PACKAGE INSERT

Brand or Product Name

Rigevidon *coated tablets*

Name and Strength of Active Substance(s)

Composition: Each tablet contains ethinylestradiol 0.03 mg and levonorgestrel 0.15 mg

Product Description

Film-coated tablet
White, biconvex, circular sugar-coated tablets of 6 mm diameter

Full list of excipients
Each tablet contains 33 mg of lactose monohydrate and 22.46 mg of sucrose.

Core:
silica, colloidal anhydrous, magnesium stearate, talc, maize starch, lactose monohydrate

Coating:
sucrose, talc, calcium carbonate, titanium dioxide (E171), copovidone K90,
Macrogol 6000, silica, colloidal anhydrous, povidone K30, carmellose sodium

Pharmacodynamics/Pharmacokinetics

Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations, ATC code: G03AA07.

Combined, estrogen-progestogen mini-pill.
Pearl index: 0.1 per cent women years.

The contraceptive efficacy of Rigevidon arises from 3 complementary actions:
- at the hypothalamic-pituitary axis by means of inhibition of ovulation,
- at the cervical mucus which becomes impermeable to migration of spermatozoids,
- at the endometrium, which becomes inappropriate for implantation

Pharmacokinetic properties

Levonorgestrel
Absorption
Levonorgestrel is rapidly and completely absorbed after oral administration of Rigevidon. The bioavailability is approximately 100% and levonorgestrel is not subject to first-pass metabolism.

Distribution
Levonorgestrel is to a large extent bound to albumin and SHBG (Sex Hormon Binding Globulin) in plasma.

Biotransformation
Metabolism is mainly by reduction of the Δ4-3-oxo group and hydroxylation at the positions 2α, 1β and 16β, followed by conjugation. The majority of the metabolites circulating in the blood are sulphates of 3α, 5β-tetrahydro-levonorgestrel, while excretion mainly takes place as glucuronides. Some of the original levonorgestrel is also circulating as 17β-sulphate. Metabolic clearance is subject to marked inter-individual variation which may partly explain the wide variation in the concentrations of levonorgestrel observed among patients.

Elimination
Levonorgestrel is eliminated with a mean $T_{½}$ of approximately 36 hours at steady state. Levonorgestrel and its metabolites are primarily excreted in the urine (40%-68%) and approximately 16%-48% is excreted in the faeces.

Ethinylestradiol
Absorption
Ethinylestradiol is rapidly and completely absorbed, and peak plasma levels are reached after 1.5 hours. Following presystemic conjugation and first-pass metabolism, the absolute bioavailability is 60%. The area under curve and C_{max} may over time be expected to increase slightly.

Distribution
Ethinylestradiol is to 98.8% bound to plasma proteins, almost entirely to albumin.

Biotransformation
Ethinylestradiol undergoes presystemic conjugation both in the small intestinal mucosa and in the liver. Hydrolysis of the direct conjugates of ethinylestradiol by the intestinal flora gives ethinylestradiol, which can be re-absorbed, thereby creating an enterohepatic circulation. The primary route of metabolism of ethinylestradiol is cytochrome P-450-mediated hydroxylation, where the primary metabolites are 2-OH-ethinylestradiol and 2-methoxy-ethinylestradiol. 2-OH-ethinylestradiol is further metabolised to chemically reactive metabolites.

Elimination
Ethinylestradiol disappears from plasma with a $T_{½}$ of approximately 29 hours (26-33 hours), plasma clearance varies from 10-30 l/hour. The excretion of conjugates of ethinylestradiol and its metabolites takes place via urine and faeces (ratio 1:1).

Preclinical safety data

Acute toxicity of ethinylestradiol and levonorgestrel is low. Because of marked species differences preclinical results possess a limited predictive value for the application of estrogens in humans.
In experimental animals estrogens displayed an embryolethal effect already at relatively low doses; malformations of the urogenital tract and feminisation of male fetuses were observed. Levonorgestrel displayed a virilising effect in female fetuses. Reproduction toxicology studies in rats, mice and rabbits revealed no hint for teratogenicity beyond the effect on sexual differentiation.
Preclinical data based on conventional studies of repeated dose toxicity, genotoxicity and carcinogenic potential revealed no particular human risks beyond those discussed in other sections of the CCDS.

Indication

Oral contraception

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

Recommended Dosage

Posology

Route of administration:
Oral

How to use Rigevidon

Tablets must be taken orally in the order directed on the blister package at about the same time every day, with some liquid if necessary.

One tablet is to be taken daily for 21 consecutive days. Each subsequent pack is started after a 7 day tablet-free interval, during which time a withdrawal bleed usually occurs. Withdrawal bleeding will usually start on the 2nd or 3rd day after the last tablet has been taken and it may not have stopped, before the next blister pack is started.

How to start the use of Rigevidon
No preceding hormonal contraceptive use in the past month.
Tablet-taking is started on day 1 of the woman's natural cycle (= the first day of her menstrual bleeding).

Changing from another combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring or transdermal patch):
Take the first tablet the day after the dose of the last active tablet of the previous contraceptive or, at the latest, the day after the usual period of stopping the tablets.
In case of vaginal ring or transdermal patch, take the first tablet the day of removal or at the latest the day scheduled for application of the new device or ring.

Changing from a progestogen-only method (progestogen-only or mini-pills, injection, implant or from a progestogen-releasing intrauterine system (IUS))
Switching from the mini-pill can be performed at any time in the cycle and Rigevidon tablet should be commenced the day after stopping.
Switching from an implant or IUS should occur on the day of removal and for an injectable contraceptive on the day scheduled for the new injection. In all cases, using an additional method of contraception for the 7 first days of treatment is recommended.

After abortion in 1st trimester
The woman may start the tablet intake immediately. In this case, it is not necessary to take further contraceptive precautions.

After delivery or abortion in 2nd trimester
The woman should be advised to start on day 21-28 after delivery in non-lactating women or abortion in the 2nd trimester, because there is an increased risk of thromboembolic disorders during the post partum period. If she starts later than this, she should be advised to use a concomitant barrier method during the first 7 days of tablet intake. However, if she already has had intercourse, pregnancy must be excluded, before she starts the tablets, or she should wait for her first menstrual bleeding.

In case of breast-feeding
See section “Fertility, pregnancy and lactation”.

Missed tablets
If the woman has forgotten tablet intake for less than 12 hours, the contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers this, and the remaining tablets should be taken at the usual time.

If the delay exceeds 12 hours, the contraceptive protection may be reduced. Handling of missed active tablets may be managed by the following two basic rules:

1. Tablets should never be delayed for longer than 7 days.
2. Seven days of uninterrupted tablet taking is required to maintain adequate suppression of the hypothalamus-pituitary-ovarian-axis.

Thus, the following advice may be given in daily practice:

Week 1:

The woman should take the last missed tablet as soon as she remembers this, even if this means that she has to take 2 tablets at the same time. Hereafter, she continues taking the tablets at the usual time point. She should use a barrier method concomitantly, e.g. a condom, for the next 7 days. If intercourse has taken place during the previous 7 days, the possibility of pregnancy must be considered. The more forgotten tablets, and the closer to the usual hormone-free interval this takes place, the greater the risk of pregnancy.

Week 2:
The woman should take the last missed tablet as soon as she remembers this, even if this means that she has to take 2 tablets at the same time. Hereafter, she continues taking the tablets at the usual time point. Provided that the tablets have been taken correctly during the 7 days preceding the first missed tablet, it is not necessary to take further contraceptive precautions. However, if this is not the case, or if more than 1 tablet has been forgotten, the woman should be advised to additionally use a barrier method (such as a condom) for 7 days.

Week 3:
The risk of contraceptive failure is imminent because of the ensuing hormone-free interval. The reduced contraceptive protection may, however, be prevented by adjusting the tablet intake. Therefore, by following one of the following two alternatives, it is not necessary to take further contraceptive precautions, provided that all tablets have been taken correctly during the 7 days preceding the first missed tablet. If this is not the case, the woman should be advised to follow the first of the two alternatives. Additionally a barrier method (such as a condom) should be used concomitantly for the next 7 days.

1. The woman should take the last missed tablet as soon as she remembers this, even if this means that she has to take 2 tablets at the same time. Thereafter, she should continue to take the tablets at the usual time point. She should start on the next blister pack immediately after taking the last tablet in the current blister pack, i.e. there will be no hormone-free interval between the blister packs. A withdrawal bleeding is unlikely until the end of the second blister pack, but she may experience spotting or break through bleeding on the days she is taking tablets.
2. The woman may also be advised to stop taking tablets from the current blister pack. In this case, she should keep a hormone-free interval of up to 7 days, including the days she forgot to take her tablets, and thereafter continue with the next blister pack.

If the woman has missed tablets and does not get a withdrawal bleeding during the first, normal hormone-free interval, the possibility of pregnancy must be considered.

Advice in case of gastro-intestinal disturbances
In case of severe gastro-intestinal symptoms (e.g. vomiting or diarrhoea), absorption of the active ingredients may not be complete and additional contraceptive measures should be taken.

If vomiting or severe diarrhoea occurs within 3 to 4 hours after taking a tablet, a new tablet should be taken as a replacement as soon as possible. The new tablet should be taken if possible within 12 hours of the usual dose time.

If more than 12 hours elapse, the same instructions as those provided for missed tablets should apply (see section “Missed tablets”).

If the woman does not wish to modify the normal tablet-taking schedule, she should take additional tablets from another blister pack.

How to delay or shift a withdrawal bleeding:
In order to delay a withdrawal bleeding, the woman should continue the next blister pack of Rigevidon, after taking the last tablet in the current pack, without a hormone-free interval. The extension can be carried on for as long as desired until the end of the second blister pack. During the extension the woman may experience break through bleeding or spotting. Regular intake of Rigevidon is resumed after the usual 7 days hormone-free interval.

To shift her withdrawal bleeding to another day of the week, rather than the one the woman is used to with the present tablet intake, she may be advised to shorten the forthcoming hormone-free interval by as many days as she likes. The shorter the interval, the greater the risk that she will not have a withdrawal bleeding and that she may have breakthrough bleeding or spotting during the second blister pack (which is also the case when delaying a period). It is important to emphasise that the hormone-free interval should not be extended.

Contraindications

Combined oral contraceptives (COCs) are not to be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during COC use, the product must be stopped immediately.

- Presence or risk of venous thromboembolism (VTE)
  - Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. deep venous thrombosis [DVT] or pulmonary embolism [PE])
  - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
  - Major surgery with prolonged immobilisation (see section Warnings and Precautions)
  - A high risk of venous thromboembolism due to the presence of multiple risk factors (see section Warnings and Precautions)
- Presence or risk of arterial thromboembolism (ATE)
  - Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) 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 Warnings and Precautions) or to the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia
- Severe hepatic disease, current or previous, as long as liver function values have not returned to normal.
- 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 levonorgestrel, ethinylestradiol or to any of the excipients of Rigevidon tablets.

Rigevidon is contraindicated for concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir (see sections ‘Warnings and Precautions’ and ‘Interaction with other medicinal products and other forms of interaction’).

Warnings and Precautions

Warnings

If any of the conditions/risk factors mentioned below is present, the benefits of combined oral contraception use should be weighed against the possible risks for each individual and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first

appearance of any of these conditions or risk factors the woman should contact her physician. The physician should then decide on whether COC use should be discontinued.

1. Circulatory disorders

Risk of venous thromboembolism (VTE)
The use of any combined hormonal contraceptive (CHC) increases the risk of venous thromboembolism (VTE) (such as deep vein thrombosis and pulmonary embolism) compared with no use. Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. The decision to use Rigevidon tablets should be taken after a discussion with the woman to ensure she understands the risk of VTE with Rigevidon tablets, 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).
Out of 10,000 women who use a levonorgestrel containing COC about 6[1] will develop VTE in one year. VTE may be is fatal in 1% to 2% of the cases.

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

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). Rigevidon tablets is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section Contraindications). 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 Contraindications).

Table: Risk factors for VTE

Risk factor	**Comment**
Obesity (body mass index 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 patch/pill/ring (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 Rigevidon tablets has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).	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

[1] 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

	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").

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)
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 deep vein thrombosis (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 pulmonary embolism (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 arterial thromboembolism (ATE)
Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (myocardial infarction) or for cerebrovascular accident (e.g. transient ischaemic attack, 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). Rigevidon tablet 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 Contraindications). 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 Contraindications).

Table: 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 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension.	
Obesity (body mass index 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).	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.

2. Tumours:

Cervical cancer
An increased risk of cervical cancer in long-term users of COCs 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 behavior and other factors such as human papilloma virus (HPV).

Breast cancer
A meta-analysis of 54 epidemiological studies showed that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation.

The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Liver tumours
In rare cases, benign liver tumors, and even more rarely, malignant liver tumors have been reported in users of COCs. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. A hepatic tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.

3. Other conditions

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

Hypertension
Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. If, during the use of a COC in preexisting hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. Where considered appropriate, COC use may be resumed if normotensive values can be achieved with antihypertensive therapy.

Liver conditions
The occurrence of acute or chronic liver abnormalities may require the discontinuation of the COC until the liver parameters return to normal.

Angioedema
In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Glucose intolerance/diabetes
Although COCs 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 COCs. However, diabetic women should be carefully monitored, particularly in the early stage of COC use.

Others
The following conditions have been reported to occur or deteriorate during both pregnancy and COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstones; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

Some cases of worsening of endogenous depression, epilepsy, Crohn's disease and of ulcerative colitis has been reported during COC use.

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 COCs.

Special attention should be paid to patients with hyperprolactinaemia.

Excipients with known effects
This medicinal product contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose free diet should take this amount into consideration.

Medical examination/consultation

Prior to the initiation or reinstitution of ethinylestradiol/levonorgestrel 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 Contraindications) and warnings (see section Warnings and Precautions). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of ethinylestradiol/levonorgestrel 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 oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases (STD).

Reduced efficacy

The efficacy of combined oral contraceptives may be reduced in the event of missed tablets (see section Recommended Dosage) vomiting or diarrhoea (see section Recommended Dosage) or concomitant medication (see section Interaction with other medicinal products and other forms of interaction).

Reduced cycle control

With all combined oral contraceptives, irregular bleeding (spotting or breakthrough 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 3 cycles.

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 some women withdrawal bleeding may not occur during the tablet-free interval. If the COC has been taken according to the directions described in section Recommended Dosage it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

ALT elevations

During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Patients who are taking ethinylestradiol-containing medicinal products must switch to an alternative method of contraception (e.g. progestin only contraception or non-hormonal methods) prior to initiating ombitasvir/paritaprevir/ritonavir and dasubuvir therapy. (See sections 'Contraindications' and 'Interaction with other medicinal products and other forms of interaction').

Interaction with other medicinal products and other forms of interaction

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

Pharmacodynamic interactions

Concomitant use with the medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (see sections 'Contraindications' and 'Warnings and Precautions'). Therefore, Rigevidon users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods)

prior to starting therapy with this combination drug regimen. Rigevidon can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Pharmacokinetic interactions
• Effects of other medicinal products on Rigevidon tablets

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

Management
Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy enzyme induction may be sustained for about 4 weeks.

Short-term treatment
Women on treatment with enzyme inducing drugs should temporarily use a barrier method or another method of contraception in addition to the COC. The barrier method must be used during the whole time of the concomitant drug therapy and for 28 days after its discontinuation.
If the drug therapy runs beyond the end of the tablets in the COC pack containing 21 tablets, the next COC pack should be started right after the previous one without the usual tablet-free interval.

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

The following interactions have been reported in the literature.

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.
Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, and HIV medication ritonavir, nevirapine and efavirenz and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (hypericum perforatum).

Substances with variable effects on the clearance of COCs:

When co-administered with COCs, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors can increase or decrease plasma concentrations of estrogen or progestins. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, an additional barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

• Effects of Rigevidon tablets 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).

• Other forms of interaction

Troleandomycin
Troleandomycin may increase the risk of intrahepatic cholestasis during coadministration with COCs.

Modafinil
Risk of reduction of contraceptive efficacy during the treatment and a cycle after discontinuation of the treatment with modafinil, because of its enzyme inducer potential.

Use normodosed oral contraceptives or another contraceptive method.

Vemurafenib
Risk of reduction of estrogen and progestogen concentrations, with a consequent risk of lack of efficacy.

Perampanel
For perampanel doses greater or equal to 12 mg/d: risk of reduced contraceptive efficacy.
Preferably use another contraceptive method, especially mechanical.

Rufinamide
Moderate reduction in ethinylestradiol concentrations. Preferably use another contraceptive method, especially mechanical.

Etoricoxib
Increased concentrations of ethinylestradiol with etoricoxib.

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 and lipid/lipoprotein fractions; parameters of carbohydrate metabolism and parameters of blood coagulation and fibrinolysis. The changes generally remain within the normal laboratory range.

Fertility, pregnancy and lactation

Pregnancy
Rigevidon is not indicated during pregnancy.If the woman becomes pregnant while using ethinylestradiol/levonorgestrel tablets, further intake must be stopped. Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect at unintentional intake of contraceptive pills in early pregnancy. The increased risk of VTE during the postpartum period should be considered when re-starting Rigevidon tablets (see section Recommended Dosage and Warnings and Precautions).

Breastfeeding
Lactation may be influenced by contraceptive pills as they may reduce the amount of breast milk and change its composition. Thus, the use of combined oral contraceptives should generally not be recommended until the nursing mother has weaned her child off breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted in breast milk. These amounts may affect the child. If the woman wishes to breastfeed, another means of contraception should be proposed.

Effects on ability to drive and use machines
Rigevidon have no effects or negligible influence on the ability to drive and use machines.

Adverse Effects/ Undesirable Effects

The following adverse effects have been reported during use of ethinylestradiol/levonorgestrel.

l Organ system	**Common** (≥1/100 and <1/10)	**Uncommon** (≥1/1000 and <1/100)	**Rare** (<1/1000)	**Very rare** (<1/10,000)	**Not known** (frequency cannot be estimated from the available data)
Neoplasms benign, malignant				Hepatocellular carcinoma,	

and unspecified (incl. cysts and polyps)				benign liver tumours (e.g. focal nodular hyperplasia, hepatic adenoma).	
Infections and infestations	Vaginitis including vaginal candidiasis				
Immune system disorders			Hypersensitivity Anaphylactic reactions with very rare cases of urticaria, angioedema, circulatory and severe respiratory disorders	Exacerbation of disseminated lupus erythematosus.	
Metabolism and nutrition disorders		Altered appetite (increase or decrease)	Glucose intolerance	Exacerbation of a porphyria	
Psychiatric disorders	Nervousness Mood swings including depression, changes in libido				
Nervous system disorders	Dizziness Headache	Migraine		Exacerbated chorea	
Eye disorders			Contact lens intolerance	Optic neuritis, retinal vascular thrombosis	
Vascular disorders		Hypertension	Venous thromboembolism (VTE), Arterial thromboembolism (ATE)	Aggravated varicose veins	
Gastrointestinal disorders	Nausea Vomiting Abdominal pain	Diarrhoea Abdominal cramps, bloating		Ischaemic colitis	Inflammatory bowel disease (Crohn's disease, ulcerative colitis)
Hepatobiliary disorders			Jaundice cholestatic	Pancreatitis, cholelithiasis, cholestasis	Hepatocellular condition (e.g. hepatitis, abnormal liver function)

Skin and subcutaneous tissue disorders	Acne	Rash Urticaria chloasma (melasma) with risk of persisting, hirsutism, hair loss	Erythema nodosum	Erythema multiforme	
Renal and urinary disorders				Haemolytic-uraemic syndrome	
Reproductive system and breast disorders	Breast pain, tenderness, enlargement and discharge, Dysmenorrhoea Irregular bleeding Change in cervical ectropion and vaginal secretion Amenorrhoea				
General disorders and administration site conditions	Fluid retention/oedema, altered weight (increase or decrease)				
Investigations		Changes in serum lipid levels, including hypertriglyceridaemia,		Reduced serum folates.	

Description of selected adverse reactions

An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section Warnings and Precautions.

The following serious adverse events have been reported in women using COCs, which are discussed in section Warnings and Precaution:

- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Hypertension
- Liver tumours
- Crohn's disease, ulcerative colitis, porphyria, systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice;

The frequency of diagnosis of breast cancer is slightly increased among OC-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 COC use is unknown. For further information, see sections Contraindications and Warnings and Precautions**.**

In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

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

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.

Overdose and Treatment
Symptoms of overdose of oral contraceptive have been reported in adults, adolescents and children aged 12 and under. Symptoms of overdose can manifest by nausea, vomiting, breast pains, dizziness, abdominal pains, drowsiness/fatigue and vaginal bleeding in young girls. There is no antidote and treatment should only be symptomatic.

Storage Conditions
Store below 30°C. Shelf-life: 2 years

Nature and contents of container

Aluminium-PVC/PVDC blister

Dosage forms and packaging available
1 x blister of 21 tablets per box
3 x blister of 21 tablets per box

Name and address of manufacturer
Gedeon Richter Plc.
H-1103 Budapest
Gyömrői út 19-21.
Hungary

Date of revision of PI
July 2018.

GEDEON RICHTER PLC.,
BUDAPEST - HUNGARY