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ORIGINAL RESEARCH ARTICLE

# Physician Awareness of the Safe Use of Cyproterone Acetate in Europe: A Survey on the Effectiveness of Additional Risk Minimization Measures

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## Abstract

**Background** Cyproterone acetate (CPA) is a synthetic progesterone derivative introduced in the 1970s and prescribed as antiandrogenic therapy for inoperable prostate cancer, sexual deviations in men, and signs of androgenization in women. In 2020, the CPA summary of product characteristics (SmPC) was revised to include an updated special warning and precaution about (1) the risk of meningioma with increasing cumulative dose and (2) contraindication in patients with meningioma or history of meningioma. A Direct Healthcare Professional Communication (DHPC) was distributed. The European Medicine Agency's Pharmacovigilance Risk Assessment Committee requested that marketing authorization holders in Europe conduct a survey to assess physicians' knowledge of the updated key safety information. The primary objective of this study was to measure physicians' awareness (i.e., did they receive and review the revised SmPC and DHPC) and level of knowledge and understanding of the key safety information pertaining to the restricted use of CPA monotherapy because of the risk of meningioma.

**Methods** This cross-sectional web-based survey was administered to dermatologists, endocrinologists, gynecologists, urologists, oncologists, psychiatrists, and general practitioners in France, Germany, Poland, Spain, and the Netherlands who had prescribed CPA monotherapy in the previous 12 months to assess awareness of the risk of meningioma associated with CPA monotherapy.

**Results** Of the 613 physicians who participated, 85% correctly indicated that CPA monotherapy should be prescribed with the lowest effective dose, 75% correctly indicated that the risk of meningioma increases with increasing cumulative CPA monotherapy doses, and 73% correctly indicated that treatment with CPA-containing products must be stopped permanently if a patient is diagnosed with meningioma. Overall, 40% of physicians reported having received the DHPC, and 42% reported having received the revised SmPC.

**Conclusions** Despite low recall of receipt of the updated SmPC and DHPC, most physicians surveyed are aware of the meningioma risk and actions to mitigate the risk.

## 1 Introduction

Cyproterone acetate (CPA) is a synthetic progesterone derivative with antiandrogenic properties that has been available since the 1970s [1]. CPA is available as monotherapy in doses of 10 mg, 50 mg, and 100 mg for oral administration and 300 mg/3 mL in a depot formulation for intramuscular administration in multiple European countries. Approved indications and doses vary across countries in which CPA monotherapy is authorized. The 10 mg and 50 mg doses of CPA monotherapy are used to treat moderate and severe signs of androgenization in women (e.g., hirsutism, androgenetic alopecia, acne, seborrhea), while formulations of 50 mg and above and depot formulations are used to reduce sex drive in hypersexuality and sexual deviations in men and as antiandrogen treatment in inoperable carcinoma of the prostate or palliative

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**Key Points**

In 2020, the product labelling of cyproterone acetate (CPA) monotherapy was updated in countries within the European Union due to the associated risk of meningioma.

In this survey of physicians who prescribe CPA monotherapy, we found that knowledge of risks associated with CPA monotherapy varied by their specialty.

Overall, most physicians surveyed are aware of the risk of meningioma associated with CPA monotherapy and actions to take to mitigate risk.

antiandrogenic treatment of prostate cancer. CPA is also often used for hormone therapy in transgender women [1, 2]. In recent years, there has been increasing evidence of an association between CPA and the development of meningioma [3–6]. A pharmacoepidemiology study conducted in France to estimate the number of meningioma cases that could be attributed to prolonged exposure to 50 mg or 100 mg doses of CPA in women between the years of 2007 and 2015 found that women exposed to high cumulative doses of CPA (≥3 g during the first 6 months of treatment) were approximately five times more likely to develop meningiomas than those who received lower cumulative doses of CPA (<3 g) [1, 7]. The report from this pharmacoepidemiologic study was issued in 2019 and spurred the French National Agency for the Safety of Medicines and Health Products to perform its own overview of cases of meningioma in patients treated with CPA. On 7 July 2019, the French National Agency for the Safety of Medicines and Health Products triggered a referral under Article 31 of Directive 2001/83/EC and requested that the Pharmacovigilance Risk Assessment Committee (PRAC) (1) assess the benefit-risk ratio of CPA-containing products and (2) issue a recommendation on whether the relevant marketing authorizations should be maintained, varied, suspended, or revoked [8]. The PRAC reviewed data from epidemiological studies—including the French Health Insurance study, post-marketing case reports, and data submitted by marketing authorization holders—and concluded that, while the absolute risk of meningioma in association with CPA use remains low (1–10 per 10,000 patients), the risk increases with the cumulative dose of CPA. Most meningioma cases occur after prolonged exposure to high dosages 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 [8]. The PRAC concluded that the benefit-risk balance of CPA-containing products remains favorable, though CPA monotherapy should be used only if other treatment options are not effective and should not be prescribed to any patient with meningioma or a history of meningioma.

In light of these findings and in alignment with the European Medicines Agency's (EMA's) guideline on good pharmacovigilance practices module XVI for risk minimization measures [9], the PRAC recommended updates to prescribing practices for CPA to reduce exposure when possible. These updates were shared with physicians through a Direct Healthcare Professional Communication (DHPC) and a revised summary of product characteristics (SmPC). The DHPC and SmPC were distributed throughout the European Union (EU) during the spring and summer of 2020, with the exception of Spain, where dissemination of the DHPC was delayed until November 2020 because of the coronavirus disease 2019 pandemic. The materials were distributed following local requirements and differed by country. The SmPC and DHPC were published on health agency websites and distributed via e-mail and/or letters from physician societies. Following the dissemination of these materials, the PRAC requested an observational, cross-sectional survey to assess physicians' awareness and level of knowledge of key safety information pertaining to the meningioma risk with the use of CPA monotherapy. In alignment with the PRAC request, this study surveyed a convenience sample of dermatologists, endocrinologists, gynecologists, urologists, oncologists, psychiatrists, and general practitioners selected from France, Germany, Poland, Spain, and the Netherlands. The objective of the study was to assess physicians' awareness and level of knowledge of the key safety information included in the revised SmPC and the DHPC regarding the risk of meningioma.

## 2 Methods

### 2.1 Study Design

The study was an observational, cross-sectional survey to assess the knowledge and understanding of the information covered in the SmPC and DHPC among a sample of physicians who had prescribed CPA monotherapy in the 12 months prior to the survey (EU PAS Register No. EUPAS41194). The questionnaire was developed and tested using best practices [10, 11]. Prior to administration, the questionnaire was tested through cognitive pre-test interviews with physicians in each country. The questionnaire was modified based on feedback from the cognitive interviews with physicians and feedback provided by health authorities. The questions were tailored

to the study aims and to the information provided in the revised SmPC and DHPC (Electronic Supplementary Material [ESM]).

The target sample size for the physician survey was a minimum of 600 participating physicians across the five countries, with a minimum of 200 physicians in France and a minimum of 100 physicians each in Germany, Poland, the Netherlands, and Spain. These sample sizes were chosen because they provide reasonable precision around our point estimates. For an individual question with an observed percentage of correct answers of 80%, the 95% confidence interval around the observed value would be 76.6 to 83.1% for a sample size of 600, 73.8 to 85.3% for a sample size of 200, and 70.8 to 87.3% for a sample size of 100. Following review and endorsement of the protocol and questionnaire by the PRAC, surveys were administered via the web between 18 October 2021 and 16 December 2021.

## 2.2 Participants

Physicians based in France, Germany, Poland, Spain, and the Netherlands and across specialties were recruited from a physician panel maintained by a third-party survey research company. Physicians were considered eligible for the survey if they had prescribed CPA monotherapy to at least one patient in the previous 12 months, worked in a hospital or office setting, and acknowledged informed consent within the survey platform. Physicians had to be a licensed and practicing dermatologist, endocrinologist, gynecologist, general practitioner, urologist, oncologist (who treats prostate cancer), or psychiatrist involved in the treatment of hypersexuality/sexual deviations to be eligible.

The recruitment targets for this survey were as follows: (1) up to 30% general practitioners; (2) 25% urologists or oncologists (minimum of five of each type); and at least five dermatologists, psychiatrists, gynecologists, and endocrinologists per country. Given the high prescribing volume of CPA monotherapy by gynecologists in France, the limit was raised so that up to 40% of participants in France could be gynecologists.

## 2.3 Questionnaire

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 (e.g., treatment should be prescribed for the shortest possible time and with the lowest effective dose).
- Risk factors associated with meningioma (e.g., risk increases with increasing cumulative doses).

In addition, the physician questionnaire included queries on the following items to characterize the physicians and their practices: their gender, age, years in practice, practice setting, and experience prescribing CPA monotherapy (ESM).

The questionnaire was administered in the local language for each country, and responses were collected anonymously. The electronic format was programmed so that respondents could not move backward in the survey to change their answers to previous questions, in order to reduce the risk of biasing previous responses based on information provided in follow-up questions. Before study implementation, the questionnaire was tested in cognitive pretest interviews with physicians in each country. The pretest interviews of the draft questionnaire helped to identify problems with questionnaire items, wording, and response choices, thereby ensuring that survey participants fully understood the final questionnaire. The cognitive testing also helped to identify cultural and 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.

## 2.4 Statistical Analysis

Data analyses were descriptive in nature and focused primarily on summarizing 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 forced to skip the question because of an answer given in a previous question (skip pattern). The analysis population consisted of respondents who were eligible for the study, provided informed consent, and completed at least one knowledge question in full.

The study protocol and questionnaire were reviewed and accepted by the relevant health authorities in the Netherlands and France per country-specific requirements before the study was initiated. The study was also communicated

to BfArM (German Federal Institute for Drugs and Medical Devices) as required.

### 2.5 Compliance with Ethical Standards

Ethics approval was obtained prior to data collection in Germany, France, and Spain. Ethical review was not required in the Netherlands or Poland.

## 3 Results

### 3.1 Participants

A total of 10,579 physicians were invited to participate in the survey. Of those, 1242 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 the predefined quota for their specialty 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 the target sample size in each country was reached.

Of the 613 physicians who completed the survey, the distribution by medical specialty for all countries combined aligned with predefined minimum recruitment targets (general practice: 30%; gynecology: 19%; urology: 15%; oncology: 11%; and dermatology: 11%). There were also at least five endocrinologists and psychiatrists for each country. Characteristics of participating physicians are given in Table 1. Most physicians characterized their practice as either office based (46%) or a university/research-oriented/teaching hospital (33%). Most physicians in this study had been practicing for over 10 years (81%), and only 4% reported that they had been practicing for 5 years or less. Sixty-five percent of the physicians identified as male.

### 3.2 Physicians' Experience Prescribing CPA Monotherapy

When asked when they had last prescribed CPA monotherapy for any indication, 69% of all physicians in the survey responded that they had written a prescription for CPA monotherapy within the previous 3 months, with 25% indicating they had prescribed it within the previous month. Results were broadly similar across individual countries; the percentage of prescriptions in the past month was lowest in the Netherlands (17%) and highest in Spain (36%) (Fig. 1A). Gynecologists (75%) and urologists (75%) were the specialties with the highest percentage of members who had written prescriptions within the previous 3 months, followed by oncologists (74%) and endocrinologists (73%); the lowest percentage was found among psychiatrists (54%) [Fig. 1B]. Physicians prescribed CPA monotherapy most commonly for androgenization in women (with a range from 46% in the Netherlands to 58% in Spain), followed by inoperable carcinoma of the prostate (ranging from 39% in Poland to 51% in Germany). These trends were consistent across the studied countries (Fig. 1C).

### 3.3 Knowledge of Indications

Physicians' knowledge of indications for CPA monotherapy was dependent on specialty. Specialties most often reporting that they had prescribed CPA monotherapy either for "moderate to severe" or "severe signs of androgenization in women" (wording depended on the approved indication in each country) in the previous 12 months were as follows: gynecologists (95%), dermatologists (90%), endocrinologists (87%), and general practitioners (63%). Among this group, 88% of participants selected at least one correct response when asked when 10 mg or 50 mg doses of CPA monotherapy should be prescribed for moderate to severe signs of androgenization in women. More physicians chose "when no satisfactory results have been achieved with other treatment options" (73%) than "when no satisfactory results have been achieved at lower dose CPA-containing products" (40%), both of which were correct responses to this question. However, when asked to respond to "After using CPA monotherapy at a dose of 10 mg (in Germany and the Netherlands only, where this dosage is available as per country label) or 50 mg (in France, Poland, and Spain only, where this dosage is available as per country label) and achieving clinical improvement of moderate to severe signs of androgenization, the patient can continue using CPA monotherapy at this dose for as long as it is necessary," only 34% of physicians correctly answered that this was a false statement, with a range from 15% in Germany to 50% in France. Gynecologists had the highest proportion of specialists correctly identifying this as false (41%); endocrinologists had the lowest proportion (27%).

Only 18% of physicians reported that they had prescribed CPA monotherapy for the reduction of sexual deviations in men, ranging from 10% in the Netherlands to 30% in Germany. Physicians who reported that in the previous 12 months they had prescribed CPA monotherapy for a reduction of sex drive in men with sexual deviations were asked when CPA monotherapy should be prescribed for this purpose in men, and 56% correctly answered that this should be done "when other interventions are considered inappropriate." Psychiatrists (63%) and urologists (60%) had the

**Table 1** 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) |
| Gynecology | 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 characterize 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 practicing medicine? (Q16) | | | | | | |
| 5 years or less | 3 (2) | 3 (3) | 13 (13) | 4 (4) | 1 (1) | 24 (4) |
| 6–10 years | 20 (10) | 5 (5) | 36 (36) | 15 (14) | 16 (16) | 92 (15) |
| 11–15 years | 34 (17) | 23 (22) | 23 (23) | 23 (21) | 27 (27) | 130 (21) |
| 16–20 years | 41 (21) | 19 (18) | 15 (15) | 24 (22) | 28 (28) | 127 (21) |
| 21–25 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 | 0 (0) | 0 (0) | 0 (0) | 1 (1) | 0 (0) | 1 (0) |
| Prefer not to answer | 5 (3) | 4 (4) | 4 (4) | 1 (1) | 0 (0) | 14 (2) |

highest percentage of correct responses to this question, as might be expected for the indication.

Forty-five percent of physicians had prescribed CPA monotherapy as antiandrogen treatment for inoperable carcinoma of the prostate in the past 12 months, with a range from approximately 39% in Poland to 51% in Germany. Seventy-five percent of these physicians correctly answered that "The use of CPA monotherapy for the treatment of inoperable prostate carcinoma and LHRH (luteinizing hormone-releasing hormone) flare remains unchanged per the summary of product characteristics (SmPC)" was true; the proportion of physicians answering this question correctly was highest among oncologists (78%), followed by urologists (74%) and general practitioners (71%).

### 3.4 Knowledge of Updated Safety Information for CPA Monotherapy

Across all countries, 43% of physicians correctly identified that a special warning and precaution about meningioma on the prescribing label for CPA monotherapy was updated in 2020. Those in France (63%) and Germany (50%) were most aware of this change (Fig. 2A). The proportion of physicians who reported they did not know what special warning and precaution was added ranged from 21% in France to 49% in Poland. Physicians specializing in gynecology (62%) and endocrinology (60%) had the highest awareness of the changes in the label regarding meningioma with use of CPA monotherapy; oncologists (30%) had the lowest awareness (Fig. 2B).

### 3.5 Knowledge of Meningioma

Physicians were asked to identify clinical signs and symptoms of meningioma from a list of seven signs and symptoms, all of which were correct (Fig. 3). 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%). Overall, physicians' knowledge of the clinical signs and

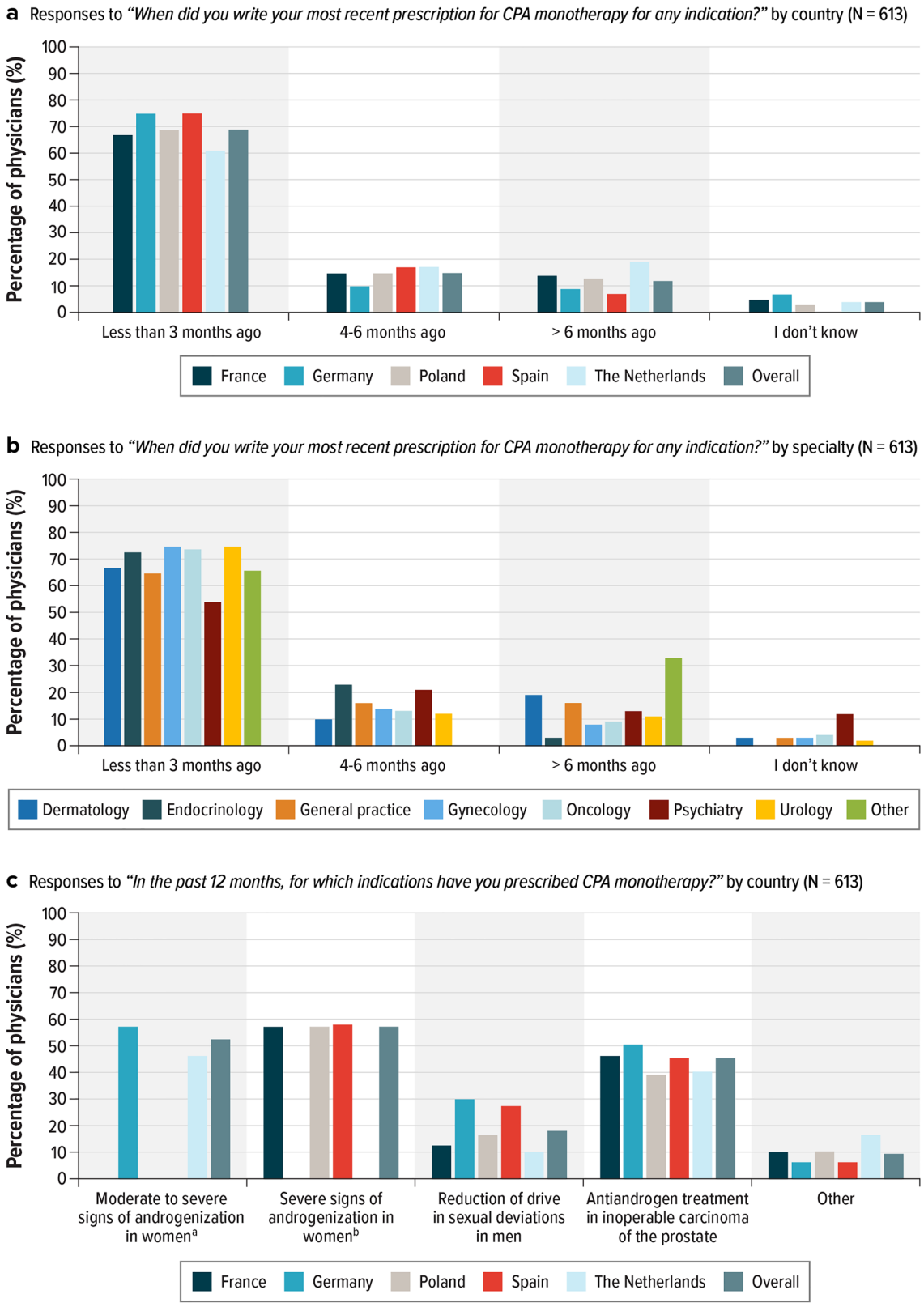


**Fig. 1** Physician's experience prescribing CPA monotherapy. **A** Responses to "When did you write your most recent prescription for CPA monotherapy for any indication?" by country ($N = 613$). **B** Responses to "When did you write your most recent prescription for CPA monotherapy for any indication?" by specialty ($N = 613$). **C** Responses to "In the past 12 months, for which indications have you prescribed CPA monotherapy?" by country ($N = 613$)

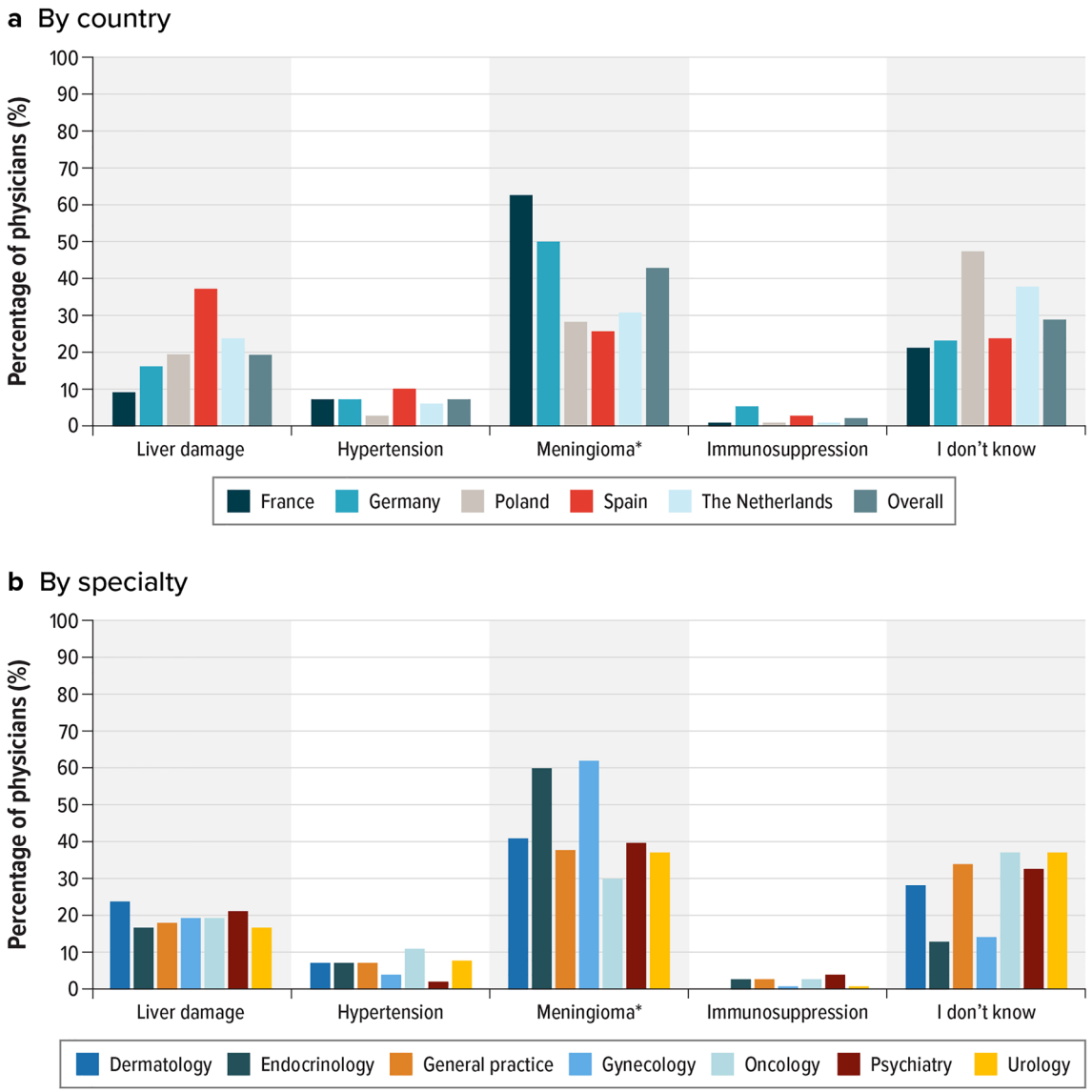


**Fig. 2** Knowledge of CPA monotherapy warning label. Responses to "What special warning and precaution was recently added in 2020 to the prescribing label for CPA monotherapy?" ($N = 613$). **A** By country. **B** By specialty. *Correct response is marked with an asterisk

symptoms of meningioma was high, with 98% of physicians correctly selecting at least one response and 66% of physicians correctly identifying all seven responses. Knowledge of the signs of meningioma was highest in Poland, where 100% of physicians selected at least one correct answer and 80% correctly identified all seven signs and symptoms (Fig. 3A). By physician specialty, dermatologists had the highest proportion who identified all seven signs and symptoms (78%), followed by psychiatrists (73%), oncologists (71%), general practitioners (67%), gynecologists (58%), and endocrinologists (50%) (Fig. 3B).

Most physicians were familiar with dose modulation guidelines to reduce the risk of meningioma with CPA monotherapy, and 74% correctly indicated that patients using CPA monotherapy should be monitored for meningioma. Approximately 85% of physicians correctly stated that CPA monotherapy should be prescribed at the lowest effective dose. Across all countries in the study, 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 (Fig. 4A).

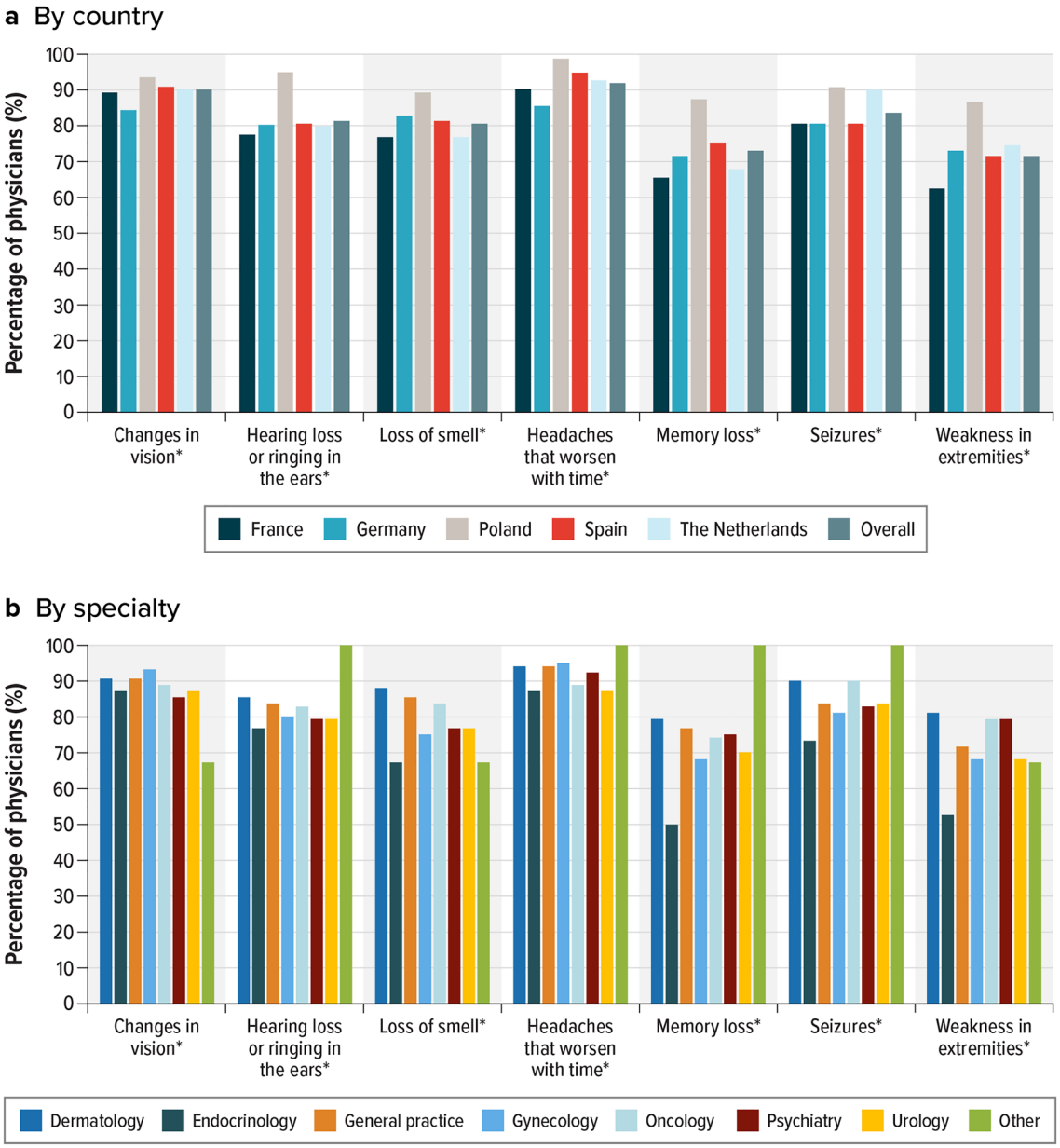


**Fig. 3** Knowledge of the clinical signs and symptoms of meningioma. Responses to "Which of the following may be clinical signs and symptoms of meningioma?" ($N = 613$). **A** By country. **B** By specialty. *Correct response is marked with an asterisk

As with knowledge of indications, there was some variability in the knowledge of meningioma related to CPA monotherapy across physician specialties. In most specialties, over 70% of physicians correctly answered that the risk of meningioma increases with increasing cumulative CPA doses and that if a patient receiving CPA treatment develops meningioma, CPA treatment must be permanently stopped. However, oncologists were an outlier: only 56% and 47% of oncologists, respectively, provided the correct answer to these questions. Across all physician specialties, oncologists had the lowest proportion of correct responses to questions regarding meningioma related to CPA monotherapy. Only 17% of oncologists correctly identified the statement "CPA monotherapy may be used in patients with a history of meningioma under carefully controlled conditions" as false. This question had a low correct response percentage overall, with only 39% of physicians indicating that CPA may not be used in patients with a history of meningiomas (Fig. 4B). Gynecologists had the highest correct response percentage (57%).

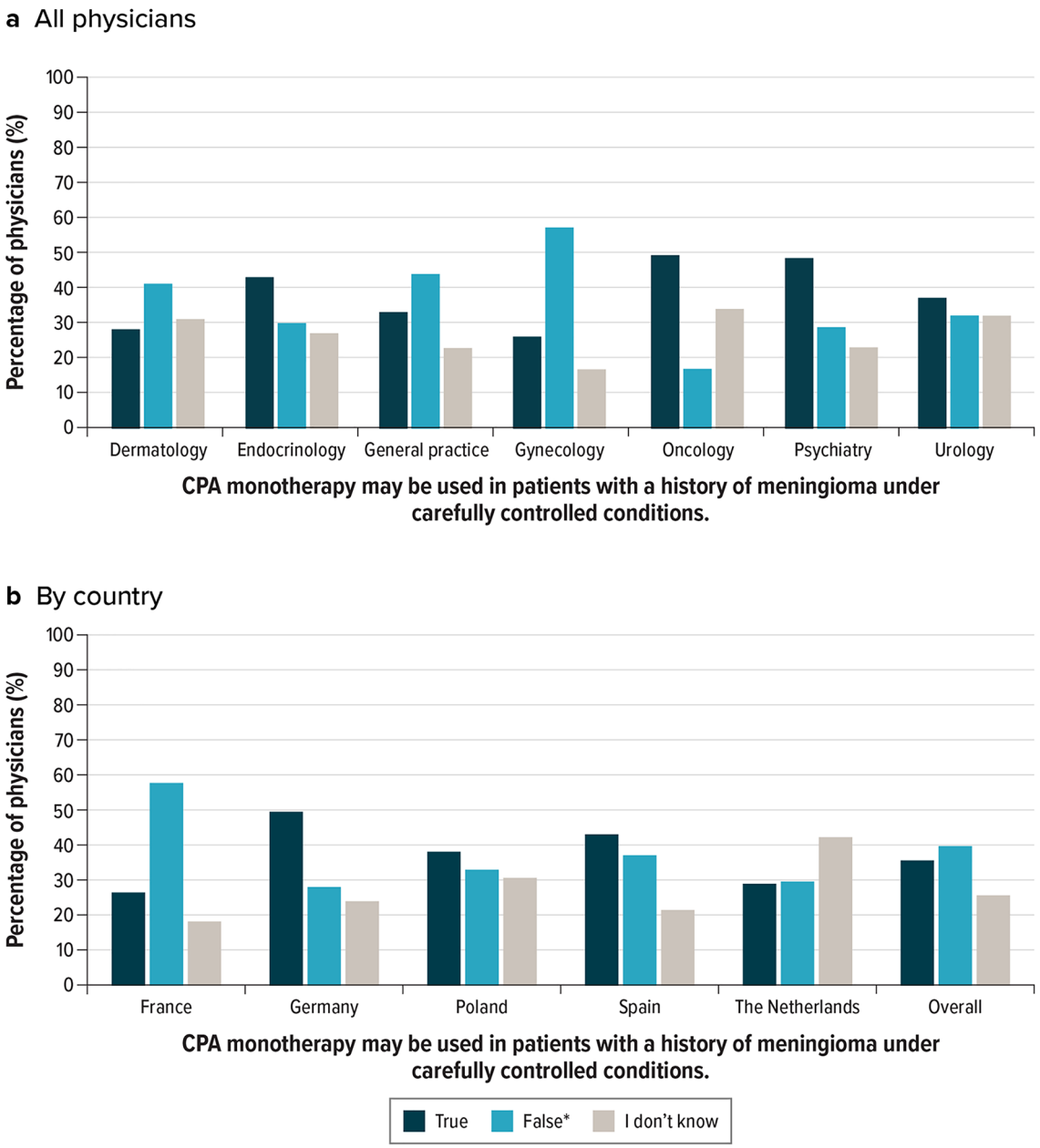


**Fig. 4** Familiarity with risks from CPA monotherapy. Responses to "Please indicate whether each of the following statements about CPA monotherapy is true or false." ($N = 613$). **A** By specialty. **B** By country. *Correct response is marked with an asterisk

## 4 Discussion

This survey of physician knowledge of updates to prescribing information for CPA regarding meningioma risk found that most physicians are knowledgeable about the association between CPA and meningioma, based on their responses to CPA dose modulation questions and awareness of updated practices. We found some variability in physician awareness of label recommendations for CPA use with respect to the risk of meningioma, and in indication-specific uses across specialties. In our study, physicians' knowledge of the clinical signs and symptoms of meningioma was high: 66% of physicians correctly identified all seven signs and symptoms, and knowledge of each of the individual signs and symptoms ranged from 72 to 92%, showing high awareness among the study participants. The signs and symptoms most familiar to physicians varied by their specialty. In general, the observed patterns of knowledge among the physicians were as expected; physicians were most knowledgeable about the indicated use of CPA monotherapy relevant to their specialties and the most important risks of meningioma, and were least knowledgeable about 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). The large majority of physicians were also aware that CPA monotherapy should be prescribed at the lowest effective dose (85%), that risk of meningioma increases with cumulative CPA dose (75%), that patients receiving CPA monotherapy should be monitored for meningioma (74%), and that CPA therapy must be stopped permanently if patients develop meningioma (73%). However, knowledge of the updates contained in the SmPC and DHPC pertaining to CPA use varied. Only 43% of physicians were aware of the updated precaution and warning of meningioma recently added to the prescribing label for CPA monotherapy. Physicians specializing in gynecology (62%) and endocrinology (60%) had the highest awareness of the updates in the label regarding meningioma with use of CPA monotherapy. Reported receipt of the DHPC and SmPC 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 the resources was high. However, while most physicians were aware of meningioma risks associated with CPA, including the dose dependence of that association, 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 the statement "CPA monotherapy may be used in patients with a history of meningioma under carefully controlled conditions" as false, with the highest knowledge among gynecologists (57%) and lowest among oncologists (17%).

Some of the differences between awareness of the association between CPA use and meningiomas and awareness of the recent DHPC and SmPC may be owing to the history of warnings issued in regard to CPA. In 2008, a study by Froelich and colleagues reporting that high doses of CPA were associated with meningioma triggered a recommendation from the EMA's Pharmacovigilance Working Party that CPA formulations over 10 mg provide information regarding an increased risk of meningioma in the product information [6, 12]. Additional studies published between 2008 and 2019, including a large population-based cohort study by Gil et al., have continued to raise this issue in the medical community [3, 13]. Additionally, the Health Authorities in France recently distributed information to healthcare providers and patients detailing the association between CPA and meningioma. In light of this, many physicians may have attributed their awareness of the risks of meningioma associated with CPA to other sources than the recent DHPC and SmPC. This may also have impacted physicians' recall of the DHPC and SmPH; if physicians were already aware of the risk, they may not recall receiving this information again. In fact, among those who recall receipt, the percentage who stated they reviewed the materials was high.

The findings of this survey on physician knowledge follow similar trends seen in other surveys conducted after the dissemination of a DHPC and SmPC for other medications. In 2017, a survey was conducted to assess physician knowledge of a DHPC issued after a safety study examining the risk of thromboembolism associated with CPA 2 mg/ethinylestradiol 35 µg (Diane-35) [14]. Similar to what was observed in this study, physicians surveyed in the Diane-35 study were generally well aware of the signs and symptoms of significant potential side effects, and knowledge was generally consistent across region and specialty. About half (51%) of physicians in the Diane-35 study reported having received the educational materials, consistent with the 42% in this study [14]. The response rate is also consistent with other surveys with quotas evaluating the effectiveness of additional risk minimization measures [15].

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 is 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 minimization measures in Europe, most participants responding correctly was considered a successful result in 9 of 11 surveys registered in the EU PAS Register [16].

Though this study represents a thorough analysis of physician knowledge of CPA and meningioma, there were some limitations. This study was designed to select a diverse and generally representative sample of physicians who have recent experience with CPA monotherapy, but there was no exhaustive list of all physicians who have prescribed or administered CPA monotherapy from which to draw a sample. It was therefore not possible to select a random sample from all relevant physicians, so a convenience sample was collected instead. The physicians who answered this survey may tend to be more engaged in professional education and awareness and therefore responded to the survey and were familiar with the risk of meningioma associated with CPA use. Additionally, because the survey was closed once the quota was reached, the study included all physicians who completed the survey before the survey met its quota. As a result, the study participants may not necessarily be representative of all physicians who have prescribed and/or administered CPA monotherapy. Our survey was conducted in late 2021, at least 11 months after the dissemination of the revised DHPC and SmPC in each country, which may account in some part for the low recall of receipt of the SmPC and DHPC.

## 5 Conclusions

The study met its objectives of evaluating physicians' knowledge and awareness of key safety information pertaining to the use of CPA, and it fulfilled the request of the health authorities. No changes were made to the additional risk minimization measures as a result of this study. In general, there was high knowledge of the risk of meningioma associated with use of CPA monotherapy and of the approved indications/dosing (when accounting for physicians' specialty prescribing experience), despite only 43% of physicians indicating their awareness of the recent changes in the warning and precaution in the prescribing label. The observed patterns of knowledge among the physicians were overall as expected. Knowledge was greatest on (1) the indicated use of CPA monotherapy (particularly when the indication was relevant to a specific specialty) and (2) the most important risks of meningioma; there was less knowledge about more complex aspects of safe CPA use, especially regarding correct use in indications that were not in the area of specialty of the respective physician.

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### Declarations

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**Conflict of Interest** Carolyn Sweeney, Brian Calingaert, and Alicia Gilsenan are full-time employees of RTI Health Solutions, an independent nonprofit research organization, which was retained by Bayer to conduct the research that is the subject of this article. Their compensation is unconnected to the studies on which they work. Carsten Moeller, Gesa Schomakers, Alen Sok, Ruth Holzmann, and Federica Pisa are employees of Bayer and may hold shares and/or stock options in the company.

**Ethical Approval** All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

**Consent to Participate** Informed consent was obtained from all individual participants included in the study.

**Consent for Publication** Not applicable.

**Availability of Data and Material** The data will not be made available.

**Code Availability** Not applicable.

**Author Contributions** All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by CS, BC, and AG. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.



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