SCHEDULING STATUS
S4

1. NAME OF THE MEDICINE
ETHODROS 3 mg / 0,02 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
24 pink active film-coated tablets:
Each ETHODROS tablet contains
Drospirenone ……3 mg
Ethinylestradiol …….0,02 mg

Excipients with known effect:
Contains sugar.
Each pink active tablet contains 44 mg lactose monohydrate.
Contains sodium.
Each pink active tablet contains 0,10 mg sodium.

4 White inactive (placebo) film-coated tablets:
The tablet does not contain active substances.

Excipients with known effect:
Contains sugar.
Each white inactive (placebo) tablet contains 89,5 mg lactose.
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 drospirenone 3 mg and ethinylestradiol 0,02 mg for PMDD has not been reported beyond 3 cycles.

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

4.2 Posology and method of administration
ETHODROS, 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 ETHODROS:
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 to 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 ETHODROS 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. In case a vaginal ring or transdermal patch has been used, the woman should start using ETHODROS 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 to 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 ETHODROS 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 strip) 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 4 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 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 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 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.

Day 15 to 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 to 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 ETHODROS 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 ETHODROS is then resumed after the inactive tablet phase.

Additional information on special populations:
Children and adolescents:
ETHODROS is only indicated after menarche.

Elderly patients:
ETHODROS is not indicated after menopause.

Patients with hepatic impairment:
ETHODROS 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:
ETHODROS 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 ETHODROS, 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 ETHODROS, the product should be stopped immediately.

- Hypersensitivity to the active substances (drospirenone and ethinylestradiol) or to any of the excipients listen 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. deep venous thrombosis, pulmonary embolism, 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).
- 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 sex-steroid 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 contraceptives.

ETHODROS is contraindicated for concomitant use with medicines containing ombitasvir/paritaprevir/ritonavir and dasabuvir.

4.4 Special warnings and precautions for use
If any of the conditions or risk factors mentioned below is present, the suitability of ETHODROS 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 ETHODROS tablets should be discontinued.

In case of suspected or confirmed venous thromboembolism (VTE) or arterial thromboembolism (ATE), combined hormonal contraceptive (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 ETHODROS 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 ETHODROS, may have up to twice this level of risk. The decision to use any medicines 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 ETHODROS, 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 ETHODROS 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/m²)
- 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 ETHODROS 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).

Tumours
The most important risk factor for cervical cancer is persistent human papilloma virus infection. Long-term use of ETHODROS 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 ETHODROS has been reported. The excess risk is reported to gradually disappear during the 10 years after cessation of drospirenone/ethinylestradiol as contained in ETHODROS use.

Benign liver tumours and, even more rarely, malignant liver tumours have been reported in users of drospirenone/ethinylestradiol, as contained in ETHODROS. 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 ETHODROS.

With the use of the higher-dosed combined oral contraceptives (COCs) (50 µg 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 ETHODROS 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 COCs (combined oral contraceptives) such as ETHODROS.

Small increases in blood pressure have been reported in many women taking drospirenone/ethinylestradiol, as contained in ETHODROS, and clinically relevant increases may occur. If a sustained clinically significant hypertension develops during the use of

ETHODROS, 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 ETHODROS 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 ETHODROS may induce or exacerbate symptoms of angioedema.

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

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

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 (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 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 ETHODROS.

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 ETHODROS.

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 ETHODROS 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 ETHODROS. 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 ETHODROS 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 ETHODROS may be reduced in the event of e.g. missed active tablets, 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 placebo tablet phase. If ETHODROS has been taken according to the directions described under section 4.2, it is unlikely that the woman is pregnant. However, if ETHODROS 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 its use is continued.

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

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

4.5 Interaction with other medicines and other forms of interaction
Interactions between ETHODROS 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 ETHODROS
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 medicinal 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 ETHODROS. The barrier method must be used during the whole time of the concomitant therapy and for 28 days after its discontinuation. If the medicinal therapy runs beyond the end of the active tablets in the ETHODROS pack, the placebo tablets must be discarded and the next ETHODROS pack should be started immediately.

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 $AUC_{(0\text{-}24h)}$ 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 ETHODROS 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 ETHODROS pack, the inactive tablets should be omitted and the next pack of ETHODROS 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 ETHODROS on other medicines
ETHODROS 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 vitro* inhibition studies and *in vivo* interaction studies in female volunteers using omeprazole, simvastatin or midazolam as marker substrate, 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 medicines containing ombitasvir/paritaprevir/ ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations.

Therefore, ETHODROS 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. ETHODROS 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 ETHODROS 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 antimineralocorticoid activity.

4.6 Fertility, pregnancy and lactation

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

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

Breastfeeding
The use of ETHODROS 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
ETHODROS 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 ETHODROS. 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.

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 nutrition disorders		Increased appetite, anorexia, hyperkalaemia, hyponatraemia, body mass 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		Asthma	

disorders			
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 disorders	Breast pain*, leukorrhoea**, vaginal moniliasis, menstrual disorder (metrorrhagia***, amenorrhoea), intermenstrual bleeding***	Vaginitis, breast discharge, 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 ETHODROS is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reactions Reporting Form**", found online under SAHPRA's publications: https://www.sahpra.org.za/Publications/Index/8.

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 (ATC): 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 to 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 plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, 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 reported to be 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. An about 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 to 100 pg/mL are reached within 1 – 2 hours after single oral administration. Absolute bioavailability as a result of presystemic 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 significant gut and hepatic first-pass metabolism. Ethinylestradiol is subject to presystemic 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 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.

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 iron oxide black (E172), iron oxide red (E172), iron oxide yellow (E172), macrogol 3350, polyviniyl alcohol-partial hydrolyzed, talc (E553b) and titanium dioxide (E171)).

White placebo film-coated tablets:
Tablet core:
Lactose anhydrous
Magnesium stearate
Povidone

Film-coating:
Opadry White (containing titanium dioxide (E171), macrogol 3350, polyviniyl alcohol-partial hydrolyzed and talc (E553b)).

6.2 Incompatibilities

Not applicable.

6.3 Shelf life
3 years.

6.4 Special precautions for storage
Store at or below 25 °C.
Keep the blister strip in the outer carton until required for use.

6.5 Nature and contents of container
PVC/PVDC/Aluminium foil blister strip, placed in an outer carton. Each blister strip contains 24 pink active film-coated tablets and 4 white placebo film-coated tablets.
Pack size: 28 tablets.

6.6 Special precautions for disposal and other handling
Return all unused or expired medicine to your pharmacist for safe disposal. Do not dispose of unused medicines in drains or sewage systems (e.g. toilets).

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

Marketed by:
United Pharma Marketing (Pty) Ltd

8. REGISTRATION NUMBER
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