ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼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 adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Drovelis 3 mg/14.2 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pink active tablet contains 3 mg drospirenone and estetrol monohydrate equivalent to 14.2 mg estetrol.

Each white placebo tablet does not contain active substances.

Excipient with known effect

Each pink active tablet contains 40 mg lactose monohydrate.

Each white placebo tablet contains 68 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

The active film-coated tablet is pink, 6 mm diameter, round, biconvex with a drop-shaped logo embossed on one side.

The placebo film-coated tablet is white to off-white, 6 mm diameter, round, biconvex with a drop-shaped logo embossed on one side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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) (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Posology and method of administration

How to take Drovelis

Oral use.

One tablet is to be taken daily for 28 consecutive days. 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. Each pack starts

with 24 pink active tablets, followed by 4 white placebo tablets. Each subsequent pack is started the day after the last tablet of the previous 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.
Withdrawal bleeding usually starts on day 2-3 after starting the white placebo tablets and may not have finished before the next pack is started. See 'Cycle control' in section 4.4.

How to start Drovelis

- *No preceding hormonal contraceptive use (in the past month)*

Tablet-taking has to start on day 1 of the woman's 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 woman's menstruation, this medicinal product will not be effective until after the first 7 consecutive days of pink active tablet-taking. A reliable barrier method of contraception such as a condom must therefore be used additionally during these first 7 days. The possibility of pregnancy should be considered before starting Drovelis.

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

The woman should start with Drovelis preferably on the day after the last active tablet (the last tablet containing the active substances) 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 transdermal patch has been used the woman should start using Drovelis preferably on the day of removal, but at the latest when the next application would have been due.

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

The woman may switch any day from the progestogen-only pill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due) but should in all of these cases be advised to additionally use a barrier method for the first 7 consecutive days of tablet-taking.

- *Following first-trimester abortion*

The woman may start immediately. When doing so, she needs not take additional contraceptive measures.

- *Following delivery or second-trimester abortion*

Women should be advised to start between day 21 and 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 CHC use or the woman has to wait for her first menstrual period.

For breast-feeding women see section 4.6.

Management of missed tablets

White 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 **missed pink active tablets**:

If the user is **less than 24 hours** late in taking any pink active tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as possible and should take further tablets at the usual time.

If she is **more than 24 hours** late in taking any pink active tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. The recommended hormone-free tablet interval is 4 days, tablet-taking must never be discontinued for longer than 4 days.

2. Seven days of uninterrupted pink active tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly, the following advice can be given in daily practice:

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

Day 8-17
The user should take the last missed tablet as soon as possible, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if she has missed more than 1 tablet, the woman should be advised to use extra precautions until she has completed 7 days of uninterrupted pink active tablet-taking.

Day 18-24
The risk of reduced reliability is imminent because of the forthcoming placebo tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. 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 extra precautions until she has completed 7 days of uninterrupted pink active tablet-taking as well.

1. The user should take the last missed tablet as soon as possible, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until the pink active tablets are used up. The 4 white placebo tablets from the last row 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 pink active tablets section of the second pack, but she may experience spotting or breakthrough bleeding on pink active tablet-taking days.

2. The woman may also be advised to discontinue pink active tablet-taking from the current blister pack. She should then take white placebo tablets from the last row for up to 4 days, including the days she missed tablets, and subsequently continue with the next blister pack.

If the woman missed tablets and subsequently has no withdrawal bleeding in the placebo tablet phase, the possibility of a pregnancy should be considered.

Advice in case of gastro-intestinal disturbances
In case of severe gastro-intestinal disturbances (e.g., vomiting or diarrhoea), absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after pink active tablet-taking, a new (replacement) tablet should be taken as soon as possible. The new pink active tablet should be taken within 24 hours of the usual time of tablet-taking if possible. If more than 24 hours elapse, the advice concerning missed tablets, as given in section 4.2 "*Management of missed tablets*", is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra pink active tablet(s) from another blister pack.

How to postpone a withdrawal bleed

To delay a period the woman should continue with another blister pack of Drovelis without taking the white placebo tablets from her current pack. The extension can be carried on for as long as wished until the end of the pink active tablets in the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of Drovelis is then resumed after the placebo tablet phase.

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming placebo tablet phase 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 (just as when delaying a period).

Special populations

Elderly
Drovelis is not indicated after menopause.

Renal impairment

Based on currently available data, Drovelis is contraindicated in women with severe renal insufficiency (see section 4.3).

Drovelis is not recommended in women with moderate renal impairment.
No dose adjustment for Drovelis is required in patients with mild renal impairment (see section 5.2).

Hepatic impairment
A study to evaluate the effect of hepatic disease on the pharmacokinetics of estetrol is presented in section 5.2. The study results indicate that the increase of estetrol plasma exposure in subjects with severe hepatic impairment (Child-Pugh class C) compared to subjects with a normal hepatic function could be of clinical relevance.

Based on currently available data, Drovelis is contraindicated in women with severe hepatic disease as long as liver function values have not returned to normal (see section 4.3).
Based on currently available data, no dose adjustment for Drovelis is required in patients with mild or moderate hepatic impairment (see section 5.2).

Paediatric population
Safety of Drovelis has been established in post-menarchal adolescents under age of 18 years. The contraceptive efficacy is expected to be the same in post-menarchal adolescents compared to users 18 years and older. Currently available safety and efficacy data are described in section 4.8, 5.1 and 5.2. There is no relevant use of Drovelis in pre-menarcheal adolescents.

4.3 Contraindications

As no epidemiological data are yet available for estetrol-containing CHCs, the contraindications for ethinylestradiol-containing CHCs are considered applicable to the use of Drovelis. CHCs should not be used in the following conditions. Should any of the conditions appear for the first time during Drovelis use, the medicinal product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE)
  - VTE - current VTE (on anticoagulants) or history of VTE (e.g., deep venous thrombosis [DVT] or pulmonary embolism [PE]).
  - Known hereditary or acquired predisposition for venous thromboembolism, such as activated protein C (APC)-resistance (including factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency.
  - Major surgery with prolonged immobilisation (see section 4.4).
  - A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4).

- Presence or risk of arterial thromboembolism (ATE)
  - ATE - current ATE, history of ATE (e.g., myocardial infarction [MI]) or prodromal condition (e.g., angina pectoris).
  - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g., transient ischaemic attack [TIA]).
  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
  - History of migraine with focal neurological symptoms.
  - A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms;
    - severe hypertension;
    - severe dyslipoproteinaemia.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Severe renal insufficiency or acute renal failure.
- Presence or history of liver tumours (benign or malignant).
- Known or suspected sex steroid-influenced malignancies (e.g., of the genital organs or the breasts).
- Undiagnosed vaginal bleeding.
- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Warnings

If any of the conditions or risk factors mentioned below is present, the suitability of Drovelis should be discussed with the woman before she decides to start using Drovelis.

In the event of aggravation, or first appearance of any of these conditions or risk factors, the woman should be advised to contact her doctor to determine whether the use of Drovelis should be discontinued. All data presented below are based upon epidemiological data obtained with CHCs containing ethinylestradiol. Drovelis contains estetrol. As no epidemiological data are yet available with estetrol containing-CHCs, the warnings are considered applicable to the use of Drovelis.

In case of suspected or confirmed VTE or ATE, CHC use must be discontinued. In case anticoagulant therapy is started, adequate alternative non-hormonal contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

Circulatory disorders

Risk of VTE
The use of any CHC increases the risk of VTE compared with no use. **Products that contain low dose ethinylestradiol (<50 µg ethinylestradiol) combined with levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. It is not yet known how the risk with Drovelis compares with these lower risk products. The decision to use any product other than one known to have the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with CHCs, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use.**

There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.

In women who do not use a CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

Epidemiological studies in women who use low dose (<50 µg ethinylestradiol) combined hormonal contraceptives have found that out of 10,000 women between about 6 and 12 will develop a VTE in one year.

It is estimated[1] that out of 10,000 women who use a CHC containing ethinylestradiol and drospirenone, between 9 and 12 women will develop a VTE in one year; this compares with about 6[2] in 10,000 women who use a levonorgestrel-containing CHC.

It is not yet known how the risk of VTE with CHC containing estetrol and drospirenone compares with the risk with low dose levonorgestrel-containing CHCs.

The number of VTEs per year with low-dose CHCs is fewer than the number expected in women during pregnancy or in the postpartum period.

VTE may be fatal in 1-2% of cases.

Extremely rarely, thrombosis has been reported to occur in CHC users in other blood vessels, e.g., hepatic, mesenteric, renal or retinal veins and arteries.

Risk factors for VTE
The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see table 1).

Drovelis is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table 1: Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index [BMI] over 30 kg/m²).	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma. Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors.	In these situations, it is advisable to discontinue use of the pill (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Drovelis has not been discontinued in advance.

[1]These incidences were estimated from the totality of the epidemiological study data, using relative risks for the different products compared with levonorgestrel-containing CHCs.
[2] Mid-point of range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6

Positive family history (VTE ever in a sibling or parent especially at a relatively early age, e.g., before 50 years).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.
Other medical conditions associated with VTE.	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.
Increasing age.	Particularly above 35 years.

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

The increased risk of thromboembolism in pregnancy, and particularly the 6-week period of the puerperium, must be considered (for information on pregnancy and lactation see section 4.6).

Symptoms of VTE (DVT and PE)
In the event of symptoms, women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of DVT can include:
- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg which may be felt only when standing or walking;
- increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of PE can include:
- sudden onset of unexplained shortness of breath or rapid breathing;
- sudden coughing which may be associated with haemoptysis;
- sharp chest pain;
- severe light headedness or dizziness;
- rapid or irregular heartbeat.

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).
Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.
If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of ATE
Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (myocardial infarction [MI]) or for cerebrovascular accident (e.g., TIA, stroke). Arterial thromboembolic events may be fatal.

Risk factors for ATE
The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table 2). Drovelis is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table 2: Risk factors for ATE

Risk factor	**Comment**
Increasing age.	Particularly above 35 years.

Smoking.	Women should be advised not to smoke if they wish to use a CHC. Women over 35 years who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension.	
Obesity (BMI over 30 kg/m^2).	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors.
Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age, e.g., below 50 years).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.
Migraine.	An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation.
Other medical conditions associated with adverse vascular events.	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE
In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of a cerebrovascular accident can include:
- sudden numbness or weakness of the face, arm or leg, especially on one side of the body;
- sudden trouble walking, dizziness, loss of balance or coordination;
- sudden confusion, trouble speaking or understanding;
- sudden trouble seeing in one or both eyes;
- sudden, severe or prolonged headache with no known cause;
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggest the event is a transient ischaemic attack (TIA).

Symptoms of myocardial infarction (MI) can include:
- pain, discomfort, pressure, heaviness, sensation of squeezing or fullness in the chest, arm, or below the breastbone;
- discomfort radiating to the back, jaw, throat, arm, stomach;
- feeling of being full, having indigestion or choking;
- sweating, nausea, vomiting or dizziness;
- extreme weakness, anxiety, or shortness of breath;
- rapid or irregular heartbeats.

Tumours
An increased risk of cervical cancer in long-term users of CHCs containing ethinylestradiol (>5 years) has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human papilloma virus (HPV).

With the use of the higher-dosed CHCs (50 µg ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to estetrol-containing CHCs remains to be confirmed.

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR=1.24) of having breast cancer diagnosed in women who are currently using CHCs containing ethinylestradiol. The excess risk gradually disappears during the course of the 10 years after cessation of CHC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent CHC users is small in relation to the overall risk of breast cancer. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in CHC users, the biological effects of CHCs or a combination of both.

In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of CHCs containing ethinylestradiol. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. Therefore, a hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking CHCs.

Hepatitis C
During clinical studies with patients treated for hepatitis C virus (HCV) infection with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, ALT elevations higher than 5 times the upper limit of normal occurred significantly more frequently in women using ethinylestradiol-containing medicinal products such as CHCs. Additionally, also in patients treated with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir, ALT elevations were observed in women using ethinylestradiol-containing medications such as CHCs. Women using medicinal products containing oestrogens other than ethinylestradiol had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination therapeutic regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin and also the regimen glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir. See also section 4.5.

Other conditions
The progestogen component in Drovelis, drospirenone, is an aldosterone antagonist with potassium sparing properties. In most cases, no increase of potassium levels would be expected. In a clinical study with drospirenone, however, in some patients with mild or moderate renal impairment and concomitant use of potassium-sparing medicinal products, serum potassium levels increased slightly, but not significantly, during intake of 3 mg drospirenone for 14 days. Therefore, it is recommended to check serum potassium during the first treatment cycle with Drovelis in patients presenting with renal insufficiency and a pretreatment serum potassium in the upper reference range, and particularly during concomitant use of potassium sparing medicinal products. See also section 4.5.

Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using CHCs.

Although small increases in blood pressure have been reported in many women taking CHCs, clinically relevant increases are rare. A relationship between CHC use and clinical hypertension has not been established. However, if a sustained clinically significant hypertension develops during the use of a CHC, then it is prudent for the physician to suspend the intake of the tablets and treat the hypertension. Where considered appropriate, CHC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

The following conditions have been reported to occur or deteriorate with both pregnancy and CHC use, but the evidence of an association with CHC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of CHCs.

Although CHCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose CHCs (containing <50 µg ethinylestradiol). However, diabetic women should be carefully observed, particularly in the early stage of CHC use.

Worsening of endogenous depression, of epilepsy, of Crohn's disease and ulcerative colitis has been reported during CHC use.

Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking CHCs.

Medical examination/consultation
Prior to the initiation or reinstitution of Drovelis a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a physical examination should be performed, guided by the contraindications (see section 4.3) and warnings (see section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of Drovelis compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis. The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of examinations should be based on established practice guidelines and be adapted to the individual woman.
Women should be advised that hormonal contraceptives do not protect against human immunodeficiency virus (HIV) infection and/or acquired immunodeficiency syndrome (AIDS) and other sexually transmitted diseases.

Reduced efficacy
The efficacy of CHCs may be reduced in the event of missed tablets (see section 4.2), gastro-intestinal disturbances during pink active tablet taking (see section 4.2) or concomitant medicinal products (see section 4.5).

Cycle control
With all CHCs, unscheduled bleeding (spotting or bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles. Unscheduled bleeding or spotting occurred in 14% to 20% of women using Drovelis. Most of these episodes concerned spotting only.

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

In a small percentage of women (6-8%), withdrawal bleeding may not occur during the placebo tablet phase. If absence of withdrawal bleeding occurs and Drovelis has been taken according to the instructions as described in section 4.2, 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.

Laboratory tests

The use of 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, e.g., corticosteroid binding globulin (CBG) and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range. Drospirenone causes an increase in plasma renin activity and plasma aldosterone induced by its mild anti-mineralocorticoid activity.

Excipients
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 essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Note: The prescribing information of concomitant medicinal products should be consulted to identify potential interactions.

Pharmacokinetic interactions

Effects of other medicinal products on Drovelis

Interactions can occur with medicinal products that induce microsomal enzymes, resulting in increased clearance of sex hormones, which may lead to breakthrough bleeding and/or contraceptive failure.

- *Management*

Enzyme induction can already be observed after a few days of treatment. Maximum enzyme induction is generally observed within a few weeks. After the cessation of medicinal product therapy, enzyme induction may be sustained for about 4 weeks.

- *Short-term treatment*

Women on treatment with enzyme-inducing medicinal products should temporarily use a barrier method or another method of contraception in addition to the CHC. The barrier method must be used during the whole time of the concomitant medicinal product therapy and for 28 days after its discontinuation. If the medicinal product therapy runs beyond the end of the pink active tablets in the CHC pack, the white placebo tablets must be discarded and the next CHC pack should be started right away.

- *Long-term treatment*

In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

The following interactions have been reported in the literature.

Medicinal products increasing the clearance of CHCs (enzyme-induction), e.g.:
barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin and HIV medicinal products (e.g. ritonavir, nevirapine and efavirenz) and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal St. John's wort (*Hypericum perforatum*).

Medicinal products with variable effects on the clearance of CHCs:
When co-administered with CHCs, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of oestrogens and progestogens. The effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medicinal products should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an

additional barrier method of contraception should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Medicinal products decreasing the clearance of CHCs (enzyme inhibitors):
The clinical relevance of potential interactions with enzyme inhibitors remains unknown. Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of oestrogens or progestogens or both.

- *Potential interactions with drospirenone*

In a multiple dose study with a drospirenone (3 mg/day) / ethinylestradiol (0.02 mg/day) combination, co-administration of the strong CYP3A4 inhibitor ketoconazole for 10 days increased the area under the curve during a 24-hour period ($AUC_{(0-24\ h)}$) of drospirenone (and ethinylestradiol) 2.7-fold (and 1.4-fold, respectively).

- *Potential interactions with estetrol*

Estetrol is predominantly glucuronised by UDP-glucuronosyltransferase (UGT) 2B7 enzyme (see section 5.2 'Pharmacokinetic properties'). No clinically relevant interaction was observed with estetrol and the strong UGT inhibitor valproic acid.

Effects of Drovelis on other medicinal products

Oral contraceptives may affect the metabolism of certain other active substances. Accordingly, plasma and tissue concentrations may either increase (e.g., ciclosporin) or decrease (e.g., lamotrigine).

Based on *in vitro* inhibition studies and *in vivo* interaction studies in female volunteers using omeprazole, simvastatin and midazolam as marker substrate, an interaction of drospirenone at doses of 3 mg with the metabolism of other active substances is unlikely.

Based on *in vitro* inhibition studies, an interaction of estetrol contained in Drovelis with the metabolism of other active substances is unlikely.

Pharmacodynamic interactions

Concomitant use with the HCV medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, may increase the risk of ALT elevations in women using ethinylestradiol containing medicinal products such as CHCs (see section 4.4). Women using medicinal products containing oestrogens other than ethinylestradiol, had a rate of ALT elevation similar to those not receiving any oestrogens; however, due to the limited number of women taking these other oestrogens, caution is warranted for co-administration with the combination therapeutic regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin and also the regimen with glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir (see section 4.4).

In patients without renal impairment, the concomitant use of drospirenone and angiotensin converting enzyme (ACE)-inhibitors or non-steroidal anti-inflammatory drugs (NSAIDs) did not show a significant effect on serum potassium. Nevertheless, concomitant use of Drovelis with aldosterone antagonists or potassium-sparing diuretics has not been studied. In this case, serum potassium should be tested during the first treatment cycle. See also section 4.4.

Paediatric population

Interaction studies have only been performed in adults.

4.6 Fertility, pregnancy and lactation

Pregnancy

Drovelis is not indicated during pregnancy.

If pregnancy occurs while taking Drovelis, further intake must be stopped.

There is limited amount of data from the use of Drovelis in pregnant women.

Studies in animals have shown reproductive toxicity (see section 5.3). Based on animal experience, harmful effects due to hormonal action of the active substances cannot be excluded.

The increased risk of VTE during the postpartum period should be considered when re-starting Drovelis (see section 4.2 and 4.4).

Breast-feeding

Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the breast milk and might affect the child.

Breast-feeding may be influenced by CHCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of CHCs should not be recommended until the breast-feeding mother has completely weaned her child and an alternative method of contraception should be proposed to women wishing to breastfeed.

Fertility

Drovelis is indicated for oral contraception. For information on return to fertility, see section 5.1.

4.7 Effects on ability to drive and use machines

Drovelis has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions with Drovelis are metrorrhagia (4.3%), headache (3.2%), acne (3.2%), vaginal haemorrhage (2.7%) and dysmenorrhoea (2.4%).

Tabulated list of adverse reactions

Adverse reactions that have been identified are listed below (see table 3).
Adverse reactions are listed according to the MedDRA system organ class and ranked under frequency groupings using the following convention: common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000).

Table 3: List of adverse reactions

System organ class	Common	Uncommon	Rare
Infections and infestations		Fungal infection Vaginal infection Urinary tract infection	Mastitis
Neoplasms benign, malignant and unspecified (including cysts and polyps)			Fibroadenoma of breast
Immune system disorders			Hypersensitivity

System organ class	Common	Uncommon	Rare
Metabolism and nutrition disorders		Appetite disorder	Hyperkalaemia Fluid retention
Psychiatric disorders	Mood disorders and disturbances[1] Libido disorder	Depression[2] Anxiety disorder[3] Insomnia Emotional disorder[4] Stress	Nervousness
Nervous system disorders	Headache	Migraine Dizziness Paraesthesia Somnolence	Amnesia
Eye disorders			Visual impairment Vision blurred Dry eye
Ear and labyrinth disorders			Vertigo
Vascular disorders		Hot flush	Hypertension Venous thrombosis Thrombophlebitis Hypotension Varicose vein
Gastrointestinal disorders	Abdominal pain Nausea	Abdominal distension Vomiting Diarrhoea	Gastroesophageal reflux disease Colitis Gastrointestinal motility disorder Constipation Dyspepsia Flatulence Dry mouth Lip swelling
Skin and subcutaneous tissue disorders	Acne	Alopecia Hyperhidrosis[5] Skin disorders[6]	Dermatitis[7] Pigmentation disorder[8] Hirsutism Seborrhoea Pruritus Swelling of face Urticaria Skin discolouration
Musculoskeletal and connective tissue disorders		Back pain	Muscle spasms Limb discomfort Joint swelling Pain in extremity
Renal and urinary disorders			Bladder spasm Urine odour abnormal
Pregnancy, puerperium and perinatal conditions			Ectopic pregnancy

System organ class	Common	Uncommon	Rare
Reproductive system and breast disorders	Breast pain Metrorrhagia Vaginal haemorrhage Dysmenorrhoea Menorrhagia	Abnormal withdrawal bleeding[9] Breast swelling Vulvovaginal disorder[10] Vaginal discharge Premenstrual syndrome Breast mass[11] Uterine spasm Uterine haemorrhage Menometrorrhagia Dyspareunia	Ovarian cyst Lactation disorders Endometrial disorder Dysfunctional uterine bleeding Pelvic pain Nipple disorder Breast discolouration Coital bleeding
General disorders and administration site conditions		Fatigue Oedema Chest pain Feeling abnormal	Malaise[12] Pain Hyperthermia
Investigations	Weight fluctuation	Hepatic enzyme increased Lipids abnormal	Blood pressure increased Renal function test abnormal Blood potassium increased Blood glucose increased Haemoglobin decreased Serum ferritin decreased Blood in urine

[1] including affect lability, anger, euphoric mood, irritability, altered mood and mood swings
[2] including depressed mood, depressive symptom, tearfulness and depression
[3] including agitation, anxiety, generalised anxiety disorder and panic attack
[4] including emotional disorder, emotional distress and crying
[5] including night sweats, hyperhidrosis and cold sweat
[6] including dry skin, rash and skin swelling
[7] including dermatitis and eczema
[8] including chloasma and skin hyperpigmentation
[9] including abnormal withdrawal bleeding, amenorrhoea, menstrual disorder, irregular menstruation, oligomenorrhoea and polymenorrhoe
[10] including vaginal odour, vulvovaginal discomfort, vulvovaginal dryness, vulvovaginal pain, vulvovaginal pruritus and vulvovaginal burning sensation
[11] including breast mass and fibrocystic breast disease
[12] including malaise and decreased performance status

Description of selected adverse reactions

An increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which is discussed in more detail in section 4.4.

The following serious adverse events have been reported in women using CHCs, which are discussed in section 4.4 Special warning and precautions for use:
- Venous thromboembolic disorders;
- Arterial thromboembolic disorders;
- Hypertension;
- Liver tumours;
- Occurrence or deterioration of conditions for which association with CHC use is not conclusive: Crohn's disease, ulcerative colitis, epilepsy, uterine myoma, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice;

- Chloasma;
- Acute or chronic disturbances of liver function may necessitate the discontinuation of CHC use until markers of liver function return to normal.
- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.

The frequency of diagnosis of breast cancer is very slightly increased among CHC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with CHC use is unknown. For further information, see sections 4.3 and 4.4.

Interactions
Breakthrough bleeding and/or contraceptive failure may result from interactions of other medicinal products (enzyme inducers) with oral contraceptives (see section 4.5).

Paediatric population
In a phase 3 study including 105 adolescents aged 12 to-17 years, Drovelis was well-tolerated for 6 cycles of use and no safety concerns were raised during the study.
The most commonly reported adverse reactions in the adolescent population were dysmenorrhoea (1.9%) and nausea (1.9%). Other adverse events were reported in ≤ 1% of the study population.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Sex hormones and modulators of the genital system, progestogens and oestrogens, fixed combinations, ATC code: G03AA18

Mechanism of action

Drovelis contains the oestrogen estetrol and the progestogen drospirenone. Estetrol is an oestrogen that is only produced during pregnancy by the human foetal liver.

Estetrol demonstrates anti-gonadotropic activity characterised by a dose-dependent decrease in both serum follicle-stimulating hormone (FSH) and luteinizing hormone (LH) levels.

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

The contraceptive effect of Drovelis is based on the interaction of various factors, the most important of which is inhibition of ovulation.

Clinical efficacy and safety

Two clinical studies were performed worldwide, one pivotal study in the EU/Russia and a supportive study in the US in women between 16 and 50 years of age for 13 cycles/1 year.

The following Pearl Indices in women 18-35 years of age were found in the pivotal EU/Russia study based on a total of 14,759 cycles in which cycles with back-up contraception and cycles with no sexual activity have been excluded:
Method failure: 0.26 (upper limit 95% confidence interval 0.77);
Method and user failure: 0.44 (upper limit 95% confidence interval 1.03).

The study in the US found higher Pearl Indices than noted in the EU/Russia study. It is known that Pearl Indices of studies performed in the US are higher than noted in EU studies, but the cause of this discrepancy is unknown.

In a randomised open-label study, 97% of women in the Drovelis group demonstrated a return to ovulation by the end of the post-treatment cycle.

Endometrial histology was investigated in a subgroup of women (n=108) in one clinical study after up to 13 cycles of treatment. There were no abnormal results.

Paediatric population
A multicenter, open-label, single-arm phase 3 study to evaluate the safety, compliance and pharmacokinetics (PK) of Drovelis in post-menarchal adolescents was conducted in Europe in 105 patients aged 12 to 17 years for 6 cycles. Scheduled and unscheduled bleeding data in adolescents showed good cycle control and acceptable pattern and were consistent with those from phase 3 Studies in adult females. Treatment with Drovelis in adolescents resulted in decreased symptoms for dysmenorrhea, indicated by a decreased Visual Analogue Scale score >30% and a decreased use of rescue medication after 3 cycles of use and remained up to the end of the study. Available pharmacokinetic data are described in section 5.2.

5.2 Pharmacokinetic properties

Estetrol

Absorption
Estetrol is rapidly absorbed after ingestion. After intake of Drovelis, average peak plasma concentrations of 18 ng/mL are reached 0.5-2 hours after single ingestion.
The overall exposure to estetrol is similar irrespective of food intake. The C_{max} of estetrol is reduced with approximately 50% after food intake.

Distribution
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.

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

Biotransformation
After oral administration, estetrol undergoes extensive phase 2 metabolism to form glucuronide and sulphate conjugates. The two main metabolites estetrol-3-glucuronide and estetrol-16-glucuronide have negligible oestrogenic activity. UGT2B7 is the dominant UGT isoform involved in the

biotransformation of estetrol into a direct glucuronide. Estetrol undergoes sulfation, mainly by specific oestrogen sulfotransferase (SULT1E1).

Elimination
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.

Linearity/non-linearity
When Drovelis is administered from 1 to 5 times the dose, estetrol plasma levels do not show any relevant deviation from dose-proportionality, after single administration as well as in steady-state conditions.

Steady-state conditions
Steady-state is achieved after 5 days. C_{max} of estetrol is about 17.9 ng/mL and is reached 0.5-2 hours after dosing. Average serum concentrations are 2.46 ng/mL. The accumulation is very limited with daily area under the curve (AUC) at steady-state 60% larger than after a single dose.

Drospirenone

Absorption
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. Bioavailability is between 76 and 85%. The overall exposure to drospirenone is similar regardless of food intake around tablet intake of Drovelis.

Distribution
Drospirenone is bound to serum albumin and does not bind to SHBG or CBG. 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.

Biotransformation
Drospirenone is extensively metabolised after oral administration. The major metabolites in plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, formed by reduction and subsequent sulfation. Drospirenone is also subject to oxidative metabolism catalyzed by CYP3A4.

Elimination
After oral administration of Drovelis, serum drospirenone levels decrease with a terminal elimination half-life observed around 34 hours. The metabolic clearance rate of drospirenone in serum is 1.5 ± 0.2 mL/min/kg. Drospirenone is excreted only in trace amounts in unchanged form. The metabolites of drospirenone are excreted with the faeces and urine at an excretion ratio of about 1.2 to 1.4. The $t_{1/2}$ of metabolite excretion with the urine and faeces is about 40 h.

Linearity/non-linearity
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
Steady-state is achieved after 10 days. C_{max} of drospirenone of about 48.7 ng/mL is 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. The accumulation is very limited with daily AUC at steady-state 80% larger than after a single dose.

Special populations

Renal impairment

Estetrol
A study to evaluate the effect of renal disease on pharmacokinetics of estetrol was performed with a single oral dose of 20 mg estetrol monohydrate administered in female subjects with normal renal function, mild renal impairment (absolute glomerular filtration rate (GFR) ≥60 to <90 mL/min), moderate renal impairment (GFR ≥30 to <60 mL/min) and severe renal impairment (GFR <30 mL/min)).

C_{max} and AUC_{inf} for estetrol were ~1.1 fold and ~1.7 fold, respectively, in mild renal impairment versus subjects with normal renal function; ~1.8 fold and ~ 2.3 fold, respectively, in moderate renal impairment versus subjects with normal renal function, and ~1.5 fold and ~2.3 fold, respectively, in severe renal impairment versus subjects with normal renal function.

Renal clearance (CLr) was decreased by 20% in the group with mild renal impairment, 40% in the group with moderate renal impairment, and 71% in the group with severe renal impairment compared to the group with normal renal function.

The study results indicate that the increase of estetrol plasma exposure in subjects with moderate and severe renal impairment compared to subjects with a normal renal function could be of clinical relevance (see section 4.2).

Drospirenone
In a study performed with drospirenone 3 mg alone administered orally for 14 days, 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. The serum drospirenone levels were on average 37% higher in women with moderate renal impairment (CLcr=30-50 mL/min) compared with those in women with normal renal function.

Hepatic impairment
Estetrol
A study has been performed with a single oral dose of 20 mg estetrol monohydrate administered in female subjects with normal hepatic function, mild hepatic impairment (Child-Pugh class A), moderate hepatic impairment (Child-Pugh class B), and severe hepatic impairment (Child-Pugh class C).
The results show that C_{max} and AUC_{inf} ratios for estetrol were ~1.7-fold and ~1.1-fold, respectively, in mild hepatic impairment versus subjects with normal hepatic function; ~1.9-fold and ~1-fold, respectively, in moderate hepatic impairment versus subjects with normal hepatic function, and ~5.4-fold and ~1.9-fold, respectively, in severe hepatic impairment versus subjects with normal hepatic function.

Drospirenone
In a single dose study, oral clearance of drospirenone (CL/F) was decreased approximately 50% in volunteers with moderate hepatic impairment as compared to those with normal liver function.

Paediatric population
Concentrations (C_{trough}) at steady state remain stable over cycles and are similar in adults and adolescents.

Other special populations

Ethnic groups
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.

5.3 Preclinical safety data

Repeated dose toxicity studies with estetrol, drospirenone or the combination have indicated expected estrogenic and gestagen effects.

At exposures exceeding those in users of Drovelis **(**~27-fold multiple for estetrol and ~3.5-fold multiple for drospirenone), ventricular histological changes, without clinical effects, were observed in monkeys after repeated administration of the combination.

Reproductive toxicity studies in rats and rabbits performed with estetrol have shown embryotoxic and fetotoxic effects in animals at clinically relevant exposures; the effects possibly dependent on uterotonic effects in late gestation.

Genotoxicity and carcinogenicity studies were not conducted with the combination. Estetrol and drospirenone are not considered to be genotoxic. However, it is known that due to their hormonal action, sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

Environmental risk assessment studies with drospirenone have shown that drospirenone may pose a risk to the aquatic environment (see section 6.6). Environmental risk assessment studies with estetrol including the Japanese medaka fish extended one generation reproduction test indicated that the predicted environmental exposure to estetrol will not affect the aquatic ecosystem.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pink active film-coated tablets

Tablet core
Lactose monohydrate
Sodium starch glycolate
Maize starch
Povidone K30
Magnesium stearate (E470b)

Tablet coating
Hypromellose (E464)
Hydroxypropylcellulose (E463)
Talc (E553b)
Cottonseed oil, hydrogenated
Titanium dioxide (E171)
Iron oxide red (E172)

White placebo film-coated tablets

Tablet core
Lactose monohydrate
Maize starch
Magnesium stearate (E470b)

Tablet coating
Hypromellose (E464)
Hydroxypropylcellulose (E463)
Talc (E553b)
Cottonseed oil, hydrogenated
Titanium dioxide (E171)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

4 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Transparent PVC/aluminium blister containing 28 film-coated tablets (24 pink active tablets and 4 white placebo tablets) in a carton with an etui storage bag and 1, 3, 6 or 13 self-adhesive weekday sticker(s).

Pack sizes: 28 (1 × 28), 84 (3 × 28), 168 (6 × 28) and 364 (13 × 28) film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

Drospirenone containing medicinal products may pose a risk to the environment (see section 5.3). Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1547/001
EU/1/21/1547/002
EU/1/21/1547/003
EU/1/21/1547/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 May 2021

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Haupt Pharma Münster GmbH
Schleebrüggenkamp 15
48159 Münster
Germany

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this medicinal product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

Prior to the launch of Drovelis in each Member State, the MAH will agree about the content and format of the educational material, including communication media, distribution modalities and any other aspects of the programme with the National Competent Authority.
The educational materials are aimed at providing guidance on how to manage risk of thromboembolic events.

The MAH shall ensure that in each Member State where Drovelis is marketed, all healthcare professionals and patients/carers who are expected to prescribe, dispense or use the product have access to:

- Prescriber's checklist;
- Information card for women.

The prescriber's checklist should aim at initiating a discussion between the prescriber and woman to assess their suitability to receive Drovelis, particularly with respect to the presence of any contraindications or risk factors for thromboembolic events.

The prescriber's checklist should contain the following key elements:

- points to cover in the consultation (risk of thromboembolism with the CHC, effect of intrinsic risk factors, to be alert for signs and symptoms of a thrombosis);
- checklist of contraindications;
- checklist for risk factors;
- reminder to inform women of situations when the risk of thromboembolism is increased and to advise women to tell healthcare professionals that they are taking a CHC.

The Information card for women is provided as part of the product packaging, the text of which is included in Annex III. The Information card for women aims to provide women with information on the risk of thromboembolism associated with combined oral contraceptive pills, the known risk factors, as well as signs and symptoms of venous and arterial thromboembolism and to emphasize the significance of the early detection of any thromboembolic event.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

Drovelis 3 mg/14.2 mg film-coated tablets
drospirenone/estetrol

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pink active tablet contains 3 mg drospirenone and estetrol monohydrate equivalent to 14.2 mg estetrol.
Each white placebo (inactive) tablet does not contain active substances.

3. LIST OF EXCIPIENTS

Also contains lactose monohydrate. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

28 (1 x 28) film-coated tablets
84 (3 x 28) film-coated tablets
168 (6 x 28) film-coated tablets
364 (13 x 28) film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest, Hungary

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1547/001
EU/1/21/1547/002
EU/1/21/1547/003
EU/1/21/1547/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Drovelis

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTER

1. NAME OF THE MEDICINAL PRODUCT

Drovelis 3 mg/14.2 mg tablets
drospirenone/estetrol

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Gedeon Richter Plc.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Start
1 → 2 → 3 → 4 → 5 → … → 28

MINIMUM PARTICULARS TO APPEAR ON STICKER

STICKER

Choose the day sticker that starts with the first day of your pill intake and place it in the frame on the front of the blister card on the "⇨" symbol.
Each day will line up with the rows of pills.
If you miss a pill, refer to your package leaflet.

MO	TU	WE	TH	FR	SA	SU
TU	WE	TH	FR	SA	SU	MO
WE	TH	FR	SA	SU	MO	TU
TH	FR	SA	SU	MO	TU	WE
FR	SA	SU	MO	TU	WE	TH
SA	SU	MO	TU	WE	TH	FR
SU	MO	TU	WE	TH	FR	SA

MINIMUM PARTICULARS TO APPEAR ON INFORMATION CARD FOR WOMEN

INFORMATION CARD FOR WOMEN

IMPORTANT INFORMATION ABOUT DROVELIS AND RISK OF BLOOD CLOTS

All combined contraceptives like Drovelis increase the risk of having a blood clot. The overall risk of a blood clot due to Drovelis is small but clots can be serious and may in very rare cases even be fatal.

It is very important that you recognise when you might be at greater risk of a blood clot, what signs and symptoms you need to look out for and what action you need to take.

In which situations is the risk of a blood clot highest?

- in the first year of using Drovelis (including if you are re-starting use after a break of 4 weeks or more)
- if you are very overweight
- if you are older than 35 years
- if you have a family member who has had a blood clot at a relatively young age (eg below 50)
- if you have given birth in the previous few weeks

If you smoke and are over 35 years old you are strongly advised to stop smoking or use a non-hormonal method of contraception.

Seek medical attention immediately if you experience any of the following symptoms:

- Severe pain or swelling in either of your legs that may be accompanied by tenderness, warmth or changes in the skin colour such as turning pale, red or blue. You may be experiencing a **deep vein thrombosis**.
- Sudden unexplained breathlessness or rapid breathing; severe pain in the chest which may increase with deep breathing; sudden cough without an obvious cause (which may bring up blood). You may be experiencing a serious complication of deep vein thrombosis called a **pulmonary embolism**. This occurs if the blood clot travels from the leg to the lung.
- Chest pain, often acute, but sometimes just discomfort, pressure, heaviness, upper body discomfort radiating to the back, jaw, throat, arm together with a feeling of fullness associated with indigestion or choking, sweating, nausea, vomiting or dizziness. You may be experiencing a **heart attack.**
- Face, arm or leg weakness or numbness, especially on one side of the body; trouble speaking or understanding; sudden confusion; sudden loss of vision or blurred vision; severe headache/migraine that is worse than normal. You may be experiencing a **stroke**.

Watch out for symptoms of a blood clot, especially if you have:

- just had an operation
- been off your feet for a long time (eg. because of an injury or illness, or if your leg is in a cast)
- a long journey (more than about 4 hours)

Remember to tell your doctor, nurse or surgeon that you are taking Drovelis if you:

- are due to or have had surgery
- are in any situation when a healthcare professional asks you if you are taking any medications

For further information please read the accompanying Patient Information Leaflet or go to [NCA web address].

If you suspect you have an undesirable effect associated with the use of your CHC, you can report it to a Healthcare professional or according to your national reporting requirements.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Drovelis 3 mg/14.2 mg film-coated tablets
drospirenone/estetrol

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Important things to know about combined hormonal contraceptives (CHCs):
- They are one of the most reliable reversible methods of contraception if used correctly.
- They slightly increase the risk of having a blood clot in the veins and arteries, especially in the first year or when restarting a combined hormonal contraceptive following a break of 4 or more weeks.
- Please be alert and see your doctor if you think you may have symptoms of a blood clot (see section 2 'Blood clots').

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Drovelis is and what it is used for

Drovelis is a contraceptive pill that is used to prevent pregnancy.
- The 24 pink film-coated tablets are active tablets that contain a small amount of two different female hormones, namely estetrol and drospirenone.
- The 4 white film-coated tablets are inactive tablets that do not contain hormones and are called placebo tablets.
- Contraceptive pills that contain two different hormones, like Drovelis, are called 'combination' or 'combined' pills. They work together to prevent ovulation (release of an egg from the ovary) and to reduce the chance of any released egg being fertilised and making you pregnant.

2. What you need to know before you take Drovelis

General notes
Before your start taking Drovelis, you should read the information on blood clots in section 2. It is particularly important to read the symptoms of a blood clot – see section 2 'Blood clots'.

Before you can begin taking Drovelis, your doctor will ask you some questions about your personal health history and that of your close relatives. The doctor will also measure your blood pressure and, depending upon your personal situation, may also carry out some other tests.

In this leaflet, several situations are described where you should stop taking the pill, or where the reliability of the pill may be decreased. In such situations, you should not have sexual intercourse or you should take extra non-hormonal contraceptive precautions, e.g., use a condom or another barrier method. Do not use rhythm or temperature methods. These methods can be unreliable because the pill alters the usual changes in temperature and cervical mucus that occur during the menstrual cycle.

Drovelis, like other hormonal contraceptives, does not prevent against human immunodeficiency virus (HIV) infection (acquired immunodeficiency syndrome, AIDS) or any other sexually transmitted disease.

Do not take Drovelis
You should not take Drovelis if you have any of the conditions listed below. If you do have any of the conditions listed below, you must tell your doctor. Your doctor will discuss with you what other form of birth control would be more appropriate.

- if you have (or have ever had) a blood clot in a blood vessel of your legs (deep vein thrombosis, DVT), your lungs (pulmonary embolus, PE) or other organs;
- if you know you have a disorder affecting your blood clotting – for instance, protein C deficiency, protein S deficiency, antithrombin-III deficiency, factor V Leiden or antiphospholipid antibodies;
- if you need an operation or if you are off your feet for a long time (see section 'Blood clots');
- if you have ever had a heart attack or a stroke;
- if you have (or have ever had) angina pectoris (a condition that causes severe chest pain and may be a first sign of a heart attack) or transient ischaemic attack (TIA – temporary stroke symptoms);
- if you have any of the following diseases that may increase your risk of a clot in the arteries:
  - severe diabetes with blood vessel damage;
  - very high blood pressure;
  - a very high level of fat in the blood (cholesterol or triglycerides);
  - a condition known as hyperhomocysteinaemia;
- if you have (or have ever had) a type of migraine called 'migraine with aura';
- if you have (or have ever had) a tumour in the liver (benign or malignant);
- if you have (or have ever had) a liver disease and your liver function is still not normal;
- if your kidneys are not working well (renal failure);
- if you have (or have ever had) or if you are suspected of having breast cancer or cancer of the genital organs;
- if you have any unexplained bleeding from the vagina;
- if you are allergic to estetrol or drospirenone, or any of the other ingredients of this medicine (listed in section 6).

If any of these conditions appear for the first time while using Drovelis, stop taking it immediately and tell your doctor. In the meantime, use a non-hormonal contraceptive. See also 'General notes' in section 2 above.

Warnings and precautions
Talk to your doctor or pharmacist before taking Drovelis.

When should you contact your doctor?

Seek urgent medical attention

- if you notice possible signs of a blood clot that may mean you are suffering from a blood clot in the leg (i.e. deep vein thrombosis), a blood clot in the lung (i.e. pulmonary embolism), a heart attack or a stroke (see 'Blood clots' section below).

For a description of the symptoms of these serious side effects please go to 'How to recognise a blood clot'.

Tell your doctor if any of the following conditions apply to you
If the condition develops, or gets worse while you are taking Drovelis, you should also tell your doctor:

- if a close relative has or has ever had breast cancer;
- if you have hereditary or acquired angioedema. Medicines containing oestrogens may induce or worsen symptoms of angioedema. See your doctor immediately if you experience symptoms of angioedema such as swollen face, tongue and/or throat and/or difficulty swallowing or hives, together with difficulty breathing;
- if you have a liver disease or the gallbladder disease;
- if you have a kidney disease;
- if you have diabetes;
- if you have depression;
- if you have epilepsy (see section 2 'Other medicines and Drovelis');
- if you have Crohn's disease or ulcerative colitis (chronic inflammatory bowel disease);
- if you have systemic lupus erythematosus (SLE – a disease affecting your natural defence system);
- if you have haemolytic uraemic syndrome (HUS – a disorder of blood clotting causing failure of the kidneys);
- if you have sickle cell anaemia (an inherited disease of the red blood cells);
- if you have elevated levels of fat in the blood (hypertriglyceridaemia) or a positive family history for this condition. Hypertriglyceridaemia has been associated with an increased risk of developing pancreatitis (inflammation of the pancreas);
- if you need an operation, or you are off your feet for a long time (see section 2 'Blood clots');
- if you have just given birth you are at an increased risk of blood clots. You should ask your doctor how soon after delivery you can start taking Drovelis;
- if you have an inflammation in the veins under the skin (superficial thrombophlebitis);
- if you have varicose veins;
- if you have or have ever had chloasma (a discolouration of the skin especially of the face or neck known as 'pregnancy patches'). In this case, avoid direct exposure to sunlight or ultraviolet light.
- if you have a disease that first appeared during pregnancy or earlier use of sex hormones (for example, hearing loss, a blood disease called porphyria, skin rash with blisters during pregnancy [gestational herpes], a nerve disease causing sudden movements of the body [Sydenham's chorea]).

BLOOD CLOTS

Using a combined hormonal contraceptive such as Drovelis increases your risk of developing a blood clot compared with not using one. In rare cases, a blood clot can block blood vessels and cause serious problems.

Blood clots can develop

- in veins (referred to as a 'venous thrombosis', 'venous thromboembolism' or VTE)
- in the arteries (referred to as an 'arterial thrombosis', 'arterial thromboembolism' or ATE).

Recovery from blood clots is not always complete. Rarely, there may be serious lasting effects or, very rarely, they may be fatal.

It is important to remember that the overall risk of a harmful blood clot due to Drovelis is small.

HOW TO RECOGNISE A BLOOD CLOT

Seek urgent medical attention if you notice any of the following signs or symptoms.

Are you experiencing any of these signs?	What are you possibly suffering from?

- swelling of one leg or along a vein in the leg or foot especially when accompanied by:
  - pain or tenderness in the leg which may be felt only when standing or walking
  - increased warmth in the affected leg
  - change in colour of the skin on the leg e.g. turing pale, red or blue
	Deep vein thrombosis

- sudden unexplained breathlessness or rapid breathing; - sudden cough without an obvious cause, which may bring up blood; - sharp chest pain which may increase with deep breathing; - severe light headedness or dizziness; - rapid or irregular heartbeat; - severe pain in your stomach; If you are unsure, talk to a doctor as some of these symptoms such as coughing or being short of breath may be mistaken for a milder condition such as a respiratory tract infection (e.g. a 'common cold').	Pulmonary embolism
Symptoms most commonly occur in one eye: - immediate loss of vision or painless blurring of vision which can progress to loss of vision;	Retinal vein thrombosis (blood clot in the eye)
- chest pain, discomfort, pressure, heaviness; - sensation of squeezing or fullness in the chest, arm or below the breastbone; - fullness, indigestion or choking feeling; - upper body discomfort radiating to the back, jaw, throat, arm and stomach; - sweating, nausea, vomiting or dizziness; - extreme weakness, anxiety, or shortness of breath; - rapid or irregular heartbeats.	Heart attack
- sudden weakness or numbness of the face, arm or leg, especially on one side of the body; - sudden confusion, trouble speaking or understanding; - sudden trouble seeing in one or both eyes; - sudden trouble walking, dizziness, loss of balance or coordination; - sudden, severe or prolonged headache with no known cause; - loss of consciousness or fainting with or without seizure; Sometimes the symptoms of stroke can be brief with an almost immediate and full recovery, but you should still seek urgent medical attention as you may be at risk of another stroke.	Stroke

- swelling and slight blue discolouration of an extremity; - severe pain in your stomach (acute abdomen).	Blood clots blocking other blood vessels

BLOOD CLOTS IN A VEIN

What can happen if a blood clot forms in a vein?
- The use of combined hormonal contraceptives has been connected with an increase in the risk of blood clots in the vein (venous thrombosis). However, these side effects are rare. Most frequently, they occur in the first year of use of a combined hormonal contraceptive.
- If a blood clot forms in a vein in the leg or foot it can cause a deep vein thrombosis (DVT).
- If a blood clot travels from the leg and lodges in the lung it can cause a pulmonary embolism.
- Very rarely a clot may form in a vein in another organ such as the eye (retinal vein thrombosis).

When is the risk of developing a blood clot in a vein highest?
The risk of developing a blood clot in a vein is highest during the first year of taking combined hormonal contraceptive for the first time. The risk may also be higher if you restart taking a combined hormonal contraceptive (the same medicine or a different medicine) after a break of 4 weeks or more. After the first year, the risk gets smaller but is always slightly higher than if you were not using a combined hormonal contraceptive.
When you stop Drovelis your risk of a blood clot returns to normal within a few weeks.

What is the risk of developing a blood clot?
The risk depends on your natural risk of VTE and the type of combined hormonal contraceptive you are taking.
The overall risk of a blood clot in the leg or lung (DVT or PE) with Drovelis is small.
- Out of 10,000 women who are not using any combined hormonal contraceptive and are not pregnant, about 2 will develop a blood clot in a year.
- Out of 10,000 women who are using a combined hormonal contraceptive that contains low-dose ethinylestradiol (<50 microgram ethinylestradiol) combined with levonorgestrel, norethisterone, or norgestimate about 5-7 will develop a blood clot in a year.
- It is not yet known how the risk of a blood clot with Drovelis compares to the risk with a combined hormonal contraceptive that contains levonorgestrel.
- The risk of having a blood clot will vary according to your personal medical history (see 'Factors that increase your risk of a blood clot' below).

	Risk of developing a blood clot in a year
Women who are **not using** a combined hormonal pill/patch/ring and are not pregnant	About 2 out of 10,000 women
Women using a combined hormonal contraceptive pill containing low-dose ethinylestradiol(<50 microgram ethinylestradiol) combined with **levonorgestrel, norethisterone or norgestimate**	About 5-7 out of 10,000 women
Women using Drovelis	Not yet known

Factors that increase your risk of a blood clot in a vein
The risk of a blood clot with Drovelis is small but some conditions will increase the risk. Your risk is higher:
- if you are very overweight (body mass index or BMI over 30 kg/m^2);
- if one of your immediate family has had a blood clot in the leg, lung or other organ at a young age (e.g. below the age of about 50 years). In this case you could have a hereditary blood clotting disorder;

- if you need to have an operation, or if you are off your feet for a long time because of an injury or illness, or you have your leg in a cast. The use of Drovelis may need to be stopped several weeks before surgery or while you are less mobile. If you need to stop Drovelis ask your doctor when you can start using it again.
- as you get older (particularly above about 35 years);
- if you gave birth less than a few weeks ago.

The risk of developing a blood clot increases the more conditions you have.
Air travel (> 4 hours) may temporarily increase your risk of a blood clot, particularly if you have some of the other factors listed.
It is important to tell your doctor if any of these conditions apply to you, even if you are unsure. Your doctor may decide that Drovelis needs to be stopped.
If any of the above conditions change while you are using Drovelis, for example a close family member experiences a thrombosis for no known reason; or you gain a lot of weight, tell your doctor.

BLOOD CLOTS IN AN ARTERY

What can happen if a blood clot forms in an artery?
Like a blood clot in a vein, a clot in an artery can cause serious problems. For example, it can cause a heart attack or a stroke.

Factors that increase your risk of a blood clot in an artery
It is important to note that the risk of a heart attack or stroke from using Drovelis is very small but can increase:
- with increasing age (beyond about 35 years);
- **if you smoke.** When using a combined hormonal contraceptive like Drovelis, you are advised to stop smoking. If you are unable to stop smoking and are older than 35 years your doctor may advise you to use a different type of contraceptive;
- if you are overweight;
- if you have high blood pressure;
- if a member of your immeddiate family has had a heart attack or stroke at a young age (less than about 50 years). In this case you could also have a higher risk of having a heart attack or stroke;
- if you, or someone in your immediate family, have a high level of fat in the blood (cholesterol or triglycerides);
- if you get migraines, especially migraines with aura;
- if you have a problem with your heart (valve disorder, disturbance of the rhythm called atrial fibrillation);
- if you have diabetes.

If you have more than one of these conditions or if any of them are particularly severe the risk of developing a blood clot may be increased even more.

If any of the above conditions change while you are using Drovelis, for example you start smoking, a close family member experiences a thrombosis for no known reason; or you gain a lot of weight, tell your doctor.

Cancer
Breast cancer has been observed slightly more often in women using combination pills, but it is not known whether this is caused by the treatment. For example, it may be that tumours are detected more in women on combination pills because they are examined by their doctor more often. After stopping the combination pill, the increased risk gradually reduces. It is important to check your breasts regularly and you should contact your doctor if you feel any lump. You should also tell your doctor if a close relative has, or ever had breast cancer (see section 2 ‘Warnings and precautions’).

In rare cases, benign (noncancerous) liver tumours, and in even fewer cases malignant (cancerous) liver tumours have been reported in pill users. Contact your doctor if you have unusual severe abdominal pain.

Cervical cancer is caused by an infection with the human papilloma virus (HPV). It has been reported to occur more often in women using the pill for more than 5 years. It is unknown if this finding is due to the use of homonal contraceptives or to other factors, such as difference in sexual behaviour.

Psychiatric disorders
Some women using hormonal contraceptives including Drovelis have reported depression or depressed mood. Depression can be serious and may sometimes lead to suicidal thoughts. If you experience mood changes and depressive symptoms contact your doctor for further medical advice as soon as possible.

Bleeding between periods
Your period will normally start while you are taking the white placebo tablets in the Drovelis pack. During the first few month that you are taking Drovelis, you may have unexpected bleeding (bleeding outside the placebo days). Mostly this bleeding is mild and usually not requiring any sanitary protection. If this bleeding occurs for more than a few months, or if it begins after some months, your doctor must find out what is wrong.

What you must do if no bleeding occurs during the placebo days
If you have taken all the pink active tablets correctly, have not had vomiting or severe diarrhoea and you have not taken any other medicines, it is highly unlikely that you are pregnant. Keep taking Drovelis as usual.
If you have not taken all the tablets correctly, or if the expected bleeding does not happen twice in succession, you may be pregnant. Contact your doctor immediately. Only start the next strip if you are sure that you are not pregnant. See also in section 3 'If you vomit or have severe diarrhoea' or in section 2 'Other medicines and Drovelis'.

Children and adolescents
Drovelis is only indicated after menarche (the first menstrual period).

Other medicines and Drovelis
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. Also tell any other doctor or dentist who prescribes another medicine (or the pharmacist) that you take Drovelis. They can tell you if you need to take additional contraceptive precautions (for example using condoms) and if so, for how long, or, whether the use of another medicine you need must be changed.
Some medicines can have an influence on the blood levels of Drovelis and can make it less effective in preventing pregnancy, or can cause unexpected bleeding. These include medicines used for the treatment of:
- epilepsy (e.g. barbiturate, carbamazepine, phenytoin, primidone, felbamate, oxcarbazepine, topiramate);
- tuberculosis (e.g. rifampicin);
- HIV and hepatitis C virus (HCV) infections (e.g. so-called protease inhibitors and non-nucleoside reverse transcriptase inhibitors such as, ritonavir, nevirapine, efavirenz);
- fungal infections (e.g. griseofulvin);
- high blood pressure in the blood vessels in the lungs (e.g. bosentan).

The herbal product St. John's wort (*Hypericum perforatum*) may also stop Drovelis from working properly. If you want to use herbal products containing St. John's wort while you are already using Drovelis you should consult your doctor first.

If you are taking these medicines or herbal products that might make Drovelis less effective, a barrier contraceptive method should also be used. The barrier method must be used during the whole time of the concomitant medicine therapy and for 28 days after its discontinuation If the concomitant medicine therapy runs beyond the end of the pink active tablets in the current pack, the white placebo tablets must be discarded and the next pack of Drovelis should be started right away.

If long-term treatment with the above mentioned medicines is necessary, you should use non-hormonal contraceptive methods. Ask your doctor or pharmacist for advice.

Drovelis may influence the effect of other medicines, e.g.:
- ciclosporin (medicine used for the treatment of suppression of tissue rejection following transplant surgery);
- lamotrigine (medicine used for the treatment of epilepsy).

The HCV combination therapeutic regimen ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin as well as regimen glecaprevir/pibrentasvir or sofosbuvir/velpatasvir/voxilaprevir may cause increases in liver function blood test results (increase in ALT liver enzyme) in women using CHCs containing ethinylestradiol. Drovelis contains estetrol instead of ethinylestradiol. It is not known whether an increase in ALT liver enzyme can occur when using Drovelis with these HCV combination therapeutic regimens. Your doctor will advise you.

Ask your doctor or pharmacist for advice before taking any medicine.

Laboratory tests
If you are having any blood or urinary test, tell your doctor that you are using Drovelis as it may affect the results of some tests.

Drovelis with food and drink
Drovelis may be taken with or without food, if necessary with a small amount of water.

Pregnancy and breast-feeding
Drovelis must not be taken by women who are pregnant, or think they may be pregnant.
If you become pregnant while taking Drovelis you should stop taking Drovelis immediately and contact your doctor.

If you want to become pregnant, you can stop taking Drovelis at any time (see section 3 ‘If you stop taking Drovelis’).

Drovelis is not recommended during breast-feeding. If you wish to take the pill while breast-feeding, you should contact your doctor.

Driving and using machines
Drovelis has no or negligible effect on the ability to drive and use machines.

Drovelis contains lactose and sodium
If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.
The pink active tablet contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

3. How to take Drovelis

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

When and how to take the tablets
The Drovelis blister contains 28 film-coated tablets: 24 pink active tablets with the active substances (number 1-24) and 4 white placebo tablets without active substances (number 25-28).
Each time you start a new blister of Drovelis, take the number 1 pink active tablet (see ‘Start’). Choose from the 7 weekday stickers, the one that begins with your starting day. For example, if you start on a Wednesday, use the day label sticker that starts with ‘Wed’. Place it in the frame on the front of the

blister card on the "⇨" symbol. Each day will line up with a row of pills. This allows you to check whether you took your daily tablet.

Take one tablet each day at about the same time, with some water if necessary.

Follow the direction of the arrows on the blister, so take the pink active tablets first and then the white placebo tablets.

Your period will start during the 4 days that you take the white placebo tablets (so-called withdrawal bleeding). Usually it will start 2 to 4 days after the last pink active tablet intake and may not have finished before the next blister is started.
Start taking your next blister immediately after the last white placebo tablet, even if your period has not finished. This means that you will always start a new blister on the same day of the week, and also that you have your period on roughly the same days each month.

Some users may not have their period every month during the intake of the white placebo tablets. If you have taken Drovelis every day according to these instructions, it is unlikely that you are pregnant.

Starting your first pack of Drovelis

If you have not used a contraceptive with hormones in the previous month
Begin with Drovelis on the first day of the cycle (that is the first day of your period). If you start Drovelis on the first day of your menstruation you are immediately protected against pregnancy.
You may also begin on day 2-5 of the cycle, but then you must use extra protective measures (for example, a condom) for the first 7 days of tablet-taking.

Changing from a combined hormonal contraceptive, or combined contraceptive vaginal ring or patch
You can start Drovelis preferably on the day after the last active tablet (the last tablet containing the active substances) of your previous pill, but at the latest on the day after the tablet-free days of your previous pill finish (or after the last inactive tablet of your previous pill). When changing from a combined contraceptive vaginal ring or patch, follow the advice of your doctor.

Changing from a progestogen-only-method (progestogen-only pill, injection, implant or a progestogen-releasing Intra-Uterine Device [IUD])
You may switch any day from the progestogen-only pill (from an implant or an IUD on the day of its removal, from an injectable when the next injection would be due) but in all of these cases you must use extra protective measures (for example, a condom) for the first 7 consecutive days of tablet-taking.

After a miscarriage or an artificial abortion
Follow the advice of your doctor.

After having a baby
You can start Drovelis between 21 and 28 days after having a baby. If you start later than day 28, you must use a barrier method (for example, a condom) during the first 7 days of Drovelis use. If, after having a baby, you have had sex before starting Drovelis, you must first be sure that you are not pregnant or you must wait until your next period.

If you are breast-feeding and want to start Drovelis (again) after having a baby
Read the section on "Breast-feeding".

Ask your doctor or pharmacist what to do if you are not sure when to start.

If you take more Drovelis than you should
There are no reports of serious harmful results of taking too many Drovelis tablets.
If you take several tablets at once, then you may feel sick or vomit or bleed from the vagina. Even girls who have not yet started to menstruate but have accidentally taken this medicine may experience such bleeding.

If you have taken too many Drovelis tablets, or you discover that a child has taken some, ask your doctor or pharmacist for advice.

If you forget to take Drovelis
The last 4 white tablets of the strip are the placebo tablets. If you forget one of these tablets, this has no effect on the reliability of Drovelis. Throw away the forgotten white placebo tablet.

If you miss a **pink, active tablet** (tablets 1-24 of your blister-strip), you must do the following:

- if you are **less than 24 hours late** taking a pink active tablet, the protection against pregnancy is not reduced. Take the tablet as soon as possible and then take the following tablets again at the usual time.

- if you are **more than 24 hours late** taking a pink active tablet, the protection against pregnancy may be reduced. The greater the number of tablets that you have forgotten, the greater is the risk of becoming pregnant.

The risk of incomplete protection against pregnancy is greatest if you forget a pink active tablet at the beginning or at the end of the strip. Therefore, you should keep to the following rules (see also the diagram):

More than one tablet forgotten in this strip:
Contact your doctor.

One pink active tablet forgotten between days 1-7
Take the forgotten tablet as soon as possible, even if that means that you have to take two tablets at the same time. Continue taking the tablets at the usual time and use extra precautions, for example, a condom, for the next 7 days while taking the tablets correctly. If you have had sex in the week before forgetting the tablet you must realize that there is a risk of a pregnancy. In that case, contact your doctor.

One pink active tablet forgotten between days 8-17
Take the forgotten tablet as soon as possible, even if that means that you have to take two tablets at the same time. Continue taking the tablets at the usual time. The protection against pregnancy is not reduced, and you do not need to take extra precautions.

One pink active tablet forgotten between days 18-24
You can choose between two possibilities:

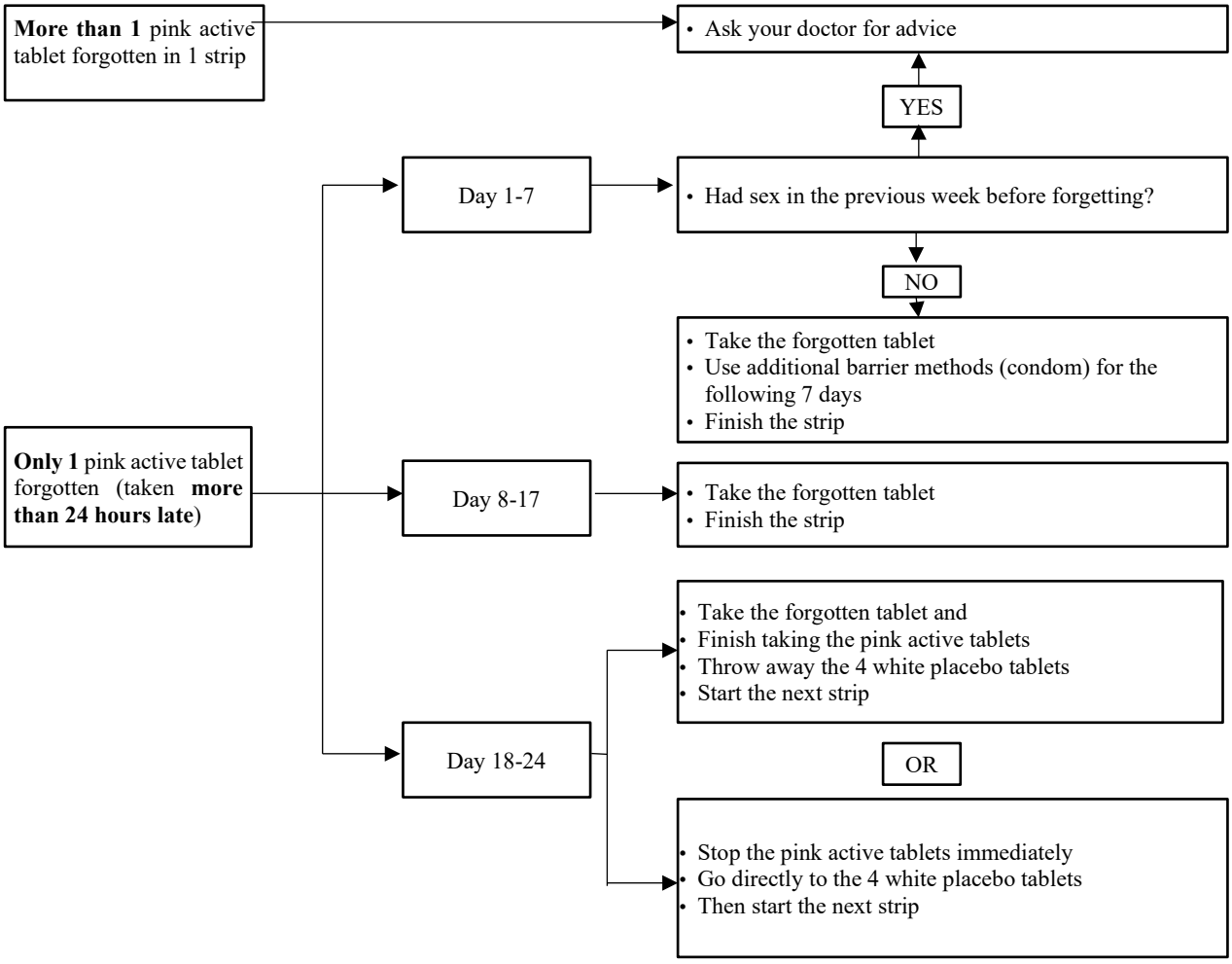
1. Take the forgotten tablet as soon as possible, even if that means that you have to take two tablets at the same time. Continue taking the tablets at the usual time. Instead of taking the white placebo tablets on this strip, throw them away, and start the next strip (the starting day will be different).
   Most likely, you will have a period at the end of the second strip - while taking the white placebo tablets - but you may have light or menstruation-like bleeding during the second strip.

2. You can also stop the pink active tablets and go directly to the 4 white placebo tablets. Before taking the white placebo tablets, record the day on which you forgot your tablet. The placebo period should not exceed 4 days. If you want to start a new strip on the day you always start, take the white placebo tablets for less than 4 days.

If you follow one of these two recommendations, you will remain protected against pregnancy.

If you have forgotten any of the tablets in a strip, and you do not have a bleeding during the placebo days, this may mean that you are pregnant. You must contact your doctor before you start the next strip.

Schedule if you are more than 24 hours late taking pink active tablets



More than one tablet forgotten in this strip
Follow the advice of your doctor.

If you vomit or have severe diarrhoea
If you vomit within 3-4 hours of taking a pink active tablet or you have severe diarrhoea, there is a risk that the active substances in the pill will not be fully taken up by your body. The situation is almost the same as forgetting a tablet. After vomiting or diarrhoea, you must take another pink active tablet from a reserve strip as soon as possible. If possible take it within 24 hours of when you normally take your pill. If this is not possible or 24 hours have passed, you should follow the advice given under 'If you forget to take Drovelis'.

Delaying your period: what you need to know
Even if it is not recommended, you can delay your period by not taking the white placebo tablets from the 4th row and going straight to a new strip of Drovelis and finishing it. You may experience light or menstruation-like bleeding while using this second strip. Finish this second strip by taking the 4 white placebo tablets. Then start your next strip. You might ask your doctor for advice before deciding to delay your menstrual period.

If you want to change the starting day of your period
If you take the tablets according to the instructions, then your period will begin during the placebo days. If you have to change this day, reduce the number of placebo days – when you take the white placebo tablets – but never increase them (4 is the maximum). For example, if you start taking the white placebo tablets on Friday, and you want to change this to a Tuesday (3 days earlier) you must start a new blister 3 days earlier than usual. You may not have any bleeding during the shortened

period of white placebo tablet intake. While using the next blister you may have some spotting (drops or flecks of blood) or breakthrough bleeding on pink active tablet -taking days.

If you are not sure what to do, speak with your doctor or pharmacist.

If you stop taking Drovelis
You can stop taking Drovelis at any time. If you do not want to become pregnant, first ask your doctor about other methods of birth control.
If you stop taking Drovelis because you want to get pregnant, it is best to wait until you have had a natural period before trying to become pregnant. This will help you to calculate the expected delivery date more easily.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you get any side effect, particularly if severe and persistent, or have any change to your health that you think may be due to Drovelis, please talk to your doctor.

An increased risk of blood clots in your veins (VTE) or blood clots in your arteries (ATE) is present for all women taking combined hormonal contraceptives. For more detailed information on the different risks from taking combined hormonal contraceptives please see section 2 'What you need to know before you take Drovelis'.

The followig side effects have been linked with the use of Drovelis:

Common (may affect up to 1 in 10 people):
- mood disorder and disturbance, libido disorder;
- headache;
- abdominal pain, nausea;
- acne;
- breast pain, painful periods, vaginal bleeding (during or outside periods, heavy irregular bleeding);
- weight fluctuation.

Uncommon (may affect up to 1 in 100 people):
- fungal infection, vaginal infection, urinary tract infection;
- changes in appetite (appetite disorder);
- depression, emotional disorder, anxiety disorder, stress, problems sleeping;
- migraine, dizziness, 'pins and needles', drowsiness;
- hot flush;
- abdominal (belly) swelling, vomiting, diarrhoea;
- hair loss, excessive sweating (hyperhidrosis), dry skin, rash, skin swelling;
- back pain;
- swollen breasts, lumps in the breast, abnormal genital bleeding, pain with intercourse, fibrocystic breast disease (presence of one or more cysts in a breast), heavy periods, no periods, menstrual disorders, premenstrual syndrome, contractions of the uterus, uterine or vaginal bleeding including spotting, vaginal discharge, vulvovaginal disorder (dryness, pain, odour, discomfort);
- fatigue, swelling of parts of your body e.g. ankles (oedema), chest pain, feeling abnormal;
- blood tests showing increased liver enzymes, changes in certain blood fats (lipids).

Rare (may affect up to 1 in 1,000 people):
- breast inflammation;
- benign breast mass;

- hypersensitivity (allergy);
- fluid retention, increased potassium levels in the blood;
- nervousness;
- forgetfulness;
- dry eye, visual blurring, visual impairment;
- giddiness;
- high or low blood pressure, inflammation of a vein with the formation of a blood clot (thrombophlebitis), varicose vein;
- constipation, dry mouth, indigestion, lip swelling, flatulence, bowel inflammation, gastric reflux, abnormal bowel contractions;
- allergic skin reactions, golden brown pigment patches (chloasma) and other pigmentation disorders, male pattern hair growth, excessive hair growth, skin conditions such as dermatitis and itchy dermatitis, dandruff and oily skin (seborrhoea) and other skin disorders;
- muscle and joint cramps, pain and discomfort;
- urinary tract pain, abnormal urine smell;
- pregnancy that occurs outside the womb (ectopic pregnancy);
- ovarian cyst, increased spontaneous milk flow, pelvic pain, breast discolouration, bleeding during intercourse, endometrial disorders, nipple disorders, abnormal uterine bleeding;
- malaise and feeling generally unwell, increase in body temperature, pain;
- incease in blood pressure, changes in blood tests (abnormal kidney function test, increased blood potassium, increased blood glucose, decreased haemoglobin, decresed iron stores in blood, blood in urine);
- harmful blood clots in a vein for example:
  - in a leg or foot (i.e. DVT)
  - in a lung (i.e. PE)
  - heart attack
  - stroke
  - mini-stroke or temporary stroke-like symptoms, known as a transient ischaemic attack (TIA)
  - blood clots in the liver, stomach/intestine, kidneys or eye

  The chance of having a blood clot may be higher if you have any other condition that increase this risk (see section 2 for more information on the conditions that increase the risk for blood clots and the symptoms of a blood clot).

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Drovelis

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Drovelis contains

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

The other excipients are:

Pink active film-coated tablets:
Tablet core:
Lactose monohydrate (see section 2 'Drovelis contains lactose and sodium'), sodium starch glycolate (see section 2 'Drovelis contains lactose and sodium '), maize starch, povidone K30, magnesium stearate (E470b).
Tablet coating:
Hypromellose (E464), hydroxypropylcellulose (E463), talc (E553b), cottonseed oil, hydrogenated, titanium dioxide (E171), iron oxide red (E172).

White placebo film-coated tablets:
Tablet core:
Lactose monohydrate (see section 2 'Drovelis contains lactose and sodium'), maize starch, magnesium stearate (E470b).
Tablet coating:
Hypromellose (E464), hydroxypropylcellulose (E463), talc (E553b), cottonseed oil, hydrogenated, titanium dioxide (E171).

What Drovelis looks like and contents of the pack
The active film-coated tablets are pink, 6 mm diameter, round, biconvex with a drop-shaped logo embossed on one side.
The placebo film-coated tablets are white to off-white, 6 mm diameter, round, biconvex with a drop-shaped logo embossed on one side.

Drovelis is presented in blisters of 28 film-coated tablets (24 pink active tablets and 4 white placebo tablets) packed in a carton. In addition to the blister(s), the Drovelis box contains an etui-storage bag and 1, 3, 6, or 13 self-adhesive sticker(s) marked with days of the weeks. The numbers of self-adhesive stickers depend on the number of blisters.

Pack sizes: 28 (1 × 28), 84 (3 × 28), 168 (6 × 28) and 364 (13 × 28) film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

Manufacturer
Haupt Pharma Münster GmbH
Schleebrüggenkamp 15
48159 Münster
Germany

Gedeon Richter Plc.
Gyömrői út 19-21.
1103 Budapest
Hungary

This leaflet was last revised in

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.