PROFESSIONAL INFORMATION

RUBY

SCHEDULING STATUS

S3

1. NAME OF THE MEDICINE

RUBY, 3 mg/0,03 mg, film coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each active film coated tablet contains drospirenone 3 mg and ethinylestradiol 0,03 mg.

RUBY contains sugar (lactose monohydrate 62,00 mg and lactose anhydrous 89,50 mg).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film coated tablets.

21 active round, yellow film coated tablets. 7 round, plain, white inactive film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

RUBY is indicated for the prevention of pregnancy (oral contraception).

4.2 Posology and method of administration

Method of administration

Oral use.

Taking RUBY *for the first time*

The first tablet should be started on the first day of the menstrual cycle (day 1 of the cycle) by selecting the appropriate tablet for that day of the week (e.g. MON for Monday). One tablet should be taken daily (preferably after the evening or at bedtime) for 28 consecutive days. The tablet is swallowed whole with

some liquid.

Withdrawal bleeding usually starts on day 2 to 3 after starting the inactive white tablets and may not have finished before the next pack is started. Each subsequent pack is started the day after the last tablet of the current pack. If RUBY is started during the last part of the week, the very first cycle may be slightly shortened.

How to start RUBY

No preceding hormonal contraceptive uses (in the past month)

Tablet-taking has to start on day 1 of natural cycle (i.e., the first day of the menstrual bleeding). An additional barrier method is recommended for the first 7 days of tablet-taking during the first cycle.

Changing from another combined oral contraceptive, vaginal ring, or transdermal patch to RUBY

The first RUBY tablet should be taken on the day after the last active tablet of the previous combined oral contraceptive, but at the latest on the day following the usual tablet-free or inactive tablet interval of the previous combined oral contraceptive.

In case a vaginal ring or transdermal patch has been used, the woman should start using RUBY preferably on the day of removal, but at the latest when the next application would have been due.

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

Switching from mini pills to RUBY can be done on any day, from an implant or intrauterine system on the day of its removal and from an injectable when the next injection would be due.

In all these cases additional contraceptive precautions are required for the first 7 days of tablet-taking.

Following 1st trimester abortion or miscarriage

Oral contraception may be started immediately. Additional contraceptive precautions are not required.

Following delivery or 2nd trimester abortion or miscarriage

For use in lactation – see section 4.6.

Oral contraception can be started by non-lactating women 21 to 28 days after a delivery or 2nd trimester abortion. If oral contraception is started later, one of the barrier methods as additional contraceptive precaution is also required for the first 7 days.

If intercourse has already taken place, pregnancy should be excluded before tablet intake is started, or it should be delayed until the first menstrual bleeding.

Management of missed tablets

Missed hormone-free white film-coated tablets can be disregarded. However, they should be discarded to avoid unintentionally prolonging the hormone-free white tablet phase. The following advice only refers to missed hormone-containing yellow film-coated tablets:

If the user is less than 12 hours late in taking the yellow active tablet

Contraceptive protection is not reduced, and additional contraceptive precautions are not required.

Take the tablet as soon as you remember and take the next tablet on the scheduled time.

If the user is more than 12 hours late in taking the yellow active tablet

If she is more than 12 hours late in taking any active tablet, contraceptive protection may be reduced.

The management of missed tablets can be guided by the following two basic rules:

- Tablet-taking must never be discontinued for longer than 7 days.
- Uninterrupted tablet-taking for 7 days are required to attain adequate suppression of the hypothalamic-pituitary-ovarian axis.

Accordingly the following advice can be given in daily practice:

First 7 days of active tablet-taking (Day 1 to 7)

The user should take the last missed tablet as soon as she remembers, 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 for the next 7 days. If intercourse took place in the preceding 7days, the possibility of a pregnancy should be considered. The more tablets that are missed and the closer they are to the inactive tablet phase, the higher the risk of a pregnancy.

Second 7 days of active tablet-taking (Day 8 to 14)

The user should take the last missed tablet as soon as she remembers, 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 this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

Third 7 days of active tablet-taking (Day 15 to 21)

The risk of reduced reliability is imminent because of the forthcoming inactive tablet phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. If either of the following two options is adhered to, there is 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, the woman should be advised to follow the first of these two options, and also to use extra precautions for the next 7 days.

1. The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time until the active tablets are used up. The 7 inactive tablets must be discarded. The next pack must be started right away. The user is unlikely to have a withdrawal bleed until the end of the active tablets section of the second pack, but she may experience spotting or breakthrough bleeding

on active tablet-taking days.

2. The woman may also be advised to discontinue active tablet-taking from the current pack. She should then have a tablet-free interval of up to 7 days, including the days she missed tablets, and subsequently continue with the next pack, starting in the silver section with the tablet for the appropriate day of the week.

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

Inactive tablet-taking

Missing any of the white inactive tablets can be ignored but beginning a new cycle on time is essential. However, they should be discarded to avoid unintentionally prolonging the inactive tablet phase.

Advice in case of gastrointestinal disturbances

In case of severe gastrointestinal disturbances, absorption may not be complete and additional contraceptive measures should be taken.

If vomiting occurs within 3 to 4 hours after active tablet taking, the advice concerning missing tablets is applicable. If the woman does not want to change her normal tablet-taking schedule, she must take the extra tablet(s) needed from another pack.

Postponing a period

In order to postpone the menstrual bleeding, a new pack of RUBY should be started without taking the inactive white tablets from the current pack. The extension can be carried on for as long as wished until the end of the second pack. During the use of the second pack, breakthrough-bleeding or spotting may occur. Regular intake of RUBY can be restored after the usual 7 white inactive tablets or tablet-free days.

Special populations

Geriatric patients

Not applicable. RUBY is not indicated after menopause.

Patients with hepatic impairment

RUBY is contraindicated in women with severe hepatic diseases (see section 4.3).

Patients with renal impairment

RUBY is contraindicated in women with severe renal insufficiency or acute renal failure (see section 4.3).

Paediatric population

Children and adolescents

RUBY is only indicated after menarche. There are no data indicating that safety and efficacy in this young age group is different from that known in women aged above 18 years.

4.3 Contraindications

RUBY should not be used in the following conditions. Should any of the conditions appear for the first time during RUBY use, the product should be stopped immediately.

- hypersensitivity to drospirenone, ethinylestradiol or to any of the ingredients of RUBY (see section 6.1)
- hereditary or acquired predisposition for venous or arterial thrombosis, such as activated protein C-resistance, antithrombin-III-deficiency, protein C- deficiency, protein S deficiency, hyperhomocysteinaemia and antiphospholipid antibodies (anticardiolipin-antibodies, lupus anticoagulant)
- deep venous thrombosis or pulmonary embolism (present or history)
- arterial thrombosis (e.g. cerebrovascular accident, myocardial infarction) or prodromal conditions

(e.g. angina pectoris, transient ischemic attack) (present or history)

- severe or multiple risk factor(s) for arterial factors:
  - diabetes mellitus with vascular symptoms
  - uncontrolled hypertension
  - severe dyslipoproteinaemia
  - smoking tobacco
  - underlying abnormality of the coagulation system
- active and severe hepatic disease (presence or history), cholestatic or active
- severe renal insufficiency or acute renal failure. Potassium excretory capacity may be limited in patients with renal insufficiency. These patients must be monitored for hyperkalaemia when additionally, concomitant potassium sparing medicines are taken (see sections 4.4 and 4.5)
- hepatic tumours, benign or malignant (presence or history)
- personal and family history of breast cancer
- previous proven deep-vein thrombosis (DVT)
- previous pulmonary embolism
- inherited thrombophilia
- patients known with inherited genetic mutations: BRCA1 and BRCA2 genes
- early menstrual periods (before the age of 12 years)
- history of non-cancerous breast diseases (atypical hyperplasia or lobular carcinoma in situ)
- previous treatment using radiation therapy to the chest or breast
- previous exposure to diethylstilbestrol (DES)
- known or suspected malignant conditions of the genital organs or the breasts if sex steroid-influenced
- vaginal bleeding (abnormal or undiagnosed)
- history of migraine headaches with focal neurological symptoms (see section 4.4)

- pregnancy (known or suspected)
- major surgery with prolonged immobilisation.

4.4 Special warnings and precautions for use

If any of the following conditions/risk factors mentioned below is present, appear for the first time or aggravate, the benefits of using RUBY must be weighed against possible risks for each individual woman and discussed with the woman before she decides to start using the medicine. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her medical practitioner. The medical practitioner should then decide on whether RUBY's use should be discontinued.

Circulatory disorders

An increased risk for venous (deep vein thrombosis, pulmonary embolism) and arterial (myocardial infarction, transient ischaemic attack) thromboembolism have been associated with the use of combined oral contraceptives.

The risk for venous thromboembolism is highest during the first year of use. This increased risk is present after initially starting a combined oral contraceptive, such as RUBY, (following a 4 week or greater pill-free interval) the same or a different combined oral contraceptive. Study data suggests this increased risk is mainly present during the first 3 months of use.

Overall the risk for venous thromboembolism (VTE) in users of low combined oral contraceptives is two to three-fold higher than for non-users of combined oral contraceptives who are not pregnant.

Venous thromboembolism (VTE) may be life-threatening or may have a fatal outcome (in 1- 2 % of the cases).

The occurrence of thrombosis has been reported in other blood vessels e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in combined oral contraceptives including RUBY users. There is no

consensus as to whether the occurrence of these events is associated with the use of combined oral contraceptives such as RUBY.

Symptoms of deep venous thrombosis (DVT) may include:

- unilateral swelling of the leg 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) may include:

- sudden severe pain in the chest, which may increase with deep breathing, whether or not it radiates to the left arm
- sudden onset of unexplained breathlessness or rapid breathing
- sudden onset of coughing which may bring up blood
- sense of anxiety, 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).

An arterial thromboembolic event can include cerebrovascular accident, vascular occlusion or myocardial infarction (MI).

Symptoms of a cerebrovascular accident can include:

- weakness or very marked numbness suddenly affecting one side or one part of the body (face, arm or leg)
- sudden confusion, trouble speaking, or understanding

- sudden partial or complete loss of vision, in one or both eyes, diplopia
- sudden trouble walking, dizziness, loss of balance or coordination
- any unusual, severe, prolonged headache with no known cause
- collapse or fainting with or without focal seizure
- sudden pain, swelling and slight blue discolouration of an extremity, acute abdomen.

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
- fullness, indigestion or choking feeling
- sweating, nausea, vomiting or dizziness
- extreme weakness, anxiety or shortness of breath
- rapid or irregular heartbeats.

Arterial thromboembolic events may be life-threatening or may have a fatal outcome.

Risk factors for venous thromboembolic complications when using RUBY:

- increased age
- positive family history of venous thromboembolism (if a hereditary predisposition is known or suspected, the woman should be referred to a specialist for advice before deciding about any combined oral contraceptive use)
- prolonged immobilisation, major surgery, any surgery to the legs or major trauma. It is advisable to discontinue the use of RUBY (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation in these situations. Antithrombotic treatment should be considered if the use of RUBY has not been discontinued in advance

- obesity (body mass index more than 30 kg/m^2).

Risk factors for arterial thromboembolic complications when using RUBY**:**

- increasing age
- smoking (with heavier smoking and increasing age, the risk increases further, women over 35 years should be strongly advised not to smoke if they wish to use a combined oral contraceptive)
- dyslipoproteinaemia
- hypertension
- valvular heart disease
- atrial fibrillation.

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in venous thromboembolism.

The increased risk of thromboembolism in the puerperium must be considered (see section 4.6).
The presence of one or more serious risk factors or multiple risk factors for venous arterial disease respectively, can also constitute to a contraindication. Possible symptoms of thrombosis should be reported, and anticoagulant therapy should be considered. Other medical conditions which have been associated with adverse vascular events include diabetes mellitus, systemic lupus erythematosus, haemolytic uremic syndrome, and chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease. An increase in frequency or severity of migraine may be reason for immediate discontinuation of RUBY.

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include activated protein C (APC) resistance, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin

antibodies, lupus anticoagulant).

Migraine

An increase in frequency or severity of migraine during combined oral contraceptive use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation of the combined oral contraceptive, such as RUBY (see section 4.3).

Tumours

An increased risk of cervical cancer has been reported in long-term users of combined oral contraceptives.

The most important risk factor for cervical cancer is persistent human papilloma virus infection. Some epidemiological studies have indicated that long term use of combined oral contraceptives may further contribute to this increased risk but there continues to be controversy about the extent to which this finding is attributable to confounding effects e.g., cervical screening and sexual behaviour including the use of barrier contraceptives.

Benign liver tumours, and malignant liver tumours have been reported in users of combined oral contraceptives. These tumours have led to life-threating intra-abdominal haemorrhages. 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 combined oral contraceptives. Malignancies may be life threatening or may have a fatal outcome.

Breast cancer

RUBY contains oestrogen and progestogen which, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 -2018 reported a significant increase in the risk of developing breast cancer in 55,575 women 40 - 59 years of age who

used menopausal hormone therapy (MHT). The risk increased steadily with duration of use and was slightly greater for oestrogen-progestogen than oestrogen only preparations, and the risk persisted for more than 10 years after stopping the treatment. The relative risk (RR) to develop breast cancer for oestrogen-progestogen preparations was 1.60 at 1 - 4 years and RR = 2.08 at 5 - 14 years, while that for oestrogen only preparations was 1.17 at 1 - 4 years and 1.33 at 5 - 14 years.

There was no risk of developing breast cancer in women who started MHT at 60 years of age.

All women on RUBY should receive yearly breast examinations by a healthcare provider and perform monthly breast self-examinations. Mammography evaluations should be done based on patient age, risk factors, and prior mammogram results.

Other conditions

Potassium sparing medication

The progestogen component in RUBY is an aldosterone antagonist with potassium sparing properties. Potassium excretion capacity may be limited in patients with renal insufficiency. In a clinical study, drospirenone intake did not show an effect on serum potassium concentration in patients with mild or moderate renal impairment. A theoretical risk for hyperkalaemia can be assumed only for patients with renal impairment whose pre-treatment serum potassium is in the upper reference range, and who are additionally using potassium sparing medicines. Therefore, it is recommended to check serum potassium during the first treatment cycle in patients presenting with renal insufficiency and a pre-treatment serum potassium in the upper reference range, and particularly during concomitant use of the following medicines during the first treatment cycle (see sections 4.3 and 4.5):

- angiotensin-converting enzyme (ACE) inhibitors
- angiotensin II receptor antagonists
- aldosterone antagonists
- potassium sparing diuretics
- nonsteroidal anti-inflammatory drugs (NSAIDs) (used for long term treatment).

Hypertriglyceridaemia

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

Blood pressure

Although small increases in blood pressure have been reported in many women taking combined oral contraceptives such as RUBY, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of combined oral contraceptives use is justified. If, during the use of a combined oral contraceptive in pre-existing hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, RUBY must be withdrawn. Where considered appropriate, combined oral contraceptives 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 combined oral contraceptives use but the relevance of an association with RUBY is inconclusive:

- jaundice and/or pruritus related to cholestasis
- gallstone formation
- porphyria
- systemic lupus erythematosus
- haemolytic uremic syndrome
- Sydenham’s chorea
- herpes gestationis
- otosclerosis related hearing loss.

Angioedema

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

Cholestatic jaundice

Acute or chronic disturbances of liver function may necessitate the discontinuation of RUBY use until markers of liver function return to normal. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus, which previously occurred during pregnancy or during previous use of sex steroids, necessitates the discontinuation of RUBY.

Diabetes mellitus

Although RUBY 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 RUBY due to its low ethinylestradiol content of 0,03 mg per tablet. However, diabetic women should be carefully observed, particularly in the early stage of RUBY use.

Crohn’s disease and ulcerative colitis

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

The following conditions may develop or worsen with the use of RUBY:

Chloasma

May occur occasionally, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation when taking RUBY.

Respiratory

Asthma may worsen in women using RUBY.

Depressed mood and depression

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 medical practitioner in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

Medical examination/consultation

Prior to the initiation or reinstitution of RUBY 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, 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 human immunodeficiency virus (HIV) infections (acquired immunodeficiency syndrome (AIDS)) and other sexually transmissible diseases.
The efficacy of combined oral contraceptives may be reduced in the event of missed tablets, vomiting or severe diarrhoea (see section 4.2), or concomitant medication (see section 4.8) which may interact with combined oral contraceptives.

Reduced cycle control

Irregular bleeding (spotting or breakthrough bleeding) may occur especially during the first months of use. The evaluation of any irregular bleeding is only meaningful after an adaption of about three 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 inactive tablet phase. If RUBY has been taken according to the directions described under section 4.2, it is unlikely that the woman is pregnant. However, if RUBY 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 RUBY use is continued.

Concomitant antibiotic therapy:

Oral contraceptive failure may occur with concomitant antibiotic therapy. For maximal protection, additional non-hormonal contraception is recommended for the duration of antibiotic therapy and for seven days thereafter. Those on long-term antibiotic therapy need to only take extra precautions for the first two weeks of antibiotic therapy. Spotting and breakthrough bleeding are possible signs of diminished contraceptive effectiveness.

Lactose:

RUBY contains lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take RUBY.

4.5 Interaction with other medicines and other forms of interaction

Medicines that increase clearance and clearance efficacy by enzyme induction:

An increased clearance of sex hormones, which lead to reduced contraceptive protection and increased breakthrough bleeding, have been associated with the concomitant use of hydantoins, barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, and HIV medicines ritonavir, nevirapine and efavirenz and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and the herbal remedy St. John's wort (*Hypericum perforatum*).

Women on short-term treatment (up to one week) with any of the above-mentioned classes of medicines or individual medicines should temporarily use a barrier method in addition to the combined oral contraceptive (i.e. during the time of concomitant medicine administration) and 28 days after use.

Long-term treatment: stopped

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

Antibiotics (interference with enterohepatic circulation)

Some clinical reports suggest that enterohepatic circulation of oestrogens may decrease when certain antibiotic medicines are given, which may reduce ethinylestradiol concentrations (e.g. penicillins, tetracyclines).

Reduced contraceptive effectiveness is also known with antibiotics such as ampicillin and tetracyclines and the antifungal, griseofulvin.

Long-term users of antibiotic therapy should be advised to use an alternative or additional method of contraception to avoid an unplanned pregnancy.

Women on rifampicin treatment should use a barrier method in addition to the combined oral contraceptive during the time of rifampicin administration and for 28 days after its discontinuation. If

concomitant medicine administration runs beyond the end of the active tablets in the RUBY blister pack, the next RUBY pack should be started without the usual inactive tablet interval.

The dose of RUBY may be increased in women receiving chronic treatment with hepatic enzyme inducing medicines. If a high contraceptive dosage appears to be unsatisfactory or unreliable (in the case of irregular bleeding) another non-hormonal, method of contraception should be advised.

Substances interfering with the metabolism of combined oral contraceptives such as RUBY (enzyme inhibitors):

Inhibitors of the cytochrome P450 systems are unlikely to influence the metabolism of drospirenone as the main metabolites are generated without the involvement of this system.

The clinical relevance of potential interactions with enzyme inhibitors remains unknown.

Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the oestrogen or the progestin or both.

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 $AUC_{(0-24h)}$ of drospirenone and ethinylestradiol 2,7 fold and 1,4 fold respectively.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1,4 to 1,6-fold respectively when taken concomitantly with a combined hormonal contraceptive containing 0,035 mg ethinylestradiol.

Effects of combined oral contraceptives such as RUBY on other medicines:

RUBY may affect the metabolism of certain other medicines. 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 market substrates, an interaction of drospirenone at doses of 3 mg with the metabolism of other medicines is unlikely.

Clinical data suggests that ethinylestradiol is inhibiting the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

Other interactions

The following medications have the potential to increase potassium levels and should be tested for serum potassium during the first treatment cycle (see sections 4.3 and 4.4):

- ACE inhibitors
- angiotensin II receptor antagonists
- aldosterone antagonists
- potassium sparing diuretics
- NSAIDs (used for long term treatment).

However, in studies evaluating the interaction of drospirenone (combined with estradiol) with an ACE inhibitor or indomethacin, no clinically or statistically significant differences in serum potassium concentrations were observed.

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

Changes in laboratory test

The use of RUBY may influence the results of certain laboratory tests e.g. the liver, thyroid, adrenal and renal functions, plasma levels of proteins (e.g. corticosteroid binding globulin and lipid/lipoprotein

fractions) and carrier proteins, parameters of carbohydrate metabolism, parameters of coagulation and fibrinolysis. Changes generally remain within the normal laboratory range.

Drospirenone causes an increase in plasma rennin activity and plasma aldosterone is induced by its mild antimineralocorticoid activity.

4.6 Fertility, pregnancy and lactation

Pregnancy

RUBY is contraindicated during pregnancy. The use of RUBY should be discontinued if pregnancy is confirmed.

Breastfeeding

RUBY may reduce the production and change the composition of breast milk. Therefore, the use of RUBY is not recommended until the breastfeeding mother has completely weaned her child. Small amounts of the contraceptive steroids and/or their metabolites may be excreted with the milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of RUBY. There are no studies on whether RUBY affects mental or physical abilities to execute tasks or activities requiring mental alertness, judgment and/or sound coordination and vision.

4.8 Undesirable effects

a. Summary of the safety profile

The most serious adverse effects associated with the use of combined oral contraceptives are also listed under section 4.4.

b. Tabulated list of adverse reactions

System Organ Class	**Frequency**	**Side effects**
Immune system disorders	Less frequent	Asthma, hypersensitivity
Endocrine disorders	Frequency unknown	Pancreatitis, gall stone formation, changes in glucose tolerance or effect on peripheral insulin resistance, Crohn's disease, ulcerative colitis, chloasma
Psychiatric disorders	Frequent Less frequent	Depression/depressive mood, emotional lability, decrease and loss of libido Increased libido
Nervous system disorders	Frequent	Headache, drowsiness
Eye disorders	Less frequent	Contact lens intolerance
Ear and labyrinth disorders	Frequency unknown	Hypoacusis

Vascular disorders	Frequent Less frequent Frequency unknown	Migraine Hypertension, hypotension Venous thromboembolism (VTE), arterial thromboembolism (ATE), venous and arterial thromboembolic events* (peripheral deep venous occlusion, thrombosis and embolism/pulmonary vascular occlusion, thrombosis, embolism and infarction/myocardial infarction and stroke not specified as haemorrhagic)*
Gastrointestinal disorders	Frequent Less frequent	Nausea, abdominal pain Vomiting, diarrhoea
Hepatobiliary disorders	Frequency unknown	Liver tumours (benign and malignant), jaundice, alterations in liver function tests
Skin and subcutaneous tissue disorders	Less frequent Frequency unknown	Acne, eczema, pruritis, alopecia, hirsutism Erythema nodosum*, erythema multiforme*

Reproductive system and breast disorders	Frequent	Vaginal discharge, vaginal candidiasis, menstrual disorders, intermenstrual bleeding, breakthrough bleeding or spotting, breast tenderness, breast pain
	Less frequent	Breast hypertrophy, vaginal infection
	Frequency unknown	Breast secretion, malignant neoplasms
General disorders and administrative site conditions	Less frequent	Fluid retention, weight loss or gain, fatigue, fever

*Post-marketing reported adverse events.

c. Description of selected adverse reactions

Increased risk of adverse effects:

As discussed in section 4.4, women using combined hormonal contraceptives (CHCs) are at increased risk of arterial and venous thrombotic and thromboembolic events, including myocardial infarction, stroke, transient ischaemic attacks, venous thrombosis and pulmonary embolism.

Serious adverse effects in women using combined oral contraceptives (COCs):

Venous thromboembolic disorders, arterial thromboembolic disorders, hypertension, liver tumours.

Deterioration or occurrence of the following serious adverse effects are inconclusive in women using COCs:

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 (which may necessitate discontinuation), symptoms of angioedema that may be induced or exacerbated in those women with hereditary angioedema exogenous oestrogens.

Interactions:

Concomitant use with enzyme inducing medicines may result in breakthrough bleeding and/or contraceptive failure (see section 4.5).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are requested to report any suspected adverse reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on the SAHPRA website. An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za, to ensure safety of the product.

4.9 Overdose

Signs and symptoms:

Nausea, vomiting and slight vaginal bleeding in young girls.

Management of overdose:

There is no known antidote, and the treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Progestogens and oestrogens, fixed combinations

ATC code: G03AA12

Pharmacological classification: A 18.8 Ovulation controlling agents

Mechanism of action:

Drospirenone and ethinylestradiol act to suppress gonadotropins, which is achieved through inhibition of ovulation and alterations to both the cervical mucus and endometrium. Drospirenone (progestogen) possesses antiandrogenic and mild antimineralocorticoid properties, but no oestrogenic, glucocorticoid and antiglucocorticoid activity.

5.2 Pharmacokinetic properties

Drospirenone

Absorption:

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations of drospirenone in serum of about 37 ng/mL are reached at about 1 to 2 hours after single ingestion. Bioavailability is between 76 % and 85 %. Concomitant ingestion of food has no influence on bioavailability.

Distribution:

Drospirenone is widely distributed with the apparent volume distribution of about 3,7 to 4,2 L/kg. Drospirenone does not bind to sex hormone binding globulin (SHBG) or corticosteroid binding globulin (CBG). Only 3 to 5 % of the total medicine concentrations are present as free steroid, 95 to 97 % are non-specifically bound to albumin. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of drospirenone.

Biotransformation:

Drospirenone is extensively metabolised with a half-life of about 30 hours. The major metabolites in the

plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulphate, both of which are formed without involvement of the P450 system.

Drospirenone is metabolised to a minor extent by cytochrome P450 3A4 based on *in vitro* data. The clearance rate from serum is about 1,2 to 1,5 mL/min/kg. When drospirenone was acutely co-administered with ethinylestradiol, no direct interaction was found.

Elimination:

Drospirenone serum levels decrease in two phases. The terminal disposition phase is characterised by a half-life of approximately 31 hours. Drospirenone is not excreted in unchanged form. Its metabolites are excreted at a biliary to urinary ratio of about 1,2 to 1,4. The half-life of metabolite excretion with the urine and faeces is about 1,7 days.

Steady-state conditions:

Drospirenone pharmacokinetics are not influenced by SHBG levels. Following daily ingestion, medicine serum levels increase about two to threefold reaching steady-state conditions during the second half of a treatment cycle. Maximum steady-state concentrations of drospirenone in serum of about 70 ng/mL are reached after 8 days of treatment. Serum drospirenone levels accumulate by a factor of about 3 as a consequence of the ratio of terminal half-life and dosing interval.

Pharmacokinetics in special patient groups

Effect on renal impairment:

Steady-state serum drospirenone levels in women with mild renal impairment (creatinine clearance CLcr, 50 to 80 mL/minute) were comparable to those of women with normal renal function (CLcr, > 80 mL/minute). The serum drospirenone levels were on average 37 % higher in women with moderate renal impairment (CLcr, 30 to 50 mL/minute) compared to those in women with normal renal function. Drospirenone was well tolerated by all groups. Drospirenone treatment did not show any clinically

significant effect on serum potassium concentration. Severe renal impairment was not studied.

Effect on hepatic impairment:

In women with moderate hepatic impairment (Child-Pugh B), mean serum drospirenone concentration – time profiles were comparable with those of women with normal hepatic function during the absorption/distribution phases, with similar C_{max} values.

The mean terminal half-life of drospirenone for the volunteers with moderate hepatic impairment was about 1,8 times greater than for volunteers with normal hepatic function.

An approximately 50 % decrease in apparent oral clearance (CL/f) was seen in volunteers with moderate hepatic impairment as compared to those with normal liver function. The observed decline in drospirenone clearance in volunteers with moderate hepatic impairment compared to normal volunteers did not translate to any apparent difference in terms of serum potassium concentrations between the two groups of volunteers.

Ethinylestradiol

Absorption:

Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations of about 54 to 100 pg/mL are reached within 1 to 2 hours. During absorption and first-liver passage, ethinylestradiol is metabolised extensively resulting in a mean oral bioavailability of about 45 % with a large interindividual variation of about 20 to 65 %. Concomitant intake of food reduced the bioavailability of ethinylestradiol in about 25 % of the investigated subjects while no change was observed in the others.

Distribution:

The bioavailability is 40 % after oral administration and serum ethinylestradiol is widely distributed (4 - 5 litres per kilogram) in the body. It is highly protein bound, but unlike naturally occurring oestrogens which are mainly bound to sex hormone binding globulin, ethinylestradiol is principally bound to albumin

(approximately 98 %) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 2,8 to 8,6 L/kg was determined.

Biotransformation:

Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulphate. The clearance rate was reported to be about 2,3 to 7 mL/min/kg.

Elimination:

It is extensively metabolised with a half-life of about 24 hours. Ethinylestradiol is excreted in the urine and faeces as glucuronide and sulphate conjugates and undergoes enterohepatic circulation. Ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6.

Steady-state conditions:

Steady-state conditions of ethinylestradiol are reached during the second half of a treatment cycle when serum medicine levels are higher by 40 to 110 %, as compared to a single dose.

5.3 Preclinical safety data

In laboratory animals, the effects of drospirenone and ethinylestradiol were confined to those associated with the recognised pharmacological action. In particular, reproduction toxicity studies revealed embryotoxic and fetotoxic effects in animals which are considered as species specific. At exposures exceeding those in users of at above normal doses, effects on sexual differentiation were observed in rat foetuses but not in monkeys.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core active:

Crospovidone (XL and XL-10)

Lactose monohydrate

Magnesium stearate

Maize starch

Polysorbate 80

Povidone K-30

Pregelatinised starch

Tablet core inactive:

Lactose anhydrous

Magnesium stearate

Povidone K-30

Coating, active Opadry II yellow

Polyvinyl alcohol – partially hydrolysed

Titanium dioxide

Macrogol

Talc

Iron oxide yellow

Coating inactive,Opadry II white:

Polyvinyl alcohol

Titanium dioxide

Macrogol/PEG

Talc

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

Store at or below 25 ºC.

Keep in outer container until required for use.

6.5 Nature and contents of container

Aluminium/PVC/PVDC foil blister strips containing 28 tablets packed in an outer carton.

6.6 Special precautions for disposal

No special requirements.

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

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