Summary of the Swiss Risk Management Plan (RMP)

Name of the medicinal product:	Drovelis (Estetrol/Drospirenone 14.2 mg/3 mg, film-coated tablets)
Active substance:	Estetrol/Drospirenone
Version number of the current RMP:	1.0
Name of the marketing authorisation holder:	Gedeon Richter (Schweiz) AG
Data lock point for the RMP:	18 November 2022
Date of RMP:	18 January 2023

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary of "Drovelis (Estetrol/Drospirenone 14.2 mg/3 mg, film-coated tablets)", is a concise document and does not claim to be exhaustive. As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorization. Please note that the reference document which is valid and relevant for the effective and safe use of "Drovelis" in Switzerland is the "Arzneimittelinformation/ Information sur le médicament" (see www.swissmedic.ch) approved and authorized by Swissmedic. "Gedeon Richter (Schweiz) AG" is fully responsible for the accuracy and correctness of the content of the published summary RMP of "Drovelis".

Part VI: Summary of the risk management plan

Summary of risk management plan for Drovelis (estetrol/drospirenone)
This is a summary of the risk management plan (RMP) for Drovelis. The RMP details important risks of Drovelis, how these risks can be minimised, and how more information will be obtained about Drovelis 's risks and uncertainties (missing information).

Drovelis's SmPC and its package leaflet give essential information to healthcare professionals and patients on how Drovelis should be used.

This summary of the RMP for Drovelis should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of Drovelis's RMP.

I. The medicine and what it is used for

Drovelis is authorised for oral contraception. It contains estetrol and drospirenone as the active substances.

Further information about the evaluation of Drovelis's benefits can be found in Drovelis's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

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

Important risks of Drovelis, together with measures to minimise such risks and the proposed studies for learning more about Drovelis'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 Drovelis, 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*.

If important information that may affect the safe use of Drovelis is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Drovelis 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 Drovelis. 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);

List of important risks and missing information	
Important identified risks	Venous thromboembolism
	Arterial thromboembolism
Important potential risks	None
Missing information	Exposure during pregnancy

II.B Summary of important risks

Identified risk: Venous thromboembolism (VTE)	
Evidence for linking the risk to the medicine	The increased risk of VTE (blood clots in the veins) in women taking combined oral contraceptives (COCs) has been known for many years and is very small. The risk of blood clots in the veins varies between COCs, depending on the dose of estrogen and on the type of progestin (a hormone) they contain, and ranges from 5 to 12 cases of blood clots per 10,000 women who use them for a year. This compares with 2 cases of blood clots in the veins each year per 10,000 women who are not using COCs (EMA/35464/2014). Blood clots in the veins of the legs may lead to a painful swelling of the legs (deep vein thrombosis [DVT]) and very occasionally to life threatening or fatal events if the clots are dislodged and travel to the lungs (pulmonary embolism [PE]). In clinical studies investigating the recommended dose of Drovelis in 3790 women, there was one report of deep venous thrombosis and another report of superficial thrombophlebitis (blood clot in vein near the surface of the skin) but there were no cases of pulmonary embolism. As a risk of VTE has been identified with other COCs, the possibility of VTE events occurring during treatment with Drovelis cannot be ruled out.
Risk factors and risk groups	Risk factors for VTE include: obesity (BMI >30 Kgm^2), prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma, positive family history (VTE ever in a sibling or parent especially at a relatively early age e.g. before 50 years), increasing age (particularly above 35 years) and presence of other medical conditions associated with VTE (e.g. cancer, systemic lupus erythematosus, haemolytic uremic syndrome, chronic inflammatory bowel disease [Crohn's disease or ulcerative colitis)] and sickle cell disease).

Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.1, 4.3, 4.4,4.6, 4.8* *PL section 2, 4* Additional risk minimisation measures: *Educational materials:* **Important information for women:** *Information card for women* **Physician educational material:** *Checklist for prescribers*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Prospective non-interventional comparative cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Identified risk: Arterial thromboembolism (ATE)	
Evidence for linking the risk to the medicine	The small increased risk of ATE (blood clots in the arteries) in women taking COCs has been known for many years and is very low. In the completed clinical studies, no ATE events were observed. However, as a risk of blood clots in the arteries has been identified with other COCs, the possibility of ATE events occurring during treatment with Drovelis cannot be ruled out. Along with other factors, ATE can potentially cause a cerebrovascular accident (stroke) or a myocardial infarction (heart attack). In the clinical studies, no strokes and no heart attacks were observed.
Risk factors and risk groups	Risk factors for arterial ATE include: increasing age (particularly above 35 years), smoking, hypertension, obesity (BMI >30 Kgm^2), positive family history (ATE ever in a sibling or parent especially at relatively early age e.g. below 50 years), migraines and other medical conditions associated with adverse vascular events (e.g. diabetes mellitus, hyperhomocysteinemia, valvular heart disease and atrial fibrillation, dyslipoproteinemia and systemic lupus erythematosus).
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.3, 4.4, 4.8* *PL section 2, 4* Additional risk minimisation measures: *Educational materials:* **Important information for women:** *Information card for women* **Physician educational material:**

	Checklist for prescribers
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Prospective non-interventional comparative cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

Missing information: Exposure during pregnancy	
Risk minimisation measures	Routine risk minimisation measures: *SmPC section 4.6, 5.3* *PL section 2* Additional risk minimisation measures: *None*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: *Prospective non-interventional comparative cohort study* See section II.C of this summary for an overview of the post-authorisation development plan.

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 Drovelis.

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

Study short name and title:

International Active Surveillance Study: Native Estrogen Estetrol (E4) Safety Study (INAS-NEES)

Purpose of the study:

The COC containing E4 and drospirenone (DRSP) (E4/DRSP) is a novel oral contraceptive containing a fixed dose of E4 (14.2 mg) and DRSP (3 mg). E4 is a natural oestrogen only produced during pregnancy by the foetal liver. When combined with the progestin DRSP, ovulation is inhibited. The E4/DRSP combination may have less impact on hepatic and haemostasis parameters in comparison to combinations of ethinyl estradiol (EE) and levonorgestrel (LNG) or EE and DRSP. Yet, it is unknown whether this regimen has an impact on the cardiovascular risk associated with the use of hormonal contraceptives.

The primary objective is to characterise and compare the risks of E4/DRSP with EE/LNG, in a study population that is representative of the actual users of these preparations. This includes an estimate of the absolute risk of rare serious adverse outcomes. The main clinical outcome of interest is VTE, i.e., DVT of the lower extremities and PE. Secondary objectives include measuring the occurrence of unintended pregnancy, assessing the risk of ATE, describing the drug utilisation pattern, describing the baseline risk profile for VTE and ATE, and investigating outcomes associated with foetal exposure to E4/DRSP.