Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Benign and malignant liver tumours	SmPC lists contraindication for patients with benign or malignant liver tumours or a known history of such tumours. Extensive wording provided in SmPC section "Special warnings and precautions for use" describing the risk, including mention of potential complications and recommendation to consider the differential diagnosis in case of occurrence of corresponding signs or symptoms.	None proposed
Insulin resistance	SmPC provides information in section "Special warnings and precautions for use" that treatment may have an effect on peripheral insulin resistance and glucose tolerance, that there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs, such as CPA/EE, and that diabetic women should be carefully observed while taking COCs.	None proposed
Crohn's Disease and ulcerative colitis	SmPC provides information in section "Special warnings and precautions for use" that ulcerative colitis and Crohn's disease have been associated with COC use.	None proposed
Pancreatitis (hypertriglyceridemia associated)	SmPC section "Special warnings and precautions for use" provides information that women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis.	None proposed
Increase in onset or deterioration of depression	SmPC section "Undesirable effects" provides information that depressed mood and mood changes are reported in COC users	None proposed
Potential for off-label use	Label harmonization by the EU wide implementation of the indication wording adopted by PRAC: "*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, <product name> should only be used after topical therapy or systemic antibiotic treatments have failed. Since <product name> is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives (see section 4.3)*".	Educational material • Prescribers checklist • Patient information card for HCP handout

VI.2 Elements for a public summary

VI.2.1 Overview of disease epidemiology

Acne is a common skin condition characterized by areas of skin with seborrhoea (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 such as the face, the upper part of the chest, and the back. Severe acne is inflammatory, but acne can also manifest in non-inflammatory 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.

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

IMPORTANT IDENTIFIED RISKS		
Risk	**What is known**	**Preventability**
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 the patient smokes; • if the patient's close relative has had	If any of the stated risk factors applies to the patient, it is important to tell the doctor that the patient is 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 the patient is older than 35 years. The patient should stop taking tablets and see the doctor immediately if possible signs of a blood clot are noticed, 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 hearing, sense of

IMPORTANT IDENTIFIED RISKS		
Risk	**What is known**	**Preventability**
	a blood clot in the leg, lung or other organ at a young age; • if the woman is overweight, must have an operation or is off her feet for a long time because of an injury or illness; • if the patient has leg in a plaster cast.	smell, or taste; • dizziness or fainting; • weakness or numbness in any part of the body; • severe pain in the abdomen; • severe pain or swelling in either of the patient's 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 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 the patient smokes; • if the patient is overweight; • if the patient has high blood pressure; • if the patient's close relative has had a heart attack or stroke at a young age; • if the patient has a high level of fat in the blood (cholesterol or triglycerides); • if the patient gets migraines; • if the patient has a problem with the heart (valve disorder, disturbance of the rhythm).	If any of the stated risk factors applies to the patient, it is important to tell the doctor that the patient is 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 the patient is older than 35 years. The patient should stop taking tablets and see the doctor immediately if possible signs of a blood clot are noticed, 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 hearing, sense of smell, or taste; • dizziness or fainting; • weakness or numbness in any part of the body; • severe pain in the abdomen; • severe pain or swelling in either of the patient's legs.
Liver disorders	CPA/EE should not be used if the patient has liver problems. Acute or chronic disturbances of liver function may occur. 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, the patient should visit the doctor regularly for a physical examination.

IMPORTANT IDENTIFIED RISKS		
Risk	**What is known**	**Preventability**
Increased blood pressure	CPA/EE should not be used if the patient has high blood pressure.	Before starting treatment with CPA/EE the woman should inform the doctor if she has high blood pressure. When using oral contraceptives, the patient should visit the doctor regularly for a physical examination.
Effect on hereditary angioedema	In women with hereditary angioedema, exogenous oestrogens may induce or exacerbate symptoms of angioedema.	Before starting treatment with CPA/EE the woman should inform the doctor if she is allergic to cyproterone acetate, ethinylestradiol or any of the other ingredients of this medicine.

IMPORTANT POTENTIAL RISKS	
Risk	**What is known (including reason why it is considered a potential risk)**
Breast cancer	CPA/EE should not be used if the patient has or has 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.
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.
Benign and malignant liver tumours	CPA/EE should not be used if the patient has or has 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.
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.
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.
Inflammation of the pancreas (in patients with a high lipid concentration)	CPA/EE should not be used if the patient has or has ever had pancreatitis with a high lipid concentration of the blood.
Increase in onset or deterioration of depression	CPA/EE should be stopped if the patient develops severe depression.

IMPORTANT POTENTIAL RISKS	
Risk	**What is known (including reason why it is considered a potential risk)**
Use in unapproved indications (Off-label use)	CYP/EE is 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 the patient if the patient's doctor considers that treatment with a hormonal contraceptive is appropriate. The woman should only take CYP/EE if her 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

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals (HCP) 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 Patient Information Leaflet (PIL). The measures in these documents are known as routine risk minimisation measures.

This medicine has special conditions and restrictions for its safe and effective use (additional 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: 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 Healthcare professionals should use the prescriber's checklist in conjunction with the summary of product 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

List of studies in post authorisation development plan

Study / activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final reports (planned or actual)
PASS, pursuant to Article 107i of Directive 2001/83/EC, European Commission decision dated 25 July 2013 (non-interventional, category 3)	To evaluate the effectiveness of the risk minimisation activities.	Venous thromboembolic events; Arterial thromboembolic events (incl. cardiovascular disease and stroke)	Planned	Planned for 30 June 2016
DUS (Survey), pursuant to Article 107i of Directive 2001/83/EC, European Commission decision dated 25 July 2013 (non-interventional, category 3)	To characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription.	Potential for off-label use. Responsible prescribing in accordance with the harmonized label adopted by PRAC across EU countries for CPA/EE (indication and contraindication for concomitant hormonal contraceptive use).	Started	Planned for 31 May 2016
DUS (Database), pursuant to Article 107i of Directive 2001/83/EC, European Commission decision dated 25 July 2013 (non-interventional, category 3)	To characterise prescribing practices for the medicinal products during typical clinical use in representative groups of prescribers and to assess main reasons for prescription.	Potential for off-label use. Responsible prescribing in accordance with the harmonized label adopted by PRAC across EU countries for CPA/EE (indication and contraindication for concomitant hormonal contraceptive use).	Planned	Planned for March 2016

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 (survey and database) 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: Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.2	29 June 2015	Based on the request from the Dutch Agency (MEB request, dated Nov 2014), the important potential risk "Potential for off-label use" is included in all relevant parts of the RMP.	Additional amendments: Milestones changed.