Drug Utilization Study:

Indications for prescribing CPA/EE products among physicians in Denmark

Post Authorization Safety Study:

Knowledge about safety precautions among physicians in Denmark prescribing CPA/EE products

Study reports

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Background

The combination of cyproterone acetate (CPA) 2 mg and ethinylestradiole (EE) 35 mcg was introduced in 1985. The product is currently marketed in most European countries and indicated for the treatment of moderate to severe androgen-sensitive acne with or without seborrhea and/or hirsutism in women of reproductive age.

At the initiative from the French Medicines Regulatory Agency (ANSM), the European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) in 2013 made a detailed review of data from multiple sources to assess the product safety profile, in particular the risk of thromboembolic (TE) events. Other drug effects, e.g. the efficacy in the three different approved indications were also reviewed.

Based on the review PRAC concluded that the benefits of CPA/EE outweigh the risk provided a number of safety precautions are observed to reduce the risk of serious adverse reactions, especially increased risk of thromboembolism in some potential users of the product. The indication alopecia was dropped due to insufficient evidence for efficacy. The Coordination Group for Mutual Recognition and Decentralized Procedures, CMDh, endorsed PRAC's recommendations.

Marketing Authorization Holders (MAHs) must prepare a core Risk Management Plan (RMP) and submit it to the National Competent Authorities (NCA), in Denmark, The Danish Health and Medicines Authority (DHMA), for evaluation and approval. From 1985 and up to now no regulatory authority request or MAH concern has required a RMP for the product.

Part of this RMP is that two studies must be conducted: 1) a Drug Utilization Study (DUS) and 2) a Post Authorization Safety Study (PASS) to assess the impact of a direct Healthcare Professional (HCP) Communication (DHCPC) taking place in June 2013 and more recently HCP educational material from Orifarm Generics A/S. This communication announced the two main changes that followed the PRAC review: 1) adjustment of indications for use of the product, alopecia dropped based on insufficient data for efficacy and 2) the new safety precautions to be observed when prescribing the product, during its use and when restarting treatment after an interruption. In addition the DHCPC is to be followed by development and distribution of educational material both for health care professionals (HCPs) and users of the product, especially to highlight contraindications and the new safety precautions to reduce the risk of adverse reactions especially thromboembolism in high-risk predisposed subjects. The educational material will include:

- Specification of the revised indications for the product and its safe use
- Information about risk factors, precautions, warnings and contraindications
- Information about the duration of treatment to assess symptom relief from treatment and the need for regular reevaluation of continued treatment
- Information about symptoms and signs of thromboembolic complications

A combined protocol for the two studies providing a detailed description of the DUS and PASS studies has been made and forwarded for review to the National Competent Authorities (NCAs) in countries where Zyrona has a marketing authorisation: DHMA in Denmark, Medicinal Products Agency (MPA) in Sweden and Norwegian Medicines Agency (NOMA) in Norway. The protocol included the physician questionnaire that was used for the studies. The educational material for HCPs and for product users was also submitted to the concerned NCAs for review.

The original plan was to use the unique public Danish electronic registries to identify relevant physicians prescribing the product to be approached for the study. However, it turned out that the relevant database medstat.dk containing the necessary information about physicians prescribing the product, is not allowed to reveal this information, also not in blinded format, due to Danish legislation. Therefore it has only been possible to approach a random sample of physicians predominantly from general practice (GPs) and ask for their help to perform the studies. Below please find the report describing the outcome of the studies.

Methods and results

The request for help and the questionnaire was sent to a total of 123 Danish physicians predominantly working in general practice (GP) in February 2015. If no response had been obtained within two weeks, a reminder was sent. If after a further two weeks there was still no response, a second and final reminder was sent.

Of the 123 physicians approached totally 38 (31%) responded. Three informed that they did not use the product and that they were therefore unable to answer the questionnaire. Three others informed they did not wish to be involved with anything that could associate them with the pharmaceutical industry and that they therefore did not wished to complete the questionnaire.

Therefore a total of 32 completed questionnaires were available. A summary of the replies to the questionnaire is shown in table 1 in the end of this document. Table 1 shows the number of respondents answering ***yes*** and ***no*** to the different questions and what percentage this was.

Answers with relevance for the DUS part of the studies

None of the physicians indicated they used the product as sole hormonal contraceptive or combined it with other oral hormonal contraceptives. A majority of 28 (88%) indicated they only used the product in women of reproductive age, whereas four answered no to this question. Half of the replying physicians said that the product was indicated in women with moderate to severe acne, whereas the other half answered no to this question. None said they used the product in women with alopecia. A majority of 29 (91%) informed that they used the product in women with moderate to severe androgen sensitive acne, if local or systemic antibiotics had not worked. Nine (28%) replied they did not use the product in women with hirsutisme.

Answers with relevance for the PASS part of the studies

All 32 physicians (100%) correctly indicated that the main safety concern with the product is an increased risk of venous and/or arterial thrombotic events. A minority of five physicians (16%) indicated that the product could worsen migraine, whereas none indicated weight gain as a main safety concern.

A majority of 30 (94%) correctly answered it took at least 3 months before relief of symptoms could be evaluated. All physicians indicated that need for continued treatment should be evaluated regularly.

A majority of 30 to 31 (94 to 97%) correctly indicated the contraindications for using the product. Likewise a majority of 31 to 32 (97 to 100%) provided correct answers about special warnings and precautions for using the product.

General comments to the studies

It was expected that it would be difficult to persuade a random sample of general practitioners to respond a survey based on a questionnaire about a product with limited use. Thus it is unlikely that all or a majority of GPs to use the product regularly. Three of 38 responding physicians (8%) said they never used the product. Some of the non-responding physicians may also belong to this category of physicians. Therefore an unknown fraction of the physicians approached in this way for the studies may have been irrelevant.

For these studies 31% of the approached physicians replied to the questionnaire after one initial approach supplied by up to two additional reminders sent within a period of a month. Three of the responders (8%) were unwilling to contribute to the studies by answering the questionnaire, as they did not want to have anything to do with something that came from or could in anyway associate them with the pharmaceutical industry.

Evaluation of the DUS part

None of the physicians indicated they used the product for hormonal contraception alone or in combination with other hormonal contraceptives. Also none used the product against alopecia, which is no longer an approved indication based on insufficient data to indicate efficacy. Four physicians indicated that the product was not only used in women of reproductive age. This cannot be readily explained, but may be due to confusion when answering the questionnaire.

Seventy percent of responders used the product in women with hirsutisme, whereas 30 percent did not. Only half indicated they used the product in women with moderate to severe androgen sensitive acne. However 29 of 32 (91%) said they used the product in this indication, when local or systemic antibiotic had failed. These disparate answers could indicate some confusion among physicians as to how these questions was to be understood and should be answered. The indication for using the product is correct, but the product is only approved for use when treatment with antibiotics has been tried and has failed.

Conclusions for the DUS part

In general the product is used in accordance with the approved indications. Importantly the product is not used solely for contraception or in combination with other hormonal contraceptives. The only potential finding noted was that a few physicians indicated the product was/could be used in women outside reproductive age. How this should be interpreted cannot be answered. It could however be due to confusion about the question when rapidly answering the questionnaire.

Evaluation of the PASS part

All responding physicians correctly knew that venous and/or arteriolar thrombotic events are the main safety concern with the product. A minority also indicated migraine as a main safety concern. This may be due to confusion as some forms of migraine are associated with an increased risk of thrombotic events. In such forms of migraine the product should not be used or only used after special consideration as the risk of thrombosis is increased.

All or nearly all knew that it takes at least 3 months to evaluate relief of symptoms and that continuation of treatment must be evaluated regularly. Contraindications and special warnings/precautions for use were close to correct for all physicians. One physician had indicated no instead of yes to all contraindications. Again this may have been due to confusion when rapidly answering the questions.

Conclusions for the PASS part

A dominant picture of correct answers was obtained.

Overall conclusions of the studies

The studies support that in daily clinical practice Danish physicians comply with the adjusted indications for use of the product. The data supports that the product is not used solely for hormonal contraception or in combination with other hormonal contraceptives. The main safety concern with the product is well understood as well as the time it takes to assess symptom relief and the need to evaluate treatment continuation regularly. Contraindications and special warnings and precautions for use are very well understood.

Thus the studies support that the DHCPC of June 2013 - to announce PRAC's decision to adjust the approved indications for use of the product and to introduce new safety precautions when prescribing the product – in combination with HCP educational material has been perceived and is followed in clinical practice by Danish physicians in the first months of 2015.

Table 1. Replies from 32 physicians about their use of CPA/EE products in clinical practice

		YES N - %	NO N - %
Indications for prescribing CPA/EE products	*Kindly indicate, yes or no, to the below statements to describe your current use of the products in clinical practice, i.e. your indications:*		
	• Used solely for hormonal contraception?.....	0 – 0	32 - 100
	• Used in combination with other hormonal contraceptives?.....	0 – 0	32 - 100
	• Used only in women of reproductive age?.....	28 – 84	4 – 16
	• Used in women with moderate to severe androgen sensitive acne?.....	16 – 50	16 – 50
	• Used in women with alopecia?.....	0 – 0	32 – 100
	• Used in women with moderate to severe androgen sensitive acne, if local or systemic antibiotic has failed?.....	29 – 91	3 – 9
	• Used in women with hirsutism?.....	23 – 72	18 - 28
Main safety concerns with CPA/EE products	*Kindly indicate, yes or no, to the below statements to describe the main safety concerns with the products:*		
	• Increased risk of **venous** and/or arterial thrombotic events?.....	32 – 100	0 – 0
	• Worsening of migraine?.....	5 – 16	27 – 84
	• Weight gain?.....	0 – 0	32 – 100
Evaluation of **efficacy / need of continued treatment**	*Kindly indicate, yes or no, to the below statements about the duration of treatment to evaluate efficacy and evaluation of the need for continued treatment:*		
	• Time to evaluate symptom relief: ≥ 3 months?.....	30 - 94	2 – 6
	• Evaluate need of treatment continuation regularly?.....	32 – 100	0 – 0
Contraindications for using products	*Kindly indicate, yes or no, to the below statements to describe contraindications to treatment with the products?*		
	• Concomitant with other oral hormonal contraceptives?.....	31 – 97	1 – 3
	• Venous thrombosis: Present/past, e.g. deep vein or pulmonary emboli?.....	31 – 97	1 – 3
	• Arterial thrombosis: Present/past, e.g. MI, angina, stroke, TCI?.....	30 – 94	2 - 6
	• Severe/multiple risk factors for thrombosis, e.g. diabetes with vascular symptoms, severe hypertension or dyslipidemia?.....	31 – 97	1 – 3

	• Hereditary/acquired high risk for venous/arterial thrombosis?……..	31 – 97	1 - 3
Special Warnings and **precautions for use**	*Kindly indicate, yes or no, to the below statements to describe when treatment with product must be weighed, thoroughly considered?*		
	• High CV risk due to polycystic ovarian syndrome?……..	31 – 97	1 – 3
	• Increased risk of thrombotic events?……	32 – 100	0 – 0
	• Symptoms of arterial or venous thrombosis?……..	32 – 100	0 – 0
	• High risk of venous thrombosis, e.g. age, family history, obesity, immobilization, surgery, trauma, cancer?……	32 – 100	0 - 0
	• High risk of arterial thrombosis, e.g. age, smoking, obesity, dyslipidemia, hypertension, migraine (± increased frequency/severity), atrial fibrillation, valvular heart disease, family history, diabetes mellitus, puerperium, immobilization, systemic LE?……..	32 – 100	0 - 0