PROFESSIONAL INFORMATION

RUBAZ

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

RUBAZ 3 mg / 0,02 mg film coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

24 active pink film coated tablets:

Each tablet contains 3 mg drospirenone and 0,02 mg ethinylestradiol.

Each tablet contains sugar (lactose monohydrate 44 mg).

4 inactive (placebo) white film coated tablets:

The tablet does not contain active substances.

Each tablet contains sugar (lactose anhydrous 89,5 mg).

For the full list of excipients, see section 6 .1.

3. PHARMACEUTICAL FORM

Film coated tablets.

The active tablets are round, pink film coated tablets.

The inactive (placebo) tablets are round, white film coated tablets.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

- oral contraceptive
- treatment of moderate acne vulgaris in women seeking oral contraception
- treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who have chosen oral contraception as their method of birth control. The efficacy of RUBAZ for PMDD was not

assessed beyond 3 cycles.

RUBAZ has not been evaluated for treatment of premenstrual syndrome (PMS).

4.2 Posology and method of administration

Posology

RUBAZ, when taken correctly, has a failure rate of approximately 1 % per year. The failure rate may increase when pills are missed or taken incorrectly.

Tablets must be taken in the order directed on the package, at about the same time every day, with some liquid if needed. One tablet is taken daily for 28 days. Each subsequent pack is started the day after the last intake of the previous pack. A withdrawal bleed usually starts on day 2 to 3 after starting the white placebo tablets and may not be finished before the next pack is started.

How to start RUBAZ:

No preceding hormonal contraceptive use (in the past month):

Tablet-taking has to start on day 1 of the woman's natural cycle (i.e. the first day of her menstrual bleeding). Starting on days 2 - 5 is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

Changing from a combined hormonal contraceptive (combined oral contraceptive), vaginal ring or transdermal patch:

The woman should start with RUBAZ preferably on the day after the last active tablet of her previous combined oral contraceptive, but at the latest on the day following the usual tablet-free or inactive tablet interval of her previous combined oral contraceptive. If a vaginal ring or transdermal patch has been used, the woman should start using RUBAZ preferably on the day of removal, but at the latest when the next application would have been due.

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

The woman may switch any day from the minipill, from an implant or the intrauterine system on the day of its removal and 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 days of tablet-taking.

Following first-trimester abortion:

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

Following delivery or second-trimester abortion:

For breastfeeding women see section 4.6.

Women should be advised to start at day 21 - 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 of tablet-taking. However, if intercourse has already occurred, pregnancy should be excluded before the actual start of RUBAZ use or the woman has to wait for her first menstrual period.

Management of missed tablets:

Missed white tablets (from the last row of the blister) are placebos and thus can be disregarded to avoid unintentionally prolonging the placebo tablet phase. The following advice only pertains to missed active tablets:

If the user is **less than 12 hours** late in taking any active tablet, contraceptive protection is not reduced.

The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

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:

1. Active tablet-taking must never be discontinued for longer than four days;
2. 7 days of uninterrupted 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 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 7 days, 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.

Day 8 - 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.

Day 15 - 24:

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 use extra precautions for the next 7 days as well.

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 4 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 4 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.

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 - 4 hours after active tablet-taking, the advice concerning missed 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.

How to delay a period:

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

Special populations

Children and adolescents:

RUBAZ is only indicated after menarche.

Elderly patients:

RUBAZ is not indicated after menopause.

Patients with hepatic impairment:

RUBAZ is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal (see section 4.3).

Patients with renal impairment:

RUBAZ is contraindicated in patients with severe renal impairment or acute renal failure (see section 4.3).

Method of administration

For oral use only.

4.3 Contraindications

Combined oral contraceptives, such as RUBAZ, should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during treatment with RUBAZ, the product should be stopped immediately.

- hypersensitivity to the active substances (drospirenone and ethinylestradiol) or to any of the excipients listed in section 6.1
- known hereditary or acquired predisposition for venous or arterial thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency, hyperhomocysteinaemia, antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant)
- presence or a history of venous or arterial thrombotic/ thromboembolic events (e.g. myocardial infarction, or of a cerebrovascular accident)
- presence or history of prodromata of a thrombosis (e.g. transient ischaemic attack, angina pectoris)
- history of migraine with focal neurological symptoms

- diabetes mellitus with vascular involvement
- the presence of a severe or multiple risk factor(s) for venous or arterial thrombosis (see section 4.4)
- personal and family history of breast cancer
- previous proven deep-vein thrombosis (DVT)
- previous pulmonary embolism
- inherited thrombophilia
- active liver disease
- patients known with inherited genetic mutations: BRCA1 and BRCA 2 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)
- active and severe hepatic disease as long as liver function values have not returned to normal
- severe renal insufficiency or acute renal failure with a creatinine clearance of < 30 mL/min
- presence or history of liver tumours (benign or malignant)
- known or suspected sexsteroid-influenced malignancies (e.g. of the genital organs or the breasts)
- undiagnosed vaginal bleeding
- known or suspected pregnancy
- major surgery with prolonged immobilisation
- severe hypertension, severe dyslipoproteinaemia
- depression not well-controlled with treatment
- a history of depression with the use of hormonal contraception
- RUBAZ is contraindicated for concomitant use with the medicines containing ombitasvir/ paritaprevir/ritonavir and dasabuvir (see section 4.5).

4.4 Special warnings and precautions for use

If any of the conditions or risk factors mentioned below is present, the suitability of RUBAZ should be discussed with the woman.

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 RUBAZ should be discontinued.

In case of suspected or confirmed venous thromboembolism (VTE) or arterial thromboembolism (ATE), combined hormonal contraceptives (CHC) use should be discontinued. In case anticoagulant therapy is started, adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

Circulatory disorders

An association between the use of drospirenone/ethinylestradiol, as in RUBAZ tablets and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis and pulmonary embolism has been reported.

Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products, such as RUBAZ, may have up to twice this level of risk. The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with RUBAZ, 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 reported evidence that the risk is increased when the same CHC is re-started or a different CHC is started after a break in use of 4 weeks or more. This increased risk is reported to be mainly present during the first 3 months.

Overall, the risk for venous thromboembolism (VTE) in users of low estrogen dose combined oral contraceptives is reported to be two- to threefold higher than for non-users of combined oral contraceptives who are not pregnant.

VTE may be life-threatening or may have a fatal outcome.

Venous thromboembolism, manifesting as deep venous thrombosis and/or pulmonary embolism, may occur. The occurrence of thrombosis has been reported in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries, in RUBAZ users.

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

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

The risk of venous or arterial thrombotic/thromboembolic events or of a cerebrovascular accident increases with:

- age
- smoking (with heavier smoking and increasing age the risk increases further, especially in women over 35 years of age)
- a positive family history (i.e. venous or arterial thromboembolism ever in a sibling or parent at a relatively early age). If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any combined oral contraceptive use
- obesity (body mass index over 30 kg/m^2)
- dyslipoproteinaemia
- hypertension
- migraine
- valvular heart disease
- atrial fibrillation
- prolonged immobilisation, major surgery, any surgery to the legs, or major trauma, 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 combined oral contraceptive use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilisation.

The increased risk of thromboembolism in the puerperium, must be considered (see section 4.6).

Other medical conditions which have been associated with adverse circulatory events include diabetes mellitus, cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease.

An increase in frequency or severity of migraine during RUBAZ tablets use (which may be prodromal of a cerebrovascular event) may be a reason for its immediate discontinuation.

Biochemical factors that may be indicative of a 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).

Breast cancer

RUBAZ contains drospirenone and ethinylestradiol which, on prolonged use, may increase the risk of developing breast cancer. A meta-analysis of prospective epidemiological studies from 1992 to 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 to develop breast cancer in women who started MHT at 60 years of age.

All women on RUBAZ 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.

Tumours

The most important risk factor for cervical cancer is persistent human papilloma virus infection. Long-term use of RUBAZ may further contribute to an increased risk of cervical cancer.

A slightly increased relative risk (RR = 1,24) of having breast cancer diagnosed in women who are currently using drospirenone/ ethinylestradiol, as contained in RUBAZ, has been reported. The excess risk is reported to gradually disappear during the 10 years after cessation of drospirenone/ ethinylestradiol as contained in RUBAZ use.

Benign liver tumours and, even more rarely, malignant liver tumours have been reported in users of drospirenone/ethinylestradiol, as contained in RUBAZ. In isolated cases, these tumours have been reported to lead to life-threatening 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 RUBAZ.

With the use of the higher-dosed combined oral contraceptives (COCs) (50 microgram ethinylestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower-dosed COCs remains to be confirmed.

Other conditions

The progestin component in RUBAZ is an aldosterone antagonist with potassium-sparing properties. In most cases, no increase of potassium levels is to be expected. In a reported clinical study, however in some patients with mild or moderate renal impairment and concomitant use of potassium-sparing medicines serum potassium levels slightly, but not significantly, increased during drospirenone intake. 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 potassium-sparing medicines.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis

when using combined oral contraceptives such as RUBAZ.

Small increases in blood pressure have been reported in many women taking drospirenone/ ethinylestradiol, as contained in RUBAZ, and clinically relevant increases may occur. If a sustained clinically significant hypertension develops during the use of RUBAZ, then it is prudent for the medical practitioner to withdraw it and treat the hypertension.

The occurrence or deterioration of the following conditions have been reported with drospirenone/ ethinylestradiol as contained in RUBAZ use: 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 estrogens such as RUBAZ may induce or exacerbate symptoms of angioedema.

Acute or chronic disturbances of liver function may necessitate the discontinuation of RUBAZ. Recurrence of cholestatic jaundice which first occurred during pregnancy or previous use of sex steroids necessitates the discontinuation of RUBAZ.

RUBAZ may have an effect on peripheral insulin resistance and glucose tolerance. Hence diabetic women should be carefully observed while taking RUBAZ.

Worsening of endogenous depression and epilepsy, has been reported during COC use.

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

Crohn's disease and ulcerative colitis have been reported with combined oral contraceptives such as RUBAZ.

Chloasma may 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 RUBAZ.

ALT elevations

Patients treated for hepatitis C virus infections (HCV) with the medicines containing ombitasvir/ paritaprevir/ritonavir and dasabuvir with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) have been reported significantly more frequent in women using ethinylestradiol-containing medicines such as combined hormonal contraceptives (CHCs).

Medical examination/consultation

A complete medical history and physical examination should be taken, and pregnancy must be ruled out prior to the initiation or reinstitution of RUBAZ use, guided by the contraindications (see section 4.3) and warnings (see section 4.4), and should be repeated periodically.

Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of RUBAZ. The frequency and nature of these assessments should be based on established practice guidelines and be adapted to the individual woman, but should generally include special reference to blood pressure, breasts, abdominal and pelvic organs, including cervical cytology and relevant laboratory tests.

Women should be advised that RUBAZ does not protect against HIV infections (AIDS) and other sexually transmitted diseases (STDs). Women should be advised that additional barrier contraceptive measures are needed to prevent transmission of STDs and HIV infection.

Reduced efficacy

The efficacy of RUBAZ may be reduced in the event of e.g. missed active tablets (see section 4.2), gastrointestinal disturbances during active tablet taking (see section 4.2) or concomitant medicine (see section 4.5).

Reduced cycle control

Irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. 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 RUBAZ have been taken according to the directions described under section 4.2, it is unlikely that the woman is pregnant. However, if RUBAZ have 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 its use is continued.

Lactose

Each pink active film coated tablet contains 44 mg lactose monohydrate. Each white inactive (placebo) film coated tablet contains 89,5 mg lactose anhydrous. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Sodium

RUBAZ contains less than 1 mmol sodium (0,023 g) per tablet, that is to say ‘essentially sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

Interactions between RUBAZ and other medicines may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature.

Effects of other medicines on RUBAZ

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 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 RUBAZ. The barrier method must be used during the whole time of the concomitant therapy and for 28 days after its discontinuation. If the therapy runs beyond the end of the active tablets in the RUBAZ pack, the placebo tablets must be discarded, and the next RUBAZ 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.

Hepatic metabolism:

Interactions can occur with medicines that induce microsomal enzymes, which can result in increased clearance of sex hormones (e.g. phenytoin, barbiturates, bosentan, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St John’s wort).

Also, HIV protease (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine, efavirenz), and combinations of them, including combinations with HCV inhibitors have been reported to potentially affect hepatic metabolism and can increase or decrease plasma concentrations of estrogen or progestins. The net effect of these changes may be clinically relevant in some cases.

Concomitant administration of strong CYP3A4 inhibitors can increase plasma concentrations of the

estrogen or the progestin or both.

In a reported 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 reported 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.

Enterohepatic circulation of estrogens may decrease when certain antibiotics are given, which may reduce ethinylestradiol concentrations (e.g. penicillins, tetracyclines).

Women on treatment with any of these medicines should temporarily use a barrier method in addition to RUBAZ or choose another method of contraception.

With microsomal enzyme-inducing medicines, the barrier method should be used during the time of concomitant medicine administration and for 28 days after their discontinuation. Women on treatment with antibiotics (except rifampicin and griseofulvin) should use the barrier method until 7 days after discontinuation. If the period during which the barrier method is used runs beyond the end of the active tablets in the RUBAZ pack, the inactive tablets should be omitted and the next pack of RUBAZ should be started with the active tablets (i.e. without the usual inactive tablet interval).

The main metabolites of drospirenone in human plasma are generated without involvement of the cytochrome P450 system. Inhibitors of this enzyme system are therefore unlikely to influence the metabolism of drospirenone.

Effects of RUBAZ on other medicines

RUBAZ may affect the metabolism of certain other medicines. Plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

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

The reported clinical data suggests that ethinylestradiol may inhibit the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

Pharmacodynamic interactions

Concomitant use with the medicines containing ombitasvir/paritaprevir/ ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations.
Therefore, RUBAZ users must switch to an alternative method of contraception (e.g. progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination regimen.
RUBAZ can be restarted 2 weeks following completion of treatment with this combination regimen.

There is a potential for an increase in serum potassium in women taking RUBAZ with other medicines that may increase serum potassium levels. Such medicines include angiotensin II receptor antagonists, potassium-sparing diuretics, and aldosterone antagonists. 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 reported.

No formal interaction studies were reported with tuberculosis or HIV treatments.

Note: The package insert information of concomitant medicines should be consulted to identify

potential interactions.

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 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.

4.6 Fertility, pregnancy and lactation

Pregnancy

RUBAZ is contraindicated during pregnancy (see section 4.3). If pregnancy occurs during treatment with RUBAZ further intake should be stopped.

The increased risk of VTE during the postpartum period should be considered when restarting RUBAZ.

Breastfeeding

The use of RUBAZ is not recommended during breastfeeding. Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Therefore, the use of COCs should generally not be 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 during COC use. These amounts may affect the child.

Fertility

RUBAZ is indicated for the prevention of pregnancy.

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 reported. No effects on ability to drive and use machines have been reported in users of combined oral contraceptives such as RUBAZ. However, patients should be advised that they may experience undesirable effects such as somnolence, dizziness or vertigo during treatment (see section 4.8). Therefore, caution should be recommended when driving a vehicle or operating machinery.

4.8 Undesirable effects

The frequencies of adverse reactions (ARs) reported with drospirenone/ ethinylestradiol are summarised in the table below. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Tabulated list of adverse reactions

System organ class	**Frequency category**		
	Frequent	**Less frequent**	**Frequency not known**
Infections and infestations		Candidiasis	
Blood and lymphatic system disorders		Anaemia, thrombocythemia	
Immune system disorders		Allergic reaction	Hypersensitivity
Endocrine disorders		Endocrine disorder	
Metabolism and		Increased appetite,	

nutrition disorders		anorexia, hyperkalaemia, hyponatraemia, body weight changes, fluid retention, hypertriglyceridaemia	
Psychiatric disorders	Depressive mood, emotional lability	Changes in libido, nervousness, somnolence, anorgasmia, insomnia	Altered mood
Nervous system disorders	Headache, migraine	Dizziness, paraesthesia, vertigo, tremor	
Eye disorders		Conjunctivitis, dry eye, eye disorder	Contact lens intolerance
Ear and labyrinth disorders		Hypoacusis	
Cardiac disorders		Tachycardia	
Vascular disorders		Hypertension, hypotension, thromboembolism,	

		varicose vein, phlebitis, vascular disorder, epistaxis, syncope, venous thromboembolism (VTE), arterial thromboembolism (ATE), cerebrovascular accidents	
Respiratory, thoracic and mediastinal disorders		Asthma	
Gastrointestinal disorders	Nausea	Vomiting, dyspepsia, flatulence, gastritis, abdominal pain, diarrhoea, abdomen enlarged, gastrointestinal disorder, gastrointestinal fullness,	

		hiatus hernia, oral candidiasis, constipation, dry mouth	
Hepatobiliary disorders		Biliary pain, cholecystitis, liver tumours (benign and malignant), liver function disturbances	
Skin and subcutaneous tissue disorders		Acne, eczema, pruritus, rash, chloasma, alopecia, dermatitis acneiform, dry skin, erythema nodosum, hypertrichosis, skin disorder, skin striae, contact dermatitis, photosensitive dermatitis, skin nodule	Urticaria, erythema multiforme
Musculoskeletal and connective tissue disorders		Back pain, pain in extremity, muscle cramps	
Reproductive system and	Breast pain*, leukorrhoea**,	Vaginitis, breast discharge,	

breast disorders	vaginal moniliasis, menstrual disorder (metrorrhagia***, amenorrhoea), intermenstrual bleeding***	vaginal candidiasis, pelvic pain, breast enlargement, fibrocystic breast, uterine / vaginal bleeding*, genital discharge, hot flushes, dysmenorrhoea, hypomenorrhoea, vaginal dryness, papanicolaou smear suspicious, decreased libido	
General disorders and administration site conditions		Asthenia, increased sweating, oedema, (generalised oedema, peripheral oedema, face oedema), malaise	

* including breast tenderness

** including vaginal discharge

*** bleeding irregularities usually subside during continued treatment.

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 professionals are requested to report any suspected adverse drug reactions to SAHPRA via the Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.
An email can be sent directly to the company, pharmacovigilance@pharmadynamics.co.za
to ensure the safety of the product.

4.9 Overdose

On the basis of general experience with combined oral contraceptives, symptoms that may occur in case of taking an overdose of active tablets are nausea; vomiting; and, in young girls, slight vaginal bleeding. Treatment should be symptomatic and supportive.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 21.8.2 Progesterones with estrogens.

Pharmacotherapeutic group: Progestogens and estrogens, fixed combinations.

ATC code: G03AA12.

The contraceptive effect of combined oral contraceptives is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion.

Drospirenone exerts antiandrogenic activity.

Drospirenone is devoid of androgenic, estrogenic, glucocorticoid and anti-glucocorticoid activity.

5.2 Pharmacokinetic properties

Drospirenone

Absorption:

Orally administered drospirenone is reported to be rapidly and almost completely absorbed. Maximum

concentrations of the active substance in serum of about 35 ng/mL are reported to be reached at about 1 - 2 hours after single ingestion. Bioavailability is reported to be between 76 % and 85 %. It has been reported that the intake of food had no influence on the extent of absorption of drospirenone, but the maximum concentration was reduced in comparison to intake on an empty stomach.

Distribution:

After oral administration, serum drospirenone levels have been reported to decrease in two phases which are characterised by half-lives of 1,6 ± 0,7 hours and 27,0 ± 7,5 hours, respectively. Drospirenone is reported to bind to serum albumin and does not bind to sex hormone binding globulin (SHBG) or corticoid binding globulin (CBG). Only 3 - 5 % of the total serum active substance concentrations are present as free steroid. The ethinylestradiol-induced increase in SHBG does not influence the serum protein binding of drospirenone. The mean apparent volume of distribution of drospirenone is reported to be 3,7 ± 1,2 L/kg.

Biotransformation:

Drospirenone is reported to be extensively metabolised after oral administration. 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 by cytochrome P450 3A4 and has reportedly demonstrated a capacity to inhibit this enzyme and cytochrome P450 1A1, cytochrome P450 2C9 and cytochrome P450 2C19 *in vitro*.

Elimination:

The metabolic clearance rate of drospirenone in serum is reported to be 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 half-life of metabolite excretion with the urine and faeces is about 40 hours.

Steady-state conditions:

During a treatment cycle, maximum steady-state concentrations of drospirenone in serum of about 60 ng/mL are reported to be reached between day 7 and day 14 of treatment. Serum drospirenone levels accumulated by a factor of about 3 as a consequence of the ratio of terminal half-life and dosing interval. Further accumulation of drospirenone levels beyond treatment cycles was reported between cycles 1 and 6 but thereafter, no further accumulation was reported.

Special populations

Effect of renal impairment

Steady-state serum drospirenone levels in women with mild renal impairment (creatinine clearance CL_{cr}, 50 – 80 mL/min) were comparable to those of women with normal renal function (creatinine clearance CL_{cr}, > 80 mL/min). The serum drospirenone levels were on average 37 % higher in women with moderate renal impairment (CL_{cr}, 30 – 50 mL/min) compared to those in women with normal renal function. It has been reported that drospirenone treatment did not show any clinically significant effect on serum potassium concentration.

Effect of hepatic impairment

In women with moderate hepatic function (Child-Pugh B), mean serum drospirenone concentration-time profiles were reported to be comparable to those of women with normal hepatic function during the absorption/distribution phases, with similar C_{max}, values. The decline in serum drospirenone concentrations during the terminal disposition phase was reported to be about 1,8 times greater for the volunteers with moderate hepatic impairment than for the volunteers with normal hepatic function. About a 50 % decrease in apparent oral clearance (CL/f) was reported in volunteers with moderate hepatic impairment as compared to those with normal liver function. The reported decline in drospirenone clearance in volunteers with moderate hepatic impairment compared to normal volunteers did not translate into any apparent difference in terms of serum potassium concentrations between the two groups of volunteers.

Ethinylestradiol

Absorption:

Orally administered ethinylestradiol is reported to be rapidly and completely absorbed. Peak serum concentrations of about 88 - 100 pg/mL are reported to be reached within 1 - 2 hours after single oral administration. Absolute bioavailability as a result of pre-systemic conjugation and first-pass metabolism is reported to be approximately 60 %. Concomitant intake of food has been reported to reduce the bioavailability of ethinylestradiol in about 25 % of the investigated subjects while the maximum concentration was reduced in all subjects.

Distribution:

Serum ethinylestradiol levels decrease in two phases, the terminal disposition phase is characterised by a half-life of approximately 24 hours. Ethinylestradiol is reported to be highly but non-specifically bound to serum albumin (approximately 98,5 %) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 5 L/kg was determined.

Biotransformation:

Ethinylestradiol is subject to pre-systemic conjugation in both the 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 metabolic clearance rate of ethinylestradiol is reported to be about 5 mL/min/kg.

Elimination:

Ethinylestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinylestradiol are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions:

Steady-state conditions are reported to be reached during the second half of a treatment cycle and

serum levels of ethinylestradiol accumulate by a factor of about 1,4 to 2,1.

5.3 Preclinical safety data

No information of relevance available.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Pink active film coated tablets:

Tablet core:

Croscarmellose sodium

Lactose monohydrate

Magnesium stearate

Polysorbate 80

Povidone

Pregelatinised starch.

Film coating:

Opadry Pink (containing black iron oxide, red iron oxide, yellow iron oxide, macrogol, polyvinyl alcohol-partial hydrolysed, talc and titanium dioxide).

White placebo film coated tablets:

Tablet core:

Lactose, anhydrous

Magnesium stearate

Povidone.

Film coating:

Opadry White (containing titanium dioxide, macrogol, polyvinyl alcohol-partial hydrolysed, and talc).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years.

6.4 Special precautions for storage

Store at or below 25 °C.

Keep blister strip in outer carton until required for use.

6.5 Nature and contents of container

One PVC/PVDC/aluminium foil blister strip in an outer carton.

Pack size: 28 (24 + 4) tablets.

6.6 Special precautions for disposal and other handling

None.

7. HOLDER OF CERTIFICATE OF REGISTRATION

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8. REGISTRATION NUMBER

A50/21.8.2/0342

9. DATE OF FIRST AUTHORISATION

10 August 2022

10. DATE OF REVISION OF THE TEXT

16 January 2024