Date: 21 June 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Drovelis

International Non-Proprietary Name: drospirenone, estetrol monohydrate

Pharmaceutical Form: coated tablet

Dosage Strength(s): 3 mg drospirenone /
15 mg estetrol monohydrate corresp. to 14.2 mg estetrol

Route(s) of Administration: oral

Marketing Authorisation Holder: Gedeon Richter (Schweiz) AG

Marketing Authorisation No.: 68228

Decision and Decision Date: approved on 5 May 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC_{0-24h}	Area under the plasma concentration-time curve for the 24-hour dosing interval
BMI	Body mass index
CHC	Combined hormonal contraceptives
CI	Confidence interval
C_{max}	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DRSP	Drospirenone
E2	Estradiol
E4	Estetrol
ECG	Electrocardiogram
ED_{50}	Median effective dose
EE	Ethinylestradiol
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
EV	Estradiol valerate
FDA	U.S. Food and Drug Administration
FSH	Follicle-stimulating hormone
GLP	Good Laboratory Practice
HPLC	High performance liquid chromatography
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International non-proprietary name
ITT	Intention-to-treat
IV	Intravenous
LDH	L-lactate dehydrogenase
LH	Luteinising hormone
LNG	Levonorgestrel
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MPR	Metabolite/parent ratio
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PASS	Post-Authorisation Safety Study
PBPK	Physiology-based pharmacokinetics
PD	Pharmacodynamics
PI	Pearl index
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics

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PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)
PSUR	Periodic Safety Update report
PVC	Polyvinyl chloride
QD	Every day
RMP	Risk Management Plan
SAE	Serious adverse event
SGGG	Swiss Society for Gynaecology and Obstetrics
SHBG	Sex hormone-binding globulin
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
T_{max}	Time to reach C_{max}
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
UGT	Uridine 5'-diphospho-glucuronosyltransferase
VTE	Venous thromboembolism

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance estetrol of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

Oral contraception.

The decision to prescribe Drovelis should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Drovelis compares with other combined hormonal contraceptives (CHCs).

2.2.2 Approved Indication

Oral contraception in women aged 18 and over.

The decision to prescribe Drovelis should take into consideration the individual woman's current risk factors, particularly with regard to venous thromboembolism (VTE). The relative risk of VTE with Drovelis should also be compared with that of other combined hormonal contraceptives (CHCs) (see "Contraindications" and "Warnings and precautions").

2.2.3 Requested Dosage

Summary of the applied standard dosage:

The tablets must be taken every day at about the same time, if necessary with a little liquid, in the order shown on the blister pack. Stickers marked with the 7 days of the week are provided, and the two relevant weekday stickers should be stuck on the tablet blister as an indicator of when the first tablet has been taken. The tablets are taken continuously. One tablet is to be taken daily for 28 consecutive days.

2.2.4 Approved Dosage

(See appendix)

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2.2.5 Regulatory History (Milestones)

Application	12 October 2020
Formal control completed	8 December 2020
List of Questions (LoQ)	25 March 2021
Answers to LoQ	21 June 2021
Predecision	4 October 2021
Answers to Predecision	24 November 2021
Labelling corrections	17 February 2022
Answers to Labelling corrections	23 February 2022
Final Decision	5 May 2022
Decision	approval

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3 Medical Context

There are two forms of hormonal contraception: combined hormonal contraceptives (CHCs) and progestin-only products. CHCs derive their contraceptive efficacy largely from their progestogen component. Although the estrogen component also contributes to efficacy, its primary role is to stabilise the menstrual cycle.

The primary mechanism of action of CHCs is ovulation inhibition. Other mechanisms also contribute to their contraceptive efficacy, including changes to the endometrium and cervical mucus. CHCs have the desirable side effect of regularising the menstrual cycle and reducing bleeding intensity. They can often also reduce dysmenorrhoea.

A large number of CHCs are available in Switzerland. The progestogens contained in them vary in terms of partial effects (e.g. androgenic or antiandrogenic). These effects determine the individual desirable – in addition to contraception – and undesirable effects of the preparation in question.

Drospirenone (DRSP), the progestogen contained in Drovelis, has been approved in several CHCs in Switzerland and has recently been approved as a progestin-only pill. DRSP is a derivative of spironolactone and possesses both antiandrogenic and antimineralocorticoid properties. CHCs that contain DRSP are therefore supposed to cause sodium retention to a lower degree than other CHCs; on the other hand, they are associated with a risk of hyperkalaemia, particularly in patients with reduced renal function.

Generally, the estrogen component in CHCs is ethinylestradiol (EE). Two preparations containing “natural” estrogens have been available for several years now: a combination of estradiol valerate (EV) and dienogest since 2009 and a combination of estradiol (E2) and nomegestrol acetate since 2012. With E2 or EV, stable menstrual cycles are harder to achieve than with EE.

In Drovelis, in contrast, the estrogen component is estetrol (E4), an estrogen that was first described in 1965, but which has not been approved in any medicinal product until now. Physiologically, this estrogen is only produced by the foetal liver during the foetal period. It enters the maternal blood via the placenta and can be detected in the mother from the ninth week of pregnancy. Peak maternal concentrations of 0.4–1.2 ng/ml are reached towards the end of pregnancy. However, foetal concentrations are over ten times higher, at up to 13 ng/ml. Estetrol synthesis stops after birth. It is not known whether estetrol plays a physiological role in the mother too or whether the concentrations measurable in pregnant women are “contamination” via the placenta.

Estetrol is being developed for two indications: hormonal contraception and hormone replacement in the (post-) menopause. It binds specifically to the estrogen receptors, displaying an affinity for the α receptor that is 4-5 times greater than its affinity for the β receptor. Unlike the other estrogens, estetrol metabolism does not produce active metabolites. (This is in contrast to estradiol, which is metabolised into estriol and estrone, creating equilibrium between the various estrogens.)

Venous and arterial thromboembolic events are one of the major risks associated with CHCs. The severity of this risk depends primarily on the EE dose. Whereas preparations containing high doses of EE used to be approved, most modern CHCs contain an EE dose of between 15 and 30 µg. A small number of preparations still contain 50 µg of EE, but preparations containing higher doses are no longer authorised. Any further reduction in EE dose would affect the stability of the menstrual cycle. In general terms, a declining EE dose negatively affects the bleeding pattern.

EE’s 17α ethinyl group gives it significant influence on hepatic metabolism, which in turn affects haemostatic parameter synthesis. It is assumed that “natural” estrogens such as estradiol or estetrol do not affect hepatic metabolism as significantly as EE. CHCs containing E2 or EV had therefore been expected to present a lower risk of thromboembolic events than CHCs containing EE. However, this has yet to be confirmed for the two authorised preparations referred to above.

The risk is also dependent on the type of progestogen. A distinction is made here between second and third-generation CHCs (and those with more recent progestogen components such as norelgestromin, which it is as yet not possible to categorise). The third-generation preparations (containing progestogens such as desogestrel and gestodene) present an increased risk of thromboembolic events compared with their second-generation counterparts (particularly those containing levonorgestrel). Combinations of EE and DRSP (sometimes referred to as fourth-

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generation CHCs) present a significantly increased risk of thromboembolic events compared to second-generation CHCs. Overall, there is a certain amount of evidence to suggest an increase of the risk of thromboembolic events particularly with progestogens with antiandrogenic properties (such as DRSP). Androgens are able to antagonise the negative effects of the estrogens on haemostasis to a certain extent. Progestogens with antiandrogenic properties cannot provide this protection.

The information for healthcare professionals of CHCs has been updated over recent years to reflect what is now known about the risk of thromboembolic events. The underlying data indicate that the number of events per year involving CHCs containing EE and DRSP is between 9 and 12 per 10,000 women, compared with 5 to 7 cases for CHCs containing EE and levonorgestrel. For details, please also refer to the information about thromboembolic risk of hormonal contraceptives on the Swissmedic website www.swissmedic.ch.

Drovelis was developed with the aim of finding an estrogen-progestogen combination that would be effective in suppressing ovarian function (i.e. providing effective contraception) while simultaneously providing a predictable and acceptable bleeding profile. A further goal was to reduce the risk of thromboembolic events compared with the EE / DRSP combination.

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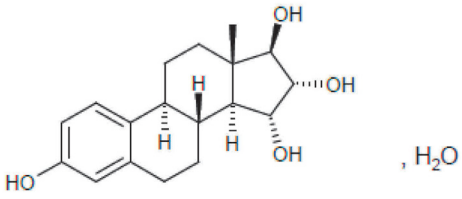
4 Quality Aspects

4.1 Drug Substance

INN: Estetrol [estetrol monohydrate (INNM)]
Chemical name: (8*R*,9*S*,13*S*,14*S*,15*R*,16*R*,17*R*)-13-methyl 6,7,8,9,11,12,14,15,16,17decahydrocyclopenta[a]penthanthrene-3,15,16,17-tetrol monohydrate
Molecular formula: $C_{18}H_{24}O_4.H_2O$
Molecular mass: 322.40 g/mol (estetrol monohydrate)
304.38 g/mol (estetrol, anhydrous)
Molecular structure:

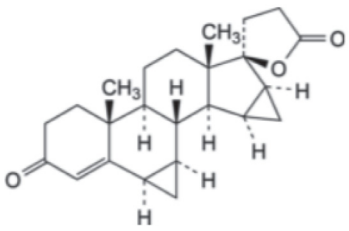


Estetrol monohydrate is a white to off-white crystalline solid, poorly soluble in water and aqueous solution. Estetrol monohydrate is slightly hygroscopic.

The drug substance is manufactured by multiple step chemical synthesis with final isolation by crystallisation. The crystallised product is milled.

The drug substance specification includes relevant tests for proper quality control, encompassing tests relating to identification, assay, impurities and particle size.
Appropriate stability data has been presented and justify the established re-test period.

INN: Drospirenone
Chemical name: 3-Oxo-6α,7α,15α,16α-tetrahydro-3′*H*,3″*H*-dicyclopropa[6,7:15,16]-17α-pregn-4-en-21,17-carbolactone
Molecular formula: $C_{24}H_{30}O_3$
Molecular mass: 366.5 g/mol
Molecular structure:



A monograph for drospirenone exists in the Ph. Eur. and Certificates of Suitability from the EDQM have been presented.

4.2 Drug Product

The drug product is presented as a pink film-coated tablet for oral administration with a dosage strength of 15 mg estetrol monohydrate (equivalent to 14.2 mg estetrol). The film-coated tablets are pink, round, biconvex, with a drop-shaped logo embossed on one side.

Additionally, white to off-white, round, biconvex placebo film-coated tablets, with a drop-shaped logo embossed on one side for oral administration are presented.

The composition of the drug product is adequately described, qualitatively and quantitatively.

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Suitable pharmaceutical development data has been provided for the finished product composition and manufacturing process, including establishment of the Quality Target Product Profile (QTPP), the Critical Quality Attributes (CQA) and the Critical Process Parameters (CPP).
The manufacturing process is described narratively and in sufficient detail, taking into account pharmaceutical development data. Batch manufacturing formulas and in-process controls are included.
Adequate validation data pertaining to the commercial manufacturing process is presented in the dossier.
The drug product specification covers relevant physicochemical characteristics; identification, assay and purity tests are included as well. They allow for proper control of the finished drug product. The control methods are validated according to international guidelines. Batch data show consistent quality of the drug product.
Both film-coated tablets – drug product and placebo – are packaged in blisters comprising a PVC foil and aluminium foil.
Appropriate stability data have been generated in the packaging material intended for commercial use and following the relevant international guidelines. The data show good stability of the finished product and allow for a clear assignment of the shelf life.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Nonclinical studies were conducted to characterise estetrol, as drospirenone is the progestogenic component of several marketed combined oral contraceptives. A 13-week oral repeat-dose toxicity study was conducted with the estetrol/drospirenone combination in female monkeys.

5.1 Pharmacology

Estetrol showed activity against estrogen receptors α or β *in vitro*, which was about 400- to 450-fold less compared to estradiol. Estetrol exhibited a stimulatory effect on the proliferation of human breast epithelial (HBE) and the human breast cancer cell line MCF-7 of about 1% of that of estradiol.
Oral administration of estetrol to female rabbits inhibited ovulation and implantation at exposures corresponding to 0.20-fold human exposure (ED_{50} values 0.735 mg/kg and 0.055 mg/kg twice daily).
The potency of estetrol, including vaginal estrogenic response such as weight increase and epithelial cornification, was dose-dependent and about 5.5% of the potency of ethinyl estradiol *in vivo*.
In summary, the *in vitro* and *in vivo* primary pharmacodynamic data suggest that estetrol has estrogenic activity but is less potent than estradiol and ethinyl estradiol.
In a secondary pharmacodynamic screening assay, no substantial off-target activity was identified.
Estetrol showed no adverse effects in a core battery of *in vitro* and *in vivo* safety pharmacology studies assessing the cardiovascular, respiratory and central nervous system effects.

5.2 Pharmacokinetics

The pharmacodynamics of estetrol was studied in mice, rats, and monkeys. Following repeated oral administration, maximum mean plasma concentrations were observed at 30 minutes in mice and rats and at 0.5-1.5 h in monkeys (T_{max}). Oral bioavailability was 70%. Both C_{max} and AUC increased dose-dependently.
In vitro plasma protein binding across species (female mouse, rat, monkey and woman) was close to 50% and there was no indication of a concentration relationship for any species.
After a single oral dose of 15 mg/kg [^{14}C]-estetrol to female rats, there was rapid tissue distribution of radioactivity. No preferential melanin binding was observed. Plasma radioactivity concentrations declined rapidly within 24 hours. At 24 hours after dosing, only the gastrointestinal tract, bladder, adrenal gland, kidney, liver, pancreas, salivary gland, and thyroid gland exhibited quantifiable radioactivity. Radioactivity was found in the brain up to 1 h postdose.
Estetrol was metabolised in hepatocytes of mice, rats and humans, with each species showing a specific pattern of metabolites. Two major metabolites were identified in humans (glucuronide M6 and sulphation product M8), which were also found in hepatocytes of the animal species. None of the quantifiable metabolites was unique to humans and all were adequately covered in the toxicity studies.
Estetrol was primarily eliminated via the biliary/faecal route in rats and mice, in contrast to the urinary route of elimination in humans. Based on its pharmacology, estetrol is likely to pass the placental barrier and be secreted in milk.

5.3 Toxicology

The toxicological profile was evaluated in mice, rats, rabbits and monkeys. The choice of rats and monkeys as the rodent and non-rodent species for toxicological assessment is considered appropriate, as the metabolism and pharmacology of estetrol are comparable in both species and in humans. The route (oral) and frequency of administration in the nonclinical studies were consistent with the proposed clinical setting. The duration of the studies supports chronic use.
Estetrol was well tolerated in repeated dose studies up to 39 weeks in female cynomolgus monkeys. Mortality was observed only in monkeys after combined administration at estetrol and drospirenone doses of 30/6 mg/kg/day, corresponding to 63-fold and 5.3-fold human exposure, respectively. The reasons for the increased mortality in the combination group are unknown.

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As expected, given the pharmacological mode of action, the main target organs in all species were the genital organs and mammary glands. Oestrous cycles were interrupted after the start of dose administration, and increases in uterus weights and a higher incidence and severity of squamous metaplasia of the cervix were observed. In monkeys, the mammary glands showed dose-dependent hypertrophic/hyperplasic changes even after the recovery period. Most observed effects after repeated oral administration of estetrol were due to the pharmacological mode of action. Lower thymus weights were observed in all species, and minor vacuolation in islet cells and cell death were observed in the pancreas of monkeys that had been given estetrol/drospirenone, this being associated with elevated glucose levels. Exposure at the NOAEL in the 13-week estetrol/drospirenone (3/0.6 mg/kg/day) combination study in monkeys was 8.17-fold (for estetrol) and 1.2-fold (for drospirenone) human exposure at the recommended clinical dose.
Estetrol was genotoxic in Ames test, but was not mutagenic in the mouse lymphoma assay at up to 1 mM and did not induce DNA damage at up to 2000 mg/kg/day *in vivo*. The negative *in vivo* data overrule the positive Ames results according to ICH S2.
In 2-year carcinogenicity studies in rats and mice, estetrol induced uterine and cervical epithelial neoplasms, mammary gland neoplasms and pituitary gland neoplasms. All neoplastic and non-neoplastic proliferative lesions were explained by the estrogenic properties of estetrol. Dose levels not considered carcinogenic by the applicant in mice and rats (0.125 mg/kg/day and 0.27 mg/kg/day) were associated with estetrol exposures corresponding to 0.08-fold human exposure levels in mice and 0.32-fold human exposure levels in rats.
In the fertility and early embryonic development studies in rats, body weight gain and food consumption were dose-dependently reduced. A dose-dependent increase in the number of non-cycling females was observed. Oestrus cycle and body weights recovered within three weeks of treatment being stopped. Post-recovery mating, fertility, gestation indices or implantations assessed after the recovery were not affected.
In embryo-foetal development studies in rats, there was a dose-related increase in the incidence of skeletal malformations at 1 and 3 mg/kg/day (shortening, thickening and bending of the long bones and scapula). The NOAEL values for maternal and embryo-foetal development were 0.3 mg/kg/day. No exposure levels are reported for this study, but extrapolations from the range-finding embryo-foetal development study in rats indicate that the exposure at NOAEL is lower than human exposure levels at therapeutic dose.
In rabbits, a dose-related reduction in maternal food consumption and body weight and a compensatory increase in food consumption and body weight after discontinuation was observed at ≥ 0.05 mg/kg/day, associated with slight developmental delays in foetuses. The NOAEL for maternal toxicity and embryo-foetal development was 0.05 mg/kg/day, with corresponding exposure values of 0.11-fold the human exposure.
In the pre- and postnatal developmental toxicity studies in rats, clinical signs, mortality, premature sacrifices and low body weights were observed in dams at ≥ 0.5 mg/kg/day. In the F1 generation, pup mortality was observed at ≥ 0.5 mg/kg/day. Behavioural parameters, pairing performance or fertility were unaffected. The NOAEL for gestation was 0.5 mg/kg/day, the NOAEL for lactation was 0.17 mg/kg/day. The NOAEL for F1 post-weaning development, sexual maturation, physical and behavioural development, mating and fertility was 1.5 mg/kg/day, corresponding approximately to human exposure at therapeutic dosing.
Estetrol does not absorb light within the range of natural sunlight. Therefore, the risk for phototoxicity is low. The RMP adequately describes the safety concerns identified in nonclinical studies and relevance to human usage.
There are no safety concerns with regard to impurities or excipients.
Based on the ERA, the risk to the environment is low.

5.4 Nonclinical Conclusions

The submitted documentation was sufficient to conduct a risk assessment for Drovelis. The pharmacology and toxicological profile of estetrol are considered sufficiently characterised. Observed adverse effects were mostly related to the pharmacological action of the ingredients. Safety margins

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for carcinogenicity and reproductive and developmental toxicology are low but can be accepted for the requested indication as observed carcinogenicity is related to the pharmacological mode of action in rats and Drovelis is counter-indicated for pregnant and lactating women. The relevant information has been included in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

ADME of estetrol as monosubstance

The pharmacokinetics of estetrol as monosubstance were investigated in healthy female subjects, who represent the intended treatment population.

Absorption

Estetrol was rapidly absorbed and reached maximum concentrations within 1 h postdose.

The absolute bioavailability of estetrol has not been determined. However, the urinary recovery of the radioactive dose in a mass balance study indicated that at least 69% of an oral dose was absorbed.

PK after multiple doses

Following multiple doses of 15 mg QD, steady-state was reached by ~7 days postdose and estetrol accumulated mildly (1.8-fold).

Dose proportionality

Estetrol AUC and C_{max} increased dose-proportionally both after administration of a single dose (5-45 mg) or multiple doses (15-75 mg).

Distribution

In vitro, estetrol plasma protein binding was determined to be 45.4 - 50.4% and was not dependent on the estetrol concentration (range of 1-50 ng /ml). Estetrol showed no binding to human SHBG.

In vitro assessment of blood-plasma partitioning indicated an equal distribution of estetrol between plasma and blood cells.

The volume of distribution was not determined due to lack of data after IV administration. However, the mean apparent volume of distribution (V/F) determined after oral administration of 15 mg estetrol was high (range: 4450 - 7460 L).

Secondary peaks in the plasma-concentration time profile indicated that estetrol undergoes enterohepatic recirculation, which is known for other estrogens as well.

Metabolism and excretion

Estetrol is primarily metabolised by glucuronidation and to a minor extent by sulfate conjugation.

In a mass balance study, estetrol-C16-glucuronide was the main metabolite in plasma, accounting for 61.3% of radioactivity. Estetrol-C3-glucuronide represented 15.3%, estetrol ~7.4% and an estetrol glucuronide and sulfate conjugate 9.1% of radioactivity in 0-2 h plasma.

UGT2B7, and to a lesser extent, UGT1B4 have been identified as the isoforms responsible for formation of the main metabolite, estetrol-C16-glucuronide. The UGT isoforms responsible for formation of the other metabolites are unknown.

Estetrol-C16-glucuronide and estetrol-C3-glucuronide, are not believed to contribute to the intended pharmacological activity.

In a mass balance study, 68.97% of the total radioactive dose was recovered in urine. Estetrol-C3-glucuronide and estetrol-C16-glucuronide were the main radioactive species in urine and accounted for 15.9% and 46.0% of the dose within 0-120 h postdose, respectively.

Only 21.88% of the total radioactive dose was recovered in faeces, and estetrol was the only radioactive species detected in faeces. This unmetabolised estetrol detected in faeces might represent hydrolysed glucuronides and/or estretrol excreted in bile or unabsorbed.

Across studies, the mean terminal half-life of estetrol ranged between ~20-30 h.

PK of esterol in combination with drospirenone

Potential mutual pharmacokinetic interactions between estetrol and drospirenone have not been systematically investigated. However, cross-study comparisons indicate that the two active substances did not relevantly influence each other.

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Following multiple doses of estetrol/drospirenone (15/3 mg), the steady state C_{max} for estetrol was 17.9 ng/ml and AUC_{0-24h} was 59.1 ng*h/ml. The steady state C_{max} of drospirenone was 48.7 ng/ml and AUC_{0-24h} was 519 ng*h/ml.

Thus, the therapeutic concentrations of estetrol are 10-40-fold higher than the concentrations in maternal blood during pregnancy (0.4-1.2 ng/ml).

Food effect

Upon concomitant administration of estetrol/drospirenone with a high-fat, high-calorie meal, the C_{max} of estetrol was reduced by 49% and the C_{max} of drospirenone was reduced by 25%, while AUC was bioequivalent for both substances. Drovelis has been administered independently of food intake in the phase 3 study. Based on these data, administration irrespective of food is acceptable.

Special Populations / Intrinsic Factors

No dedicated studies were submitted to assess the effect of renal or hepatic impairment on the PK of estetrol. A contraindication for subjects with severe renal or hepatic impairment is warranted due to the effect on drospirenone exposure and related safety aspects.

The PK of estetrol and drospirenone were similar in healthy Japanese and Caucasian women.

Due to enterohepatic recirculation, estetrol has complex PK. It has therefore not been possible to develop a PopPK model capable of adequately describing the PK of estetrol. Thus, the influence of covariates on the PK of estetrol could not be assessed in a PopPK analysis.

Interactions

In vitro studies

The interaction potential of estetrol has been investigated for all relevant CYPs, UGTs and transporters at clinically relevant concentrations. Details are provided in the attached information for healthcare professionals (see Appendix).

Clinical interaction studies

UGT inhibitors

Concomitant administration of estetrol/drospirenone with the general UGT inhibitor valproate caused a 1.36-fold increase in estetrol C_{max} and a 1.25-fold increase in estetrol AUC_{0-t}. The increased exposure of estetrol was associated with mildly decreased metabolite exposures The geometric mean Cmax and AUC values for drospirenone were similar for both treatments. The mild increase in estetrol exposure is not considered to be clinically relevant, and no dose adjustments or restriction for concomitant use of UGT inhibitors are required.

Enterohepatic recirculation

Estetrol undergoes enterohepatic recirculation. The exact extent has not been determined but is assumed to be less pronounced than for other estrogens. Based on theoretical considerations, the interaction potential with drugs that might affect enterohepatic recirculation is considered to be low.

Further information and recommendations with regard to concomitant medications are addressed in the attached information for healthcare professionals (see Appendix).

Pharmacodynamics

Mechanism of Action and Primary Pharmacology

In a proof of concept study, two doses of estetrol monotherapy (10 mg and 20 mg) were investigated. Although this monotherapy reduced E2 levels, there was no suppression of FSH and LH and ultrasound scans showed no evidence of follicle growth suppression. Between 30 and 60% of the subjects ovulated, depending on the dose administered. However, other phase I and II studies demonstrated suppression of hormone concentrations and adequate inhibition of ovarian activity for the combination of 14.2 mg estetrol and 3 mg DRSP that has now been authorised. While hormonal suppression was slightly lower with estetrol / DRSP than with the comparators, in the light of the findings from the phase III studies, this does not seem to be clinically relevant.

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Return of ovulation was also investigated. The findings provided sufficient evidence that the ovarian suppression caused by Drovelis is fully reversible. The study findings led the Marketing Authorisation Holder to conclude that the preparation is less sensitive to administration errors, such that if the patient forgets to take it, no additional measures are required until more than 24 hours have elapsed since the missed dose. However, Swissmedic is of the opinion that women in a wealthy western industrial nation such as Switzerland give higher priority to contraceptive protection and that it is reasonable, given the prevailing circumstances here, to use additional precautionary contraceptive methods if this is felt to be appropriate. In light of this, the data were not considered to be adequate to support a recommendation that differs from the one issued for other CHCs and, as with all other preparations, additional measures should therefore be taken if 12 hours have passed since a missed dose.

Secondary Pharmacology (Safety)

Potential for prolongation of the QT interval

A potential effect of estetrol/drospirenone on the QT interval was assessed following administration of the therapeutic dose (15/3 mg for 10 days) and of a supratherapeutic dose (75/15 mg for 10 days). No relevant potential for prolongation of the QT interval was observed, as the upper boundary of the 90% CI of ΔΔQTcF was below 10 msec at all postdose timepoints.

6.2 Dose Finding and Dose Recommendation

A total of 3 dose-finding studies were submitted. These investigated various estetrol dosages on the one hand and combinations with various progestogens on the other. The aim was to find a combination that would provide adequate follicle growth suppression as well as an acceptable bleeding pattern. As expected, higher estetrol doses not only resulted in greater suppression of ovarian activity but also in a more stable menstrual cycle. It was thus deduced from the findings of the first of these studies that an estetrol dosage >10 mg was needed for adequate cycle control. Of the progestogens investigated, DRSP performed somewhat better on cycle control than levonorgestrel. However, the study in question only investigated DRSP in combination with 5 and 10 mg estetrol, whereas levonorgestrel was also investigated with 20 mg E4. It is therefore not known whether DRSP would still have had an advantage over levonorgestrel at the higher estrogen dosage.

The second study combined 15 or 20 mg estetrol with 3 mg DRSP or 0.15 mg levonorgestrel. Good inhibition of ovulation was observed in all four groups. However, the incidence of bleeding was somewhat lower with the combinations containing DRSP than with those containing levonorgestrel. It was lowest in the group taking 15 mg estetrol plus DRSP. This combination was therefore chosen for further development.

Estetrol / DRSP was also compared with authorised preparations. One study used Qlaira® as a comparator, a four-phase preparation containing estradiol valerate and dienogest. In this study, the combination of 15 mg estetrol and 3 mg DRSP tended to cause less bleeding than the comparator. Another study used Yaz® as a comparator, a preparation containing DRSP that uses a 24/4 regimen. Here, hormonal suppression was less strong with the product containing estetrol than with the one containing EE. However, since an adequately low Hoogland score was achieved in both cases, this difference was not regarded as clinically relevant.

Overall, with regard to bleeding pattern, the chosen dosage is comprehensible. However, for contraceptive efficacy, even a lower E4 dose and the choice of a progestogen with lower thromboembolic risk (i.e. levonorgestrel) would have been sufficient. There was a critical discussion of whether menstrual cycle stability should really be used as a priority criterion, even if it results in a relatively high estrogen dose and the choice of a progestogen that is known to be associated with an increased risk of thromboembolic events. In view of the phase III findings, however, the submitted combination was ultimately felt to be acceptable.

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6.3 Efficacy

Two phase III studies of comparable design were conducted to demonstrate safety and efficacy of Drovelis. Study C301, which was conducted in Europe and Russia, is the pivotal study, whereas study C302, which was conducted in North America, is supportive. As is customary for investigations of hormonal contraceptives, both were open, uncontrolled studies lasting 13 cycles (i.e. one year).

Swissmedic agrees with the classification of the American study as supportive. It is known from other contraception studies that the Pearl Index (PI) is generally substantially higher there than in Europe, and this was also the case in the studies with Drovelis.

The European study enrolled women aged 18 and over, whereas women aged 16 or over were eligible to take part in the American study. However, the actual number of participants aged under 18 was very small.

The PI was calculated in two different ways in each study, the calculation based on the American definition being defined as the primary endpoint. This means that the denominator only takes account of those cycles in which no back-up contraception was used and in which sexual intercourse could be proven to have taken place on the basis of the patient's journal. (The European definition of cycles at risk does not require proof of intercourse, only the non-use of back-up contraception). The numerator includes all pregnancies that occurred up to 7 days after the last dose of study medication was taken. (Here the European definition only includes pregnancies that occur up to 2 days after the last dose was taken).

Study C301 enrolled a total of n=1577 women, study C302 n=2148. As is customary with hormonal contraceptives, primary analysis in each study focused on the ≤35 age group, since fertility naturally declines with increasing age. This age group accounted for n=1373 subjects in the pivotal study, n=1939 in the supportive study. The average age of subjects in both studies was around 27. As would be expected, there were differences in BMI. 23% of subjects in the American study had a BMI ≥30kg/m^2, whereas the figure for the European study was just under 6%.

Around half the subjects in both studies were new users or switchers; however, new users were defined as women who had not used hormonal contraception in the 3 months prior to enrolment. "True new users" – i.e. women who had never used hormonal contraception before – were rare in both studies. There was a substantial difference in the proportion of new users between the studies – just under 60% in the American study compared to around 40% only in the European study.

Based on 13,692 cycles at risk, the pivotal study found a PI of 0.47 (95% CI 0.15–1.11) for the primary population analysed, i.e. women aged ≤35. The value for the entire study population (i.e. including subjects over 35) was 0.41 (95% CI 0.13–0.96). All the pregnancies that occurred during the study occurred in the ≤35 age group (and in trial subjects with a BMI ≤30kg/m^2). With these findings, contraceptive efficacy was shown. The EMA criterion for adequate study size for hormonal contraceptives – that the difference between the point estimate and upper limit of the confidence interval must not exceed 1 – was also fulfilled by a clear margin.

The findings for the secondary endpoints (i.e. different calculation methods for the PI and cumulative pregnancy rate) were consistent on this point. The calculated PI for method errors only in women ≤35 years old was 0.29 (95% CI 0.06–0.83).

In the supportive study, the PI for the primary endpoint for the ≤35 age group was 2.65 (95% CI 1.73–3.88). The PI for method errors in this study was 1.55 (upper limit of 95% CI: 2.60). While these values were not acceptable for European standards, they are still within a range known for American contraception studies. The substantially higher PI in this study is therefore not of concern.

In addition to the risk of pregnancy, bleeding pattern was also analysed as a secondary endpoint. No particular abnormalities were found, particularly in a historical comparison with other CHCs, and the results appear acceptable overall. Bleeding (withdrawal bleeding) occurred on a median of 5 days per cycle.

In addition, subjects completed two health questionnaires. However, the baseline evaluation in most cases was (very) good and there were virtually no changes in the course of the study. Overall, these data made little contribution to the assessment of the application.

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6.4 Safety

Safety assessment was primarily based on the pooled data from 5 phase II/III studies in which the requested dosage regimen was administered for at least 3 cycles. 96% of the data were from the 2 phase III studies, each of which involved an exposure period of 13 cycles. Overall the data pool contained n=3575 subjects who had received at least one dose of study medication and a further n=215 women for whom this could not be definitively ascertained. However, only 61% of the subjects included in the data pool completed the study in which they participated. The figure was 78% for the European study and just 54.5% for the American study.

In total, there is data for 35,677 cycles, equivalent to 2735 woman years.

The observed safety profile matched that expected from a CHC. The results did not differ in a relevant way from the experience with authorised CHCs, and neither disadvantages nor relevant advantages by use of a "natural" estrogen were identified.

The most common AEs were headaches (6.4%), metrorrhagia (4.6%), viral infections of the upper respiratory tract (3.9%) and acne (3.7%).

The incidence of SAEs was 1.1%, the majority of which were classified as unrelated. The most common SAE was spontaneous abortion (0.2%). However, SAEs involving psychiatric symptoms, where classification as "unrelated" may be questioned, were also relatively common. Depressive disorders are a particular undesirable effect of hormonal contraceptives mentioned in a separate warning in the information for healthcare professionals. Here again, though, there is nothing to indicate that Drovelis could be different from authorised CHCs in any relevant way.

The following three SAEs were classified as related: one case of venous thrombosis in the pivotal study involving a subject with no risk factors; one case of exacerbation of pre-existing depression; one ectopic pregnancy.

The rate of discontinuations owing to AEs was 9.4%. A distinction was made here between AEs relating to bleeding disorders and other AEs. The former resulted in premature discontinuation in 6.6% of cases, the latter in 2.8%. The most common individual reasons for dropping out were metrorrhagia (1.1%), acne (0.9%), vaginal bleeding (0.7%) and menorrhagia (0.6%).

During development of the product, there was one death in study C302 resulting from an accidental overdose of alprazolam and fentanyl (confirmed by autopsy) in a drug-dependent subject (marijuana, cocaine and heroin). It seems plausible to classify this death as unrelated.

Subgroup analyses of the safety data by age, BMI, ethnicity and smoking status as well as by new users versus switchers did not reveal any relevant abnormalities.

DRSP is associated with a known (slight) risk of hyperkalaemia by virtue of its anti-mineral corticoid effect. However, the studies provided no evidence of relevant elevated potassium levels, and there was no case in which (transitory) elevated potassium levels required specific treatment. In this respect, Drovelis seems to be comparable overall to authorised CHCs containing DRSP.

The increase in SHBG with Drovelis was lower than with a combination of EE and DRSP, supporting the assumption that estetrol, in contrast to EE, does not result in relevant SHBG induction.

The studies recorded bleeding pattern as a secondary efficacy endpoint with the aim of demonstrating good cycle stability. However, relevant bleeding disorders were also documented as AEs. 14–20% of subjects in the phase III studies experienced intermenstrual bleeding, mostly in the form of spotting. Regular withdrawal bleeding was maintained in over 90% of subjects.

Specific safety aspects

In response to preclinical findings (see relevant section) hinting that estetrol might be **cardiotoxic**, ECGs and echocardiograms were taken in some studies. Furthermore, LDH 1 and LDH 2 (plus troponin) were determined in addition to the usual laboratory parameters, including during phase III. These tests did not reveal any abnormalities, meaning no risk to humans is discernible at present. At a maximum of 13 cycles, however, the observation period is still limited (and a very rare side effect might not be discernible in the current population of only around 4000 women exposed).

In accordance with the EU Guideline on hormonal contraceptives, the effect of Drovelis on **haemostatic** parameters was investigated in a dedicated study. These investigations used EE/LNG

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and EE/DRSP as comparators. Compared with the comparators, Drovelis produced the smallest or least detrimental changes on most parameters.

However, the current data are insufficient to permit any statement on the relative severity of the **risk of thromboembolic events** compared to other CHCs (particularly those containing levonorgestrel). Two venous thromboembolic events were recorded in the clinical studies. In addition to the case mentioned above as an SAE in the pivotal study, there was one case involving a subject under supratherapeutic dosage in phase I. Overall, there was no evidence of an increased risk compared to other CHCs (as would be expected with EE/DRSP).

Since the FDA also requires an investigation of **endometrial** safety for CHCs, an endometrial biopsy was examined in a subgroup of n=170 subjects in the pivotal study. Ultrasound measurements of endometrial thickness were also presented from other studies. In line with expectations, the findings from these investigations revealed no abnormalities.

However, no data are as yet available on the issue of possible impact on **bone density**. In general terms, however, CHCs are not regarded as critical on this point by virtue of the estrogen component they contain. However, this is dependent on the type and particularly the dose of estrogen. As yet, it is not known whether estetrol exhibits an osteoprotective effect strong enough to antagonise the negative impact of the progestogen on the bones. This issue is particularly critical in young women who have yet to reach full skeletal maturity. However, since the estrogen dose in Drovelis is relatively high, any associated risk would tend to be unlikely.

For further details, please refer to the “Warnings and precautions” and “Undesirable effects” sections of the information for healthcare professionals.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Drovelis is an oral combined hormonal contraceptive (CHC) comprising a novel estrogen component (estetrol) and a progestogen component (DRSP) that is already in use in several hormonal contraceptives.

Benefits

The ADME characteristics of esterol have been characterised sufficiently.

In 3 phase II studies, estretrol was examined in different doses and in combination with different progestogens. A combination of 15 mg estetrol and 3 mg DRSP was found to be most beneficial in terms of effect on bleeding patterns, while the different combinations of estetrol dose and progestogen type were not found to make any material difference to ovarian activity suppression.

Pivotal study C301 demonstrated the contraceptive efficacy of this combination. Data from the supportive phase III study conducted in America (C302) supported its findings.

The bleeding pattern is also acceptable. There are no discernible benefits or disadvantages compared with other CHCs.

Uncertainties regarding benefit

The number of cycles at risk may have been slightly overestimated by virtue of the way they were recorded. However, this is not expected to have any relevant impact on the efficacy findings.

Since only 13 adolescents under the age of 18 were enrolled in phase III, the data for this age group are limited.

Risks

Overall, the safety profile of Drovelis matches the one expected from a CHC.

In its submission, the Marketing Authorisation Holder suggested that the preparation would have an advantage over CHCs containing EE, citing two considerations in particular: The first is the assumption that “natural” estrogens such as estradiol (valerate) – and also estetrol – exert less influence on haemostatic parameter synthesis because they have less impact on liver metabolism than EE, and thus present a lower risk of thromboembolic events. Secondly, the Marketing Authorisation Holder argued with findings from a phase I study examining haemostatic parameters where Drovelis tended to perform better than EE plus DRSP and EE plus levonorgestrel. However,

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these are surrogate parameters and cannot be used to assess the actual risk in everyday clinical practice. Yet, the data currently available from the phase III studies are too limited to permit comparisons with other CHCs (for which comprehensive epidemiological data are available). For this reason, a PASS study will be conducted of the type performed for other newly authorised CHCs in recent years to determine the relative risk of such events (particularly compared to CHCs containing levonorgestrel).

In general terms, a combination with levonorgestrel would be more beneficial in terms of associated risk of thromboembolic events than a combination with DRSP. Data obtained from dose-finding studies do not indicate any relevant differences in ovarian suppression between combinations containing levonorgestrel and those containing DRSP. DRSP was chosen solely on bleeding pattern-related reasons. However, given that the combination with DRSP was the only one to be developed and ultimately submitted for authorisation, these are secondary considerations.

Uncertainties regarding risks

There are no data available in subjects with renal or hepatic impairment. The resulting uncertainty could however, be mitigated by restrictive wording in the information for healthcare professionals.

Morphological changes to the heart were observed in animal studies. In response to these findings, LDH 1, LDH 2 and troponin were measured in part of the clinical trials, and ECGs and/or echocardiograms were also taken. The findings have not highlighted any relevant abnormalities as yet. However, it is unclear whether these limited data are sufficient to exclude a risk to humans with sufficient certainty. PSURs should therefore put a particular focus on possible effects on the heart in the post-marketing setting.

Since patients with severe heart failure or complicated heart valve disease as well as women with a history of pregnancy-related cardiomyopathy were excluded from the phase III studies, it is not possible to assess the potential risk of heart-related undesirable effects in at-risk patients.

Overall, longtime safety data is still rare.

Final risk-benefit profile

Drovelis is an oral combined hormonal contraceptive containing the new estrogen component estetrol (E4) and the established progestogen drospirenone. The contraceptive efficacy of this combination as well as an acceptable bleeding pattern were demonstrated in 2 phase III studies. The risks associated with Drovelis seemed in line with those associated with existing authorised CHCs. However, claims of any possible advantages compared to other CHCs have yet to be adequately proven.

The risk-benefit profile for adult users is positive overall. However, in view of the as yet unassessable relative risk of thromboembolic events, particularly compared to second-generation CHCs, the risk-benefit profile for minors (i.e. the particularly vulnerable population of adolescents) is negative. Drovelis will therefore only be authorised for adults until respective data from the above mentioned PASS study are available.

Moreover, with reference to thromboembolic events, all the precautions listed in the information for healthcare professionals of all CHCs authorised to date apply, for example the requirement to consider the current guidelines issued by the SGGG (“expert letters”).

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Drovelis was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

Drovelis 3 mg/ 14.2 mg film-coated tablets

Composition

Active substances

Drospirenone, estetrol (as estetrol monohydrate)

Excipients

Each pink active tablet contains:
Tablet core:
Lactose monohydrate (40 mg), sodium starch glycolate (type A) (corresponds max. 0.31 mg sodium), maize starch, povidone K-30, magnesium stearate (E470b)
Tablet coating:
Hypromellose (E464), hydroxypropylcellulose (E463), talc (E553b), hydrogenated cottonseed oil, titanium dioxide (E171), red iron oxide (E172)

Each white placebo tablet contains:
Tablet core:
Lactose monohydrate (68 mg), maize starch, magnesium stearate (E470b)
Tablet coating:
Hypromellose (E464), hydroxypropylcellulose (E463), talc (E553b), hydrogenated cottonseed oil, titanium dioxide (E171)

Pharmaceutical form and active substance quantity per unit

Each pink active film-coated tablet contains 3 mg drospirenone and estetrol monohydrate equivalent to 14.2 mg estetrol.
Each white placebo film-coated tablet does not contain active substances.

Indications/Uses

Oral contraception in women aged 18 and over.

The decision to prescribe Drovelis should take into consideration the individual woman’s current risk factors, particularly with regard to venous thromboembolism (VTE). The relative risk of VTE with

Drovelis should also be compared with that of other combined hormonal contraceptives (CHCs) (see “Contraindications” and ”Warnings and precautions”).

Dosage/Administration

CHCs such as Drovelis should only be prescribed by a doctor with appropriate experience who is able to provide the patient with a comprehensive explanation of the advantages and disadvantages of all available contraceptive methods, as well as a general and a gynaecological examination.
A CHC should always be prescribed in accordance with the current guidelines of the Swiss Society of Gynaecology and Obstetrics.

The tablets must be taken every day at about the same time, if necessary, with a little liquid, in the order shown on the blister pack. Stickers marked with the 7 days of the week are provided, and the relevant weekday sticker should be stuck on the tablet blister as an indicator of when the first tablet has been taken.

Tablet taking is continuous. One tablet is to be taken daily for 28 consecutive days. Each subsequent pack is started the day after the last tablet of the previous pack. Withdrawal bleeding usually starts on day 2-3 after starting the placebo tablets and may not have finished before the next pack is started. See ”Cycle control”.

Start of intake

- *Women who have not used a hormonal contraceptive in the last month*

Tablet-taking has to start on day 1 of menstrual cycle, i.e. the first day of her menstrual bleeding, and when doing so, no additional contraceptive measures are necessary.
If the first tablet is taken on days 2 to 5 of the menstruation, this medicinal product will not be effective until after the first 7 consecutive days of pink active tablet-taking. A non-hormonal contraceptive method (e.g. a condom; but not the Knaus-Ogino calendar method or the temperature method) must therefore be used additionally during these first 7 days. The possibility of pregnancy should be considered before starting Drovelis.

- *Changing from another CHC (combined oral contraceptive (COC), vaginal ring or contraceptive patch)*

The application with Drovelis preferably starts on the day after the last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC.
In case a vaginal ring or contraceptive patch has been used Drovelis should preferably be used on the day of removal, but at the latest when the next application would have been due.

- *Changing from a progestogen-only-method (minipill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)*

The switch can be done any day from the minipill (from an implant or a progesterone-releasing IUS at the earliest on the day of its removal, from an injectable when the next injection would be due) but it should in all of these cases be advised to additionally use a non-hormonal contraceptive method for the first 7 consecutive days of tablet-taking.

- *Following first-trimester abortion*

The intake of Drovelis may start immediately. When doing so, she does not need to take additional contraceptive measures.

- *Following delivery or second-trimester abortion*

When deciding at what time after a birth or after an abortion in the 2nd trimester the use of a CHC such as Drovelis can be (re)started, it must be taken into account that the risk of venous thromboembolic events is increased postpartum (during up to 12 weeks; see “Warnings and precautions”).
Women should be advised to start taking Drovelis at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of COC use or the woman has to wait for her first menstrual period.

Management of forgotten tablets

Placebo tablets from the last row of the blister can be disregarded. However, they should be discarded to avoid unintentionally prolonging the placebo tablet phase.

The following advice only refers to **forgotten active tablets**.

If it is noticed **within 12 hours** that the tablet was forgotten to be taken at the usual time, the tablet must be taken immediately. The following tablets are to be taken again at the usual time of day. In this way contraceptive protection will not be affected.

If she is **more than 12 hours** late in taking any pink tablet, contraceptive protection may be reduced. The following two basic rules apply to the missed intake:

1. Tablet-taking must never be discontinued for longer than 7 days (the recommended hormone-free tablet interval is 4 days).
2. At least seven days of regular tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

This results in the following procedure depending on the intake week:

Day 1-7
The user should take the forgotten tablet as soon as the missed dose is noticed, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a non-hormonal contraceptive method such as a condom must be used until she has completed 7 days of uninterrupted pink tablet-taking. If intercourse took place in the preceding 7 days, the possibility of a pregnancy must be considered.
The more tablets are missed and the closer they are to the placebo phase, the higher the risk of a pregnancy.

Day 8-14
The forgotten tablet should be taken as soon as the missed dose is noticed, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the intake of the tablets has been done regularly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if the user has missed more than 1 tablet, the woman must be advised to use extra non-hormonal contraceptive methods until she has completed 7 days of uninterrupted pink tablet-taking.

Day 15-24
There is a risk of reduced reliability because of the forthcoming placebo phase. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, she should follow the first of these two options and use an extra non-hormonal contraceptive method until she has completed 7 days of uninterrupted pink tablet-taking as well.

1. The user should take the forgotten tablet as soon as the missed dose is noticed, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until the active tablets are used up. The 4 placebo tablets from the last row won’t be taken and must be discarded. The next blister pack must be started right away. The user is unlikely to have a withdrawal bleed until the end of the active tablets section of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.
2. The intake of the active tablets from the current blister pack is discontinued. After an interval of up to 4 days without taking the tablets (including the days on which the tablets were forgotten to be taken), the women should continue with the next blister pack.

If there is no withdrawal bleed in the next placebo phase, the possibility of a pregnancy must be considered.

Procedure in the case of gastrointestinal disorders

In case of severe gastro-intestinal disturbances – regardless of their cause (e.g. also medication-induced diarrhoea) - absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after active tablet-taking, the basic rules given in *Management of forgotten tablets"* are applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) from another blister pack.

How to postpone a withdrawal bleed

To delay a period, tablet taking should be continued with another blister pack of Drovelis without taking the 4 placebo tablets from the current pack. The extension can be carried on for as long as wished (the longest until the end of the active tablets in the second pack). During the extension there might be breakthrough-bleeding or spotting. Regular intake of Drovelis is then resumed after the placebo phase.

Shifting withdrawal bleed

To shift the periods to another day of the week, the forthcoming placebo phase can be shortened by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the subsequent pack

Mode of administration

Oral use.

Special dosage instructions

Children and adolescents

Limited data are available on the use of Drovelis in adolescents. Until further safety data are available, Drovelis is not approved for use in adolescents (see "Warnings and precautions "). There is no indication in pre-menarche girls.

Elderly patients

There is no indication after menopause.

Patients with impaired hepatic function

Drovelis has not been studied in patients with hepatic impairment. Drovelis is contraindicated in women with severe hepatic disease.

Patients with impaired renal function

Drovelis has not been specifically studied in patients with renal impairment. Drovelis is contraindicated in severe renal insufficiency. In women with mild to moderate renal insufficiency, potassium levels should be monitored.

Contraindications

- existence or risk of venous thromboembolism (VTE)
  - venous thromboembolism – existing VTE (also under therapy with anticoagulants) or a history of VTE (e.g. deep vein thrombosis or pulmonary embolism);
  - presence of strong risk factors for venous thromboembolic events such as hereditary or acquired predisposition to venous thromboembolic events such as APC resistance (including factor V Leiden mutation), antithrombin III deficiency, protein C deficiency or protein S deficiency;
  - simultaneous presence of multiple risk factors for venous thromboembolic events, as described in the section “Warnings and precautions”.
- existence or risk of arterial thromboembolism (ATE)
  - existing or previous arterial thromboembolic events and their prodromes (e.g. angina pectoris, myocardial infarction, transient ischemic attack, cerebrovascular insult)
  - presence of strong risk factors for arterial thromboembolic events such as
    - diabetes mellitus with vascular complications
    - severe arterial hypertension
    - severe dyslipoproteinemia
    - migraine with focal neurological symptoms (also in the anamnesis)
    - hereditary or acquired predisposition to arterial thromboembolism,
    - such as hyperhomocysteinemia or antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant)
  - simultaneous presence of multiple risk factors for arterial thromboembolic events, as described in the section “Warnings and precautions”;
- existing or previous severe liver disease, as long as abnormal liver function parameters persist;
- severe renal insufficiency and acute renal failure;
- existing or previous benign or malignant liver tumours;
- existing or suspected malignant diseases of the genital organs or of the mammae, if they are sex hormone dependent;
- unexplained vaginal bleeding;
- suspected or existing pregnancy;
- hypersensitivity to the active substances or to any of the excipients of Drovelis.

Warnings and precautions

The use of a CHC increases the risk of venous thromboembolism (VTE) and arterial thromboembolism (ATE) compared to non-use. Warnings and precautions, which are described below, must be taken into account before each prescription (see “Risk of venous thromboembolism (VTE)” and “Risk of arterial thromboembolism (ATE)”). It is important to make the patient aware of the information about venous and arterial thrombosis (including the risk of using Drovelis compared to other CHCs), in particular the possible symptoms of VTE and ATE and the known vascular risk factors and what to do if thrombosis is suspected.
The benefits of using a CHC such as Drovelis should be weighed against the diseases/risks listed below – taking into account the severity of each individual or the combination of several factors – and discussed with each patient before deciding to prescribe Drovelis (see also “Contraindications”). The patient should also be instructed to read the package leaflet carefully and to follow the advice given in it.

Medical examination

Before starting or restarting the use of a CHC such as Drovelis, a thorough personal and family history should be taken, and a thorough general and gynaecological examination should be carried out, taking into account the “Contraindications” and “Warnings and precautions”, in order to be able to determine any illnesses requiring treatment and their risk factors and to exclude pregnancy. These examinations generally include blood pressure, mammae, abdomen, pelvic organs (incl. cervical cytology) and relevant laboratory studies.
During the use of the CHC, these examinations must be repeated at regular intervals, whereby frequency and type should be adapted to the individual user and should be based on the guidelines of the Swiss Society for Gynaecology and Obstetrics (SGGG). During these controls, the contraindications (e.g. a transient ischemic attack) and risk factors (e.g. family history of venous or arterial thrombosis, see “Risk factors for VTE” and “Risk factors for ATE”) should be checked again, as these may appear for the first time while using a CHC.

Reasons for immediate discontinuation

The user must be informed that if one of the above-mentioned contraindications appear or one of the following situations occurs, she must consult a doctor as soon as possible, who will then decide on the further use of the CHC:

- first appearance or exacerbation of migraine-like symptoms or more frequent occurrence of unusually severe headaches;
- sudden visual, hearing, speech or other perceptual disorders;
- first signs of thromboembolic events (see “Symptoms of VTE (deep vein thrombosis and pulmonary embolism)” and “Symptoms of ATE”);

- at least 4 weeks before planned surgery and during immobilisation (e.g. after an accident or surgery);
- clinically relevant increase in blood pressure (in the case of repeated measurement);
- occurrence of jaundice, hepatitis, or generalised pruritus;
- severe upper abdominal pain or enlargement of the liver;
- severe depressive states;
- pregnancy or suspected pregnancy.

All the information below is based on data obtained with CHCs containing ethinylestradiol. Drovelis contains Estetrol as the estrogen component. No information is yet available on possible differences in the risk profile between ethinylestradiol and estetrol. It can be assumed that these warnings also apply in a comparable way to the use of Drovelis.

Risk of venous thromboembolism (VTE)

The use of each CHC increases the risk of VTE compared to non-use. Products containing low-dose ethinylestradiol (< 50 micrograms ethinylestradiol) in combination with levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. It is not yet known how high this is under Drovelis compared to these low-risk medicines.
The decision to use the medicine should only be made after talking to the patient to make sure she understands:

- The risk of VTE associated with taking Drovelis.
- How do pre-existing individual risk factors affect this risk?
- The highest risk increase for VTE is in the first year of use (especially during the first 3 months).
- Existing data suggests that this increased risk exists both at the time of first use of a CHC and when re-using the same or another CHC (after at least a 4-week or longer application-free interval).
- Drovelis is a medicine. In the event of an accident or surgery, the user must inform the attending doctor that she is taking Drovelis.

About 2 out of every 10,000 women who do not use CHCs and are not pregnant suffer a VTE over the course of a year. For an individual woman, however, the risk may be significantly higher depending on her underlying risk factors (see below).

Epidemiological studies in women who use CHCs containing low dose ethinylestradiol (<50 µg) and drospirenone have found that out of 10,000 women about 9-12 will develop a VTE in one year; approximately 5-7 out of every 10,000 women who use CHCs containing levonorgestrel.

It is not yet known how the risk of the combination of estetrol and drospirenone compares to that of a combination of ethinylestradiol and levonorgestrel.

The number of VTEs per year when using low-dose CHCs is lower than the expected number during pregnancy or in the postpartum period.

VTEs are fatal in 1-2% of cases.

Very rarely, users of CHCs have reported venous thrombosis outside the extremities, such as sinus vein thrombosis or thrombosis in hepatic, mesenteric, renal or retinal veins.

Risk factors for VTE

The risk of venous thromboembolic complications in users of CHC may increase significantly if the user has additional risk factors, especially if several risk factors are present at the same time (see table). In particular, the benefit-risk assessment should take into account the fact that the risk of venous thromboembolic events may be over-additive if a combination of risk factors is present. In such case, the overall risk for a VTE must be considered. Drovelis is contraindicated if a woman has multiple risk factors present at the same time, exposing her to a high risk of venous thrombosis.

Table 1: Risk factors for VTE

Risk factor	Comment
Obesity (body mass index [BMI] over 30 kg/m²).	The risk increases significantly with increasing BMI. Especially important if other risk factors are present.
Prolonged immobilisation, major surgery, any leg or hip surgery, neurosurgical procedure or severe trauma.	In these cases, it is advisable to stop taking the film-coated tablets (in the case of elective operations at least four weeks in advance) and to resume taking them at the earliest two weeks after regaining full mobility. If necessary, another contraceptive method should be used to prevent unwanted pregnancy. A drug-based thrombosis prophylaxis must be considered if Drovelis has not been previously discontinued.
Positive family history (any venous thromboembolism in a sibling or parent, especially at a relatively young age, e.g. younger than 50).	If a genetic predisposition is suspected, the patient should be referred to a specialist for advice before a decision is made about taking Drovelis. If the examination shows evidence of thrombophilia, the use of Drovelis is contraindicated.
Other conditions associated with an increased risk of VTE.	Systemic lupus erythematosus, haemolytic uremic syndrome, inflammatory bowel disease (Crohn's disease or ulcerative colitis), sickle cell anaemia, malignant diseases.
Increasing age.	Especially over the age of 35.

Note: Temporary immobilisation such as a flight of more than 4 hours duration may also be a risk factor for a VTE, especially in women with other risk factors.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.

It should be noted that the risk of thromboembolic events is higher in the postpartum period. There is data to suggest that the risk of thrombosis may be higher for up to 12 weeks after delivery.

Symptoms of VTE (deep vein thromboembolism and pulmonary embolism)

The patient is advised to seek medical attention immediately if one or more of the following symptoms occur and to inform the healthcare professional that she is taking Drovelis.

- Symptoms of deep vein thrombosis may be
    - unilateral swelling in one leg and/or the foot or along a vein in the leg;
    - feeling of tightness or pain in one leg, even if these are only noticeable when standing or walking;
    - overheating, redness or discoloration of the skin on the affected leg.
- Symptoms of pulmonary embolism can be
    - sudden inexplicable shortness of breath, rapid breathing, effort intolerance;
    - sudden onset of coughing, possibly with bloody sputum;
    - sudden severe pain in the chest, which may increase with deep breathing;
    - severe drowsiness, dizziness, or anxiety;
    - tachycardia or arrhythmias.

Some of these symptoms (e.g., ‘shortness of breath’, ‘coughing’) are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

Risk of arterial thromboembolism (ATE)

Epidemiological studies have also linked the use of hormonal contraceptives to an increased risk of arterial thromboembolic events (such as myocardial infarction, stroke or transient ischemic attacks). Before deciding to prescribe Drovelis, the patient must be informed about this risk and, in particular, how any pre-existing individual risk factors may further increase that risk.
Thrombosis in other blood vessels (such as hepatic, mesenteric, renal or retinal arteries) has been reported very rarely in CHC users.

Risk factors for ATE

There is an increased risk of cerebrovascular insult or other arterial thromboembolic complications in women with CHC, especially in women who already have risk factors for such diseases (see table 2). In particular, the benefit-risk assessment must take into account the fact that the risk for arterial thromboembolic events may be over-additive if a combination of risk factors is present. In such case, the overall risk for an ATE must be considered. Drovelis is contraindicated for patients who are at high risk of ATE due to the presence of a serious risk factor or of multiple risk factors.

Table 2: Risk factors for ATE

Risk factor	Comment
Increasing age.	Especially over the age of 35.
Smoking.	Women are advised not to smoke if they would like to use a CHC such as Drovelis. Women over the age of 35 who continue to smoke are strongly advised to use a different method of contraception.
Arterial hypertension.	
Diabetes mellitus	In diabetic women with pre-existing vascular complications, the use of CHC is contraindicated.
Dyslipoproteinemia	
Valvular heart disease	
Atrial fibrillation	
Obesity (body mass index over 30 kg/m²)	The risk increases significantly with increasing BMI. Especially important in women with additional risk factors
Positive family history (any arterial thromboembolism in a sibling or parent especially at relatively young age, i.e. younger than 50).	If a genetic predisposition is suspected, the patient should be referred to a specialist for advice before a decision is made about taking Drovelis. If the examination shows evidence of thrombophilia, the use of Drovelis is contraindicated.
Migraine.	An increase in the frequency or severity of a migraine while taking Drovelis may be a prodrome symptom of a cerebrovascular event and may be a cause for immediate discontinuation.

Other diseases associated with increased risk for ATE..	Hyperhomocysteinemia, systemic lupus erythematosus, sickle cell anaemia, malignant diseases.

Symptoms of ATE

The patient is advised to seek medical attention immediately if one or more of the following symptoms occur and to inform the healthcare professionals that she is taking Drovelis.
Symptoms of cerebrovascular insult may be

- sudden numbness or weakness of the face, an arm or a leg, especially on one half of the body;
- sudden confusion;
- indistinct articulation or problems with understanding;
- sudden vision problems in one or both eyes;
- sudden walking disorders;
- vertigo;
- balance or coordination disorders;
- sudden severe or prolonged headache of unknown cause;
- loss of consciousness or fainting with or without seizure.

Symptoms of myocardial infarction may be

- pain, discomfort, pressure, heaviness, a feeling of tightness or tension in the chest, in the arm or behind the breastbone;
- complaints that radiate in the back, jaw, neck, arm or stomach;
- feeling of fullness, stomach upset or gagging;
- sweating, nausea, vomiting or dizziness;
- extreme weakness or anxiety or shortness of breath;
- tachycardia or arrhythmias

Other symptoms of vascular occlusion may be

- sudden pain, swelling or slight cyanosis of a limb;
- acute abdomen.

Suspected hereditary or acquired predisposition to thromboembolic complications

If there is a suspicion of a hereditary or acquired predisposition to thromboembolic complications, a coagulation-physiological examination by a specialist is indicated, which may result in a determination of certain haemostatic parameters.

Tumour diseases

In some epidemiological studies, an increased risk of cervical carcinoma has been reported with long-term use of CHC (>5 years). However, to what extent this result is influenced by other factors such as human papillomavirus (HPV) infection (the strongest risk factor), the frequency of cervical screening or sexual behaviour is still the subject of controversy.

A meta-analysis of 54 epidemiological studies has shown that the relative risk (RR) of being diagnosed with breast cancer is slightly elevated in women using CHCs (RR = 1.24). After discontinuation of the CHC, the increased risk gradually diminishes and is no longer detectable after 10 years. Because breast cancers are rare before the age of 40, the additional number of breast cancers diagnosed is low in relation to the overall risk of breast cancer in women using or until recently using CHC. These studies provide no evidence of causality. The observed increase in risk may be due to both CHC early detection and to the biological effects of the CHC, or both. Breast carcinomas in women who had used a CHC tended to be less advanced at the time of diagnosis than in women who had never used a CHC.

In rare cases, benign and, even more rarely, malignant, liver tumours have been reported with the use of sex hormones such as those contained in Drovelis. In individual cases, these tumours have led to life-threatening intra-abdominal haemorrhages. A liver tumour should be considered in the differential diagnosis if severe upper abdominal pain, enlarged liver, or signs of intra-abdominal haemorrhage occur in women on CHC.

Depressive disorders

Depression or depressive moods are known to be possible undesirable effects when using sex hormones, including hormonal contraceptives (see also the section on “Undesirable effects”). Such disorders can occur shortly after the start of treatment. Depression can be severe and is a risk factor for suicide or suicidal behaviour. Users of hormonal contraceptives should therefore be informed about possible symptoms of depressive disorders. The user is strongly advised to contact a doctor immediately if she experiences mood swings or other symptoms of depression while using the contraceptive.
Users with a history of severe depression should be carefully monitored. If severe depression recurs while using Drovelis, the medicine must be discontinued.

Cycle control

With all CHCs, especially during the first months of use, unscheduled bleeding (spotting or bleeding) may occur. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles. In the phase III trials, unscheduled bleeding or spotting occurred in 14%

to 20% of women using Drovelis. Most of these episodes concerned spotting only (not requiring any sanitary protection).
In a phase II study, 16.9% of women experienced unscheduled bleeding in the 6th cycle of use. Regular withdrawal bleeding occurred in 96.5% of women.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered, and adequate diagnostic measures should be initiated to exclude malignancy or pregnancy. These may include curettage.

Withdrawal bleeding may not occur during the placebo tablet phase. With Drovelis, this was the case in 6-8% of users in the studies. If Drovelis has been taken according to the instructions as described in section “Dosage/Administration”, pregnancy is unlikely. However, pregnancy must be ruled out before Drovelis use is continued, if Drovelis has not been taken as directed, or if two consecutive withdrawal bleeds do not occur.

Other precautions

Women who use a hormonal contraceptive should not be treated concomitantly with St. John’s wort preparations (*Hypericum perforatum*), because the contraceptive effect may be compromised as a result. Intermediate bleeding and isolated cases of unwanted pregnancies have been reported (see also “Interactions”).

In patients with renal insufficiency, the potassium excretion capacity may be limited. In a clinical study, drospirenone showed no effect on the serum potassium concentration in patients with mild to moderate renal insufficiency. A theoretical risk of hyperkalemia can be suspected in patients with renal insufficiency, in women whose serum potassium values were in the upper reference range before treatment and in women taking potassium-sparing drugs.

In women with existing or familial hypertriglyceridemia, taking a CHC may increase the risk of pancreatitis.

Although small increases in blood pressure are reported relatively frequently with the use of CHC, clinically relevant increased values are rare. If the use of a CHC results in a clinically significant increase in blood pressure, the CHC should be discontinued. Where appropriate, recommencing the use of the CHC may be considered when blood pressure levels (under antihypertensive treatment) have returned to normal.

Reduced glucose tolerance has been reported in those taking CHCs. Diabetics and women with reduced glucose tolerance should therefore be carefully monitored during the use of a CHC,

especially during the first few months. An adjustment of the antidiabetic therapy, however, is generally not required.

Acute or chronic disorders of liver function may require cessation of the CHC until liver function has returned to normal.

If cholestatic jaundice that has occurred for the first time during a pregnancy or during previous use of sex steroid hormones, reoccurs, use of the CHCs must be discontinued.

In patients with hepatitis C who were simultaneously taking an ethinylestradiol-containing CHC, an increase in ALT was observed significantly more frequently when the drug combination ombitasvir/paritaprevir/ritonavir was used with or without dasabuvir (including cases of an increase to more than five times, and in individual cases, more than 20 times, the upper limit of the normal range) than in patients who were treated exclusively with the antiviral drugs (see “Interactions”). Similar ALT elevations were also observed with anti-HCV drugs containing glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir. In contrast, when estradiol or estradiol valerate-containing hormone preparations were used, the ALT values were comparable to those in patients without estrogen therapy. However, the number of women taking such estrogens was small; no such data are available for Estetrol. Therefore, caution is advised even if Drovelis is administered concomitantly with one of the above-mentioned combinations of active ingredients.

Estrogens can increase the lithogenicity of bile. Cholelithiasis and other gallbladder diseases (e.g. cholecystitis) have been reported in association with the use of hormonal contraceptives.

In women with hereditary and/or acquired angioedema, exogenous estrogens may induce or exacerbate the symptoms of angioedema.

The following conditions can occur or be adversely affected during pregnancy as well as during the use of a CHC, but the available data do not allow clear conclusions to be drawn about an association with the use of a CHC: cholestatic jaundice and/or pruritus; cholelithiasis; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; chorea minor; herpes gestationis; otosclerosis-related hearing loss. The use of CHCs has also been associated with the occurrence of regional Crohn’s disease and ulcerative colitis.

In predisposed women, the use of CHCs may occasionally cause a chloasma that is exacerbated by intense sun exposure. Women who are prone to this should therefore not expose themselves to strong UV radiation.

Users must be informed that the use of hormonal contraceptives does not protect against HIV infection and sexually transmitted diseases.

Adolescents after menarche

Because the specific risk of thromboembolic events with Drovelis cannot be assessed to date, particularly when compared to second-generation contraceptives (see “Risk of venous thromboembolism (VTE)”), Drovelis is not approved for use in adolescents <18 years of age pending further (epidemiologic) data.

Excipients

Each pink film-coated tablet contains 40 mg, each white film-coated placebo tablet 68 mg, of lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say is essentially ”sodium-free”.

Interactions

To identify potential interactions, the product information of concomitantly administered medicinal products should also be consulted.

Pharmacokinetic interactions

Influence of other drugs on the pharmacokinetics of hormonal contraceptives

Enzyme inducers

Interactions between hormonal contraceptives and medicines that induce microsomal enzymes (especially cytochrome P450 enzymes) and thereby cause increased clearance of sex hormones can lead to decreased contraceptive efficacy and breakthrough bleeding. This applies, for example, to barbiturates, bosentan, carbamazepine, felbamate, modafinil, oxcarbazepine, phenytoin, primidone, rifabutin, rifampicin and topiramate, as well as to medicines containing St. John’s wort (*Hypericum perforatum*).

An enzyme induction can already be observed after a few days. The maximum enzyme induction is generally reached after 2-3 weeks and can persist for 4 or more weeks after discontinuation of these drugs.
Women on short-term treatment with any of these medicines should be encouraged to temporarily use a non-hormonal contraceptive method in addition to CHC or to choose a different type of contraception. The barrier method should be used during the concomitant use of the medicinal product and for a further 28 days after discontinuation of the treatment. If concomitant use of an

enzyme inducer is continued beyond the end of the current pack of Drovelis, the next pack of Drovelis should be started immediately after taking the active ingredient-containing film-coated tablets, i.e. skipping the 4 placebo film-coated tablets.

In the case of a long-term treatment with medicinal products that induce enzyme induction in the liver, alternative, non-hormonal methods of contraception should be used.

In addition, it is known that various inhibitors of HIV/HCV protease and non-nucleoside reverse transcriptase can lead to a decrease or an increase in the plasma concentrations of estrogens or gestagens. These changes may be clinically relevant in some cases.
In particular, although protease inhibitors such as ritonavir or nelfinavir (including combinations thereof) are known to be potent inhibitors of CYP3A4, when administered concomitantly with steroid hormones they may have enzyme-inducing properties and thereby reduce the plasma levels of estrogens and gestagens.

Enzyme inhibitors

CYP3A4-inhibitors

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), macrolide antibiotics (clarithromycin, erythromycin), cobicistat, diltiazem and verapamil may increase the plasma levels of estrogens and/or gestagens and thereby lead to an increase in the incidence of undesirable effects.
In a multiple-dose study with a combination of drospirenone (3 mg/day) and ethinylestradiol (0.02 mg/day), simultaneous administration for 10 days of the strong CYP3A4 inhibitor ketoconazole increased the $AUC_{(0-24h)}$ of drospirenone by a factor of 2.68 (90% CI: 2.44, 2.95). The $AUC_{(0-24h)}$ of ethinylestradiol increased by a factor of 1.40 (90% CI: 1.31, 1.49).

UGT-inhibitors

Estetrol is predominantly glucuronised by UDP-glucuronosyltransferase (UGT) 2B7 enzyme (see ‘Pharmacokinetics’). Co-administration of a single dose of estetrol/drospirenone (15 mg/3 mg) with the UGT inhibitor valproic acid (500 mg 2x daily for 11 days with a final single dose on Day 12) resulted in an increase in the exposure of estetrol compared to taking estetrol alone: the Geometric Mean ratio (90% confidence interval) of estetrol C_{max} was 1.36 (1.11 – 1.65), estetrol $AUC_{(0-tlast)}$ was 1.25 (1.09 – 1.42), and estetrol $AUC_{(0-inf)}$ was 1.13 (1.03 – 1.24). This increase in estetrol exposure is judged to be clinically irrelevant and no dose adjustment is recommended.

Transporters

In vitro studies indicated that estetrol is a substrate of P-gp and BCRP transporters. Co-administration of drugs that affect the activity of these transporters is however unlikely to result in a clinically relevant drug interaction.

Interference with enterohepatic circulation

In the case of the concomitant, short-term (up to 10-day) use of antibiotics that do not interact with the CYP3A4 enzyme system, pharmacokinetic interactions are not expected. When advising the patient, however, it should be taken into account that the underlying disease (e.g. venereal disease) for which the antibiotic is used may require the additional use of a barrier method.
There is insufficient data on the possible interactions in respect of long-term co-medication with antibiotics (e.g. in the case of osteomyelitis or borreliosis). If pregnancy is to be safely avoided, additional use of a barrier method is recommended in such cases, during antibiotic therapy and during the first 7 days after stopping taking the drug.
If diarrhoea and/or vomiting occur during antibiotic therapy, the information given in the section “Procedure in the case of gastrointestinal disorders” under the section “Dosage/Administration” must also be observed.

Influence of hormonal contraceptives on the pharmacokinetics of other drugs

Hormonal contraceptives can also influence the pharmacokinetics of some other drugs through various mechanisms of interaction. They can inhibit the hepatic microsomal enzymes or induce hepatic conjugation, in particular glucuronidation. Accordingly, the plasma and tissue concentrations of other drugs can either be increased (e.g. cyclosporin) or decreased (e.g. lamotrigine, see below). Furthermore, the pharmacological effect of selected substances of the following classes of drugs can be influenced: Analgesics, antidepressants, antidiabetics, antimalarials, benzodiazepines, beta-blockers, corticosteroids, and oral anticoagulants. The changes in plasma levels resulting from these interactions are not clinically relevant in all cases.
Drospirenone showed weak to moderate inhibition of the cytochrome P450 enzymes CYP1A1, CYP2C9, CYP2C19 and CYP3A4 *in vitro*. However, based on the findings of clinical interaction studies with omeprazole, simvastatin and midazolam as marker substrates, an interaction of 3 mg drospirenone with the cytochrome P-450 metabolism of other drugs is unlikely.
A possible influence of estetrol on the activity of numerous enzymes and transport proteins has been investigated in *in vitro* studies. Based on these data, it is unlikely that estetrol induces the CYP450 enzymes CYP1A2, CYP2B6 or CYP3A4 at clinically relevant doses. Inhibition of the CYP enzymes CYP3A4, CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6 and CYP2E1 as well as the UGT enzymes UGT1A1, UGT1A3, UGT1A4, UGT1A6, UGT1A7, UGT1A8, UGT1A9, UGT1A10, UGT2B4, UGT2B7, UGT2B10, UGT2B15 and UGT2B17 is also unlikely. The same is true for

inhibition of the drug transporters P-gp, BCRP, OAT1, OAT3, OCT2, MATE1 and MATE2-K. *In vitro* data indicate a minimal inhibition of OATP1B1/3 by estetrol.

Lamotrigine

An interaction study with the anti-epileptic lamotrigine and a combined oral contraceptive (0.03 mg ethinylestradiol/0.15 mg levonorgestrel) showed a clinically relevant increase in lamotrigine clearance with a corresponding significant decrease in lamotrigine plasma levels when these drugs were administered concomitantly. Such a reduction in plasma concentrations may be associated with reduced seizure control. It is not known to what extent these findings can be applied to other combined contraceptives with other gestagen components and/or other estrogen doses. However, it can be assumed that these preparations have a comparable potential for interaction.
Therefore, if a patient on lamotrigine starts taking Drovelis for the first time, the dose of lamotrigine may need to be adjusted and the lamotrigine concentration should be closely monitored at the start of therapy. It should also be noted in particular that there may be a significant increase in the level of lamotrigine (possibly toxic) if the hormonal contraceptive is discontinued (and possibly during the 4-day treatment breaks).

Pharmacodynamic interactions

Serum potassium should be monitored if Drovelis is taken at the same time as medicinal products that increase serum potassium concentrations (angiotensin II receptor antagonists, potassium-sparing diuretics, aldosterone antagonists). Possible interactions were investigated in studies in which a combination of drospirenone and estradiol was administered. There were no clinically relevant or statistically significant differences in the serum potassium concentrations when administered together with an ACE inhibitor or NSAIDs (e.g. indomethacin).

Interactions of unknown mechanism

In clinical studies, the co-administration of CHC-containing ethinylestradiol together with one of the active ingredient combinations ombitasvir/paritaprevir/ritonavir with or without dasabuvir; glecaprevir/pibrentasvir; or sofosbuvir/velpatasvir/voxilaprevir used in the treatment of HCV infections, showed a significantly more frequent increase in ALT compared with patients who were treated exclusively with the antiviral active ingredients (including cases of an increase to over five times, and in individual cases to over 20 times, the upper limit of the normal range [ULN]). When using estradiol or estradiol valerate simultaneously, however, the incidence of a clinically relevant increase in ALT was not higher than in patients without estrogen therapy, although the number of cases was limited. No corresponding data are available for Estetrol. Due to insufficient experience with estrogens other than ethinyl estradiol, caution should be exercised in the case of concomitant use with one of the above-mentioned active substance combinations.

Pregnancy, lactation

Pregnancy

Drovelis is contraindicated during pregnancy. Before starting to take the medicine pregnancy should be ruled out. If pregnancy occurs while taking the drug or is suspected, the drug should be discontinued immediately and the doctor should be consulted.
There is evidence of fetal risks based on animal studies (see “Preclinical Data”). However, most epidemiological studies conducted to date have not provided clear evidence of embryotoxic or teratogenic effects when combinations of estrogens and progestins have been inadvertently used during pregnancy.

Lactation

The drug should not be taken during breastfeeding as milk production may be reduced and milk quality may be altered and low concentrations of active substance may be measured in the milk. If possible, non-hormonal contraceptive methods should be used until the child is completely weaned. On the postpartum risk of thromboembolic events in the mother, see “Dosage/Administration” and “Warnings and precautions”.

Fertility

Drovelis is indicated for oral contraception. For information on return to fertility, see ”Properties/Effects”.

Effects on ability to drive and use machines

No studies on the ability to drive or use machines have been performed.

Undesirable effects

The most serious adverse effects associated with the use of CHCs are described in section “Warnings and Precautions” (see there). Serious adverse effects include, in particular, arterial and venous thromboembolism.
The most commonly reported undesirable effects when taking Drovelis were bleeding disorders (10%), headache (3%), acne (3%), vaginal haemorrhages (3%) and dysmenorrhoea (2%).

Undesirable effects are listed below according to the MedDRA system organ class and frequency that were observed in 5 clinical studies involving a total of altogether around 3700 female subjects using Drovelis.
The following frequency conventions are used: common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000).

Infections and infestations

Uncommon: Fungal infections, vaginal infections, urinary tract infections
Rare: Mastitis

Neoplasms benign, malignant and unspecified (including cysts and polyps)
Rare: Fibroadenoma of breast

Blood disorders
Rare: decreased haemoglobin, decreased serum ferritin

Immune system disorders
Rare: Hypersensitivity reactions, lip swelling, facial swelling

Metabolism and nutrition disorders
Common: Weight fluctuation
Uncommon: Appetite disorders, changes in serum lipids
Rare: Hyperkalaemia, fluid retention, increased blood glucose

Psychiatric disorders
Common: Mood disorders and disturbances, libido changes
Uncommon: Depressions, anxiety disorders, insomnia, emotional disorders
Rare: Nervousness

Nervous system disorders
Common: Headache
Uncommon: Migraine, dizziness, paraesthesia, sleepiness
Rare: Amnesia

Eye disorders
Rare: Visual impairment, blurred vision, dry eye

Vascular disorders
Uncommon: Hot flush
Rare: Venous thromboembolic events (e.g. deep vein thrombosis, pulmonary embolism), arterial thromboembolic events (e.g. transient ischaemic attack, stroke, myocardial infarction), increased blood pressure , hypotension, varices

Gastrointestinal disorders

Common: Abdominal pain, nausea
Uncommon: Distended abdomen, vomiting, diarrhoea
Rare: Gastroesophageal reflux, colitis, gastrointestinal motility disorders, constipation, dyspepsia, flatulence, dry mouth

Diseases of the liver and gall bladder
Uncommon: Elevation of liver enzymes

Skin and subcutaneous tissue disorders
Common: Acne
Uncommon: Alopecia, hyperhidrosis (including night sweats), dry skin, rash, skin swelling
Rare: Dermatitis, pigmentation disorders (like e.g. chloasma), hirsutism, seborrhoea, pruritus, urticaria, skin discolouration

Musculoskeletal,connective tissue and bone disorders
Uncommon: Back pain
Rare: Muscle spasms, joint swelling, pain and other limb complaints

Renal and urinary disorders
Rare: Bladder spasm, abnormal urine odour, haematuria, abnormal kidney function tests

Reproductive system and breast disorders
Very common: bleeding disorders (10% e.g. metrorrhagia, menorrhagia, irregular menstruation)
Common: Breast pain, dysmenorrhoea
Uncommon: Amenorrhoea, breast swelling, vulvovaginal complaints (including foetor vaginalis, vulvovaginal dryness, vulvovaginal pain, vulvovaginal pruritus and vulvovaginal burning sensations), fluor vaginalis, premenstrual syndrome, breast mass (including fibrocystic breast disease), uterine spasm, dyspareunia
Rare: Ovarian cyst, lactation disorders, endometrial changes, pelvic pain, nipple disorders, breast discolouration, coital bleeding, ectopic pregnancy

General disorders
Uncommon: Fatigue, oedema, chest pain, abnormal sensations
Rare: Malaise, performance reduction, pain, hyperthermia

In addition, the following adverse events have been reported in users of other CHCs (see also "Warnings and precautions"): changes in glucose tolerance, pancreatitis, cholelithiasis, cholestatic jaundice, erythema nodosum, erythema multiforme.
These reports are predominantly from experience with ethinylestradiol-containing CHCs. However, it cannot be excluded that the corresponding effects may also occur during treatment with Drovelis. A causal relationship with the use of CHCs is not certain in most cases.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected new or severe adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

There has not been any experience of overdose of Drovelis. On the basis of general experience with combined hormonal contraceptives, symptoms that may possibly occur in case of taking an overdose of active tablets are nausea, vomiting and withdrawal bleeding. Vaginal bleedings may even occur in girls before their menarche, if they accidentally take the medicinal product. There are no specific antidotes and further treatment should be symptomatic.

Properties/Effects

ATC code

G03AA18

Mechanism of action

Drovelis contains the estrogen estetrol and the progestogen drospirenone. Estetrol is a physiological estrogen that is only produced during pregnancy during fetal period by the human fetal liver.

Estetrol shows high selectivity for estrogen receptors (ER) and binds preferentially to ERα, with an affinity of approximately 5% as compared to ethinylestradiol and estradiol. Non-clinical pharmacology studies show that estetrol displays dose-dependent estrogenic responses with potencies estimated to range between 1% and 10% of ethinylestradiol or estradiol, depending on the parameter evaluated. In humans, estetrol demonstrates anti-gonadotropic activity with characteristic dose-dependent decrease in both follicle-stimulating hormone (FSH) and luteinising hormone (LH).

The progestogen drospirenone possesses progestagenic, antigonadotropic, antiandrogenic and antimineralocorticoid properties. It has no estrogenic, glucocorticoid or antiglucocorticoid activity. These properties are pharmacologically similar to the natural hormone progesterone.

As with all CHCs, the contraceptive effect of Drovelis is based on various factors, the most important of which are ovulation inhibition and alteration of the cervical secretion. In addition, as a result of morphological and enzymatic changes, the endometrium provides unfavorable conditions for nidation. Furthermore, the hormonal changes induced by CHC lead to more regular cycles and reduced bleeding intensity.
After discontinuation of Drovelis, ovulation occurred in 97% of the subjects already in the first cycle.

Pharmacodynamics

Not specified.

Safety pharmacodynamics

The effect of Drovelis on haemostasis and other metabolic parameters, in particular SHBG, was investigated in a randomised, open-label trial with a total of n=98 women over 6 cycles using haemostatic biomarkers compared to combinations of ethinylestradiol with levonorgestrel or drospirenone. 38 women received Drovelis. No relevant changes in haemostasis parameters were found with Drovelis. However, these are surrogate markers that have limited predictive value for the risk of thromboembolic events in clinical practice.
With Drovelis, there was only a slight increase in sex hormone-binding globulin (SHBG).

Clinical efficacy

In a pivotal study conducted in the EU and Russia over 13 cycles in n=1577 women aged 18-50 years, the Pearl Index values were as follows:

Age group 18-35 years:
Method failure: 0.29 (upper limit 95% confidence interval 0.83);
Method and user failure: 0.44 (upper limit 95% confidence interval 1.03).

Age group 18-50 years:
Method failure: 0.25 (upper limit 95% confidence interval 0.72);
Method and user failure: 0.38 (upper limit 95% confidence interval 0.89);

In addition to the usual exclusion criteria in contraception studies, which result from the contraindications for CHC, the pivotal study also excluded women with severe heart failure or complicated valvular heart disease, as well as those with a history of pregnancy-associated cardiomyopathy at the anamnesis.
Histological examination of the endometrium in a subgroup of women (n=108) in the pivotal study revealed no abnormal findings after up to 13 treatment cycles.

Pharmacokinetics

Absorption

Estetrol

Estetrol is rapidly absorbed after oral ingestion. After intake of Drovelis, average peak plasma concentrations of 17.9 ng/mL are reached 0.5-2 hours after single ingestion.
The absolute bioavailability of estetrol has not been determined.
The overall exposure to estetrol is similar irrespective of food intake. The C_{max} of estetrol is reduced with approximately 50% after food intake.

Drospirenone

Drospirenone is rapidly and almost completely absorbed. After intake of Drovelis, C_{max} of about 48.7 ng/mL is reached at about 1-3 h after multiple ingestion. Absolute bioavailability is between 76 and 85%.
Concomitant intake of food - in contrast to fasting - does not influence bioavailability.

Distribution

Estetrol

Estetrol is subject to enterohepatic recirculation.
Estetrol does not bind to SHBG. Estetrol displayed moderate binding to human plasma proteins (45.5% to 50.4%) and human serum albumin (58.6%), and low binding to human alpha-glycoprotein (11.2%). Estetrol is equally distributed between red blood cells and plasma.

Drospirenone

Drospirenone binds to 95-97% nonspecifically to serum albumin and does not bind to SHBG (steroid hormone-binding globulin) or CBG (corticoid-binding globulin). Only 3-5% of the total serum concentrations of the active substance are present as free steroid. The mean apparent volume of distribution of drospirenone is 3.7 ± 1.2 L/kg.

Metabolism

Estetrol

Estetrol is mainly metabolically eliminated with the formation of glucuronide and sulphate conjugates. In human plasma at 0-2 h after the oral administration of 15 mg (2.8 MBq) of [^{14}C]-estetrol, 6.9% of total radioactivity was identified as unchanged estetrol, 61.3% as estetrol-16-glucoronide, 15.3% as estetrol-3-glucoronide, 11.0% as estetrol-glucoronide-sulfate and 5.5% was represented by various unassigned metabolites. The two main metabolites estetrol-3-glucuronide and estetrol-16-glucoronide have negligible estrogenic activity. UGT2B7 is mainly responsible for the formation of estetrol 16-glucoronid. It is unknown which UGT isoform is responsible for the formation of estetrol-3 glucoronid.

Drospirenone

Drospirenone is almost completely metabolised. The major metabolites in plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydrodrospirenone-3-sulfate, formed by reduction and subsequent sulfation. Drospirenone is also subject to oxidative metabolism catalysed by CYP3A4.

Elimination

Estetrol

The terminal elimination half-life ($t_{1/2}$) of estetrol was observed to be around 24 hours under steady state conditions.
Following administration of a single oral solution of 15 mg [^{14}C]-estetrol, approximately 69% of the total recovered radioactivity was detected in urine and 21.9% in faeces. In the urine (collected at 0-2 h post-dose) no unchanged estetrol was detected. 77.7% of total radioactivity was identified as estetrol-16-glucoronide, 16.3% as estetrol-3-glucoronide, 2.1% as estetrol-glucoronide-sulfate and 1.0% was represented by unassigned metabolites. In the faeces (collected at 48-72 h post-dose), 94.6% of total radioactivity was identified as unchanged estetrol. The glucuronide and glucuronide-sulfate conjugate metabolites were not detected in human faeces.

Drospirenone

Drospirenone serum levels decrease biphasically with a terminal half-life of approx. 31 hours.
The metabolic clearance is 1.2-1.4 mL/min/kg. Drospirenone is excreted unchanged in traces. Its metabolites are excreted 54-58% in the faeces and 42-46% in the urine, the elimination half-life of the metabolites is approx. 40 hours.
Linearity/non-linearity

Estetrol

In the dose range of 15–75 mg, estetrol plasma levels do not show any relevant deviation from dose-proportionality, after single administration as well as in steady-state conditions.

Drospirenone

Drospirenone plasma levels do not show any relevant deviation from dose-proportionality over the 3-15 mg dose range, after single administration as well as in steady-state conditions.

Steady-state conditions

Estetrol

Steady-state is achieved after 5 days. C_{max} of estetrol are about 17.9 ng/mL and are reached 0.5-2 hours after intake. Average serum concentrations are 2.46 ng/mL. Estetrol accumulates slightly, with an accumulation rate of 1.8.

Drospirenone

Steady-state is achieved after 10 days. C_{max} of drospirenone of about 48.7 ng/mL are reached after about 1-3 hours after dosing. The mean concentration during steady state over a 24-hour dosing period is approximately 22 ng/mL. Drospirenone accumulates after multiple intake to 2-3 times the normal dose.

Kinetics in specific patient groups

Hepatic impairment

No studies were conducted to evaluate the effect of hepatic disease on the pharmacokinetics of estetrol. In patients with moderate hepatic insufficiency, the AUC of drospirenone was doubled, the terminal half-life was prolonged by a factor of 1.8 and clearance was reduced by 50%.

Renal impairment

No studies were performed to evaluate the effect of renal disease on the pharmacokinetics of estetrol. Steady-state serum drospirenone levels in women with mild renal impairment (creatinine clearance (CLcr)=50-80 mL/min) were comparable to those of women with normal renal function. In women with moderate renal impairment (CLcr=30-50 mL/min), the serum drospirenone levels were on average 37% higher compared with those in women with normal renal function (see Dosage/Administration").

Children and adolescents

The pharmacokinetics of estetrol and drospirenone after intake of Drovelis have not been investigated in children and adolescents.

Genetic polymorphisms

No clinically relevant differences in the pharmacokinetics of estetrol or drospirenone between Japanese and Caucasian women have been observed after single dose administration of Drovelis.

Preclinical data

Repeated dose toxicity

In monkeys, ventricular histological changes were observed after repeated administration of the combination at a higher dose than in users of Drovelis (~27-fold multiple for estetrol and ~3.5-fold multiple for drospirenone), but without clinical effects.

Reproductive toxicity

Reproductive toxicity studies performed with estetrol have shown embryotoxic and fetotoxic effects in animals at clinically relevant exposures.

Genotoxicity/carcinogenicity

Genotoxicity and carcinogenicity studies were not conducted with the combination. Estetrol and drospirenone are not considered to be genotoxic. However, it is well-known that, due to their hormonal action, sex steroids can promote the growth of certain hormone-dependent tissues and tumors.
In 2-year carcinogenicity studies, estetrol caused an increase in uterine and cervical epithelial neoplasia, uterine stromal neoplasia, mammary gland neoplasms and pituitary gland neoplasia in mice and an increase in mammary gland neoplasia in rats. All neoplastic and non-neoplastic proliferative lesions were explained by the estrogenic properties of estetrol. Doses that were non-carcinogenic resulted in plasma exposures below those at therapeutic doses.

Other information

Influencing diagnostic methods

Contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of (carrier) proteins as for example the corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism as well as of coagulation and fibrinolysis. Changes are generally within the appropriate normal laboratory range. Drospirenone may cause an increase in plasma renin activity and plasma aldosterone induced by its mild anti-mineralocorticoid activity.

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the container.

Special precautions for storage

Do not store above 30°C.
Keep out of the reach of children.

Authorisation number

68228 (Swissmedic)

Packs

Drovelis 3 mg/14.2 mg film-coated tablets: Packs of:
1x28 film-coated tablets [B]
3x28 film-coated tablets [B]
6x28 film-coated tablets [B]
13x28 film-coated tablets [B]

Marketing authorisation holder

Gedeon Richter (Schweiz) AG, 1207 Geneva

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