physicians. When combining the results for physicians selecting either response, more than 60% were at least correctly aware of the requirement that an MRI is required every 2 years (Annex 2, Table 4, Question 9b).

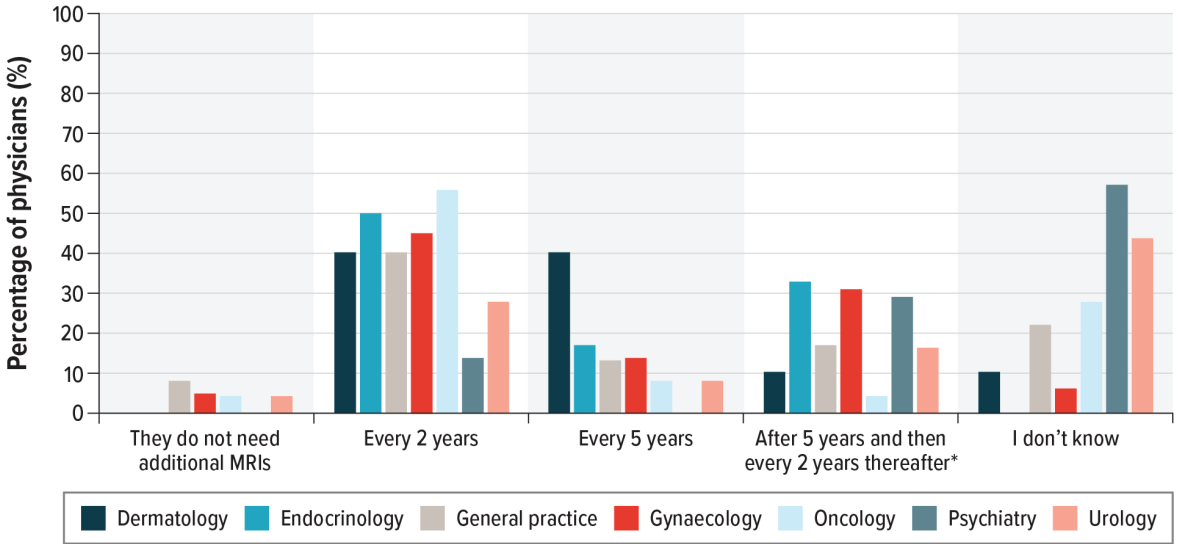
Figure 32: Responses to Question 9b: After the first MRI, how frequently should an MRI be performed on a patient being treated with CPA monotherapy? (N = 200)



* Correct response is marked with an asterisk.

As shown in Figure 33, endocrinologists (33%), gynaecologists (31%), and psychiatrists (29%) had the highest proportion of specialists select the correct response "after 5 years and then every 2 years thereafter." When combining these results with the more conservative response of "every 2 years," 83% of endocrinologists, 76% of gynaecologists, and 60% of oncologists were aware of this requirement (Annex 3, Table 4, Question 9a).

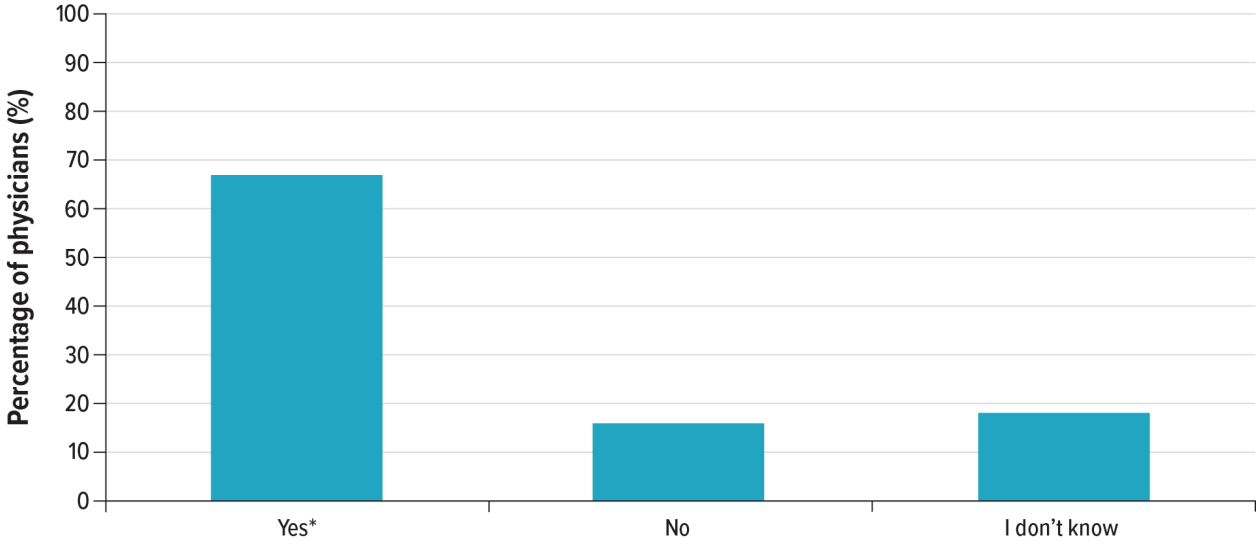
Figure 33: Responses to Question 9b by specialty. After the first MRI, how frequently should an MRI be performed on a patient being treated with CPA monotherapy? (N = 200)



* Correct response is marked with an asterisk.

Physicians in France were also asked whether patients being treated with CPA were required to sign a consent form. A total of 67% physicians correctly indicated "yes" to the question as shown in Figure 34 (Annex 2, Table 4, Question 9a and Question 9c).

Figure 34: Responses to Question 9c. Are patients who are being treated with CPA monotherapy required to sign a consent form? (N = 200)

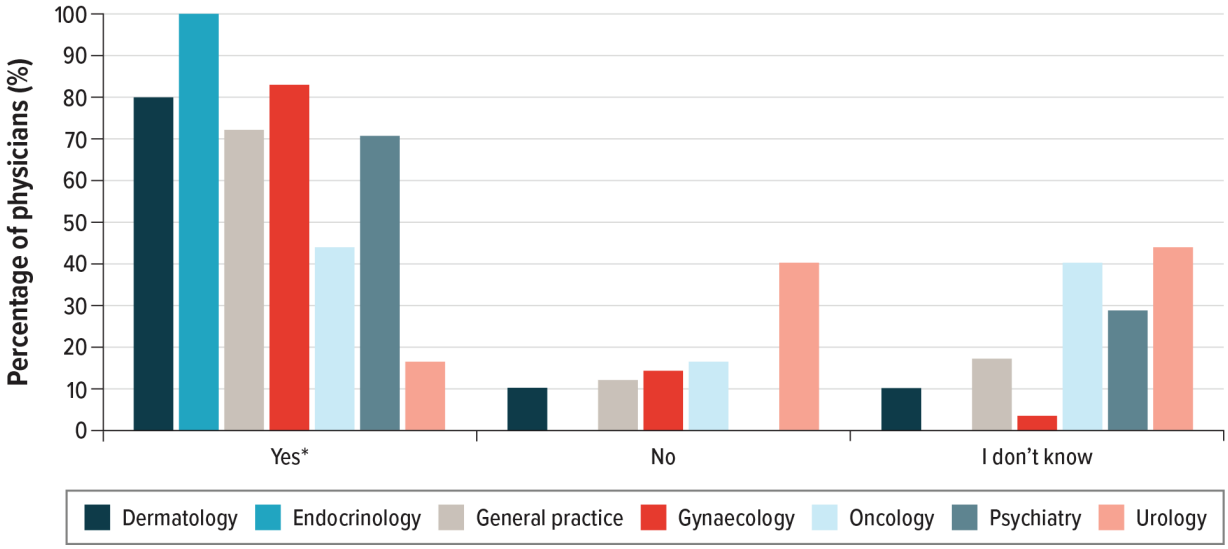


* Correct response is marked with an asterisk.

As shown in Figure 35, endocrinologists (100%), gynaecologists (83%), and dermatologists (80%) had the highest proportion of specialists correctly respond "yes" to the question "Are patients who are being treated with CPA monotherapy required to sign a consent form?" Urologists (16%) and oncologists (44%) had the lowest proportion of specialists selecting the correct response, with a

large proportion of these specialists selecting "I don't know" (44% and 40%, respectively). (Annex 3, Table 4, Question 9a).

Figure 35: Responses to Question 9c by specialty. Are patients who are being treated with CPA monotherapy required to sign a consent form? (N = 200)



* Correct response is marked with an asterisk.

10.3.6 Sources of information about CPA monotherapy, including receipt and use of the SmPC and DHPC for CPA monotherapy

Physicians participating in the study were asked to indicate what sources of information they had received about CPA monotherapy.

As summarised in Table 5, 42% of physicians reported receiving the revised SmPC. Of those, 69% indicated they reviewed it. Receipt of the SmPC was highest in Spain (61%) and lowest in the Netherlands (15%). Review of the SmPC was also highest in Spain (81%) and similar among the other 4 countries (63%-69%). Among the physicians who reported receiving the revised SmPC, 46% reported receiving it via email. The next most frequently reported method of dissemination selected was via post mail/letter (43%). Email was the most frequently reported method of dissemination in Spain (70%) and lowest in the Netherlands (13%). Post mail/letter was the most frequently reported response in Germany and France (77% and 62%, respectively) (Annex 2, Table 6, Question 14 and Question 14a).

Similarly, 40% of physicians reported receiving the DHPC. Of those, 82% indicated they reviewed it. The reported rate of receipt ranged from 63% in France to 7% in the Netherlands. Among those who said they received the DHPC, reported review of the letter ranged from 57% in the Netherlands to a high of 86% in Germany. Among the physicians who reported receiving the DHPC, 62% reported receiving it via post mail/letter. The next most frequently reported method of dissemination selected was via email (49%). Email was the most frequently reported method of dissemination in Spain (88%) and lowest in Germany (18%). Post mail/letter was the most frequently reported response in Germany, the Netherlands, and France (86%, 86%, and 73%, respectively) (Annex 2, Table 6, Question 14 and Question 14b).

Table 5: Receipt and review of revised SmPC and DHPC (Questions 14 and 14b)

Question	Number of physicians (%)					
	France n = 200	**Germany n = 103**	**Poland n = 100**	**Spain n = 110**	**Netherlands n = 100**	**Overall N = 613**
Revised SmPC						
Received	95 (48)	43 (42)	36 (36)	67 (61)	15 (15)	256 (42)
Reviewed[a]	60 (63)	27 (63)	25 (69)	54 (81)	10 (67)	176 (69)
DHPC						
Received	125 (63)	56 (54)	8 (8)	50 (45)	7 (7)	246 (40)
Reviewed[b]	102 (82)	48 (86)	5 (63)	42 (84)	4 (57)	201 (82)

DHPC = Direct Healthcare Professional Communication; SmPC = summary of product characteristics.
[a] Percentages are calculated among those physicians who either selected "SmPC" or "None of the above" to "Which of the following sources of information about CPA monotherapy did you receive?"
[b] Percentages are calculated among those physicians who either selected "DHPC" or "None of the above" to "Which of the following sources of information about CPA monotherapy did you receive?"

Physicians who reported receiving information about CPA monotherapy were asked when they last read the source of information about CPA monotherapy. A total of 26% of physicians reported reading information about CPA monotherapy 1 to 3 months ago, 22% reported 3 to 6 months ago, and 26% reported more than 6 months ago, as shown in Table 6. Results in Spain show more recent review than the other 4 countries, with 27% reporting review within the past 4 weeks or less (range for other 4 countries, 8%-13%) (Annex 2, Table 6, Question 15).

Table 6: Time since last reviewed information about CPA monotherapy

Question	Number of physicians (%)					
	France n = 195	**Germany n = 97**	**Poland n = 78**	**Spain n = 104**	**Netherlands n = 70**	**Overall N = 544**
When did you last read sources of information about CPA monotherapy? Select the most recent option. (Q15)						
Within the last week (including today)	4 (2)	1 (1)	4 (5)	6 (6)	3 (4)	18 (3)
Within the last 4 weeks	15 (8)	8 (8)	6 (8)	22 (21)	3 (4)	54 (10)
Within the last 3 months	54 (28)	24 (25)	16 (21)	31 (30)	14 (20)	139 (26)
Within the last 6 months	43 (22)	20 (21)	17 (22)	19 (18)	19 (27)	118 (22)
More than 6 months ago	55 (28)	24 (25)	23 (29)	22 (21)	19 (27)	143 (26)
I don't remember	24 (12)	20 (21)	12 (15)	4 (4)	12 (17)	72 (13)

CPA = cyproterone acetate.

10.4 Other analyses

This section provides a general summary of the knowledge question results by the stratification variables that was explored. As opposed to the previous section where the results of stratification are presented on a question-by-question basis, this section summarises the results of each stratification variable across the entire set of knowledge questions.

10.4.1.1 Gender

There was not a noticeable difference in knowledge by gender. The 14 physicians who declined to report their gender did display noticeably worse knowledge than their counterparts who were willing to identify their gender.

10.4.1.2 Number of years practising medicine

There was not a linear pattern between years practising medicine and how well the physicians did on the knowledge questions. Overall, the physicians falling into the category of the shortest duration in practice (5 years or less) and the longest (> 25 years) demonstrated better knowledge than those in the 4 intermediate categories.

10.4.1.3 Practice setting

Physicians who reported primarily being based in an office setting did noticeably better on the knowledge questions than those based either in a university/research-oriented/teaching hospital or in another hospital setting. These results were dramatic, with the physicians from the office-based setting having the highest proportion correct on the majority of the questions and only 2 of the responses being more than 10% below either of the other practice settings.

10.4.1.4 Time since last read sources of information about CPA monotherapy

Physicians who indicated that they had last read the sources of information about CPA monotherapy within the last week did noticeably better on the knowledge questions than any of the other categories of time since last reading the sources of information.

10.4.1.5 Time since last wrote a prescription for CPA monotherapy

There did not appear to be any association between the time physicians last wrote a prescription for CPA monotherapy and their results on the knowledge questions.

10.5 Adverse events/adverse reactions

This study was not designed to collect information on individual adverse events or adverse drug reactions, which are better collected using other study designs. No adverse events were reported.

11. Discussion

11.1 Key results

Overall, 43% of physicians were aware of the additional precaution and warning of meningioma recently added to the prescribing label for CPA monotherapy. The risk of meningioma had already been included in the original SmPC, but additional warning language was added in 2020 per the requirements of the PRAC. It is possible physicians were aware of the previous risk and did not realise that additional language was added. The survey did not measure this knowledge, so any previous knowledge of the SmPC before its revision is unknown. French physicians were more aware of the added warning, with 63% selecting the correct response. Higher awareness in France is expected because of the enhanced communication and regulatory actions in France around the association of CPA with meningioma. Physicians in Spain and Poland had the lowest awareness, with 26% and 28%, respectively, selecting meningioma. More than 60% of gynaecologists and endocrinologists were aware of the added warning for meningioma.

Overall, physicians' knowledge of the clinical signs and symptoms of meningioma was high, with 66% of physicians correctly identifying all 7 correct responses. Knowledge of each of the signs and symptoms individually ranged from 72% to 92%, showing high awareness among the study participants.

Most physicians knew that CPA monotherapy should be prescribed with the lowest effective dose, with 85% selecting the correct response. Seventy-five percent of physicians correctly reported that the risk of meningioma increases with increasing cumulative doses of CPA monotherapy. Similarly, 73% of physicians correctly reported that treatment with CPA-containing products must be permanently stopped if a patient is diagnosed with meningioma.

Physicians were not as aware of the proper use of CPA monotherapy in patients with a history of meningioma. Overall, 39% of physicians correctly identified as false the statement, "CPA monotherapy may be used in patients with a history of meningioma under carefully controlled conditions." Although this question tested fine during the cognitive pretesting, it is possible there was some confusion in interpreting the question with use of the term "may," which may have resulted in the low positive response rate. Knowledge was highest in France, with 57% selecting the correct response; all other countries ranged from 27% to 36%. When responses were stratified by physician specialty, correct responses ranged from 17% for oncologists up to 57% for gynaecologists. It is possible that the selected response among oncologists is because of the nature in which they would use CPA monotherapy. One element to consider is that oncologists would be prescribing for patients with inoperable carcinoma, and it may be their clinical opinion that treating a patient at the risk of an additional life-threatening condition may justify treatment with CPA despite the existing label.

Overall, 69% of physicians had written a prescription for CPA monotherapy within the past 3 months, with 25% indicating they had prescribed it within the past month.

Androgenisation in women was the highest selected indication for which CPA monotherapy had been prescribed in the past 12 months (ranging from 46% in the Netherlands to 58% in Spain). Among physicians who had prescribed CPA monotherapy for androgenisation in women within the past 3 months, 73% correctly responded that CPA monotherapy should be prescribed for androgenisation when no satisfactory results have been achieved with other treatment options. Endocrinologists had the highest proportion of specialists selecting the correct response. In addition, 40% of these physicians were aware of the indications of the 10 mg or 50 mg doses (when no satisfactory results have been achieved with lower dose CPA-containing products). Among them, gynaecologists had the highest proportion of specialists selecting the correct response (49%). Knowledge about long-term use of CPA monotherapy was low among this subset of physicians, as only 34% correctly identified as false the statement, "After using CPA monotherapy at a dose of 10 mg or 50 mg and achieving clinical improvement of moderate to severe signs of androgenisation, the patient can continue using CPA monotherapy at this dose for as long as it is necessary." Gynaecologists had the highest proportion of specialists selecting the correct response (41%).

Physicians who indicated they had prescribed CPA monotherapy for sexual deviations in men (18% of all physicians, 77% of psychiatrists) were moderately aware about the appropriateness of using CPA monotherapy for that indication. Fifty-six percent of such physicians correctly identified that CPA monotherapy should only be used when other interventions are considered inappropriate. The proportion of physicians selecting the correct response ranged from 43% in France to 63% in Poland and was highest among endocrinologists (86%), followed by psychiatrists (63%), urologists (60%), and gynaecologists (60%).

In total, 45% of physicians indicated that in the past 12 months they had prescribed CPA monotherapy for antiandrogen treatment in inoperable carcinoma of the prostate. Among this sample of physicians, 75% of physicians correctly indicated the use of CPA monotherapy for the treatment of inoperable prostate carcinoma and LHRH flare remains unchanged per the SmPC. The proportion

of physicians selecting the correct response ranged from 68% in France to 90% in Poland and was highest among oncologists (78%), followed by urologists (74%) and general practitioners (71%).

Physician knowledge of the dosage forms of CPA monotherapy for which the occurrence of meningiomas has been reported was low: 36% of physicians correctly reported 50 mg, 29% correctly reported 100 mg, and 24% correctly reported 300 mg. Physicians in France had the highest awareness, with 61% of physicians selecting at least 1 correct response. Gynaecologists had the highest proportion of physicians selecting the correct response over any other specialty, with 45%, 37%, and 29% correctly selecting doses 50 mg, 100 mg, and 300 mg, respectively.

Physician knowledge of the approved indications for CPA monotherapy was good, with most physicians correctly identifying the appropriate indication. Knowledge of approved indications was higher among specialties that most often prescribed for the specific indication. For example, by specialty, almost all endocrinologists (97%), dermatologists (93%), and gynaecologists (92%) correctly identified "severe signs of androgenisation" as an approved indication of CPA monotherapy 50 mg. Likewise, nearly all oncologists (93%) and urologists (92%) correctly identified "treatment of inoperable carcinoma of the prostate" as an approved indication for this dosage. Seventy-nine percent of psychiatrists correctly identified "reduction of drive in sexual deviations in men," whereas the proportion of other physician specialties ranged from 33% to 60%. The results suggest that knowledge closely reflects the clinical practice experience for the specific indication.

Physicians in France were asked questions specific to additional requirements around use of CPA monotherapy in France. In total, 43% of the French physicians correctly identified that an MRI should be performed on a patient at the initiation of treatment with CPA monotherapy. Psychiatrists (71%) and endocrinologists (67%) had the highest proportion of specialists correctly respond; urologists (20%) and oncologists (36%) had the lowest proportion of specialists selecting the correct response.

Twenty-one percent of French physicians were correctly aware of the how often an MRI should be performed on a patient after the first MRI (i.e., after 5 years and then every 2 years thereafter). The most frequently selected response to the question was "every 2 years," which was selected by 42% of physicians. When combining the results for physicians selecting either response, more than 60% were at least correctly aware that an MRI is required every 2 years, which is more conservative than the actual requirement. Endocrinologists (33%), gynaecologists (31%), and psychiatrists (29%) had the highest proportion of specialists select the correct response, "after 5 years and then every 2 years thereafter." When combining these results with the more conservative response of "every 2 years," 83% of endocrinologists, 76% of gynaecologists, and 60% of oncologists were aware of this requirement.

Sixty-seven percent of physicians in France were aware that patients being treated with CPA monotherapy are required to sign a consent form. Endocrinologists (100%), gynaecologists (83%), and dermatologists (80%) had the highest proportion of specialists selecting the correct response. Urologists (16%) and oncologists (44%) had the lowest proportion of specialists selecting the correct response, with a large proportion of these specialists selecting "I don't know" (44% and 40%, respectively).

In total, 42% of physicians reported that they received the revised SmPC. Of those, 69% reported that they read the document. A similar percentage of physicians (40%) reported that they received the DHPC. Of those, 82% of physicians reviewed the DHPC. There was variation across the

countries in the receipt of the revised SmPC and DHPC. The proportions of reported receipt of the SmPC varied from 15% in the Netherlands to 61% in Spain. The proportion that reported receipt of the DHPC varied from 7% in the Netherlands to 63% in France.

11.2 Limitations

As with all voluntary, cross-sectional surveys that depend on healthcare professionals agreeing to participate, some limitations are inherent. Many methodologic and operational challenges are well recognised.[5] Although the study was designed to select a diverse and generally representative sample of physicians who have recent experience with CPA monotherapy, there was no exhaustive list of all physicians who have prescribed or administered CPA monotherapy from which to draw a sample; hence, it was not possible to select a random sample of all physicians. Therefore, the study participants may not necessarily represent all physicians who have prescribed/administered CPA monotherapy. In addition, as is true with most surveys, it was possible that participants who completed the questionnaire differed from nonparticipants in characteristics measured in the questionnaire (e.g., knowledge, reading). The direction and magnitude of any bias was not possible to quantify because physicians who did not wish to participate in the survey did not respond to the invitation, and characteristics of the invited physicians were not otherwise available. We could not compare physician and practice characteristics of the physician participants with what is known about the overall prescribing population because that information was not available to us.

The overall response rate for the survey (5%) is somewhat artificial because responses were not allowed once country quotas for specialties were met. Thus, the true response rate, although unmeasurable, would be higher.

In general, physician response rates for surveys have been somewhat low historically. Some literature has suggested that it is common for response rates for physician surveys to be below 20%.[6] A variety of factors related to survey methodology may account for the low response rates of physicians to survey studies (e.g., method of contact, mode of survey administration, use of incentives).[7,8] However, physician-related factors that may also be related to low response rates include the following: (1) lack of time, which, if coupled with the increasing number of requests for participation in survey studies, may discourage participation and (2) lack of interest or low relevance of the survey topic to motivate participation. Other factors identified as contributing to the low response are incorrect or incomplete contact information of listings, physicians being away or retired, and office policies of not participating in any survey.[9]

Low response rates may result in a higher likelihood that participating physicians are not representative of all prescribing physicians. Thus, the resulting estimates of physician understanding about CPA monotherapy may be biased. If participants discontinued the survey because they did not know how to answer the knowledge questions, the frequency of substantial physician knowledge will be overestimated. The level of missing data was minimal; most participants who began the survey completed all items of the questionnaire. As is true with most surveys, it is possible that participants who completed the questionnaire differed from nonparticipants in characteristics measured in the questionnaire (e.g., knowledge of or reading the SmPC and DHPC). The direction and magnitude of such potential participant bias is not known. Although a comparison of participating physician characteristics with nonparticipating physicians was not possible within the panel recruitment framework, the diversity of physician characteristics and experience with CPA monotherapy in the final sample gave some assurance that the target population was well represented. However, despite efforts to ensure a representative sample of physicians, participants

may have differed from nonparticipants on key characteristics measured in the questionnaire (e.g., knowledge, reading the educational materials).

In addition, the sample does not account for individuals who could not participate because of the mode of data collection (i.e., internet access). However, it is anticipated that the vast majority of physicians had internet access.

The study collected data from 613 physicians across 5 countries and 7 different specialties. Although we report country-specific and specialty-specific findings, low sample sizes among some subgroups limit drawing country-specific or specialty-specific conclusions for some questions. This is particularly true of the knowledge questions that were only asked in France.

The DHPC was distributed and published on websites in April 2020 in Germany, France, Poland, and the Netherlands and was delayed to November 2020 in Spain. The SmPC was updated between June and August across all 5 countries. Distribution of the DHPC was independent of the study. The survey was conducted after physicians should have received the materials and had a chance to use the information in their practice, which allows for evaluation of how well they understand the safety information provided in the educational materials and apply it to their practices. However, many of the countries were undergoing various stages of lockdown due to the global COVID-19 pandemic during the time when the materials were disseminated and the SmPC was updated. The effect of the pandemic on physician knowledge or receipt of the materials was not evaluated and is unknown; however, it is possible that the recall of the action was impacted.

11.3 Interpretation

Knowledge and behaviour may be influenced by many factors, including availability and access to information, years of experience, practice setting, country-specific healthcare systems, literacy and numeracy, cultural differences, beliefs, and motivation.

No a priori thresholds of correct responses to the knowledge questions were specified for this study. Having a minimum of 60% of respondents selecting the correct response for each question would be considered reassuring regarding physician awareness and knowledge of the product's safety information. In a review of survey-based studies evaluating the effectiveness of risk-minimisation measures in Europe, most participants responding correctly was considered a successful result in 9 of 11 surveys registered in the EU PAS Register.[10]

For this study, the following questions were answered correctly by at least 60% of participants:

- The risk of meningioma increases with increasing cumulative doses of CPA monotherapy (75%)
- Treatment with all CPA-containing products must be permanently stopped if a patient treated with CPA monotherapy is diagnosed with meningioma (73%)
- CPA monotherapy should be prescribed with the lowest effective dose (85%)
- Patients using CPA monotherapy should be monitored for meningioma in accordance with clinical practice (74%)

- Clinical signs and symptoms of meningioma
  - Changes in vision (90%)
  - Hearing loss or ringing in the ears (82%)
  - Loss of smell (81%)
  - Headaches that worsen with time (92%)
  - Memory loss (73%)
  - Seizures (84%)
  - Weakness in extremities (72%)
- Use of CPA monotherapy at doses of 10 mg or 50 mg should only be prescribed in women for moderate to severe signs of androgenisation when no satisfactory results have been achieved with other treatment options (73%)
- There are no changes in the SmPC regarding the use of CPA monotherapy to treat inoperable prostate carcinoma and LHRH flare (75%)
- In France only
  - Patients treated with CPA monotherapy are required to sign a consent form (67%)

There is a requirement in France to perform an MRI at the initiation of CPA monotherapy, a follow-up MRI 5 years after the first MRI, and then subsequent MRIs every 2 years for as long as the patient remains on CPA monotherapy. It was observed that a low percentage of physicians were aware of the MRI requirement at initiation of CPA monotherapy, and that most physicians thought the requirement for follow-up MRIs was every 2 years, which is more conservative than the actual requirement. It is possible that the physician who most recently prescribed CPA monotherapy is not necessarily the same physician who initiated treatment and prescribed the initial MRI; thus, there may be confusion around the MRI requirement. Given the low sample size of some specialties in France, it is difficult to interpret the results to support or refute this theory.

Less than half of physicians reported receipt of the revised SmPC and DHPC (42% and 40%, respectively). Reported receipt varied across countries and was quite low in the Netherlands and Poland. It was encouraging to see that, among physicians who reported receipt of the SmPC and DHPC, review of either resource was high.

The percentage of physicians reporting receipt of the revised SmPC and DHPC is within the range of similar prior studies. A recent publication[11] reported the results of a multinational survey of 800 European physicians that assessed the receipt of educational materials. For that study, physician-reported receipt of the educational materials ranged from 16% to 69% across the participating countries. A study evaluating a risk management plan in more than 400 physicians in Europe showed that only 31% of participating physicians received the educational materials that had been disseminated to physicians.[12] Another PASS that surveyed more than 750 physicians in Europe reported 46% of physicians had received the DHPC.[13] An additional risk-minimisation study of more than 1,100 physicians in several countries in Europe reported that 25.8% of physicians had received both the educational materials and DHPC. A total of 40.2% reported that they had received neither of them.[14] Another risk-minimisation study in 332 healthcare providers in Europe reported a

similar trend, with 20% to 26% reporting receipt of the education materials, and 47% to 57% of participants indicating they had not received any education materials.[15]

11.4 Generalizability

As noted in Section 10.2, the study achieved great diversity in physician characteristics within the 5 countries, allowing for stratification of results by those characteristics. We saw 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 of evaluating whether physicians received and reviewed the revised SmPC and DHPC and assessing physicians' knowledge and understanding of key safety information pertaining to the restrictions for use of CPA.

In general, the knowledge of the risk of meningioma associated with use of CPA monotherapy was high; however, only 43% of physicians indicated their awareness of the recent changes in the warning and precautions in the prescribing label. In general, the observed patterns of knowledge among the physicians were as expected—with greatest knowledge on the indicated use of CPA monotherapy relevant to the per-specialty indication and most important risks of meningioma and less knowledge on more complex aspects of safe use, especially correct use in indications that were not in the area of specialty of the respective physician (e.g., questions specific to the dosage of CPA monotherapy).

Of the 42% of physicians who confirmed receipt of the revised SmPC and the 40% who confirmed receipt of the DHPC, 69% and 82%, respectively, reported they had read each document. This is in line with other risk-minimisation surveys and could be because of recall bias, given that the survey was launched more than 6 months after distribution of the DHPC in most countries and more than 4 months after SmPC approval.

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Appendices

Annex 1. List of stand-alone documents

Annex 2. Results tables, overall and by country

Annex 3. Results tables, by specialty

Annex 4. Signature pages

Annex 1: List of stand-alone documents

Table 7: List of stand-alone documents

Document name	Final version and date (if available)*
Physician questionnaire	01 SEP 2021
Statistical analysis plan	19 NOV 2021

Annex 2: Results tables, overall and by country

0305974_Safe-CAM analysis tables_Over

Annex 3: Results tables, by specialty

0305974_Safe-CAM analysis tables_Spec

Annex 4: Signature pages

The signatories agree that the study was conducted under the conditions described in the protocol.

Signatories

- PPD (Principal Investigator)
- PPD (Study Medical Expert)
- PPD (Study Statistician, Internal)
- PPD (Study Statistician, External)
- PPD (Study Conduct Responsible and Study Epidemiologist, Internal)
- PPD (Study Epidemiologist, External)
- PPD (Study Safety Lead)
- PPD (Qualified Person Responsible for Pharmacovigilance)
- PPD (MAH Contact Person)
- PPD (Regulatory Affairs Responsible, External)

Signature Page - Principal Investigator

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Report version and date	v 1.0, 05 MAY 2022
IMPACT study number	21490
Study type / Study phase	Observational, post-approval Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☒ YES ☐ NO
EU PAS register number	EUPAS41194
Medicinal product / Active substance	Androcur (cyproterone) and its generics/INN: Cyproterone; ATC code: G03HA01
Study Initiator and Funder	Bayer Pharma AG on behalf of a group of MAHs

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD
RTI Health Solutions

Date, Signature: 5/13/2022, PPD

Signature Page – OS Medical Expert

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Report version and date	v 1.0, 05 MAY 2022
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The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 5/16/2022, _____ PPD _____

Signature Page – OS Statistician (Internal)

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Report version and date	v 1.0, 05 MAY 2022
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Print Name: PPD

Date, Signature: 5/13/2022, PPD

Signature Page – OS Statistician (External)

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
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The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD
RTI Health Solutions

Date, Signature: 5/13/2022, _____ PPD _____

Signature Page – OS Conduct Responsible and OS Epidemiologist (Internal)

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Report version and date	v 1.0, 05 MAY 2022
IMPACT study number	21490
Study type / Study phase	Observational, post-approval Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☒ YES ☐ NO
EU PAS register number	EUPAS41194
Medicinal product / Active substance	Androcur (cyproterone) and its generics/INN: Cyproterone; ATC code: G03HA01
Study Initiator and Funder	Bayer Pharma AG on behalf of a group of MAHs

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 5/13/2022, _____ PPD _____

Signature Page – OS Epidemiologist (External)

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
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Print Name: PPD
RTI Health Solutions

Date, Signature: 5/13/2022, _____ PPD _____

Signature Page – OS Safety Lead

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Report version and date	v 1.0, 05 MAY 2022
IMPACT study number	21490
Study type / Study phase	Observational, post-approval Postmarket surveillance, Phase IV (Post-Market Clinical Follow-Up study) ☒ PASS Joint PASS: ☒ YES ☐ NO
EU PAS register number	EUPAS41194
Medicinal product / Active substance	Androcur (cyproterone) and its generics/INN: Cyproterone; ATC code: G03HA01
Study Initiator and Funder	Bayer Pharma AG on behalf of a group of MAHs

The undersigned confirms that s/he has read this report and confirms that to the best of her/his knowledge it accurately describes the conduct and results of the study.

Print Name: PPD

Date, Signature: 5/13/2022, _____ PPD _____

Signature Page – Qualified Person responsible for Pharmacovigilance (QPPV)

Title	Study to Evaluate Physician Awareness and Knowledge of Safety and Safe Use Information for Androcur and Other Cyproterone Acetate Monotherapies in Europe: an Observational Post-Authorisation Joint Safety Study (Safe-CAM)
Report version and date	v 1.0, 05 MAY 2022
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Signature Page – MAH contact person (Regulatory Affairs)

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Signature Page –Regulatory Affairs responsible (External)

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