Attachment 1: Product information for AusPAR YAZFlex Drospirenone and ethinyloestradiol (as betadex clathrate) Bayer Australia Ltd PM-2010-03613-3-5 Final 14 October 2014. This Product Information was approved at the time this AusPAR was published.

PRODUCT INFORMATION

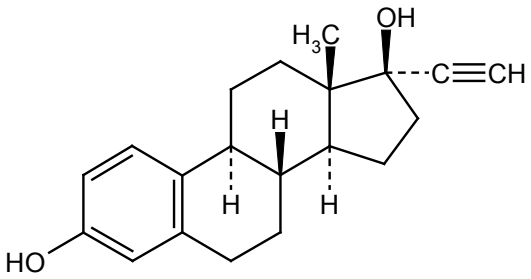
YAZ® FLEX

NAME OF THE MEDICINE

YAZ Flex is a combined oral contraceptive (COC) tablet containing the synthetic progestogen, drospirenone and the synthetic oestrogen, ethinyloestradiol (as betadex clathrate).

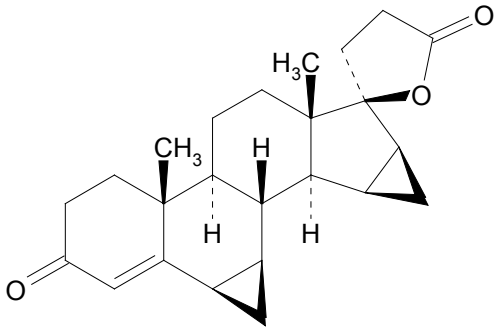
Ethinyloestradiol betadex-clathrate is an inclusion complex of the compendially described substances ethinyloestradiol and betadex and when dissolved in water it dissociates into the active moiety ethinyloestradiol and the ligand betadex.

The chemical name for ethinyloestradiol is 19-nor-17a-pregna-1,3,5(10)-trien-20-yne-3, 17b–diol and has the following structural formula:



Chemical Formula: C_{20} H_{24} O_2
Molecular Weight: 296.41
CAS No: 57-63-6

The chemical name for drospirenone is 6b, 7b,15b, 16b-dimethylene-3-oxo-17a-pregn-4-ene-21, 17-carbolactone and has the following structural formula:



Chemical formula: C_{24} H_{30} O_3
Molecular weight: 366.50
CAS No: 67392-87-4

DESCRIPTION

Ethinyloestradiol is a white to creamy white, odourless, crystalline powder. It is insoluble in water and soluble in alcohol, chloroform, ether, vegetable oils, and aqueous solutions of alkali hydroxides.

Drospirenone is a white to off-white crystalline powder. It is freely soluble in methylene chloride, soluble in acetone, methanol, sparingly soluble in ethylacetate and ethanol 96% (v/v) and practically insoluble in hexane and water.

Each YAZ Flex tablet contains drospirenone 3 mg and ethinyloestradiol (as betadex clathrate) 20 mg and the excipients: lactose, maize starch, magnesium stearate, hypromellose, purified talc, titanium dioxide and iron oxide red.

PHARMACOLOGY

Pharmacodynamic properties

The contraceptive effect of combined oral contraceptives is based on the interaction of various factors, the most important of which are seen as the inhibition of ovulation and the changes in the cervical secretion. As well as protection against pregnancy, combined oral contraceptives have several positive properties which, next to the negative properties (see PRECAUTIONS, ADVERSE 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 oestrogen-related sodium retention. In combination with ethinyloestradiol, drospirenone displays a favourable lipid profile with an increase in high density lipoprotein (HDL). Drospirenone exerts antiandrogenic activity. Drospirenone does not counteract the ethinyloestradiol-related sex hormone binding globulin (SHBG) increase which is useful for binding and inactivating the endogenous androgens.

Drospirenone is devoid of any androgenic, oestrogenic, 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 Combined Oral Contraceptives (COCs) (50 µg ethinyloestradiol), 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 combined oral contraceptives such as YAZ Flex remains to be confirmed.

The flexible extended-cycle oral contraceptive regimen of YAZ Flex may reduce bleeding associated problems such as dysmenorrhoea, headache and breast tenderness.

Pharmacokinetics

Drospirenone

<u>Absorption</u>

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 extent of absorption but the maximum concentration was reduced as compared to drug intake on an empty stomach.

<u>Distribution</u>

After oral administration, serum drospirenone levels decrease in two phases which are characterised 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 SHBG or corticoid binding globulin (CBG). Only 3 - 5% of the total serum drug concentrations are present as free steroid. The

ethinyloestradiol-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 metabolised after oral administration. The major metabolites in the plasma are the acid form of drospirenone, generated by opening of the lactone ring, and the 4,5-dihydro-drospirenone-3-sulfate, both of which are formed without involvement of the P450 system. Drospirenone is metabolised by cytochrome P450 3A4 and has demonstrated a capacity to inhibit this enzyme and cytochrome P450 1A1, cytochrome P450 2C9 and cytochrome P450 2C19 *in vitro*.

Elimination

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

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, > 80mL/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

In women with moderate impairment of 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 the volunteers with moderate hepatic impairment was 1.8 times greater than for the volunteers with normal hepatic function.

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 (2 factors that can predispose a patient to hyperkaelemia) 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 ethinyloestradiol 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 ethinyloestradiol.

Ethinyloestradiol

Absorption

Orally administered ethinyloestradiol 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. Absolute bioavailability as a result of presystemic conjugation and first-pass metabolism is approximately 60%. Concomitant intake of food had a variable effect. The maximum concentration was reduced in all subjects and the bioavailability of ethinyloestradiol was reduced in about 25% of the investigated subjects.

Distribution

Serum ethinyloestradiol levels decrease in two phases, the terminal disposition phase is characterised by a half-life of approximately 24 hours. Ethinyloestradiol 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 5L/kg was determined.

Metabolism

Ethinyloestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinyloestradiol is primarily metabolised by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed, and these are present as free metabolites and as conjugates with glucuronides and sulfate. The metabolic clearance rate of ethinyloestradiol is approximately 5 mL/min/kg.

Elimination

Ethinyloestradiol is not excreted in unchanged form to any significant extent. The metabolites of ethinyloestradiol 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 ethinyloestradiol accumulate by a factor of about 1.4 to 2.1.

CLINICAL TRIALS

YAZ Flex is a flexible, extended-cycle oral contraceptive based on the conventional COC YAZ. YAZ contains 24 hormone tablets and 4 placebo tablets. The contraceptive and therapeutic effects for YAZ also apply to YAZ Flex as both formulations are identical with respect to the hormone tablet.

Contraception

The contraceptive efficacy and safety of YAZ Flex was examined in two multi-centre open trials evaluating the YAZ Flex regimen. The contraceptive reliability was analysed using two different methods, the Pearl Index (PI) and a life table analysis.

The first pivotal study A40196 was a randomised, parallel group study to evaluate the bleeding pattern, contraceptive efficacy and safety of the YAZ Flex regimens (YAZ Flex, YAZ extend and YAZ) in 1067 women between the ages of 18 to 35 years. This study was conducted in Europe and Canada. YAZ Flex (Group A) women were advised to schedule their withdrawal bleeding between days 25 and 120 of the intake cycle when intracyclic bleeding occurs. The YAZ extend (Group B) dosage regimen consisted of 120 active cycle taken without interruption, irrespective of the occurrence of (unintended) bleeding episodes. The YAZ (Group C) took 24 active tablets followed by 4 placebo tablets. This was a two year study: Year 1 comprised the randomised parallel group treatment and Year 2 was an extension period during which all subjects who continued, received YAZ Flex. The Pearl Index (PI) was calculated on the YAZ Flex group in both Year 1 and Year 2, totalling 1268 woman-years (WY) of exposure. The PI_U (unadjusted PI) was 0.63 with an upper two sided 95% confidence interval of 1.24 based on 8 pregnancies. The PI_A (adjusted PI) was 0.59 with an upper two sided 95% confidence interval of 1.22.

The probability of pregnancy was calculated using the Kaplan Meier estimator. The Kaplan-Meier estimator after one year of treatment with YAZ Flex was 1.42%, the probability of contraceptive protection was 98.58% with a 95% CI of (0.9709; 0.9931).

The number of bleeding and spotting days within the first year of treatment for the YAZ Flex regimen was 41.0 days versus 65.8 days for the YAZ group. The difference was statistically significant ($p<0.0001$). When compared against the YAZ extend group, the YAZ Flex group had less bleeding days on average, 41 compared with 60.9 (67%). Table 1 displays the number and proportion of bleeding or spotting days during one year of treatment- FAS.

Table 1: Number and proportion of bleeding or spotting days during one year of treatment- FAS.

Treatment	n	Mean	SD	Min	Q1	Median	Q3	Max
Days of bleeding including spotting								
A: YAZ Flex	640	41.0	29.07	2	20.0	34.0	56.0	219
B: YAZ extend	209	60.9	51.13	1	21.0	45.0	89.0	298
C: YAZ 24+4	215	65.8	26.95	5	51.0	68.0	78.0	161
Proportion of bleeding and spotting days								
A: YAZ Flex	640	13.34	11.11	0.5	6.45	10.62	17.34	100.0
B: YAZ extend	209	23.06	20.71	0.3	8.06	16.40	33.09	100.0
C: YAZ 24+4	215	20.36	9.76	3.0	15.32	19.09	22.85	100.0

The mean length of withdrawal bleeding over the first two extended cycles by comparison with the monthly cycles of the YAZ subjects was longer in Group A (7.5 – 9.8 days) and

Group B (9.8 – 10.5 days). The mean length of withdrawal bleeding in Group C was between 4.4 – 5.2 days.

Subject satisfaction was 62% with YAZ Flex subjects reporting "very satisfied", 33.5% reporting "quite satisfied", and 86% indicating preparedness to recommend the regimen to a friend.

The second pivotal study (A48294) was a three-arm, active controlled study evaluating the efficacy and safety of the YAZ Flex regimens in 1864 women between the ages of 18 to 45 years. This study was conducted in the United States. The YAZ extend group (Group B) in study A40196 was replaced with the YAZ Stop&Go regimen in this study. The YAZ Stop&Go regimen is similar to the YAZ Flex regimen (Group A) except that women were allowed to schedule their withdrawal bleeding at any time between days 25 and 120 of the intake cycle independent of the occurrence of intracyclic bleeding. The PI_U for YAZ Flex was 1.65 with an upper two sided 95% confidence interval of 2.64 based on 17 pregnancies and 1032 WY of exposure. The PI_U for the two flexible extended regimens (YAZ Flex and YAZ Stop&Go) was 1.92.

The probability of pregnancy was calculated using the Kaplan Meier estimator. For YAZ Flex, the estimation of cumulative failure rate was 1.63% (95% CI; 1.01, 2.61), indicating a probability of contraceptive protection on 98.4%. For the YAZ Flex/YAZ Stop&Go pooled population, it was 1.83% (95% CI; 1.21, 2.75), and probability of protection 98.2%.

Subjects in the extended flexible treatment regimens had improved bleeding pattern, including reduction in overall bleeding when compared to the conventional YAZ regimen.
The mean number of bleeding and spotting days in the first year of treatment for the YAZ Flex group was 39.9 compared with 51.8 for the YAZ group ($p<0.0001$). In the subset of subjects who completed ≥ 350 days of treatment, the mean number of bleeding and spotting days was as follows: YAZ Flex 46.6 days, YAZ Stop&Go 53.0 days and YAZ 65.1 days.

Women were satisfied with the extended cycle length, the ease of following the regimen and the instructions in Study A48294. Table 2 displays the satisfaction rates reported in Study A48294 for the extended flexible treatment regimens.

Table 2: Satisfaction rates reported in Study A48294 for YAZ Flex and YAZ Stop&Go regimens.

Treatment regimen	Extended cycle length	Following the regimen instructions	Understanding the regimen instructions
YAZ Flex	85%	94%	95%
YAZ Stop&Go	90.2%	98%	98%

A third study (A47505) evaluated the efficacy and safety of the flexible extended (YAZ Flex) in comparison with the conventional YAZ regimen in the treatment of primary dysmenorrhoea in 223 women. This study was a five month multicentre, open label, randomised, controlled, parallel group study. The total number of bleeding and spotting days (first 90 day reference period, mean ± SD) were 19.9 ±13.0 for YAZ Flex compared with 25.3±9.1 for the YAZ group. Similarly, the number of bleeding episodes was less with YAZ Flex, 2.4±1.7 compared with 3.5±1.0 whereas mean length of bleeding and spotting episodes was greater and more variable at 7.8±9.0 compared with 5.2±1.8 for the YAZ

regimen. Table 2 displays the number of days with dysmenorrhoeic pain over 140 days of treatment.

Table 2: Number of days with dysmenorrhoeic pain over 140 days of treatment.

Parameter (over 140 days treatment days) Days with:	**YAZ Flexible (mean±SD)**	**YAZ conventional mean±SD (n)**	**Treatment difference in days**	**95% confidence interval**
Dysmenorrhoeic pain	10.6 ± 7.8 (112)	14.9 ± 8.9 (102)	-4.2 (p=0.0003)	(-6.5, -2.0)
At least moderate dysmenorrhoeic pain	4.0 ± 3.1 (112)	6.5 ± 5.3 (102)	-2.5	(-3.7, -1.3)
Pelvic pain	12.2 ± 9.1 (112)	15.6 ±9.5 (102)	-3.4	(-5.9, -0.9)
Dysmenorrhoeic pain associated with withdrawal bleeding	5.2 ±6.3 (112)	9.3 ±6.5 (102)	-4.1	(-5.8, -2.4)
Dysmenorrhoeic pain associated with unscheduled bleeding	5.4 ± 4.3 (112)	5.5 ± 4.4 (102)	-0.1	(-1.3, 1.0)
Use of rescue medication	4.7 ± 5.1 (112)	5.7 ± 6.0 (102)	-1.0	(-2.5, 0.5)
Interference with daily activities	6.9 ± 7.0 (112)	9.0 ± 8.3 (102)	-2.2	(-4.2, -0.1)

Acne

YAZ as an acne therapy was evaluated in two pivotal multi-centre, double blind, randomised placebo controlled studies of 6 month duration. A total of 451 YAZ and 442 placebo subjects were included in the final integrated analysis. Patients had moderate acne defined in the protocol as a minimum of 40 lesions (i.e. at least 20 inflammatory lesions and at least 20 non-inflammatory lesions) and were between ages of 14 to 45. The primary efficacy endpoints were the percent change in total lesions, inflammatory lesions, non-inflammatory lesions, and the percentage of subjects with a “clear” or “almost clear” rating on the Investigator’s Static Global Assessment (ISGA) on day 15 of cycle 6. The results for the primary efficacy variables are provided in the Table below:

	YAZ (n=451)	**Placebo (n=442)**	**Difference**	***p*-value**
Mean change in Total Lesion Count (%)	-45.3	-29.1	-16.1	<0.0001
Mean change in Inflammatory Lesion Count (%)	-50.3	-34.9	-15.3	<0.0001
Mean Change in Non-Inflammatory Lesion Count (%)	-41.3	-23.2	-18.1	<0.0001

	YAZ (n=451)	Placebo (n=442)	Difference	*p*-value
ISGA Success (Percent of Subjects rated "Clear" or "Almost Clear")	18.6	6.8	Odds Ratio 3.413 (2.146, 5.426 95% C.I.)	<0.0001

In addition, there was a statistical difference (p = <0.0001) in the percentage of patients considered improved at the final assessment by the investigator for YAZ (87.6%) as compared to placebo (66.0%) [odds ratio; 3.83 95% CI 2.58, 5.80].

There are no clinical data with YAZ Flex.

INDICATIONS

YAZ Flex is indicated for use as:

- an oral contraceptive.
- treatment of moderate acne vulgaris in women who seek oral contraception

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).
- History of migraine with focal neurological symptoms
- Diabetes mellitus with vascular involvement.
- The presence of a severe or multiple risk factor(s) for venous or arterial thrombosis may also constitute a contraindication (see PRECAUTIONS).
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia.
- Severe hepatic disease as long as liver function values have not returned to normal.
- Severe renal insufficiency or acute renal failure.
- 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 any of the ingredients contained in YAZ Flex.

PRECAUTIONS

If any of the conditions/risk factors mentioned below are 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 take it. In the event of aggravation, exacerbation or first appearance of any of these conditions or risk factors, the woman should contact her doctor. The doctor should then decide whether COC use should be discontinued.

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 (MI), deep venous thrombosis (DVT), pulmonary embolism (PE) and of cerebrovascular accidents. These events occur rarely.

Venous thromboembolism (VTE), manifesting as DVT and/or PE, may occur during the use of all COCs. The risk for VTE is highest during the first year a woman takes a COC. 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, multinational, cohort study (EURAS[1] and LASS[2]) on the safety of OC use, suggests that this increased risk is mainly present during the first 3 months.

Two prospective cohort studies (EURAS and Ingenix), each evaluating the risk of venous and arterial thromboembolism and death, were initiated separately at the time of ethinyloestradiol/drospirenone 30 µg/3 mg approval in Europe and the United States. The first (EURAS) showed the risk of thromboembolism (particularly venous thromboembolism) and death in ethinyloestradiol/drospirenone 30 µg/3 mg users to be comparable to that of other oral contraceptive preparations, including those containing levonorgestrel (a so-called second generation COC).

In the EURAS study, the VTE incidence rate for all OC users ranged from 8.0 to 9.9 per 10,000 WY. The overall incidence rate for past OC users was 4.7 VTE/10,000 WY, which was further specified to 19.4 VTE/10,000 WY for pregnant past OC users and 2.3 VTE/10,000 WY for non pregnant past OC users. The second prospective cohort study (Ingenix) also showed a comparable risk of thromboembolism in ethinyloestradiol/drospirenone 30 µg/3 mg users compared to users of other COCs, including those containing levonorgestrel. In this second study, COC comparator groups were selected based on their having similar characteristics to those being prescribed ethinyloestradiol/drospirenone 30 µg/3 mg.

Another large population based study (Heit et al) found an incidence rate of 20 VTE/10,000 WY in pregnant or postpartal women and 4.6 in non pregnant women of reproductive age. All of these rates tend to be higher than those reported in the past. Based on this data it can be assumed that the VTE risk in users of OC users is roughly twice as high for non pregnant non OC users. The absolute attributable risk (approximately 4 VTEs per 10,000 WY of use) was found to be slightly higher in these studies than reported in the past. Nevertheless the risk in OC users remains lower than the VTE risk associated with pregnancy and the first weeks following delivery.

Two additional epidemiological studies, one case control study (van Hylckama Vlieg et al.) and one retrospective cohort study (Lidegaard et al.) suggested that the risk of venous

thromboembolism occurring in ethinyloestradiol/drospirenone 30 µg/3 mg users was higher than that for users of levonorgestrel-containing COCs and lower than that for users of desogestrel/gestodene-containing COCs (so called third generation COCs). In the case-control study, however, the number of ethinyloestradiol/drospirenone 30 µg/3 mg cases was very small (1.2% of all cases making the risk estimates unreliable). The relative risk for ethinyloestradiol/drospirenone 30 µg/3 mg users in the retrospective cohort study was greater than that for users of other COC products when considering women who used the products for less than one year. However, these one-year estimates may not be reliable because the analysis may include women of varying risk levels. Among women who used the products for 1 to 4 years, the relative risk was similar for users of ethinyloestradiol/drospirenone 30 µg/3 mg to that of other COC products. Two further retrospective database studies (Parkin et al., Jick et Hernandez) published in 2011, suggested a greater risk for VTE in users of drospirenone-containing COCs compared to levonorgestrel-containing COCs. However, the number of drospirenone cases in the Parkin et al. study was very small.

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

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 a venous (includes PE and DVT) or arterial thrombotic/ thromboembolic (includes MI, vascular occlusion and cerebrovascular accident) event can include: unilateral leg pain and/or swelling; pain or tenderness in the leg which may be felt only when standing or walking; increased warmth in the affected leg; red or discoloured skin on the leg; sudden severe pain in the chest which may increase with deep breathing; 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; rapid or irregular heartbeat; sudden onset of unexplained shortness of breath or rapid breathing; sudden onset of coughing which may bring up blood; sudden, severe prolonged headache with no known cause; sudden partial or complete loss of vision; diplopia; sense of anxiety; dizziness; slurred speech or aphasia; sudden confusion; vertigo; collapse with or without focal seizure; weakness or very marked numbness suddenly affecting one side or one part of the body; motor disturbances; ‘acute’ abdomen; fullness, indigestion or choking feeling; sweating; nausea; vomiting.

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).

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 event 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);
- overweight;
- dyslipoproteinaemia;
- hypertension;
- migraine;
- valvular heart disease;
- atrial fibrillation;
- prolonged immobilisation (e.g. long haul flights), 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 remobilisation.

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

The increased risk of thromboembolism in the puerperium must be considered (see Use in Pregnancy).

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

An increase in frequency or severity of migraine during 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, hyperhomocysteinaemia, antithrombin-III deficiency, protein C deficiency, protein S deficiency, antiphospholipid antibodies (anticardiolipin antibodies, lupus anticoagulant).

When considering the risk/benefit profile of YAZ Flex, the doctor should take into account that the 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 (< 50 µg ethinyloestradiol).

Tumours

The most important risk factor for cervical cancer is persistent Human Papillomavirus (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 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 taking 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 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 haemorrhages. A liver tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

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

Other conditions

Potassium excretion capacity may be limited in patients with renal insufficiency. In a clinical study, drospirenone intake did not show an effect on the serum potassium concentration in patients with mild or moderate renal impairment. A theoretical risk for hyperkalaemia can be assumed only for patients whose pre-treatment serum potassium is in the upper reference range, and who are additionally using potassium sparing medicines.

Women with hypertriglyceridemia, or a family history thereof, may be at an increased risk of pancreatitis when taking 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 ethinyloestradiol-induced increases in blood pressure observed in normotensive women taking other combined oral contraceptives. However, if a sustained clinically significant hypertension develops during the use of a COC, it is prudent for the doctor to withdraw the COC and treat the hypertension. 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; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

In women with hereditary angioedema exogenous oestrogens 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 taking low dose COCs (containing < 50 µg ethinyloestradiol). 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.

Worsening of depression has been observed in patients taking COCs.

Each YAZ Flex tablet contains 48.18 mg of lactose. Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption who are on a lactose free diet should take this amount into consideration.

Medical examination / consultation

Prior to the initiation or reinstitution of YAZ Flex, a complete medical history (including family history) should be taken and pregnancy must be ruled out. This should be repeated at least annually during the use of YAZ Flex. Periodic medical assessment is important 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 taking YAZ Flex. The frequency and nature of these assessments should be adapted to the individual woman but should generally include special attention to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests.

Sexually Transmitted Infections including Human Immunodeficiency Virus (HIV) infections and (Acquired Immune Deficiency Syndrome) AIDS

Women should be advised that oral contraceptives do not protect against HIV infections (AIDS) and other sexually transmissible infections (STIs). Women should be advised that additional barrier contraceptive measures are needed to prevent transmission of STIs.

Reduced efficacy

The efficacy of COCs may be reduced in the event of missed YAZ Flex tablets, gastro-intestinal disturbances or concomitant medication (see DOSAGE AND ADMINISTRATION and INTERACTIONS WITH OTHER MEDICINES).

Reduced cycle control

The flexible regimen is designed to delay menstruation. With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, even during the fixed phase of the cycle especially during the first few months of use. Evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three months. The fixed phase is between days 1 – 24. Irregular bleeding is unscheduled and cannot be predicted. The hormonal withdrawal bleeding following the 4-day tablet-free interval can be scheduled. The flexible regimen of YAZ Flex allows withdrawal bleeding to be scheduled during the flexible phase. The flexible phase is between days 25 - 120.

If bleeding irregularities persist even after induction of withdrawal bleeding 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 tablet-free interval. If the COC has been taken according to the directions described in the section DOSAGE AND ADMINISTRATION, 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.

Information for the Patient

A Consumer Medicine Information leaflet is available. Please advise your patient to read this information carefully.

Carcinogenicity

Long-term carcinogenicity studies were performed in mice and rats with drospirenone, ethinyloestradiol and with a combination of both products. After 2 years oral treatment of mice and rats with drospirenone alone there were no increases in the incidence of neoplastic lesions. Exposure to drospirenone (based on AUC) was up to 3-fold (mice) and 8-fold (rats) than that anticipated in humans at the recommended clinical dose. In contrast, treatment with the combination of drospirenone and ethinyloestradiol resulted in an increased rate of neoplastic lesions in the mammary glands and uteri of mice and rats and in the pituitary glands of mice. The tumour pattern was similar but the incidence increased even further in animals receiving ethinyloestradiol alone, indicating that ethinyloestradiol was responsible for the increase in neoplastic lesions. Co-administration of drospirenone decreased the carcinogenic potential of ethinyloestradiol in the mouse pituitary and in the mouse and rat uterus and mammary gland.

The ethinyloestradiol-induced tumours in rodents have previously been seen with other ethinyloestradiol-containing products, and are considered attributable to species-specific effects of oestrogens on prolactin secretion in rodents.

Although, long-term animal studies did not definitively indicate a tumourigenic potential for the clinical use of either drospirenone or ethinyloestradiol, it should be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissues and tumours.

Genotoxicity

There is limited evidence available in the literature suggesting that oestrogens may be weakly genotoxic at high doses. Ethinyloestradiol was negative in studies for DNA-adduct formation in cultured human liver slices and in assays for gene mutations (bacterial or mammalian cells in vitro) and gave equivocal results in assays for chromosomal damage *in vitro* (clastogenic effects were not consistently seen and occurred at high concentrations). *In vivo* studies did not confirm these results.

Drospirenone was found to induce chromosome aberrations in human peripheral lymphocytes. However, drospirenone was not mutagenic in bacterial and mammalian cell gene mutation assays *in vitro*, and was not clastogenic in mouse micronucleus assays *in vivo*. Interactions between drospirenone and the DNA of liver cells which indicate a

genotoxic potential were found in *in vitro* and *in vivo* studies in rats. No such finding was observed in human liver cells *in vitro*.

Use in Pregnancy

Pregnancy Category B3[1]

Drospirenone and/or its metabolites crossed the placenta and entered the foetus when administered orally to pregnant rats and rabbits. Treatment of pregnant rats with a combination of drospirenone and ethinyloestradiol resulted in a dose-dependent increased incidence of embryolethality due to increased pre- and post-implantation losses. There was no indication of teratogenic effects of drospirenone in rats or rabbits.

Dose-dependent feminisation of male foetuses and virilisation of female foetuses were seen following administration of a combination of drospirenone and ethinyloestradiol to female rats in the last third of pregnancy. Feminising effects in male foetuses were consistent with drospirenone's anti-androgenic activity and were observed at an estimated systemic exposure approximately 8-13 fold than that anticipated clinically (based on AUC). Virilisation of female foetuses was seen following systemic drospirenone exposure of approximately 2 to 5-fold than that anticipated clinically (based on AUC). This effect has previously been described for oestrogens in rats. When pregnant monkeys received a combination of drospirenone and ethinyloestradiol by daily oral administration during the major period of organogenesis and sexual organ differentiation, abortion rates were increased in a dose-dependent manner. However there were no indications of teratogenicity.

Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who take COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during early pregnancy. The data regarding the use of YAZ Flex during pregnancy are limited to permit conclusions concerning negative effects of YAZ Flex on pregnancy, health of the fetus or neonate. No relevant epidemiological data are available yet.

YAZ Flex is contraindicated during pregnancy. The possibility of pregnancy should be considered in any patient who may be experiencing symptoms of pregnancy, especially if the user has not adhered to the prescribed schedule. If pregnancy occurs during treatment with YAZ Flex, further intake must be stopped.

If YAZ Flex is taken according to the instructions as described under DOSAGE and ADMINISTRATION and conditions possibly impairing contraceptive effectiveness are ruled out, it is unlikely the woman is pregnant. Scheduled withdrawal bleeding does not occur every 4 weeks. The frequency of withdrawal bleeding is reduced when the tablets are taken continuously for up to 120 days depending on when the user decides to have her 4-day tablet-free interval. The absence of withdrawal bleeding cannot always be used as an early sign of an unexpected pregnancy and as such may be difficult to recognise. Pregnancy is

[1] **Category B3**

Drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human fetus having been observed. Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans.

unlikely if YAZ Flex is taken as directed, if for any reason pregnancy is, a pregnancy test should be performed.

Use in Lactation

Lactation may be influenced by COCs as they may reduce the quantity and change the composition of breast milk. Small amounts of the contraceptive steroids and/or their metabolites may be excreted in the milk. Therefore the use of COCs should generally not be recommended until the nursing mother has completely weaned her child.

Children and Adolescents

YAZ Flex is only indicated after menarche.

Use in the Elderly

YAZ Flex is not indicated after menopause.

Patients with Hepatic Impairment

YAZ Flex is contraindicated in women with severe hepatic diseases as long as liver function values have not returned to normal (see CONTRAINDICATIONS).

Patients with Renal Impairment

YAZ Flex is contraindicated in women with severe renal insufficiency or acute renal failure (see CONTRAINDICATIONS).

Effect on 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.

INTERACTIONS WITH OTHER MEDICINES

Effects of Other Medicines on YAZ Flex

Interactions can occur with medicines that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to break-through bleeding and/or oral contraceptive failure.

Women on treatment with any of these medicines 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. During the period the barrier method is used, tablet taking should not be interrupted by a tablet-free interval.

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 (*Hypericum perforatum*).

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

When co-administered with COCs, many HIV/Hepatitis C Virus (HCV) protease inhibitors and non-nucleoside reverse transcriptase inhibitors can increase or decrease plasma concentrations of oestrogen or progestogen. These changes may be clinically relevant in some cases.

Antibiotics (interference with Enterohepatic Circulation)

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

Women prescribed antibiotics (except rifampicin or griseofulvin) should use a barrier method until 7 days after completing a course of antibiotics. During the period the barrier method is used, tablet-taking should not be interrupted by a tablet-free interval.

Substances decreasing the clearance of COCs (enzyme inhibitors)

Strong and moderate CYP3A4 inhibitors such as azole antifungals (e.g. ketoconazole, itraconazole, voriconazole, fluconazole), verapamil, macrolides (e.g. clarithromycin, erythromycin), diltiazem and grapefruit juice can increase plasma concentrations of the oestrogen or the progestogen or both.

Effects of COCs on Other Medicines

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

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

Other Interactions

There is a theoretical potential for an increase in serum potassium in women taking YAZ Flex with other medicines that may increase serum potassium levels. Such medicines include angiotensin-II-receptor antagonists, potassium-sparing diuretics, and aldosterone antagonists. However, in studies evaluating the interaction of drospirenone (combined with oestradiol) with an ACE inhibitor or indomethacin, no clinically or statistically significant differences in serum potassium concentrations were observed.

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

ADVERSE EFFECTS

The most serious adverse reactions associated with the use of oral contraceptives are indicated under PRECAUTIONS (see also CONTRAINDICATIONS).

Clinical trial data

The table below includes the adverse drug reactions for YAZ in combination with the adverse drug reactions reported in the clinical trials with YAZ Flex (N = 2623).

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Infections and infestations			Candidiasis
Blood and lymphatic system disorders			Anaemia Thrombocythemia
Immune system disorders			Allergic reaction
Endocrine disorders			Endocrine disorder
Metabolism and nutrition disorders			Increased appetite Anorexia Hyperkalaemia Hyponatraemia
Psychiatric disorders	Emotional lability Depresssion/ depressive mood	Decrease and loss of libido Nervousness Somnolence	Anorgasmia Insomnia
Nervous system disorders	Headache	Dizziness Paresthesia	Vertigo Tremor
Eye disorders			Conjunctivitis Dry eye Eye disorder
Cardiac disorders			Tachycardia
Vascular disorders	Migraine	Varicose vein Hypertension	Phlebitis Vascular disorders Venous and arterial thromboembolic events** Epistaxis Syncope
Gastrointestinal disorders	Nausea	Abdominal pain Vomiting Dyspepsia Flatulence Gastritis Diarrhoea	Enlarged abdomen Gastrointestinal disorder Gastrointestinal fullness Hiatus hernia Oral candidiasis Constipation Dry mouth
Hepatobiliary disorders			Biliary pain Cholecystitis

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Skin and subcutaneous tissue disorders		Acne Pruritus Rash	Chloasma Eczema Alopecia Dermatitis acneiform Dry skin Erythema nodosum Erythema multiforme Hypertrichosis Skin disorder Skin striae Contact dermatitis Photosensitive dermatitis Skin nodule
Musculoskeletal and connective tissue disorders		Back pain Pain in extremity Muscle cramps	
Reproductive system and breast disorders	Breast pain Unscheduled uterine/Genital tract bleeding not further specified* Metrorrhagia Amenorrhoea	Vaginal candidiasis Pelvic pain Breast enlargement Fibrocystic breast Genital discharge Hot flushes Vaginitis Menstrual disorder Dysmenorrhea Hypomenorrhea Menorrhagia Vaginal dryness Papanicolaou smear suspicious	Dyspareunia Vulvovaginitis Postcoital bleeding Withdrawal bleeding Breast cyst Breast hyperplasia Breast neoplasm Cervical polyp Endometrial atrophy Ovarian cyst Uterine enlargement
General disorders and administration site conditions		Asthenia Increase sweating Oedema (Generalised oedema, Peripheral oedema, Face oedema)	Malaise
Investigations		Weight increase	Weight decrease

***Bleeding irregularities usually subside during continued treatment.**

*** Estimated frequency, from epidemiological studies encompassing a group of combined oral contraceptives. Frequency was borderline to Very Rare. Venous and arterial thromboembolic events' summarises 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 haemorrhagic.*

In addition, the following undesirable effects have been reported in users of COCs and the association has been neither confirmed nor refuted:

Common: breast tenderness
Uncommon: breast hypertrophy, fluid retention
Rare: vaginal discharge, breast discharge, contact lens intolerance.

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

DOSAGE AND ADMINISTRATION

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.

One tablet is to be taken daily at about the same time with some liquid. Tablet taking is continuous for at least 24 consecutive days.

During days 25 – 120 a woman may decide to take a 4-day tablet-free break but not before day 24. A tablet-free interval should not be longer than 4 days.
A 4-day tablet free interval has to be taken after 120 days of continuous tablet-taking. After each 4-day tablet-free interval, a new cycle starts with a minimum of 24 days to a maximum of 120 days.

During the 4-day tablet-free interval, bleeding usually occurs and may not have finished before the next YAZ Flex tablet is taken.

In the event of continued spotting and/or bleeding (three consecutive days) during days 25 – 120, a 4-day tablet-free interval is recommended. This will reduce the total number of days of bleeding.

YAZ Flex can only be used in combination with a dedicated CLYK tablet dispenser. CLYK is a tablet dispenser designed to support the user follow the YAZ Flex regimen. The instructions for use is provided with the CLYK tablet dispenser. The instructions for use should be read carefully before and during use.

How to start YAZ Flex

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 of the menstrual cycle is allowed, but during the first cycle a barrier method is recommended in addition for the first 7 days of tablet-taking.

Changing from another combined hormonal contraceptive (combined oral contraceptive/COC) or vaginal ring.

The woman should take YAZ Flex on the day following the usual tablet-free or placebo tablet interval of her previous COC.

In case a vaginal ring has been used, the woman should start taking YAZ Flex preferably on the day of removal of the ring, 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, an implant, IUS on the day of its removal or 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 tablet-taking immediately. When doing so, she need not take additional contraceptive measures.

Following delivery or second-trimester abortion.

For breastfeeding women see PRECAUTIONS - Use in Lactation.

Women should be advised to start on 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

If the woman is **less than 24 hours** late in taking a YAZ Flex tablet, contraceptive protection is not reduced. The woman should take the YAZ Flex tablet as soon as she remembers and continue to take the tablets at the usual time.

If the woman is **more than 24 hours** late in taking a YAZ Flex tablet, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. The recommended tablet-free interval is 4 days, tablet-taking must never be discontinued for longer than 7 days.

2. Seven days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

The following advice can be given in daily practice:

Day 1-7

The user should take the last missed YAZ Flex tablet as soon as she remembers, even if this means taking two YAZ Flex tablets at the same time. Subsequent tablets should be taken at the 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 YAZ Flex tablets missed and the closer they are to the tablet-free interval the higher the risk of a pregnancy.

Day 8-24

The user should take the last missed YAZ Flex tablet as soon as she remembers, even if this means taking two YAZ Flex tablets at the same time. Subsequent tablets should be taken at the usual time. If the woman has taken her tablets correctly in the 7 days preceding the first missed YAZ Flex tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than one tablet, the woman should be advised to use extra contraceptive precautions until she has taken the tablets continuously for at least 7 days without interruption.

Day 25-120

Contraceptive efficacy may be reduced if tablets are missed and particularly if the missed tablet extends the 4-day pill break. 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 no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed YAZ Flex tablet the user has taken the tablets correctly. If this is not the case, the user should be advised to follow one of these options and use extra contraceptive precautions for the next 7 days as well.

1. The woman should take the last missed YAZ Flex tablet as soon as she remembers, even if this means taking two YAZ Flex tablets at the same time. She then continues to take tablets at her usual time until she has taken at least 7 YAZ Flex tablets in a row without interruption.

2. The woman may also decide to have a tablet-free interval of 4 days, including the days she missed tablets in order to induce withdrawal bleeding, and subsequently start a new cycle of YAZ Flex.

If the woman missed tablets and subsequently has no withdrawal bleed in the tablet-free interval, 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 tablet-taking, absorption may not be complete. In such an event, 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) from the tablet dispenser.

OVERDOSAGE

There has not yet been any clinical experience of overdose with YAZ Flex. On the basis of general experience with COCs, symptoms that may occur in case of overdose of YAZ Flex tablets are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and further treatment should be symptomatic.

In cases of overdose, it is advisable to contact the Poisons Information Centre (131126) for recommendations on the management and treatment of overdose.

PRESENTATION AND STORAGE CONDITIONS

YAZ Flex tablet: 30 light pink round tablets debossed on one side with the letters "DS" in a regular hexagon, each containing ethinyloestradiol 20 µg and drospirenone 3 mg.

YAZ Flex tablets are contained in a dispenser pack. Each dispenser pack contains 30 light pink tablets. The dispenser pack containing the 30 YAZ Flex tablets are to be inserted into the Clyk tablet dispenser immediately for use. Please refer to the instructions for use provided with the Clyk tablet dispenser.

YAZ Flex is available in packs containing 1 x 30 dispenser pack and Clyk tablet dispenser (starter kit), 1 x 30 dispenser pack, 3 x 30 dispenser pack or 4 x 30 dispenser pack.

Not all pack sizes may be marketed.

Store below 30°C.

NAME AND ADDRESS OF SPONSOR

Bayer Australia Ltd
ABN 22 000 318 714
875 Pacific Highway
Pymble NSW 2073

POISON SCHEDULE OF THE MEDICINE

S4

DATE OF FIRST INCLUSION IN THE ARTG

6 March 2012

DATE FOR MOST RECENT AMENDMENT

17 July 2014

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