Part VI: Summary of the risk management plan

Summary of risk management plan for Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets and Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets

This is a summary of the risk management plan (RMP) for Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets and Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets. The RMP details important risks of Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets and Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets, how these risks can be minimised, and how more information will be obtained about Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets and Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets's risks and uncertainties (missing information).
Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets and Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets's summary of product characteristics (SmPC) and the package leaflets give essential information to healthcare professionals and patients on how Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets and Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets should be used.
Important new concerns or changes to the current ones will be included in updates of Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets and Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets's RMP.

I. The medicine and what it is used for

Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets and Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets are authorised for mainly hormonal contraception (see SmPC for the full indications). These contain Chlormadinone acetate and ethinylestradiol as the active substances and these are given by orally.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets and Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets, together with measures to minimise such risks and the proposed studies for learning more about Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets and Chlormadinone

acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets's risks, are outlined below.
Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets and Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets, these measures are supplemented with *additional risk minimisation measures* mentioned under relevant important risks, below.
In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets and Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets and Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Summary of safety concerns	
Important identified risks	#3. Venous thromboembolism #4. Arterial thromboembolism
Important potential risks	#2. Meningioma
Missing information	None

II.B Summary of important risks

Important Identified Risk #1. Venous thromboembolism	
Evidence for linking the risk to the medicine	Increased VTE risk is an established class effect of COCs. The results of the investigations with CMA/EE demonstrate that CMA/EE has a small effect on the haemostatic system: the procoagulatory activity increased (slightly increased prothrombin fragment 1+2), the anticoagulatory activity changed (slightly increased protein C activity, decreased protein S activity and slightly decreased AT III activity) and the fibrinolytic system was activated (slightly increased concentration of D-dimer and fibrinogen degradation products). The changes may be interpreted as the expression of the balanced level regulation of the haemostatic system. They were as expected and there is no evidence of an increased risk of thromboembolism. Although the changes do not appear to have any clinical consequence, as for other oral contraceptives, the use of CMA/EE is not recommended in the presence of, or if there is a history of, arterial or venous thrombosis, for example deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), stroke or if there are prodromal signs of thrombosis, for example, transient ischemic attack or angina pectoris. During the clinical development programme of CMA/EE 2mg/0.03mg, a total of over 47 238 cycles in 1855 subjects was investigated. In total, there were 5 thromboembolic events (in 1 woman without an additional risk factor, and in 2 women with at least possible additional risk factors). A 6-cycle PMS trial of CMA obtained data on 21 820 women comprising 125 634 cycles. There was a report of 1 woman with a pulmonary embolism and a report of 1 woman with a superficial venous thrombosis of a leg vein. Therefore, the much larger exposure in this PMS trial of CMA compared to the pre-marketing clinical trials gives an incidence for venous thrombosis of 2.1 per 10 000 [95% CI 0.25;7.47] woman-years at risk, a result which is comparable to values published with other oral contraceptives. In a 12 cycle PMS trial with 2620 patients (29 262 cycles in total), 1 venous thromboembolic event was documented. The rate of venous thromboembolism per 10000 women years was determined as 4.4 (95% confidence limit [1.6076, 10.2296]). In another PMS (KUSS), which included 21,352 women over 13 cycles (85,430 cycles in total), there was a report of 1 woman with a venous thromboembolic event (thrombosis of the left lower leg). The rate of venous thromboembolism per 10,000 women years was determined as 1.5 (95% confidence limit [0.0385, 8.4782]).
Risk factors and risk groups	VTE is a multifactorial disorder that arises as a result of genetic and environmental factors that interact. Several reasons may be accounted for the occurrence of thromboembolism including hereditary (e.g., Factor V Leiden mutation, protein C deficiency) or acquired (e.g., immobilisation following a trauma, surgery; burns, toxins, varicose veins, obesity, tumour, pregnancy, cardiac diseases, some medicines changing the balance between

<table>
<tr><td></td><td>procoagulant and anticoagulant factors involved in the blood coagulation cascade).

It has been shown that risk of VTE is highest during the first year a woman starts hormonal contraceptives or when she re-starts after a period of non-use of at least one month. After an initially higher risk during the first year of use, the risk decreases to a constant lower level. The risk of VTE is also higher in the presence of intrinsic risk factors. The risk factors are summarized in the table below.

Risk factors forVTE
<table><tr><th>Acquired</th><th>Hereditary</th><th>Mixed/Unknown</th></tr><tr><td>Age>40
Previous thrombosis
Immobilization
Major surgery
Orthopaedic surgery
Malignancy
COCs
HRT
Pregnancy/puerperium
Antiphospholipid syndrome
Myeloproliferative disorders
Polycythaemia vera</td><td>ATIII deficiency
Protein C deficiency
Protein S deficiency
Factor V Leiden (FVL)
Prothrombin 20210
Dysfibrinogenaemia
Non-O blood group</td><td>Hyperhomocysteinaemia
Resistance to activated Protein C
High levels of Factor VIII + vWF</td></tr></table>COC: combined oral contraceptives; HRT: hormone replacement therapy; ATIII: antithrombin III; vWF: von Willebrand factor.</td></tr>
<tr><td>Risk minimisation measures</td><td><u>Routine risk minimisation measures:</u>

SmPC section 4.1, 4.3, 4.4, 4.6 and 4.8
PL section 2 and 4
Prescription only medicine.

<u>Additional risk minimisation measures:</u>

No additional risk minimisation measures are proposed.</td></tr>
<tr><td>Additional pharmacovigilance activities</td><td><u>Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:</u>

Targeted follow-up form

<u>Additional pharmacovigilance activities:</u>

None.</td></tr>
</table>

Important Identified Risk #2. Arterial thromboembolism	
Evidence for linking the risk to the medicine	Increased risk of arterial thromboembolism (ATE) is an established class effect of COCs. According to the clinical trials with CMA/EE, the cumulative number of arterial thromboembolism cases is 5. Based on a patient exposure of about 4 844 205 WY for the entire authorization period, a corresponding arterial thromboembolism reporting rate per 100 000 WY of 0.10 is derived. COC users with hypertension appear to be at increased risk of myocardial infarction and stroke relative to users without hypertension according to the search of MedLine and Premedline databases. COC users with migraine appear to be at increased risk of stroke relative to nonusers with migraine. This should be taken into account recommending contraceptive methods to patients with hypertension or migraine. A multicenter, population-based, case-control study (called risk of arterial thrombosis in relation to oral contraceptives (RATIO study) was carried out to assess the risk of stroke in woman using any type of oral contraceptives versus no-oral contraceptives users. Data of 203 women with ischemic stroke and 925 control women were analysed. The results showed that the use of any type of oral contraceptives increased the risk of ischemic stroke. A 2-fold increased stroke risk compared with no use was found. The results did not show different effect between brands containing second- or third-generation progestogens. The authors did not find a differential effect according to oestrogen dose. The risk of oral contraceptives was even more elevated in combination with the presence of smoking, hypertension, hypercholesterolaemia or obesity. A meta-analysis was published on ischaemic stroke risk with oral contraceptives. The authors summarised the results of 73 studies published from January 1960 through November 1999. Current oral contraceptive use was associated with increased risk of ischaemic stroke (RR, 2.75; 95%CI, 2.24-3.38). Smaller oestrogen dosages were associated with lower risk, but risk was significantly elevated for all dosages. However, the absolute increase in stroke risk is expected to be small since incidence is very low in the population using oral contraceptives. In the MICA case-control study involving 2176 women, the relative risk (RR) of MI was not significantly increased among women taking oral contraceptives. After adjustment for cardiovascular risk factors, these RRs were 1.1 for second-generation contraceptives (levonorgestrel or norethisterone + EE) and 1.78 for third-generation contraceptives (gestodene or desogestrel + EE). The World Health Organisation (WHO) case-control study of 1309 women living in Europe or in developing countries showed that the relative risk of MI associated with oral contraceptive use was 1.1 among non-smoking

	women with normal blood pressure. However, this study also showed a strong increase in the risk of MI in women with risk factors who used oral contraception, namely non-smokers with hypertension, smokers with normal blood pressure and smokers with hypertension.
Risk factors and risk groups	ATE is a multifactorial disorder that arises as a result of genetic and environmental factors that interact. The risk of arterial thromboembolic complications or of a cerebrovascular accident in COC users increases with the age, smoking (women over 35 years should be strongly advised not to smoke if they wish to use a COC), dyslipoproteinaemia, hypertension, obesity (body mass index over 30 kg/m^2) or a positive family history (arterial thromboembolism ever in a sibling or parent at relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any COC use. Valvular heart disease and atrial fibrillation are also well-known risk factors. The presence of one serious risk factor or multiple risk factors for venous or arterial disease, respectively, can also constitute a contraindication.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3, 4,4 and 4.8 PL section 2 and 4 Prescription only medicine. Additional risk minimisation measures: No additional risk minimisation measures are proposed.
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up form Additional pharmacovigilance activities: None.

Important Potential Risk #1. Meningioma	
Evidence for linking the risk to the medicine	The risk of meningioma associated with chlormadinone acetate (CMA)-containing medicinal products, an increase of case reports of meningiomas was observed in France in 2019 and further risk minimisation measures (RMMs) were implemented at national level, including amendments of the PI of all chlormadinone 5 and 10 mg containing products to reflect the risk of meningioma. To further clarify the relationship between chlormadinone acetate (or nomegestrol acetate) and the risk of meningioma, two pharmacoepidemiological studies have been conducted by the French group, EPI-PHARE, based on data from SNDS (Système national des données de santé - French National Health Data System). Results suggested

	an increased risk of meningiomas depending on dose and duration of treatment with chlormadinone acetate (or nomegestrol acetate). On 22 September 2021, the French national competent authority (Agence nationale de sécurité du médicament et des produits de santé, ANSM) therefore triggered a referral under Article 31 of Directive 2001/83/EC resulting from pharmacovigilance data (EMEA/H/A-31/1510), and requested the PRAC to assess the impact of the above concerns on the benefit-risk balance of chlormadinone acetate-containing products (and nomegestrol-acetate-containing products) and to issue a recommendation on whether the relevant marketing authorisations should be maintained, varied, suspended or revoked. According to the outcome of the procedure, although there is no increased risk specifically in association to the use of low dose products could be identified, PRAC considered that a warning on meningioma should be reflected in the PI of low dose CMA (1- 2 mg)- o[r NOMAC (2.5 mg)]-containing products, and that the use of these products should be contraindicated in patients with meningioma or history of meningioma.
Risk factors and risk groups	The risk factors of meningioma include - Exposure to ionizing radiation: it increases the risk from six-fold to ten-fold. It includes radiation therapy for malignancies (for primary malignancies of the central nervous system and head and neck region) but also incidental radiation, like X-ray, CT scan or atomic bomb exposure. - Genetic predisposition: Approximately one-half of individuals with Neurofibromatosis type 2 (NF2) have meningiomas, and multiple meningiomas are often present. In some patient with schwannomatosis, meningiomas are detected. - Family history: based on a study by Malmer et al. meningioma diagnosis conferred a two-fold increase in meningioma risk to first degree relatives. - Hormones: due to its female predominance (having a peak during reproductive years) hormonal factors have been suggested in the development of meningioma. According to a meta-analysis of six prospective case-control studies that included over 1600 meningioma cases, significantly increased risks for all central nervous system tumours (glioma and meningioma) were found in users of estrogen-only [1.35 (1.22–1.49), 1.23 (1.06–1.42) and 1.31 (1.20–1.43), respectively] but not estrogen-progestin hormone replacement therapy [1.09 (0.99–1.19), 0.92 (0.78–1.08) and 1.05 (0.95–1.16), respectively]. Progesterone receptors have been described in meningiomas. High dose of the anti-androgenous cyproterone acetate is known to increase the risk of meningioma.

	- Breast cancer: A moderately increased risk of meningioma has been reported in women with breast cancer.
Risk minimisation measures	Routine risk minimisation measures: SmPC section 4.3 and 4.4 PL section 2 Prescription only medicine. Additional risk minimisation measures: Direct healthcare professional communication
Additional pharmacovigilance activities	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: Targeted follow-up form Additional pharmacovigilance activities: None

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets or Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg film-coated tablets, Chlormadinone acetate + Ethinylestradiol 2 mg/0.03 mg and placebo film-coated tablets or Chlormadinone acetate + Ethinylestradiol 1 mg/2 mg + 0.05 mg/0.05 mg film-coated tablets.