DIANE®-35
(Cyproterone acetate + ethinylestradiol)
EU Risk Management Plan

Part VI – Summary of Activities in the Risk Management Plan by Product

1. Summary of Risk Management Plan for Diane®-35

This is a summary of the risk management plan (RMP) for Diane®-35. The RMP details important risks of Diane®-35, how these risks can be minimised, and how more information will be obtained about Diane's®-35 risks and uncertainties (missing information).

Diane's®-35 summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Diane®-35 should be used.

2. The Medicine and what it is used for

Diane®-35 is authorised for treatment of moderate to severe acne related to androgen-sensitivity (with or without seborrhoea) and/or hirsutism, in women of reproductive age (see SmPC for the full indication). For the treatment of acne, Diane®-35 should only be used after topical therapy or systemic antibiotic treatments have failed. Since Diane®-35 is also a hormonal contraceptive, it should not be used in combination with other hormonal contraceptives (SmPC section 4.3). It contains the synthetic estrogen ethinylestradiol (EE) in combination with the antiandrogenic progestogen cyproterone acetate (CPA) as the active substance and it is taken orally.

3. Risks Associated with the Medicine and Activities to Minimise or further Characterise the Risks

Important risks of Diane®-35, together with measures to minimise such risks and the proposed studies for learning more about Diane's®-35 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 Diane®-35, 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 PBRER/PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

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3.1 List of Important Risks and Missing Information

Important risks of Diane®-35 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 Diane®-35. 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).

Table 1: Summary of safety concerns

Important identified risks	• Venous thromboembolic events • Arterial thromboembolic events (incl. cardiovascular disease and stroke)
Important potential risks	None
Missing information	None

3.2 Summary of Important Risks

Important identified risks: Venous thromboembolic events

Evidence for linking the risks to the medicine	Increased VTE risk is an established class effect in users of oestrogen-progestogen combination products, such as COCs or Diane®-35.
Risk factors and risk groups	Established risk factors for VTE in women taking oestrogen-progestogen combination products, such as COCs or Diane®-35, include age, obesity (body mass index [BMI]>30 kg/m^2), positive family history (VTE in first degree relative), prolonged immobilization, major surgery, any surgery to the legs, major trauma, long-haul flights, medical conditions associated with VTE – cancer, systemic lupus erythematosus, haemolytic uremic syndrome, chronic inflammatory bowel disease and sickle cell disease, smoking, dyslipoproteinemia, and hereditary predisposition. For example, some pro-thrombotic mutations (e.g. Factor V Leiden or G20210A prothrombin mutation) are known genetic risk factors associated with an increased VTE risk. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors.
Risk minimisation measures	**Routine risk minimisation measures:** Routine risk communication for informed decision-making:

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Important identified risks: Venous thromboembolic events

	• SmPC sections 4.2, 4.3, 4.4 and 4.8 Routine risk communication recommending specific clinical measures to address the risk: • SmPC section 4.3 and 4.4 o Concomitant use of other hormonal contraceptives is strictly contraindicated. o Medical history and physical examination are recommended, and treatment discontinuation is advised at first signs of thrombosis or blood clots. Other routine risk minimisation measures beyond the Product Information: • Cycle packs. • Prescription-only medicine. **Additional risk minimization measures:** Educational material for prescribers including Patient Information Card and Prescribers Checklist focusing on the risk factors and contraindications of VTE/ATE
Additional pharmacovigilance activities	None

BMI: Body mass index; COC: Combined oral contraceptive; SmPC: Summary of Product Characteristics; VTE: Venous thromboembolic events

Important identified risks: Arterial thromboembolic events (incl. cardiovascular disease and stroke)

Evidence for linking the risks to the medicine	Increased risk of myocardial infarction (MI) and ischemic stroke is an established class effect in users of oestrogen-progestogen combination products, such as COCs or Diane®-35.
Risk factors and risk groups	Established risk factors for arterial thrombotic/thromboembolic events in women taking COCs include age, obesity, a positive family history, smoking, dyslipoproteinemia, hypertension, migraine, valvular heart disease, and atrial fibrillation. Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, systemic lupus erythematosus, haemolytic uremic syndrome, chronic inflammatory bowel disease (Crohn's disease [CD] or ulcerative colitis [UC]) and sickle cell disease. Biochemical factors that may be indicative of hereditary or acquired predisposition for arterial thrombosis include APC resistance, hyperhomocysteinemia AT III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant). Duration of COC use has not been proven to be important in relation to the risk of MI, and no evidence was found that long duration of COC use adversely affects long-term risk of mortality due to MI [1].

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Important identified risks: Arterial thromboembolic events (incl. cardiovascular disease and stroke)	

Risk minimisation measures	**Routine risk minimisation measures:**
	Routine risk communication for informed decision-making:
	• SmPC sections 4.2, 4.3, 4.4 and 4.8
	Routine risk communication recommending specific clinical measures to address the risk:
	• SmPC section 4.3 and 4.4
	  ○ Concomitant use of other hormonal contraceptives is strictly contraindicated.
	  ○ Medical history and physical examination are recommended, and treatment discontinuation is advised at first signs of thrombosis or blood clots.
	Other routine risk minimisation measures beyond the Product Information:
	• Cycle packs.
	• Prescription-only medicine.
	Additional risk minimization measures:
	Educational material for prescribers including Patient Information Card and Prescribers Checklist focusing on the risk factors and contraindications of VTE/ATE

Additional pharmacovigilance activities	None

APC: Activated protein C; CD: Crohn's disease; COC: Combined oral contraceptive; MI: myocardial infarction; SmPC: Summary of Product Characteristics; UC: Ulcerative colitis.

3.3 Post-authorisation Development Plan

3.3.1 Studies which are conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Diane®-35.

3.3.2 Other Studies in Post-authorisation Development Plan

Not applicable.

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References

1. Tanis BC, Rosendaal FR. Venous and arterial thrombosis during oral contraceptive use: risks and risk factors. Semin Vasc Med. 2003;3(1):69-84.