

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Acne

Adult acne affects 25% of adult men and 50% of adult women at some time in their adult lives. one third of adults affected with facial acne also have acne on their back and body¹. Adult acne is caused by sebum, an oily substance produced by the skin's sebaceous glands. Sebum clogs pores, which attract bacteria and become inflamed. For some adults, breakouts are a result of hypersensitivity or overproduction of androgens (male hormones). But an imbalance in both male and female hormones (estrogen) can also cause breakouts. For women, this can happen during pregnancy, perimenopause, and menopause².

Hirsutism (is the excessive hairiness on women in those parts of the body where terminal hair does not normally occur or is minimal - for example, a beard or chest hair)

Hirsutism affects approximately 10% of women in the US. The prevalence rates of hirsutism in northern Europe are similar to those in the US; in other places they are not known with certainty³.

VI.2.2 Summary of treatment benefits

Cypromix is indicated for the treatment of acne, seborrhoea or mild forms of hirsutism in mature women for whom hormonal therapy is considered necessary. Although Cypromix also acts as an oral contraceptive, it should only be used in patients requiring hormone treatment for the above conditions. It is recommended that treatment be withdrawn 3 to 4 cycles after the indicated condition(s) has/have completely resolved and that treatment with Cypromix tablets is not continued solely to provide oral contraception. Repeat courses of Cypromix may be given if the androgen-dependent condition(s) recur.

Current (gold) standards of treatment:

Acne: Topical antibiotic clindamycin helps fight bacteria in the skin; so does tetracycline, another antibiotic, taken orally. Oral contraceptives and spironolactone, a blood pressure drug, can help balance hormones. A gel containing dapson, an antibiotic, helps fight infection and inflammation involved in acne⁴. Female hormones tend to fluctuate more than male hormones, and unlike men, hormonal treatment is an option for women⁵.

Drugs used in the hormonal treatment of acne fall into four categories: 1) androgen receptor blockers (spironolactone, flutamide, cyproterone acetate), which block the effect of androgens on the sebaceous gland; 2) oral contraceptives, which suppress ovarian androgen production; 3) glucocorticoids, which cause adrenal suppression of androgen production; and 4) enzyme inhibitors (5 α -reductase inhibitors)⁶.

Hirsutism: Cosmetic or systemic treatment may be necessary for hirsutism. The most effective strategy is to combine systemic therapy, with mechanical depilation⁷. Systemic therapies directed at hirsutism can be divided into those that decrease ovarian or adrenal androgen production and those that inhibit androgen action in the skin. Systemic treatment options include glucocorticoids, oral contraceptives, spironolactone, flutamide and cyproterone⁸.

VI.2.3 Unknowns relating to treatment benefits

Ethinylestradiol/ Cyproterone is not a new, but a well-established drug (more than 10 years in the market). The use is well established with recognized efficacy and acceptable safety. Apart from this anti-androgen effect cyproterone acetate also shows a strong progestagenic and antigonadotropic effect. Using cyproterone acetate enables to decrease or eliminate the effects of virilisation in women, whether the origin is an increased androgen level or an increased peripheral sensitivity for androgens.

VI.2.4 Summary of safety concerns

Important identified risks:

Risk	What is known	Preventability
Venous thromboembolic events(a blood clot in a vein)	<p>Do not take ethinylestradiol /cyproterone, if you have serious or multiple risk factors for developing arterial or venous thrombosis. Stop taking tablets and contact your doctor immediately if you notice possible signs of a blood clot.</p> <p>Cyproterone/Ethinylestradiol is known to cause venous blood clot</p>	Administration according to the recommendations laid out in the SmPC.
Arterial thromboembolic events (incl. cardiovascular disease and stroke) (a blood clot in an artery)	<p>Tell your doctor if any of the following conditions applies to you before starting to use cyproterone/ethinylestradiol.</p> <p>If you have a conditions like diabetes, very high blood pressure and a very high level of fat in your blood (cholesterol or triglycerides) that may increase the risk of a blood clot in arteries your doctor may then advise you to use a different treatment</p>	Administration according to the recommendations laid out in the SmPC.
Hepatobiliary disorders	Do not take cyproterone / ethinylestradiol, if you have or have had a liver disease or jaundice.	Administration according to the recommendations laid out in the SmPC.

	<p>Talk to your doctor or pharmacist before taking cyproterone / ethinylestradiol, if you have a disturbed function of liver or gall-bladder.</p>	
<p>Increased blood pressure</p>	<p>Do not take cyproterone / ethinylestradiol, if you have a condition that may increase the risk of a blood clot in your arteries such as very high blood pressure.</p> <p>The use of a combined pill has been connected with an increased risk of clots in the arteries. This risk increases further, if you have high blood pressure.</p>	<p>Administration according to the recommendations laid out in the SmPC.</p>
<p>Effect on hereditary angioedema (is the rapid edema (swelling) of the deep layers of skin)</p>	<p>Talk to your doctor or pharmacist before taking cyproterone / ethinylestradiol, if you have hereditary angioedema (attacks of temporary swelling with itching of the skin and/or mucous membranes, often as an allergic reaction). Administered estrogens (female sex hormones) can cause or exacerbate symptoms of angioedema. You should contact your doctor immediately if you acquire the symptoms of angioedema such as a swollen face, tongue, and/or throat, and/or problems with swallowing or hives together with difficult breathing.</p>	<p>Administration according to the recommendations laid out in the SmPC.</p>

Important potential risks:

Risk	What is known (Including reason why it is considered a potential risk)
Breast cancer	Breast cancer has been found slightly more often in women who take the pill than in women of the same age who do not. 10 years after stopping the pill, the risk of finding breast cancer is the same as for women who have never taken the pill. It is not certain whether the pill causes the increased risk of breast cancer. It may be that women taking the pill are examined more often, so that breast cancer is noticed earlier.
Cervical cancer	In women who have been using the pill for a rather long time, cancer of the cervix is now found more frequently. However, this may not be caused by the pill but may be related to sexual behaviour and other factors. It is still unclear how great its influence is on the development of cervical cancer. It is quite clear that the most significant cause of cervical cancer is a prolonged infection with the so-called human papilloma virus (HPV).
Benign and malignant liver tumours	<p>Tell your doctor if any of the following conditions applies to you before starting to use cyproterone / ethinylestradiol. Your doctor may then advise you to use a different treatment.</p> <ul style="list-style-type: none"> ➤ if you have or had in the past a (benign or malignant) tumour of the liver. ➤ if you have a hormone-dependent, malignant tumor in genitals, breasts or liver, or if you have a suspicion of it <p>On rare occasions, the use of the pill has led to benign liver tumours, and, very rarely, it has been associated with malignant liver tumours. Liver tumours may lead to life-threatening bleeding in the abdomen. Therefore, if you have pain in the upper abdomen, you should immediately contact your doctor</p>
Insulin resistance/decreased glucose tolerance	Talk to your doctor or pharmacist before taking cyproterone / ethinylestradiol, if you have diabetes (sugar disease)
Crohn's disease and ulcerative colitis (a type of inflammatory bowel disease that may affect any part of the gastrointestinal tract from mouth to anus)	Deterioration of Crohn's disease has been reported during combined oral contraceptive (COC) use.
Pancreatitis (in patients with hypertriglyceridemia) (Elevated levels of triglycerides)	Do not take cyproterone / ethinylestradiol, if you have or had in the past an inflammation of the pancreas gland (pancreatitis).

Increase in onset or deterioration of depression	Cyproterone / ethinylestradiol tablets can cause mood changes including depression. These side-effects may occur mainly in the first few months after starting the pill. They usually disappear after some time. Please consult your doctor immediately if needed.
Potential for off-label use	Ethinylestradiol / cyproteronacetate tablets are used to treat skin conditions such as acne, very oily skin and excessive hair growth in women of reproductive age. Due to its contraceptive properties it should only be prescribed for you if your doctor considers that treatment with a hormonal contraceptive is appropriate. You should only take Ethinylestradiol / cyproteronacetate tablets, if your skin condition has not improved after use of other anti-acne treatments, including topical treatments and antibiotics.

VI.2.5 Summary of risk minimisation measures by safety concern

MAH considers that routine pharmacovigilance is sufficient to address all the safety concerns except the following risks: Venous thromboembolism and Arterial thromboembolism.

The additional risk minimisation measures for these include the following:

Safety concern: Venous thromboembolic events (A blood clot in a vein)
Risk minimisation measure(s): Healthcare Professional and patient education
Objective and rationale: Patients and HCPs to understand the risk of venous thromboembolism and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity
<p>Proposed action:</p> <p>HCP educational materials to be provided to prescribing physicians and pharmacists including advice on:</p> <ul style="list-style-type: none"> ➤ Start and use of cyproterone/ethinylestradiol tablets ➤ Importance of adherence to dosing recommendations ➤ Management of venous thromboembolism <p>Patient booklet will inform patients what the symptoms of venous thromboembolism and the importance of informing their HCP if any occur</p>

Safety concern: Arterial thromboembolic events (A blood clot in an artery)
Risk minimisation measure(s): Healthcare Professional and patient education
Objective and rationale: Patients and HCPs to understand the risk of arterial thromboembolism and the procedures related to the appropriate management of this risk to minimise its occurrence and its severity

<p><u>Proposed action:</u></p> <p>HCP educational materials to be provided to prescribing physicians and pharmacists including advice on:</p> <ul style="list-style-type: none"> ➤ Start and use of cyproterone/ethinylestradiol tablets ➤ Importance of adherence to dosing recommendations ➤ Management of venous thromboembolism <p>Patient booklet will inform patients what the symptoms of arterial thromboembolism and the importance of informing their HCP if any occur</p>
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<p>Safety concern: Potential for off-label use</p>
<p>Risk minimisation measure(s): Healthcare Professional and patient education</p>
<p><u>Objective and rationale:</u> To ensure that the product is used only for approved indications as laid out in the SmPC thereby reducing the risk of off-label use</p>
<p><u>Proposed action:</u></p> <p>HCP educational materials to be provided to prescribing physicians and pharmacists including advice on:</p> <ul style="list-style-type: none"> ➤ Start and use of cyproterone/ethinylestradiol tablets ➤ Importance of adherence to dosing recommendations <p>Patient booklet will inform patients when the Cypromix tablets should only be used and the importance of informing their HCP in case of any adverse events.</p>

VI.2.6 Planned post authorisation development plan (if applicable)

N/A

VI.2.7 Summary of changes to the risk management plan over time

N/A