Clinical Study Synopsis

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