1. NAME OF THE MEDICINAL PRODUCT

Yaz 0.02mg/3mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

24 hormone-containing light pink film-coated tablets:

Each film-coated tablet contains 0.02 mg ethinylestradiol (as betadex clathrate), 3 mg drospirenone.

4 hormone-free white film-coated tablets.
For a full list of excipients(s), see section, “List of excipients”.

3. PHARMACEUTICAL FORM

Film-coated tablet.

The hormone-containing tablet is light pink, round with convex faces, one side marked with the letters "DS" in a regular hexagon.

The hormone-free tablet is white, round with convex faces, one side marked with the letters "DP" in a regular hexagon.

4. CLINICAL PARTICULARS

4.1 Indications

YAZ is indicated for the prevention of pregnancy in women who elect to use an oral contraceptive.

YAZ is indicated for the treatment of moderate acne vulgaris in women at least 14 years of age, who have no known contraindications to oral contraceptive therapy and have achieved menarche. YAZ should be used for the treatment of acne only if the patient desires an oral contraceptive for birth control.

YAZ is indicated for the treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who choose to use an oral contraceptive as their method of contraception. The effectiveness of YAZ for PMDD when used for more than three menstrual cycles has not been evaluated.

4.2 Dosage and method of administration

4.2.1 Method of administration

Oral use

4.2.2 Dosage regimen

How to take Yaz; 24 + 4 film-coated tablets

Combined oral contraceptives, when taken correctly, have 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 every day at about the same time with some liquid as needed. Tablet taking is continuous. One tablet is to be taken daily for 28 consecutive days. Each subsequent pack is started the day after the last tablet of the previous pack. Withdrawal bleeding usually starts on day 2-3 after starting the hormone-free white film-coated tablets and may not have finished before the next pack is started.

How to start Yaz; 24 + 4 film-coated tablets

- 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 /COC), vaginal ring, or transdermal patch

The woman should start with Yaz; 24+4 preferably on the day after the last hormone-containing tablet of her previous COC, but at the latest on the day following the usual tablet-free or hormone-free tablet interval of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Yaz; 24+4 preferably on the day of removal of the last ring or patch of a cycle pack, 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 (IUS)

The woman may switch any day from the minipill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due), but should in all of these cases be advised to additionally use a barrier method for the first 7 days of tablet-taking.

- Following first-trimester abortion

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

- Following delivery or second-trimester abortion

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 COC use or the woman has to wait for her first menstrual period.

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 film-coated tablets phase. The following advice only refers to **missed hormone-containing light pink** film-coated tablets:

If the user is **less than 24 hours** late in taking any hormone-containing 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 24 hours** late in taking any hormone-containing tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. tablet-taking must never be discontinued for longer than 4 days

2. 7 days of uninterrupted hormone-containing 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 are missed and the closer they are to the hormone-free white film-coated tablets 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 hormone-free white film-coated tablets phase. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the woman should be advised to follow the first of these two options and to 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 light pink film-coated tablets are used up. The 4 white hormone-free film-coated 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 hormone-containing light pink film-coated tablets section of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.

2. The woman may also be advised to discontinue taking the light pink film-coated tablet

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.

If the woman missed tablets and subsequently has no withdrawal bleed in the hormone-free white film-coated tablets phase, the possibility of a pregnancy should be considered.

Advice in case of gastro-intestinal disturbances

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

If vomiting occurs within 3-4 hours after taking a light pink hormone-containing film-coated tablet, the advice concerning missed tablets is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take the extra tablet(s) needed from another pack.

How to shift periods or how to delay a period

To delay a period the woman should continue with another pack of Yaz; 24 + 4 film-coated tablets without taking the hormone-free white film-coated tablets from her current pack. The extension can be carried on for as long as wished until the end of the light pink film-coated tablets in the second pack. During the extension the woman may experience breakthrough-bleeding or spotting. Regular intake of Yaz; 24 + 4 Film Tablets is then resumed after the hormone-free white tablet phase.

To shift her periods to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming hormone-free white film-coated tablets phase by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough-bleeding and spotting during the second pack (just as when delaying a period).

4.2.3 Additional information on special populations

4.2.3.1 Pediatric patients
Yaz is only indicated after menarche. There are no data suggesting the need for a dosage adjustment.

4.2.3.2 Geriatric patients
Not applicable. Yaz is not indicated after menopause.

4.2.3.3 Patients with hepatic impairment
Yaz is contraindicated in women with severe hepatic diseases. See also sections ‘Contraindications’ and ‘Pharmacokinetic properties’.

4.2.3.4 Patients with renal impairment
Yaz is contraindicated in women with severe renal insufficiency or acute renal failure. See also sections ‘Contraindications’ and ‘Pharmacokinetic properties’.

4.3 Contraindications

Combined oral contraceptives (COCs) 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 COC use,

the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE)
    - Venous thromboembolism – current VTE (on anticoagulants) or history of deep venous thrombosis [DVT], pulmonary embolism [PE]
    - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance, (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
    - Major surgery with prolonged immobilization (see under "Special Warnings and Special Precautions for Use")
    - A high risk of venous thromboembolism due to the presence of multiple risk factors (see under "Special Warnings and Special Precautions for Use")

- Presence or risk of arterial thromboembolism (ATE)
    - Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
    - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA)
    - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia, and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant)
    - History of migraine with focal neurological symptoms
    - A high risk of arterial thromboembolism due to multiple risk factors (see under "Special Warnings and Special Precautions for Use") or to the presence of one serious risk factor such as:
        - Diabetes mellitus with vascular symptoms
        - Severe hypertension
        - Severe dyslipoproteinaemia
- Hepatic dysfunction
- Use of direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these (see 'Interaction with other medicinal products and other forms of interaction')
- Renal impairment
- 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
- Hypersensitivity to the active substances or to any of the excipients
- Cholestatic jaundice of pregnancy or jaundice with prior pill use

4.4 Special warnings and precautions for use

Warnings

If any of the conditions/risk factors mentioned below is present, the benefits of COC use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start using it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her physician. The physician should then decide on whether COC use should be discontinued.

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

- Circulatory Disorders

Risk of venous thromboembolism (VTE)

Epidemiological studies have suggested an association between the use of COCs and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism and of cerebrovascular accidents. These events occur rarely.

The risk of VTE is highest during the first year of use. This increased risk is present after initially starting a COC or restarting (following a 4 week or greater pill free interval) the same or a different COC. Data from a large, prospective 3-armed cohort study suggest that this increased risk is mainly present during the first 3 months.

Overall the risk for venous thromboembolism (VTE) in users of low estrogen dose (< 50 µg ethinylestradiol) COCs is two to threefold higher than for non-users of COCs who are not pregnant and remains lower than the risk associated with pregnancy and delivery.

Post Authorization Safety Studies (PASS) have shown that the frequency of VTE diagnosis ranges between 7-10 per 10,000 woman years in low estrogen dose (< 50 µg ethinylestradiol) COC users. The most recent data suggest that the frequency of VTE diagnosis is approximately 4 per 10,000 woman years in non-pregnant non-COC users, and ranges between 20 to 30 per 10,000 pregnant women or post partum.

The increased risk of VTE associated with COC use is attributed to the estrogen component. There remains a scientific debate regarding any modulating effect on the risk of VTE by the progestin component of COCs. Epidemiological studies that compared the risk of VTE associated with use of ethinylestradiol/drospirenone to the risk with use of COCs containing levonorgestrel reported differing results ranging from no difference in risk to a three-fold increase in risk. The majority of studies investigated Yasmin.

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

Venous thromboembolism (VTE), manifesting as deep venous thrombosis and/or pulmonary embolism, may occur during the use of all COCs.

The use of any combined oral contraceptive (COC) increases the risk of venous thromboembolism (VTE) compared with no use. Products that contain levonorgestrel, norgestimate, or norethisterone are associated with the lowest risk of VTE. Other products such as YAZ 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 YAZ, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a COC is re-started after a break in use of 4 weeks or more.

In women who do not use a COC and are not pregnant, about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman, the risk may be far higher, depending on her underlying risk factors (see below).

It is estimated that out of 10,000 women who use a COC-containing drospirenone, between 9

to 12 women will develop a VTE in one year; this compares with about 6 in women who use a levonorgestrel-containing COC.

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

Symptoms of deep venous thrombosis (DVT) can 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 discolored skin on the leg.

Symptoms of pulmonary embolism (PE) can include: sudden onset of unexplained shortness of breath or rapid breathing; sudden coughing which may bring up blood; sharp chest pain which may increase with deep breathing; 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: sudden numbness or weakness of the face, arm or leg, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden, severe or prolonged headache with no known cause; loss of consciousness or fainting with or without seizure. Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity; acute abdomen.

Symptoms of 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.

The potential for an increased synergistic risk of thrombosis should be considered in women who possess a combination of risk factors or exhibit a greater severity of an individual risk factor. This increased risk may be greater than a simple cumulative risk of the factors. A COC should not be prescribed in case of a negative risk benefit assessment (see 'Contraindications').

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 further increases, 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 known or suspected, the woman should be referred to a specialist for advice before deciding about any COC use;
- obesity (body mass index over 30 kg/m^2);
- dyslipoproteinemia;
- hypertension;

- migraine;
- valvular heart disease;
- atrial fibrillation;
- prolonged immobilization, major surgery, any surgery to the legs, or major trauma. In these situations it is advisable to discontinue COC use (in the case of elective surgery at least four weeks in advance) and not to resume until two weeks after complete remobilization.

The presence of one serious risk factor or multiple risk factors for venous or arterial disease, respectively, can also constitute a contra-indication. The possibility of anticoagulant therapy should also be taken into account. COC users should be specifically pointed out to contact their physician in case of possible symptoms of thrombosis. In case of suspected or confirmed thrombosis, COC use should be discontinued. Adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

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.

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

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

Biochemical factors that may be indicative of hereditary or acquired predisposition for venous or arterial thrombosis include Activated Protein C (APC) resistance, hyperhomocysteinemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering risk/benefit, the physician should take into account that adequate treatment of a condition may reduce the associated risk of thrombosis and that the risk associated with pregnancy is higher than that associated with low-dose COCs (<0.05 mg ethinylestradiol).

- Tumours

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

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or acombination of both. The breast cancers diagnosed in ever-users tend to be less advanced

clinically than the cancers diagnosed in never-users.

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

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

- Other conditions

A theoretical risk for hyperkalemia can be assumed only for patients with renal impairment whose pretreatment serum potassium is in the upper reference range, and who are additionally using potassium sparing drugs. Potassium excretion capacity may be limited in patients with renal insufficiency. YAZ is contraindicated in renal impairment (See Section Contraindications).

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

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. The antimineralocorticoid effect of drospirenone may counteract ethinylestradiol-induced increases in blood pressure observed in normotensive women using other combined oral contraceptives. However, if a sustained clinically significant hypertension develops during the use of a COC then it is prudent for the physician to withdraw the COC and treat the hypertension. Where considered appropriate, COC 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 COC use, but the evidence of an association with COC use is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

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

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of COCs.

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing < 0.05 mg ethinylestradiol). However, diabetic women should be carefully observed while taking COCs.

Crohn's disease and ulcerative colitis have been associated with COC use.

Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking COCs.

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of COC use, guided by the contraindications and warnings, and should be repeated periodically. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. 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, abdomen and pelvic organs, including cervical cytology.

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmitted diseases.

Reduced efficacy

The efficacy of COCs may be reduced in the event of e.g. missed hormone-containing light pink film-coated tablets, gastro-intestinal disturbances during hormone-containing light pink film-coated tablet taking or concomitant medication.

Reduced cycle control

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about 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 hormone-free white film-coated tablets phase. If the COC has been taken according to the directions given, it is unlikely that the woman is pregnant. However, if the COC has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before COC use is continued.

4.5 Interactions with other medicinal products and other forms of interaction

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

Effects of other medicinal products on Yaz

Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure. There have been reports of pregnancy while taking hormonal contraceptives and antibiotics, but clinical studies in women demonstrate no evidence of an interaction between COCs and non-enzyme inducing antibiotics. Rifampicin and Griseofulvin are two enzyme

inducing antimicrobials that are known to reduce the efficacy of COC.

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

Women on treatment with any of these drugs should temporarily use a barrier method in addition to the COC or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. If the period during which the barrier method is used runs beyond the end of the hormone-containing light pink film-coated tablets in the COC pack, the hormone-free white film-coated tablets should be omitted and the next COC pack be started.

Substances increasing the clearance of COCs (diminished efficacy of COCs by enzyme-induction), e.g.:

Phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing St. John's wort.

Substances with variable effects on the clearance of COCs, e.g.:

When co-administered with COCs, many HIV/HCV protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of estrogen or progestin. These changes may be clinically relevant in some cases.

Substances decreasing the clearance of COCs (enzyme inhibitors)
Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the estrogen 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 2.68-fold (90% confidence interval (CI): 2.44, 2.95) and 1.40-fold (90%CI: 1.31, 1.49), 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 COCs on other medicinal products

COCs may affect the metabolism of certain other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporin) or decrease (e.g. lamotrigine).

In vitro, drospirenone is capable to inhibit weakly to moderately the cytochrome P450 enzymes CYP1A1, CYP2C9, CYP2C19 and CYP3A4.

Based on *in vivo* interaction studies in female volunteers using omeprazole, simvastatin or midazolam as marker substrates, a clinically relevant interaction of drospirenone at doses of 3 mg with the metabolism of other drugs is unlikely.

In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2. In clinical studies, administration of a hormonal contraceptive containing ethinylestradiol did not lead to any increase or only to a weak increase in plasma concentrations of CYP3A4 substrates (e.g. midazolam) while plasma concentrations of CYP1A2 substrates can increase weakly (e.g. theophylline) or moderately (e.g. melatonin and tizanidine).

Pharmacodynamic interactions

Co-administration of ethinylestradiol-containing medicinal products with direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir, or dasabuvir, and combinations of these has been shown to be associated with increases in ALT levels to greater than 20 times the upper limit of normal in healthy female subjects and HCV infected women (see 'Contraindications').

Other forms of interaction

Serum potassium
There is a theoretical potential for an increase in serum potassium in women taking Yaz hormone-containing light pink film-coated tablets with other drugs that may increase serum potassium levels. Such drugs 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 observed.

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 Pregnancy and lactation

4.6.1 Pregnancy

Yaz; 24 + 4 film coated-tablets is not indicated during pregnancy. If pregnancy occurs during treatment with Yaz; 24 + 4 film coated-tablets, further intake must be stopped. However, extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy.

The available data regarding the use of Yaz; 24 + 4 film-coated tablets during pregnancy are too limited to permit conclusions concerning negative effects of Yaz; 24 + 4 film-coated tablets on pregnancy, health of the fetus or neonate. No relevant epidemiological data are available yet.

The increased risk of VTE during the postpartum period should be considered when re-starting Yaz (see under "Special Warnings and Special Precautions for Use").

4.6.2 Lactation

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 nursing 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 operate machinery

No observed effects.

4.8 Undesirable effects

4.8.1 Summary of safety profile

The most commonly reported adverse reactions with Yaz when used as oral contraceptive or when used in the treatment of moderate acne vulgaris in women electing to use oral contraception are nausea, breast pain, unscheduled uterine bleeding and genital tract bleeding not further specified. They occur in ≥ 3 % of users. The most commonly reported adverse reactions with Yaz when used for the treatment of PMDD in women electing to use oral contraception are nausea, breast pain and unscheduled uterine bleeding. They occur in > 10% of users.

Serious adverse reactions are arterial and venous thromboembolism.

4.8.2 Tabulated summary of adverse reactions

The frequencies of ADRs reported in clinical trials with Yaz and Yaz Plus as oral contraceptives and Yaz in the treatment of moderate acne vulgaris in women who elect to use oral contraception (N=3565), as well as Yaz in the treatment of symptoms of PMDD in women who elect to use oral contraception (N= 289) are summarised in the table below. Within each frequency grouping, ADRs are presented in order of decreasing seriousness. Additional ADRs identified only during postmarketing surveillance, and for which a frequency could not be estimated, are listed under 'not known'.

System Organ Class (MedDRA version 12.1)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (≥ 1/10,000 to < 1/1000)	**Not known**
Psychiatric disorders	Emotional lability, Depression/ depressive mood	Decrease and loss of libido[b]		
Nervous system disorders	Migraine			

Vascular disorders			Venous thromboembolism Arterial thromboembolism Venous and arterial thromboembolic events*	
Gastrointestinal disorders	Nausea[a]			

System Organ Class (MedDRA version 12.1)	**Common** (≥ 1/100 to < 1/10)	**Uncommon** (≥ 1/1,000 to < 1/100)	**Rare** (≥ 1/10,000 to < 1/1000)	**Not known**
Skin and subcutaneous tissue disorders				Erythema multiforme
Reproductive system and breast disorders	Breast pain[a], Unscheduled uterine bleeding[a], Genital tract bleeding not further specified			

Adverse events in clinical studies were coded using the MedDRA dictionary. Different MedDRA terms representing the same medical phenomenon have been grouped together as single adverse reactions to avoid diluting or obscuring the true effect.

* - Estimated frequency, from epidemiological studies encompassing a group of combined oral contraceptives. Frequency was borderline to Very Rare.
- 'Venous and arterial thromboembolic events' summarizes the following Medical Entities:
Peripheral deep venous occlusion, thrombosis and embolism/Pulmonary vascular occlusion, thrombosis, embolism and infarction/Myocardial infarction/Cerebral infarction and stroke not specified as hemorrhagic

[a] Incidence in trials evaluating PMDD was Very Common >10/100

[b] Incidence in trials evaluating PMDD was Common ≥1/100

For venous and arterial thromboembolic events and migraine see also sections 'Contraindications', 'Special warnings and precautions for use'.

4.8.3 Adverse reactions reported in women using COCs

Adverse reactions with very low frequency or with delayed onset of symptoms which are considered to be related to the group of combined oral contraceptives are listed below (see also sections 'Contraindications', 'Special warnings and precautions for use'):

Tumours

- The frequency of diagnosis of breast cancer is very slightly increased among OC users. As breast cancer is rare in women under 40 years of age the excess number is small in relation to the overall risk of breast cancer. Causation with COC use is unknown.
- Liver tumours (benign and malignant)

Other conditions

- Erythema nodosum
- Increased risk of pancreatitis when using COCs in women suffering from hypertriglyceridemia (see section 'Special Warnings and precautions for use')
- Hypertension
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema
- Liver function disturbances
- Changes in glucose tolerance or effect on peripheral insulin resistance
- Crohn's disease, ulcerative colitis.
- Chloasma
- Hypersensitivity (including symptoms such as rash, urticaria)

Other side effects that had been reported with the use of COCs that have neither been confirmed nor refuted are:

Ear and labyrinth disorders	Hypoacusis
Eye disorders	Contact lens intolerance
Gastrointestinal disorders	Abdominal pain, vomiting, diarrhoea
General disorders and administration site conditions	Weight increased, fluid retention, weight decreased
Nervous system disorders	Headache
Psychiatric disorders	Libido increased
Reproductive system and breast disorders	Menstrual disorders, breast secretion, vaginal moniliasis, vaginitis, breast hypertrophy, vaginal discharge, breast discharge
Respiratory, thoracic and mediastinal disorders	Asthma

Skin and subcutaneous tissue disorders	Acne, eczema, pruritus
Vascular disorders	Hypotension

Interactions

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

4.9 Overdose

There has not yet been any clinical experience of overdose with Yaz hormone-containing light pink film-coated tablets. There have been no reports of serious deleterious effects from overdose in preclinical studies. On the basis of general experience with combined oral contraceptives, symptoms that may occur in case of taking an overdose of hormone-containing tablets are nausea, vomiting and withdrawal bleeding. The last may even occur in girls before their menarche, if they have accidentally taken the medicinal product. There are no antidotes and further treatment should be symptomatic.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

The contraceptive effect of COCs 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.

As well as protection against pregnancy, COCs have several positive properties which, next to the negative properties (see Warnings, Undesirable effects), can be useful in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency.

Drospirenone has antimineralocorticoid activity, counteracting estrogen-related sodium retention. In combination with ethinylestradiol, drospirenone displays a favorable lipid profile with an increase in HDL. Drospirenone exerts antiandrogenic activity. Drospirenone does not counteract the ethinylestradiol-related SHBG (sex hormone binding globulin) increase which is useful for binding and inactivating the endogenous androgens.

Drospirenone is devoid of any androgenic, estrogenic, glucocorticoid, and antiglucocorticoid activity. This, in combination with the antimineralocorticoid and antiandrogenic properties, gives drospirenone a biochemical and pharmacological profile closely resembling the natural hormone progesterone. Apart from this, with the higher dosed COCs (0.05 mg ethinylestradiol), there is evidence of a reduced risk of fibrocystic tumours of the breasts, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy and endometrial and ovarian cancer. Whether this also applies to lower-dosed COCs such as YAZ remains to be confirmed.

Clinical studies

Oral Contraceptive Clinical Trial

In the primary contraceptive efficacy study of YAZ (3 mg DRSP/ 0.02 mg EE) of up to 1 year duration, 1,027 subjects were enrolled and completed 11,480 28-day cycles of use. The age range was 17 to 36 years. The racial demographic was: 87.8% Caucasian, 4.6% Hispanic, 4.3% Black, 1.2% Asian, and 2.1% other. Women with a BMI greater than 35 were excluded from the trial. The pregnancy rate (Pearl Index) was 1.41 per 100 woman-years of use based on 12 pregnancies that occurred after the onset of treatment and within 14 days after the last dose of YAZ in women 35 years of age or younger during cycles in which no other form of contraception was used.

Premenstrual Dysphoric Disorder Clinical Trials

Two multicenter, double-blind, randomized, placebo-controlled studies were conducted to evaluate the effectiveness of YAZ in treating the symptoms of PMDD. Women aged 18-42 who met DSM-IV criteria for PMDD, confirmed by prospective daily ratings of their symptoms, were enrolled. Both studies measured the treatment effect of YAZ using the Daily Record of Severity of Problems scale, a patient-rated instrument that assesses the symptoms that constitute the DSM-IV diagnostic criteria. The primary study was a parallel group design that included 384 evaluable reproductive-aged women with PMDD who were randomly assigned to receive YAZ or placebo treatment for 3 menstrual cycles. The supportive study, a crossover design, was terminated prematurely prior to achieving recruitment goals due to enrollment difficulties. A total of 64 women of reproductive age with PMDD were treated initially with YAZ or placebo for up to 3 cycles followed by a washout cycle and then crossed over to the alternate medication for 3 cycles.

Efficacy was assessed in both studies by the change from baseline during treatment using a scoring system based on the first 21 items of the Daily Record of Severity of Problems. Each of the 21 items was rated on a scale from 1 (not at all) to 6 (extreme); thus a maximum score of 126 was possible. In both trials, women who received YAZ had statistically significantly greater improvement in their Daily Record of Severity of Problems scores. In the primary study, the average decrease (improvement) from baseline was 37.5 points in women taking YAZ, compared to 30.0 points in women taking placebo.

Acne Clinical Trials

In two multicenter, double blind, randomized, placebo-controlled studies, 889 subjects, ages 14 to 45 years, with moderate acne received YAZ or placebo for six 28 day cycles. The primary efficacy endpoints were the percent change in inflammatory lesions, non-inflammatory lesions, total lesions, and the percentage of subjects with a “clear” or “almost clear” rating on the Investigator’s Static Global Assessment (ISGA) scale on day 15 of
cycle 6, as presented in Table I:

Table I: Efficacy Results for Acne Trials*

	Study 1		Study 2	
	YAZ N=228	Placebo N=230	YAZ N=218	Placebo N=213
ISGA Success Rate	35 (15%)	10 (4%)	46 (21%)	19 (9%)
Inflammatory Lesions				
Mean Baseline Count	33	33	32	32
Mean Absolute (%) Reduction	15 (48%)	11 (32%)	16 (51%)	11 (34%)

Non-inflammatory Lesions Mean Baseline Count Mean Absolute (%) Reduction	 47 18 (39%)	 47 10 (18%)	 44 17 (42%)	 44 11 (26%)
Total lesions Mean Baseline Count Mean Absolute (%) reduction	 80 33 (42%)	 80 21 (25%)	 76 33 (46%)	 76 22 (31%)

* Evaluated at day 15 of cycle 6, last observation carried forward for the Intent to treat population

5.2 Pharmacokinetic properties

- Drospirenone

Absorption

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations of the drug in serum of about 35 ng/ml are reached at about 1-2 h after single ingestion. Bioavailability is between 76 and 85 %. The intake of food had no influence on the bioavailability of drospirenone as compared to drug intake on an empty stomach.

Distribution

After oral administration, serum drospirenone levels decrease in two phases which are characterized by half-lives of 1.6 ± 0.7 h and 27.0 ± 7.5 h, respectively. Drospirenone is bound 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 drug 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 3.7 ± 1.2 l/kg.

Metabolism

Drospirenone is extensively metabolized 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-sulfate, formed by reduction and subsequent sulfatation. Drospirenone is also subject to oxidative metabolism catalyzed by CYP 3A4.

Elimination

The metabolic clearance rate of drospirenone in serum is 1.5 ± 0.2 ml/min/kg. Drospirenone is excreted only in trace amounts in unchanged form. The metabolites of drospirenone are excreted with the feces and urine at an excretion ratio of about 1.2 to 1.4. The half-life of metabolite excretion with the urine and feces is about 40 h.

Steady-State Conditions

During a treatment cycle, maximum steady-state concentrations of drospirenone in serum of about 60 ng/ml are reached between day 7 and day 14 of treatment. Serum drospirenone levels accumulated by a factor of about 2 to 3 as a consequence of the ratio of terminal half-life and dosing interval. Further accumulation of drospirenone levels beyond treatment cycles was observed between cycles 1 and 6 but thereafter, no further accumulation was observed.

- Ethinylestradiol

Absorption

Orally administered ethinylestradiol is absorbed rapidly and completely. Peak serum concentrations of about 88 to 100 pg/ml are reached within 1 - 2 hours after single oral administration. During absorption and first-liver passage, ethinylestradiol is metabolized extensively, resulting in a mean oral bioavailability of about 45% with a large interindividual variation of about 20-65%. 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

Serum ethinylestradiol levels decrease in two phases, the terminal disposition phase is characterized by a half-life of approximately 24 hours. Ethinylestradiol is 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.

Metabolism

Ethinylestradiol is subject to significant gut and hepatic first-pass metabolism. Ethinylestradiol and its oxidative metabolites are primarily conjugated with glucuronides and sulfate. 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 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.

Special Populations

Effect of renal impairment

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

Effect of hepatic impairment

YAZ is contraindicated in patients with hepatic dysfunction (see Contraindications). The mean exposure to drospirenone in women with moderate liver impairment is approximately three times the exposure in women with normal liver function. YAZ has not been studied in women with severe hepatic impairment.

Ethnic groups

The impact of ethnic factors on the pharmacokinetics of drospirenone and ethinylestradiol was studied after single and repeated daily oral administration to young, healthy Caucasian and Japanese women. The results showed that ethnic differences between Japanese and Caucasian women had no clinically relevant influence on the pharmacokinetics of drospirenone and ethinylestradiol.

5.3 Preclinical safety data

Preclinical data reveal no special risks for humans based on conventional studies of repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction. In laboratory animals, the effects of drospirenone and ethinylestradiol were confined to those associated with the recognized pharmacological action. In particular, reproduction toxicity studies revealed embryotoxic and foetotoxic effects in animals which are considered as species specific. Ethinylestradiol-induced tumours in rodents have previously been seen with other ethinylestradiol-containing products, and are considered attributable to species-specific effects of estrogens on prolactin secretion in rodents. Although long-term animal studies did not definitely indicate a tumourigenic potential for the clinical use of either drospirenone or ethinylestradiol, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactose monohydrate
Cellulose microcrystalline (placebo tablet only)
Maize starch
Magnesium stearate (E470b)
Hypromellose (E464)
Talc (E553b)
Titanium dioxide (E171)
Iron oxide red (E172)

6.2 Shelf-life

Please refer to labels

6.3 Presentation

Yaz; 24 + 4 film coated-tablets are contained in blister packs consisting of transparent films made of polyvinyl chloride and metallic foils made of aluminum (mat side hot sealable).

Blister pack containing 28 tablets

6.4 Instructions for use/storage

Store below 30 °C.

Store all drugs properly and keep them out of reach of children.

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