VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

Indication: Treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age. For the treatment of acne, Zyrona should only be used after topical therapy or systemic antibiotic treatments have failed. Since Zyrona is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives (see section 4.3).

Hyperandrogenism and polycystic ovary syndrome are clear casual factors (trends) which result in hirsuitism and acne.

A recently published study[1] found the following concerning acne:
- During the 20s, 50.9 percent of women and 42.5 percent of men reported experiencing acne.
- During the 30s, 35.2 percent of women and 20.1 percent of men reported experiencing acne.
- During the 40s, 26.3 percent of women and 12 percent of men reported experiencing acne.
- During the 50s or older, 15.3 percent of women and 7.3 percent of men reported experiencing acne.

Acne vulgaris is the commonest skin disease that affects adolescents. 80–95% of adolescents aged 12–24 suffer from acne.[2]

Hirsutism is the presence of terminal (coarse) hairs in females in a male-like pattern; it affects between 5% and 15% of women.[3]

VI.2.2 Summary of treatment benefits

Zyrona is only suitable for use in women of reproductive age and that for acne treatment and should only be used after topical therapy or systemic antibiotic treatments have failed.

Studies in the literature comparing efficacy of cyproterone/ethinylestradiol versus other antiandrogens/ethinylestradiol show greatest efficacy of the CPA/EE combination after 12 months treatment for hirsutism.

CPA/EE combinations have a contraceptive effect similar to products formally approved as oral contraceptives.

VI.2.3 Unknowns relating to treatment benefits

None.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	**What is known**	**Preventability**
I Blood clots in the veins or arteries (incl.	Blood clots (thrombosis) present or in history or presence of risk factors for thrombosis are known	The risk can be prevented by securing that the physician and patients are well

Risk	What is known	Preventability
cardiovascular disease and stroke)Venous and/or arterial thrombotic events (incl. cardiovascular disease and stroke))	contraindications and patients with these risks should therefore not use Zyrona. Conditions/risk factors are listed in the Summary of Product Characteristics and patient information leaflet. The benefits of the use of Zyrona should be weighed against the potential risks for each individual woman, and discussed with the woman before she decides to start using Zyrona. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician must then decide on whether the use of Zyrona should be discontinued. • The use of Zyrona carries an increased risk of venous blood clots (VTE) compared with no use. The excess risk of VTE is highest during the first year a woman starts Zyrona or when restarting or switching after a pill-free interval of at least a month. Venous blood clots can be fatal in 1-2% of cases. • Studies have shown that the incidence of VTE is 1.5 to 2 times higher in users of Zyrona than in users of levonorgestrel-containing combined oral contraceptives (COCs) and may be similar to the risk for desogestrel / gestodene / drospirenone-containing contraceptives. • The user group of Zyrona is likely to include patients that may have an inherently increased cardiovascular risk such as that associated with polycystic ovarian syndrome. • Studies have also associated the use of hormonal contraceptive with an increased risk for arterial (myocardial infarction, transient ischaemic attack) blood clots. • Extremely rarely, blood clot has been reported to occur in other blood vessels, e.g. liver, kidney, cerebral or retinal veins and arteries, in hormonal contraceptive users. • Symptoms of venous or arterial thrombosis or of a cerebrovascular accident can include: unusual unilateral leg pain and / or swelling; sudden severe pain in the chest, whether or not it radiates to the left arm; sudden breathlessness; sudden onset of coughing; any unusual, severe, prolonged headache; sudden partial or complete loss of vision; double vision; slurred speech or aphasia; vertigo; collapse with or without focal seizure; weakness or very	informed about the risk and precautions. Educational material to physicians and patients has been developed. The risk is mentioned as a contraindication in the summary of Product Characteristics and patient information leaflet. The risk can be reduced by not allowing the product to be used in patients who are at risk of blood clots. The risk is mentioned as a warning in the summary of Product Characteristics and patient information leaflet.

Risk	What is known	Preventability
	marked numbness suddenly affecting one side or one part of the body; motor disturbances; 'acute' abdomen. Risk factors are: - increasing age; - smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age. Women over 35 years of age should be strongly advised not to smoke if they wish to use Zyrona); - a positive family history (i.e. venous thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any hormonal contraceptive use; - prolonged immobilisation, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation. Antithrombotic treatment should be considered if the use of Zyrona has not been discontinued in advance. - obesity (body mass index over 30 kg/m2). <u>Blood clot</u> is listed as a rare undesirable effect.	
- Hepatobiliary disorders	Current or prior severe liver disease, as long as liver function values are not normalized are a known contraindication and patients with this risks should therefore not use Zyrona. Acute or chronic liver function disturbances may necessitate discontinuation of oral contraceptive use until the liver function values are normalised. Recurrences of cholestatic jaundice which first appeared during pregnancy or previous sex hormone use also necessitate discontinuation.	There is no specific measure to prevent the occurrence of hepatobiliary disorders. The risk is mentioned as contraindication in the summary of Product Characteristics and patient information leaflet. The risk is mentioned as a warning in the summary of Product Characteristics and patient information leaflet.

Risk	What is known	Preventability
		The risk can be reduced by not allowing the product to be used in patients who are at risk of hepatobiliary disorders.
- Increased blood pressure	Although small increases in blood pressure have been reported in many women who are taking oral contraceptives, clinically significant increases in blood pressure are rare. However, if persistent clinical hypertension does develop during oral contraceptive use, the physician should discontinue the oral contraceptive and treat the hypertension. When deemed appropriate, oral contraceptive use may be resumed once normotensive values are achieved through antihypertensive therapy.	There is no specific measure to prevent the occurrence of hepatobiliary disorders. The risk is mentioned as contraindication in the summary of Product Characteristics and patient information leaflet. The risk is mentioned as a warning in the summary of Product Characteristics and patient information leaflet. The risk can be reduced by not allowing the product to be used in patients who are at risk of hepatobiliary disorders.
- Effect on hereditary angioedema	Included for the originator product Diane Mite. No further details are known by Orifarm Generics A/S.	There is no specific measure to prevent the occurrence of hepatobiliary disorders.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
- Breast cancer	Known or suspected type of cancer that could grow if it is exposed to sex hormones (e.g. breast cancer or cancer of the ovaries, uterus or cervix) is a known contraindication and patients with this risk should therefore not use Zyrona. An analysis of 54 studies has shown that women who use oral contraceptives have a slightly increased risk of being diagnosed with breast cancer. This increased risk declines gradually over the course of 10 years following the cessation of oral contraceptive use. Because breast cancer is a rare condition in women under the age of 40, the increase in the number of diagnosed breast

Risk	What is known (Including reason why it is considered a potential risk)
	cancer cases among current and former oral contraceptive users is small in relation to the risk of breast cancer over their entire life span. These studies do not provide proof of a causal link. The observed pattern of increased risk may be attributable to the earlier diagnosis of breast cancer among oral contraceptive users, the biological effects of oral contraceptives, or a combination of the two. The diagnosed cases of breast cancer among oral contraceptive users tend to be less clinically advanced than the diagnosed cases of breast cancer among non-users.
- Cervical cancer	An increased risk of cervical cancer has been reported among long-time users of oral contraceptives in some epidemiological studies, but there is still disagreement as to the extent to which this finding could be influenced by sexual behaviour and other factors, such as human papilloma virus (HPV).
- Benign and malignant liver tumours	Presence of liver tumours (benign or malignant), or history of such is a known contraindication and patients with this risk should therefore not use Zyrona. Benign liver tumours have been reported on rare occasion among oral contraceptive users, and malignant tumours have been reported even less often. These tumours have led to life-threatening intra-abdominal haemorrhages in isolated cases. A liver tumour should be taken into account in the differential diagnosis if severe pains occur in the upper abdomen, in connection with an enlarged liver, or in the presence of signs of intra-abdominal haemorrhage in women who are taking oral contraceptives.
- Insulin resistance/decreased glucose tolerance	Although oral contraceptives can have an effect on peripheral insulin resistance and glucose tolerance, there are no indications that it is necessary to alter the therapeutic regimen in diabetics who are using low-dose oral contraceptives (containing < 50 micrograms ethinylestradiol). Diabetes should however be monitored carefully during oral contraceptive use.
- Crohn’s disease and ulcerative colitis	Other medical conditions, which have been associated with adverse circulatory events, include chronic inflammatory bowel disease (e.g. Crohn's disease or chronic inflammation of the colon (ulcerative colitis)). Crohn's disease and chronic inflammation of the colon (ulcerative colitis) have been associated with the use of combination-type oral contraceptives.
- Inflammation of the pancreas associated with high fat levels in your blood (Pancreatitis (in patients with hypertriglyceridemia))	Current or prior inflammation of the pancreas, if associated with high fat levels in the blood (hypertriglyceridæmia) is a known contraindication and patients with this risk should therefore not use Zyrona. Women with high fat levels in the blood (hypertriglyceridæmia) or a familial predisposition for this condition may have an increased risk of pancreatitis when they take oral contraceptives.
- Increase in onset or deterioration of depression	Women who get severely depressed during the use of contraceptive pills should stop taking the pills and use an alternative contraceptive method while trying to determine if the symptoms are due to the oral contraceptive preparation.

Risk	What is known (Including reason why it is considered a potential risk)
	Depression/mood swings is listed as a common undesirable effect.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for Zyrona can be found in the EPAR.

This medicine has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in X's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risks:

Safety concern in lay terms (medical term)

Risk minimisation measure(s)
Objective and rationale
Summary description of main additional risk minimisation measures - Dear Healthcare Professional Communication letter - Educational material for HCPs and Patients
The product information must be in line with the PRAC recommendations so the HCPs and patients are rightly informed. Educational material for HCPs and patients respectively to educate on the use of the product.

VI.2.6 Planned post authorisation development plan

None.

VI.2.7 Summary of changes to the Risk Management Plan over time

Not applicable as this is the initial risk management plan.