VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Acne vulgaris (or simply acne) is a common human skin disease, characterized by areas of skin with seborrhea (scaly red skin), comedones (blackheads and whiteheads), papules (pinheads), nodules (large papules), pimples, and possibly scarring. Acne affects mostly skin with the densest population of sebaceous follicles; these areas include the face, the upper part of the chest, and the back. Severe acne is inflammatory, but acne can also manifest in noninflammatory forms. The lesions are caused by changes in pilosebaceous units, skin structures consisting of a hair follicle and its associated sebaceous gland, changes that require androgen stimulation. Globally acne affects approximately 650 million people, or about 9.4% of the population, as of 2010. It affects almost 90% of people during their teenage years and sometimes persists into adulthood. It is slightly more common in females than males (9.8% versus 9.0%). In those over 40 years old, 1% of males and 5% of females still have problems. Acne affects 40 to 50 million people in the United States (16%) and approximately 3 to 5 million in Australia (23%). It affects people of all ethnic groups, but in the United States tends to be more severe in Caucasians than people of African descent.

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. It refers to a male pattern of body hair (androgenic hair) and it is therefore primarily of cosmetic and psychological concern. Hirsutism is one of the most common endocrine disorders, affecting approximately 10% of women in the United States. The prevalence rates of hirsutism in northern Europe are similar to those in the United States; in other places, rates are not known with certainty.

VI.2.2 Summary of treatment benefits

Based on the available data from clinical studies and clinical experience of several years, cyproterone acetate/ ethinylestradiol represents an effective drug in the treatment of moderate to severe acne

related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age.
If administered as indicated in the Summary of Product Characteristics and taking into account the contra-indications, the warnings and precautions, cyproterone acetate/ ethinylestradiol can be considered effective in the approved indications and generally well tolerated.

VI.2.3 Unknowns relating to treatment benefits

Not applicable.

VI.2.4 Summary of safety concerns

Risk	What is known	Preventability
Important identified risks		
Blood clots in veins	Taking CPA/EE may slightly increase risk of having a blood clot (called a thrombosis).The chances of having a blood clot are only increased slightly by taking CPA/EE compared with women who do not take CPA/EE or any contraceptive pill. A full recovery is not always made and in 1-2% of cases, can be fatal. A blood clot in a vein (known as a 'venous thrombosis') can block the vein. This can happen in veins of the leg, the lung (a lung embolus), or any other organ. The risk of developing a blood clot in a vein is highest during the first year a woman uses the pill. The risk is not as high as the risk of developing a blood clot during pregnancy. The risk of blood clots increases further: • with increasing age; • if you smoke.; • if one of your close relatives has had a blood clot in the leg, lung or other organ at a young age; • if you are overweight • if you must have an operation, or if you are off your feet for a long time because of an injury or illness, or you have your leg in a plaster cast	If any of the stated risk factors applies to you, it is important to tell your doctor that you are using CPA/EE, as the treatment may have to be stopped. When using a hormonal contraceptive like CPA/EE it is advised to stop smoking, especially if you are older than 35 years. Stop taking tablets and see your doctor immediately if you notice possible signs of a blood clot, such as: • an unusual sudden cough; • breathlessness; • any unusual, severe, or long-lasting headache or worsening of migraine; • partial or complete loss of vision, or double vision; • slurring or speech disability; • sudden changes to your hearing, sense of smell, or taste; • dizziness or fainting; • weakness or numbness in any part of your body; • severe pain in your abdomen; • severe pain or swelling in either of your legs.
Blood clots in arteries	Taking CPA/EE may slightly increase risk of having a blood clot (called a thrombosis).The chances of having a blood clot are only increased slightly by taking CPA/EE compared with women who do not take CPA/EE or any contraceptive pill. A full recovery is not	If any of the stated risk factors applies to you, it is important to tell your doctor that you are using CPA/EE, as the treatment may have to be stopped. When using a hormonal contraceptive like CPA/EE it is advised to stop smoking, especially if you are older than 35 years.

Risk	What is known	Preventability
	always made and in 1-2% of cases, can be fatal. A blood clot in an artery in the heart may cause a heart attack, or in the brain may cause a stroke. The risk of blood clots increases further: • with increasing age; • if you smoke.; • if you are overweight; • if you have high blood pressure; • if a close relative has had a heart attack or stroke at a young age; • if you have a high level of fat in your blood (cholesterol or triglycerides); • if you get migraines; • if you have a problem with your heart (valve disorder, disturbance of the rhythm).	Stop taking tablets and see your doctor immediately if you notice possible signs of a blood clot, such as: • an unusual sudden cough; • breathlessness; • any unusual, severe, or long-lasting headache or worsening of migraine; • partial or complete loss of vision, or double vision; • slurring or speech disability; • sudden changes to your hearing, sense of smell, or taste; • dizziness or fainting; • weakness or numbness in any part of your body; • severe pain in your abdomen; • severe pain or swelling in either of your legs.
Liver disorders	CPA/EE should not be used if you have liver problems. Acute or chronic disturbances of liver function may occure. Therapy with CPA/EE should be stopped immediately if yellowness, inflammation of the liver or itching of the whole body occurs.	When using CPA/EE, you should visit your doctor regularly for a physical examination.
Important potential risks		
Breast cancer	CPA/EE should not be used if if you have or have ever had breast cancer. Breast cancer has been diagnosed slightly more often in women using oral contraceptives than in women of the same age who do not use oral contraceptives. It is not known whether the difference is caused by the use of oral contraceptives. It is possible that the women using oral contraceptives were examined more often and that breast cancer was therefore diagnosed earlier.	Before starting treatment with CPA/EE you should inform your doctor if you have or ever had breast cancer. When using CPA/EE, you should visit your doctor regularly for a physical examination.
Cervical cancer	Cervical cancer has been reported to occur more often in women who have used oral contraceptives for a long time. This finding is not necessarily caused by oral contraceptives but may be related to sexual behaviour and other factors.	When using CPA/EE, you should visit your doctor regularly for a physical examination.

Risk	What is known	Preventability
Benign and malignant liver tumors	CPA/EE should not be used if you have or have ever had a liver tumour (benign or malignant). Rarely, benign liver tumours, and even more rarely, malign liver tumours have been found in users of oral contraceptives. Liver tumours may cause internal bleeding.	Before starting treatment with CPA/EE you should inform your doctor if you have or ever had liver tumour. Contact your doctor immediately if you have severe abdominal pain. When using CPA/EE, you should visit your doctor regularly for a physical examination.
Insulin resistance/ decreased glucose tolerance	Although combined oral contraceptives may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using combined oral contraceptives.	Diabetic women should be carefully observed while taking CPA/EE.
Chronic inflammatory bowel disease (Crohn's disease and ulcerative colitis)	Worsening of Crohn´s disease and ulcerative colitis has been reported during combined oral contraceptive use.	Before starting treatment with CPA/EE you should inform your doctor if you have Crohn's disease or ulcerous colitis (chronic inflammatory bowel disease).
Effect on hereditary angioedema	In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.	Before starting treatment with CPA/EE you should inform your doctor if you have if you are allergic to cyproterone acetate, ethinylestradiol or any of the other ingredients of this medicine.
Inflamation of the pancreas (in patients with a high lipid concentration)	CPA/EE should not be used if you have or have ever had pancreatitis with a high lipid concentration of the blood.	Before starting treatment with CPA/EE you should inform your doctor if you have or ever had pancreatitis with a high lipid concentration of the blood.
Increased blood pressure	CPA/EE should not be used if you have high blood pressure.	Before starting treatment with CPA/EE you should inform your doctor if you have high blood pressure. When using oral contraceptives, you should visit your doctor regularly for a physical examination.

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.

These additional risk minimisation measures are for the following risks:

Blood clots in veins and Blood clots in arteries

Risk minimisation measures • **Direct Healthcare Professional Communication (DHPC)** • **Educational materials** o **Prescribers checklist** o **Patient information card for HCP handout**
Objective and rationale
– DHPC: To communicate the outcome of the review of CPA/EE and to highlight the risk of the thromboembolic events. – Educational material will be issued to inform the professionals and patients on the risks of thromboembolism.
Proposed action
• DHPC: "Dear HCP" letter was provided to healthcare professionals in January 2014. • Educational material: *Prescribers checklist* o Helathcare professionals should use the prescriber's checklist in conjunction with the summary of prodict characteristics, at regular intervals, to minimise the risk of venous thromboembolic events. Going through the prescriber's checklist indications for use, contraindications, and risk factors for developing blood clots should be checked and discussed with the patient. *Patient information card* o Patient information card serves as a reminder to the patients' about the risk factors, symptoms, and precautions in regards to developing blood clots

VI.2.6 Planned post authorisation development plan

Not applicable.

Studies which are a condition of the marketing authorisation (if applicable)

An observational Post-Authorisation Safety Study to evaluate physician knowledge of safety and safe use information for CPA/EE in Europe, and a Drug Utilization Study on the prescribing indications for CPA/EE are conditions of the marketing authorisation.

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

Table 3. Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
Not applicable.	Not applicable.	Not applicable.	Not applicable.