This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Health care professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

SCHEDULING STATUS
S4

1. NAME OF THE MEDICINE
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.

Excipients with known effect
Contains sugar (each pink active tablet contains 40 mg lactose monohydrate and each white placebo tablet contains 68 mg lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Film-coated tablets.

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
How to take DROVELIS
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 white 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, DROVELIS 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 device (IUD)*

The woman may switch any day from the progestogen-only pill (from an implant or the IUD 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 breastfeeding 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 woman 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 7 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
DROVELIS has not been specifically studied in patients with renal impairment. DROVELIS is contraindicated in women with severe renal insufficiency (see section 4.3).

Hepatic impairment
No clinical studies have been performed with DROVELIS in patients with hepatic impairment. DROVELIS is contraindicated in women with severe hepatic disease as long as liver function values have not returned to normal (see section 4.3).

Paediatric population
DROVELIS is only indicated after menarche (first menstrual cycle). The safety and efficacy of DROVELIS in adolescents aged under 16 years of age has not been established. No data are available.

Method of administration
Oral use.

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 medicine should be stopped immediately.

- Hypersensitivity to the active substances or to any of the excipients listed in section 6.1.
- 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.

4.4 Special warnings and precautions for use

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. **Medicines 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 medicines. The decision to use any medicine 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 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 in 10 000 women who use a levonorgestrel-containing CHC (a 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). These incidences were estimated from the totality of the epidemiological study data, using relative risks for the different medicines compared with levonorgestrel-containing CHCs.

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.

Thrombosis has been reported to occur in some 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 patients 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 are 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.
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 an 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.

In some cases, benign liver tumours, and malignant liver tumours have been reported in patients 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 medicines 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 medicines 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 medicines 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 medicines, 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 pre-treatment serum potassium in the upper reference range, and particularly during concomitant use of potassium sparing medicines. (See also section 4.5.)

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

Small increases in blood pressure have been reported in many women taking CHC. 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 healthcare professional 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.

In women with hereditary angioedema, exogenous oestrogens may induce or exacerbate symptoms of 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 healthcare professional 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 patient 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 medicines (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 DROVELIS.

DROVELIS contains less than 1 mmol sodium (23 mg) per tablet, that is to say it is essentially 'sodium-free'.

4.5 Interaction with other medicines and other forms of interaction
Note: The prescribing information of concomitant medicines should be consulted to identify potential interactions.

Pharmacokinetic interactions
Effects of other medicines on *DROVELIS*
Interactions can occur with medicines 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 medicine therapy, enzyme induction may be sustained for about 4 weeks.

- *Short-term treatment*

Women on treatment with enzyme-inducing medicines 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 medicine therapy and for 28 days after its discontinuation. If the medicine 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.
Medicines increasing the clearance of CHCs (enzyme-induction), e.g.: barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin and HIV medicines (e.g. ritonavir, nevirapine and efavirenz) and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and medicines containing the herbal St. John's wort (*Hypericum perforatum*).

Medicines 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 medicines 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 nonnucleoside reverse transcriptase inhibitor therapy.

Medicines 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 medicines
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 medicines containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, may increase the risk of ALT elevations in women using ethinylestradiol containing medicines such as CHCs (see section 4.4). Women using medicines 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 are 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).

Breastfeeding

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

Breastfeeding 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 breastfeeding 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 fertility, see section 5.1.

4.7 Effects on ability to drive and use machines

DROVELIS can cause side effects, such as dizziness, drowsiness, visual impairment, blurred vision or fatigue. Patients should be advised that if they experience any of these symptoms they should not drive or operate machinery.

4.8 Undesirable effects

a) 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 %).

b) 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
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 Blurred vision 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 Abnormal urine odour
Pregnancy, puerperium and perinatal conditions			Ectopic pregnancy

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	Increased hepatic enzyme Abnormal lipids	Increased blood pressure Abnormal renal function test Increased blood potassium Increased blood glucose Decreased haemoglobin Decreased serum ferritin 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 polymenorrhoea
(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

c) 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:

- 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
- in women with hereditary angioedema exogenous oestrogens may induce or exacerbate symptoms of angioedema.

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

Reporting of suspected adverse reactions:
Reporting suspected adverse reactions after authorisation of DROVELIS is important. It allows continued monitoring of the benefit/risk balance of DROVELIS. Health care providers are asked to report any suspected adverse reactions via the **"6.04 Adverse Drug Reaction Reporting Form"**, found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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 medicine.

There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Category and class: A 18.8 Ovulation controlling agents
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.

5.2 Pharmacokinetic properties
Estetrol
Absorption
Estetrol is rapidly absorbed after ingestion. After intake of DROVELIS, average peak plasma concentrations of 17,9 ng/mL are reached 0,5 – 2 hours after single ingestion.

The overall exposure to estetrol is similar irrespective of food intake. The Cmax 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 medicines 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 (t1/2) 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. Cmax 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, Cmax of about 48,7 ng/mL is reached at about 1 – 3 hours 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 catalysed 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 t1/2 of metabolite excretion with the urine and faeces is about 40 hours.

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. Cmax 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
No studies were performed to evaluate the effect of renal disease on the pharmacokinetics of estetrol. 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
No studies were conducted to evaluate the effect of hepatic disease on the pharmacokinetics of estetrol. 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
The pharmacokinetics of estetrol and drospirenone in postmenarcheal female adolescents (below 16 years of age) after intake of DROVELIS have not been investigated.

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 patients 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 has the potential of posing a risk to the aquatic environment (see section 6.6).

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
Store at or below 25 °C.
Keep the blister in the outer carton to protect from light.

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 a small 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 and other handling
Drospirenone containing medicines may pose a risk to the environment (see section 5.3).

Any unused medicine or waste material should be disposed of in accordance with local requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION
Adcock Ingram Limited
1 New Road,
Erand Gardens,
Midrand, 1685
Customer Care: 0860 ADCOCK / 232625

8. REGISTRATION NUMBER
56/18.8/0933

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
30 July 2024

10. DATE OF REVISION OF THE TEXT

adcock ingram
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