



Yaz®

Film-coated tablet

1. NAME OF THE MEDICINAL PRODUCT

Yaz 0.02 mg / 3 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

24 hormone-containing light pink film-coated tablets:

Each film-coated tablet contains 0.020 mg ethinylestradiol (as betadex clathrate), 3 mg drospirenone

4 hormone-free white film-coated tablets.

For a full list of excipient(s) see section "List of excipients"

3. PHARMACEUTICAL FORM

Film-coated tablet

4. CLINICAL PARTICULARS

4.1 Indication

Oral contraception.

Treatment of moderate acne vulgaris in women who elect to use oral contraception.

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

4.2 Dosage and method of administration

Method of administration

Oral use

Dosage regimen

How to take Yaz

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

► *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 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 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.

Reference :

Yaz 0.02/3mg film-coated tablets / CCDS / Version 18.0/ 9 Aug 2016. Directive 13 2018

► *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*

For breastfeeding women see section 'Pregnancy and lactation'

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 tablet 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 7 days (please note the recommended hormone-free tablet interval is 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 tablet phase, the higher the risk of a pregnancy.

► *Day 8-14*

The user should take the last missed tablet as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. Provided that the woman has taken her tablets correctly in the 7 days preceding the first missed tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

► *Day 15-24*

The risk of reduced reliability is imminent because of the forthcoming hormone-free white film-coated tablet 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.
2. The woman may also be advised to discontinue taking the light pink film-coated tablets 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 tablet 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.

Reference :

If vomiting occurs within 3-4 hours after taking a light pink hormone-containing film-coated tablet, the advice concerning missed tablets, as given in section 'Management of 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 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 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 tablet 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).

Additional information on special populations

Pediatric patients

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

Geriatric patients

Not applicable. Yaz is not indicated after menopause.

Patients with hepatic impairment

Yaz is contraindicated in women with severe hepatic diseases. See also sections 'Contraindications' and 'Pharmacokinetic properties'.

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 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 prodromi of a thrombosis (e.g. transient ischaemic attack, angina pectoris).
- ▶ A high risk of venous or arterial thrombosis (see 'Special warnings and precautions for use').
- ▶ History of migraine with focal neurological symptoms.
- ▶ Diabetes mellitus with vascular involvement.
- ▶ Severe hepatic disease as long as liver function values have not returned to normal.
- ▶ Yaz is contraindicated for concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir (See Section Warnings and Precautions and Section Interaction with other medicinal products and other forms of interaction).
- ▶ Severe renal insufficiency or acute renal failure.
- ▶ Presence or history of liver tumors (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.

4.4 Special warnings and precautions for use

Warnings

Circulatory Disorders

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, deep venous thrombosis, 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.

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.

Reference :

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;
- ▶ obesity (body mass index over 30 kg/m²);
- ▶ 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;
- ▶ 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.
- ▶ smoking (with heavier smoking and increasing age the risk further increases, especially in women over 35 years of age);
- ▶ dyslipoproteinemia;
- ▶ hypertension;
- ▶ migraine;
- ▶ valvular heart disease;
- ▶ atrial fibrillation;

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

The increased risk of thromboembolism in the puerperium must be considered (for information on pregnancy and lactation see section 'Pregnancy and lactation').

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).

Tumors

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

Reference :

extent to which this finding is attributable to confounding effects, e.g., cervical screening and sexual behaviour 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 a combination 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 tumors, and even more rarely, malignant liver tumors have been reported in users of COCs. In isolated cases, these tumors have led to life-threatening intra-abdominal hemorrhages. A liver tumor should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal hemorrhage occur in women taking COCs.

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

ALT elevations

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

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.

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. 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

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 (section 'Management of missed tablets'), gastro-intestinal disturbances (section 'Advice in case of gastro-intestinal disturbances') during hormone-containing light pink film-coated tablet taking or concomitant medication (section 'Interaction with other medicinal products and other forms of interaction').

Reduced cycle control

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. In some women withdrawal bleeding may not occur during the hormone-free white film-coated tablet phase. If the COC has been taken according to the directions described in section 'Dosage and method of administration', it is unlikely that the

Reference :

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 Interaction with other medicinal products and other forms of interaction

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.

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.

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).

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 cytochrome P450 mediated metabolism of other drugs is unlikely.

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

Concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (See Section Contraindications and Section Warnings and Precautions). Therefore, 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 drug regimen. Yaz can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Other forms of interactions

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.

Laboratory tests

The use of contraceptive steroids may influence the results of certain laboratory tests. Drospirenone causes an increase in plasma renin activity and plasma aldosterone induced by its mild antimineralocorticoid activity.

4.6 Pregnancy and lactation

Pregnancy

Yaz is not indicated during pregnancy. If pregnancy occurs during treatment with Yaz, further intake must be stopped. However, extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to

Reference :

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 during pregnancy are too limited to permit conclusions concerning negative effects of Yaz on pregnancy, health of the fetus or neonate. No relevant epidemiological data are available yet.

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 Undesirable effects

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 $\geq 3\%$ 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.

Tabulated list of adverse reactions

The frequencies of ADRs reported in clinical trials with Yaz and Yaz Plus (currently not registered in Malaysia) 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. Frequencies are defined as common ($\geq 1/100$ to $< 1/10$), uncommon ($\geq 1/1,000$ to $< 1/100$) and rare ($\geq 1/10,000$ to $< 1/1,000$). 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	Uncommon	Rare	Not known
Psychiatric disorders	Emotional lability, Depression/ depressive mood	Decrease and loss of libido ^b		
Nervous system disorders	Migraine			
Vascular disorders			Venous and arterial thromboembolic events*	
Gastrointestinal disorders	Nausea ^a			
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 (version 12.1). 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 $>10/100$

Reference :

^b Incidence in trials evaluating PMDD was Common $\geq 1/100$

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

The MedDRA preferred term is used to describe a certain reaction and its synonyms and related conditions. ADR term representation is based on MedDRA version 12.1.

Description of selected adverse reactions

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"):

Tumors

- 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 tumors (benign and malignant)

Other conditions

- Erythema nodosum
- Women with hypertriglyceridemia (increased risk of pancreatitis when using COCs)
- 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)

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').

4.8 Overdose

There has not yet been any clinical experience of overdose with Yaz hormone-containing light pink film-coated tablets. 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.

5.2 Pharmacokinetic properties

Drospirenone

Absorption

Reference :

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 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.

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 (CL_{cr}, >80 mL/min). The serum drospirenone levels were on average 37 % higher in women with moderate renal impairment (CL_{cr}, 30 - 50 mL/min) compared to those in women with normal renal function. 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*

In women with moderate hepatic function, (Child-Pugh B) mean serum drospirenone concentration-time profiles were comparable to those of women with normal hepatic function during the absorption/distribution phases with similar C_{max} values. The mean terminal half-life of drospirenone for volunteers with moderate hepatic impairment was 1.8 times greater than for volunteers with normal hepatic function.

An about 50 % decrease in apparent oral clearance (CL/f) was seen in volunteers with moderate hepatic impairment as compared to those with normal liver function. The observed decline in drospirenone clearance in volunteers with moderate hepatic impairment compared to normal volunteers did not translate into any apparent difference in terms of serum potassium concentrations between the two groups of volunteers. Even in the presence of diabetes and concomitant treatment with spironolactone (two factors that can predispose a patient to hyperkalemia) an increase in serum potassium concentrations above the upper limit of the normal range was not observed. It can be concluded that drospirenone is well tolerated in patients with mild or moderate hepatic impairment (Child-Pugh B).

► *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.

Ethinylestradiol

Absorption

Orally administered ethinylestradiol is absorbed rapidly and completely. Peak serum concentrations of about 33 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 approximately 60 %. 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

Reference :

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

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. However, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumors.

6. PHARMACEUTICAL PARTICULARS

List of excipients

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

Special precautions for storage

Store below 30°C
Store all drugs properly and keep them out of reach of children.

Nature and contents of container

Blister pack containing 28 tablets, 3x28 tablets or 6x28 tablets.
Not all pack sizes may be marketed.

Manufactured by

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