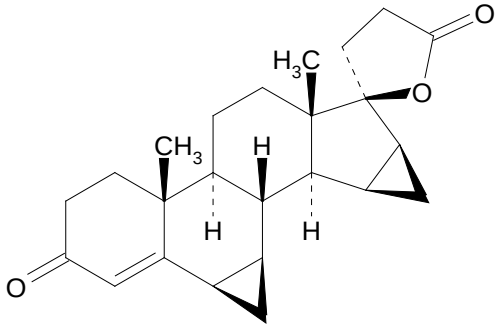
PRODUCT INFORMATION

YAZ®

NAME OF THE MEDICINE

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

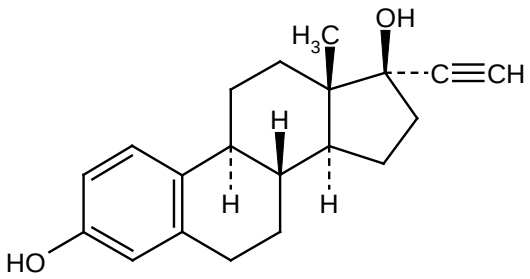
The chemical name for drospirenone is 6β, 7β, 15β, 16β-dimethylene-3-oxo-17α-pregn-4-ene-21, 17-carbolactone and has the following structural formula:



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

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-17α-pregna-1,3,5(10)-trien-20-yne-3, 17β-diol and has the following structural formula:



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

DESCRIPTION

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.

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.

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

Each white placebo tablet contains: lactose, microcrystalline cellulose, magnesium stearate, hypromellose, purified talc and titanium dioxide.

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 remains to be confirmed.

Pharmacokinetics

- **Drospirenone**

Absorption

Orally administered drospirenone is rapidly and almost completely absorbed. Maximum concentrations of the drug in serum of about 35 ng/mL are reached at approximately 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.

Distribution

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, formed by reduction and subsequent sulfation. Drospirenone is also subject to oxidative metabolism catalysed 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 approximately 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 CLcr, 50-80 mL/min) were comparable to those of women with normal renal function (CLcr, > 80 mL/min). The serum drospirenone levels were on average 37% higher in women with moderate renal impairment (CLcr, 30-50 mL/min) compared to those in women with normal renal function. Drospirenone treatment was well tolerated by all groups. Drospirenone treatment did not show any clinically significant effect on serum potassium concentration.

Effect of hepatic impairment

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 approximately 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. 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 approximately 5 L/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

Contraception

Study A12007 and Study A30713 were both large multi-centre open trials evaluating contraceptive efficacy of YAZ in 1027 and 1101 women respectively over 13 cycles. The age range was 17 to 36 years. The BMI in these studies ranged from 17 to 37.6 kg/m^2 with mean values of 22.4 (A12007) and 21.7 (A30713) respectively. The primary efficacy variable was the number of unintended pregnancies (Pearl Index). The Pearl Index (PI) is defined as the number of pregnancies divided by the exposure time in woman years (WY) multiplied by 100. Pregnancies attributed to non compliant use of the contraceptive were considered patient failure; all other pregnancies were considered method failure. In Study A12007 the PI was 1.29 with an upper two-sided 95% confidence interval of 2.30. When corrected to exclude patient failure the PI was 0.72 with an upper two-sided 95% confidence interval of 1.69. In Study A30713, the PI was 0.49 with an upper two-sided 95% confidence interval of 1.14. When corrected to exclude patient failure the PI was 0.22 with an upper two-sided 95% confidence interval of 0.80.

Study A29551 was a multi-centre open randomised study to investigate the bleeding pattern, cycle control, contraceptive reliability and general safety of YAZ in 229 women compared to ethinyloestradiol 0.02 mg + desogestrel 0.15 mg in 220 women taken for 21 days followed by pill free interval of 7-days over 7 cycles. There were no pregnancies in the YAZ group which lead to a Pearl Index of 0 with an upper two-sided 95% confidence interval of 3.40 and 3.55 for the Pearl Index and corrected index respectively.

A small fourth study (A09151) evaluated lipid and haemostatic and carbohydrate parameters in 29 women taking YAZ compared to ethinyloestradiol 0.02 mg + desogestrel 0.15 mg in 30 women taken for 21 days followed by pill free interval of 7-days over 7 cycles. No significant differences in any of the lipid, haemostatic, or carbohydrate parameters were observed between the two treatments.

The Pearl Index from the integrated efficacy analysis from these 4 studies was 0.80 with an upper two-sided 95% confidence interval of 1.30. When corrected to exclude patient failure the Pearl Index, was 0.41 with an upper two-sided 95% confidence interval of 0.85.

The Pearl Index for YAZ was calculated from data from studies in which the protocol allowed up to 24 hours delay in pill taking without a requirement for additional contraception, and in which the regimen was 24 active pills and 4 inactive pill, taken sequentially over 28 days per cycle.

The parameters of bleeding pattern and cycle control demonstrated a well-controlled and regular bleeding sequence for YAZ as compared to the comparator used. No clinically relevant changes in blood pressure or weight were observed. Irrespective of treatment duration, the mean absolute change in body weight at the final examination was -0.1 kg and the mean maximum increase in body weight versus baseline was 1.2 kg (n=1,319). The mean maximum

decrease was 1.6 kg. The majority of women treated with YAZ were satisfied or very satisfied with the treatment and reported no change or improvement in their physical or emotional well-being. The overall subjective assessment of YAZ treated women was equivalent to the comparator group.

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
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].

Premenstrual Dysphoric Disorder (PMDD)

The essential features of PMDD according to the Diagnostic and Statistical Manual-4th edition (DSM-IV) include markedly depressed mood, anxiety or tension, affective lability, and persistent anger or irritability. Other features include decreased interest in usual activities, difficulty concentrating, lack of energy, change in appetite or sleep, and feeling out of control. Physical symptoms associated with PMDD include breast tenderness, headache, joint and muscle pain, bloating and weight gain. In this disorder, these symptoms occur regularly during the luteal phase and remit within a few days following onset of menses. The disturbance markedly interferes with work or school, or with usual social activities and relationships with others. Diagnosis is made by healthcare providers according to DSM-IV criteria, with symptomatology assessed prospectively over at least two menstrual cycles. In making the diagnosis, care should be taken to rule out other cyclical mood disorders.

Two multi-centre, double-blind, randomised, placebo-controlled studies were conducted to evaluate the effectiveness of YAZ in treating the symptoms of PMDD. Women aged 18-42, > 1 year after menarche with no known contraindications for oral contraceptives and who met DSM-IV criteria for PMDD, confirmed by prospective daily ratings of their symptoms, were enrolled. Subjects with past or present psychiatric disorders other than PMDD were excluded. Both studies measured the treatment effect of YAZ using the Daily Record of Severity of Problems scale, a patient-rated instrument that assesses the symptoms that constitute the DSM-IV diagnostic criteria. The primary study was a parallel group design that included 384 evaluable reproductive-aged women with PMDD who were randomly assigned to receive YAZ or placebo treatment for 3 menstrual cycles. The supportive study, a crossover design, was terminated prematurely prior to achieving recruitment goals due to enrolment difficulties. In the supportive study, a total of 64 women of reproductive age with PMDD were treated initially with YAZ or placebo for up to 3 cycles followed by a washout cycle and then crossed over to the alternate medication for 3 cycles.

Efficacy was assessed in both studies by the change from baseline during treatment using a scoring system based on the first 21 items of the Daily Record of Severity of Problems (DRSP). Each of the 21 items was rated on a scale from 1 (not at all) to 6 (extreme); thus a maximum score of 126 was possible. In both trials, women who received YAZ had statistically significantly greater improvement in their Daily Record of Severity of Problems scores. In the primary study, the average decrease (improvement) from baseline was 37.5 points in women taking YAZ, compared to 30.0 points in women taking placebo in the full analysis set. The difference between treatment groups (-7.5) was statistically significant (p = 0.0001). In the supportive study, the average decrease from baseline for YAZ (n = 42) was -22.9, compared to -10.5 in women (n = 41) taking placebo (p = 0.0001; difference -12.47; 95% CI: -18.28, -6.66).

A statistical comparison between the treatments for the efficacy variables (full analysis set) in the PMDD Pivotal Study are presented in the table below.

	YAZ		**Placebo**		Difference (95% CI)	*p*-value
	n	Adjusted Mean Change from Baseline	n	Adjusted Mean Change from Baseline		
Primary Endpoint						
DRSP (1st 21 items)	190	-37.49	194	-29.99	-7.5 (-11.20, -3.80)	0.0001
Secondary Endpoints						
DRSP (Item 22)[1]	189	-1.98	194	-1.64	-0.33 (-0.55, -0.12)	0.0022
DRSP (Item 23)[2]	189	-1.94	194	-1.61	-0.34 (-0.55, -0.12)	0.0020
DRSP (Item 24)[3]	189	-2.10	194	-1.68	-0.42 (-0.64, -0.20)	0.0002
CGI[4] Illness Severity	209	-1.57	193	-1.36	-0.22	0.1110
CGI Efficacy Index	213	2.07 [5]	196	2.10 [5]	-0.03	0.8297
CGI Global Improvement - Observer	212	2.21 [6]	198	2.51 [6]	-0.30	0.0199

	YAZ		Placebo		Difference (95% CI)	*p*-value
	n	Adjusted Mean Change from Baseline	n	Adjusted Mean Change from Baseline		
CGI Global Improvement – Self rated	213	2.27[6]	202	2.53 [6]	-0.26	0.0573 (0.0137)[7]
SF-36[8] Mental health	200	10.15	186	8.33	1.82	0.1252
SF-36[8] Physical health	200	1.62	186	1.54	0.08	0.9247
Endicotts QoL + Satisfaction[9] (1st 14 items)	200	19.56	187	16.69	2.87 (-0.02, 5.77)	0.0519
Endicotts QoL + Satisfaction Item 16[10]	197	1.18	184	1.07	0.12 (-0.08, 0.31)	0.2429
PMS symptoms rating scales - Observer	200	-12.34	187	-10.42	-1.92 (-3.79, -0.05)	0.0446
PMS symptoms rating scales - Self rated	201	-16.76	186	-13.28	-3.49 (-5.71, -1.26)	0.0022

Table Notes:

1 Item 22 - Reduction of productivity or inefficiency at work, home or school
2 Item 23 - Interference with hobbies or social activities
3 Item 24 - Interference with relationships
4 Clinical Global Impressions
5 Treatment rating on efficacy index scale. Scores range from 0.25 to 4 with higher scores indicating therapeutic improvements with minimal side effects.
6 Subject improvement scores. The degrees of subject improvement were rated on scale of 1 (very much improved) to 7 (very much worse). Lower scores indicate improvement.
7 *p*-value from rank ANOVA, computed if Shapiro-Wilk normality test was significant at the 0.05 level
8 Self-rated quality of life survey
9 Assessed degree of enjoyment and satisfaction experienced during the week prior to menses
10 Item 16 – overall life satisfaction and contentment

INDICATIONS

YAZ is indicated for use as:

- an oral contraceptive.
- treatment of moderate acne vulgaris in women who seek oral contraception.
- treatment of symptoms of premenstrual dysphoric disorder (PMDD) in women who have chosen oral contraceptives as their method of birth control. The efficacy of YAZ for PMDD was not assessed beyond 3 cycles. YAZ has not been evaluated for treatment of PMS (premenstrual syndrome). See CLINICAL TRIALS.

CONTRAINDICATIONS

Combined hormonal contraceptives (CHCs) including YAZ 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 CHC use, the product should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE) (see PRECAUTIONS)
  - Current VTE (on anticoagulants) or history of deep venous thrombosis [DVT] or pulmonary embolism [PE]
  - Known hereditary or acquired predisposition for venous thromboembolism, such as APC-resistance (including Factor V Leiden), antithrombin-III-deficiency, protein C deficiency, protein S deficiency
  - Major surgery with prolonged immobilisation
  - A high risk of venous thromboembolism due to the presence of multiple risk factors
- Presence or risk of arterial thromboembolism (ATE) (see PRECAUTIONS)
  - Current ATE or history of ATE (e.g. myocardial infarction or stroke) or prodromal condition (e.g. angina pectoris or transient ischaemic attack [TIA])
  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (eg. anticardiolipin-antibodies and lupus anticoagulant)
  - History of migraine with focal neurological symptoms
  - A high risk of arterial thromboembolism due to multiple risk factors or to the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia
- Pancreatitis or a history thereof if associated with severe hypertriglyceridemia
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal
- Severe renal insufficiency or acute renal failure
- Use of direct-acting antiviral (DAA) medicinal products containing ombitasvir, paritaprevir or dasabuvir and combinations of these (see INTERACTIONS WITH OTHER MEDICINES)
- 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

PRECAUTIONS

If any of the conditions/risk factors mentioned below are present, the benefits of YAZ should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start taking 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 YAZ should be discontinued.

Circulatory Disorders

Epidemiological studies have suggested an association between the use of combined oral contraceptives (COCs) containing ethinyloestradiol and an increased risk of arterial and venous thrombotic and thromboembolic diseases such as myocardial infarction, stroke, deep venous thrombosis, and pulmonary embolism. These events occur rarely in average-risk women.

Risk of venous thromboembolism (VTE)

The use of any combined hormonal contraceptive (CHC) increases the risk of VTE compared with no use. The woman should be advised that her VTE risk is highest in the first ever year of use and that there is some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.

Data from a large, prospective, multinational, cohort study (EURAS and LASS) 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*., 2009) 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 and 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.

It is important that women understand that VTE associated with CHC use is rare in average-risk women. The risk in pregnancy (5-20 per 10,000 women over 9 months) and the risk in the post-partum period (45-65 per 10,000 women over 12 weeks) is higher than that as associated with CHC use.

Drospirenone containing COCs may be associated with a higher risk of VTE than COCs containing the progestogen levonorgestrel or some other progestogens. Epidemiologic studies that compared the risk of VTE reported that the risk ranged from no increase to a three-fold increase.

An additional increase in VTE risk for CHCs containing ≥ 50 µg ethinyloestradiol cannot be excluded.

The decision to use any product other than one with the lowest VTE risk should be taken only after a discussion with the woman to ensure she understands the risk of VTE with CHCs, and how her current risk factors influence this risk.

The increased risk of VTE during the postpartum period must be considered if re-starting YAZ. See Dosage and Administration, Use in pregnancy, and Use in lactation.

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

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

The risk for venous thromboembolic complications in CHC users may increase substantially in a woman with additional risk factors, particularly if there are multiple risk factors (see list below).

YAZ is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

When considering risk/benefit, the doctor should take into account that the adequate treatment of a condition may reduce the associated risk of thrombosis.

Risk factors for VTE

- Obesity (body mass index over 30 kg/m²). Risk increases substantially as BMI rises
- Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma
- Temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors
- Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50)
- Biochemical factors that may be indicative of hereditary or acquired predisposition for VTE include Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency

- Other medical conditions associated with VTE include
  - Cancer
  - Systemic lupus erythematosus
  - Haemolytic uraemic syndrome
  - Chronic inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis)
  - Sickle cell disease
- Increasing age, particularly above 35 years
- Smoking

In women at risk of prolonged immobilisation (including major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma), it is advisable to discontinue use of YAZ (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if YAZ has not been discontinued in advance.

If a hereditary predisposition to VTE is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.

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

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)

Women should be informed of the symptoms of VTE and be advised to seek urgent medical attention if VTE symptoms develop and to inform the healthcare professional that she is taking a CHC.
Symptoms of deep vein thrombosis (DVT) can include:

- unilateral swelling of the leg and/or foot 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 discoloured 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 be associated with haemoptysis
- sharp chest pain or sudden severe pain in the chest which may increase with deep breathing
- 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).

Other signs of vascular occlusion can include: sudden pain, swelling and slight blue discoloration of an extremity.

If the occlusion occurs in the eye symptoms can range from painless blurring of vision which can progress to loss of vision. Sometimes loss of vision can occur almost immediately.

Risk of arterial thromboembolism (ATE)
Epidemiological studies have associated the use of CHCs with an increased risk for arterial thromboembolism (e.g. myocardial infarction, angina pectoris, stroke or TIA). Arterial thromboembolic events may be fatal.

The risk of arterial thromboembolic complications in CHC users increases in women with risk factors. YAZ is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis. If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed.

Risk factors for ATE
- Increasing age, particularly above 35 years
- Smoking
- Hypertension
- Obesity
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).
- Biochemical factors that may be indicative of hereditary or acquired predisposition for ATE include: hyperhomocysteinaemia and antiphospholipid antibodies (e.g. anticardiolipin antibodies, and lupus anticoagulant).
- Migraine
- Other medical conditions associated with adverse vascular events:
  - Diabetes mellitus
  - Hyperhomocysteinaemia
  - Valvular heart disease
  - Atrial fibrillation
  - Dyslipoproteinaemia
  - Systemic lupus erythematosus

Women should be advised not to smoke if they wish to use a CHC. Women over 35 years who continue to smoke should be strongly advised to use a different method of contraception.

If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use.

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

Symptoms of ATE
Women should be informed of the symptoms of ATE and be advised to seek urgent medical attention if ATE symptoms develop and to inform the healthcare professional that she is taking a CHC.

Symptoms of a stroke can include:
- sudden numbness or weakness of the face, arm or leg, especially on one side of the body
- sudden trouble walking, dizziness, loss of balance or coordination
- sudden confusion, slurred speech or aphasia
- sudden partial or complete loss of vision; diplopia
- sudden, severe or prolonged headache with no known cause

- loss of consciousness or fainting with or without seizure

Temporary symptoms suggest the event is a transient ischaemic attack (TIA)

Symptoms of myocardial infarction (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
- feeling of being full, having indigestion or choking
- sweating, nausea, vomiting or dizziness
- extreme weakness, anxiety, or shortness of breath
- rapid or irregular heartbeats

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. 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; 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.

Each light pink active tablet contains 48.18 mg of lactose and each white placebo tablet contains 23.21 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

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of COC use, guided by the contraindications and warnings, and should be repeated at least annually during the use of COCs. Periodic medical assessment is also of importance because contraindications (e.g. a transient ischaemic attack, etc.) or risk factors (e.g. a family history of venous or arterial thrombosis) may appear for the first time during the use of a COC. The frequency and nature of these assessments should be adapted to the

individual woman but should generally include special reference to blood pressure, breasts, abdomen and pelvic organs, including cervical cytology, and relevant laboratory tests.

Sexually Transmitted Infections (STIs) 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 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 light pink active tablets, gastro-intestinal disturbances during active tablet taking or concomitant medication (see DOSAGE AND ADMINISTRATION and INTERACTIONS WITH OTHER MEDICINES). The more light pink active tablets are missed and the closer they are to the white placebo tablet phase the higher the risk of a pregnancy.

Reduced Cycle Control

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.

If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.

In some women withdrawal bleeding may not occur during the placebo tablet interval. If the COC has been taken according to the directions, 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.

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

[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.

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. YAZ is contraindicated during pregnancy. Pregnancy should be ruled out before the start of therapy. Should pregnancy occur during the use of YAZ, the preparation must be discontinued immediately (see also CONTRAINDICATIONS).

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.

Use in Children

YAZ is only indicated after menarche.

Use in the Elderly

YAZ is not indicated after menopause.

Patients with Hepatic Impairment

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

Patients with Renal Impairment

YAZ 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

Interactions can occur with medicines that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or oral 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 prescribed 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 medicine administration and for 28 days after their discontinuation. If the period in which the barrier method is used runs beyond the end of the active tablets in the COC pack, the white placebo tablets should be omitted and the next COC pack 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 (*Hypericum perforatum*).

- **Substances with variable effects on the clearance of COCs**

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.

- **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.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinyloestradiol by 1.4 to 1.6-fold respectively, when taken concomitantly with a COC containing 35 µg ethinyloestradiol.

Effects of COCs on Other Medicines

COCs 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 or midazolam as a marker substrates, an interaction of drospirenone

at doses of 3 mg, with the cytochrome P450 mediated metabolism of other medicines is unlikely.

In clinical studies, administration of a hormonal contraceptive containing ethinyloestradiol led to no, or a weak increase in CYP3A4 substrates (e.g. midazolam) and a weak (e.g. theophylline) to moderate (e.g. melatonin, tizanidine) increase in CYP1A2 substrates.

Pharmacodynamic interactions

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

There is a theoretical potential for an increase in serum potassium in women taking YAZ 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

Adverse drug reactions which have been associated with the use of YAZ as an oral contraceptive or in the treatment of moderate acne vulgaris.

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

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
Psychiatric disorders	Emotional lability Depression/ depressive mood	Decrease and loss of libido Nervousness Somnolence	Anorgasmia Insomnia
Nervous system disorders	Headache Migraine	Dizziness Paresthesia	Vertigo Tremor
Eye disorders			Conjunctivitis Dry eye Eye disorder
Cardiac disorders			Tachycardia
Vascular disorders		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
Skin and subcutaneous tissue disorders		Acne Pruritus Rash	Chloasma Eczema Alopecia Dermatitis acneiform Dry skin Erythema nodosum Hypertrichosis Skin disorder Skin striae Contact dermatitis Photosensitive dermatitis Skin nodule
Musculoskeletal and connective tissue disorders		Back pain Pain in extremity Muscle cramps	

System Organ Class	Common (≥ 1/100 to < 1/10)	Uncommon (≥ 1/1,000 to < 1/100)	Rare (≥ 1/10,000 to < 1/1,000)
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.

Erythema multiforme has been reported in post marketing surveillance. The frequency cannot be estimated from the available data and is therefore unknown.

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.

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 taken daily for 28 consecutive days. Each subsequent pack is started the day after the last tablet of the previous pack. A withdrawal bleed usually starts on Day 2-3 after starting the white placebo 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). The women should be instructed to take a light pink active tablet from the green section of the pack, corresponding to that day of the week. If started on Day 1 in this way, protection against pregnancy is immediate and no additional methods of contraception are required.

Starting on Days 2-5 of the menstrual cycle is allowed, but during the first 7 days of the first cycle, a barrier method is recommended in addition to tablet-taking.

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

The woman should start with YAZ preferably on the day after the last active tablet of her previous COC, but at the latest on the day following the usual tablet-free or placebo tablet interval of her previous COC. YAZ should be started by taking a light pink active tablet from the green section of the pack.

In case a vaginal ring has been used, the woman should start taking YAZ preferably on the day of removal of the ring, but at least 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 from the minipill on any day, from an implant or IUS on the day of its removal, or from an injectable when the next injection would be due. However, in all of these cases the woman must 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**

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.

For breastfeeding women see PRECAUTIONS - Use in Lactation.

Management of missed tablets

Missed white pills from the last row of the blister are placebo tablets and thus can be disregarded. However they should be discarded to avoid unintentionally prolonging the placebo tablet phase.

The risk of pregnancy increases with each light pink tablet missed. The following advice only refers to missed light pink active tablets:

If the woman is **less than 24 hours** late in taking any light pink active tablet, contraceptive protection is not reduced. The woman should take the tablet as soon as she remembers and should take further tablets at the usual time.

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

1. The placebo tablet interval for YAZ is 4 days. Active tablet-taking must never be discontinued for longer than 7 days. *Please note: YAZ is registered in Australia for use as a contraceptive using a continuous 28 day regimen consisting of 24 active tablets followed by 4 inactive tablets; the stated efficacy in preventing pregnancy is based on this regimen.*

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

Accordingly the following advice can be given in daily practice:

- **Day 1-7**

The woman should take the last missed light pink active tablet as soon as she remembers, even if this means taking two light pink active 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 light pink active tablets are missed and the closer they are to the white placebo tablet phase the higher the risk of a pregnancy.

- **Days 8-14**

The woman should take the last missed light pink active tablet as soon as she remembers, even if this means taking two light pink active 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 light pink active tablet, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than one light pink active 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 placebo 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 light pink active tablet the user has taken all tablets correctly. If this is not the case, the user 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 woman should take the last missed light pink active tablet as soon as she remembers, even if this means taking two light pink active tablets at the same time. She then continues to take tablets at her usual time until all the light pink active tablets are taken. The 4 white placebo tablets from the last row must be discarded. The next pack must be started right away. The user is unlikely to have a withdrawal bleed until the end of the active tablets of the second pack, but she may experience spotting or breakthrough bleeding on tablet-taking days.

2. The woman may also be advised to discontinue tablet-taking from the current pack. She should then have a tablet-free interval of up to 4 days, including the days she missed tablets, and subsequently continue with the next pack.

If the woman missed tablets and subsequently has no withdrawal bleed in the placebo tablet interval, the possibility of a pregnancy should be considered.

How to delay a period

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

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, (see above), is applicable. If the woman does not want to change her normal tablet-taking schedule, she should take the extra tablet(s) needed from another pack.

OVERDOSAGE

There has not yet been any clinical experience of overdose with YAZ. On the basis of general experience with COCs, symptoms that may occur in case of overdose of active 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.

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 active tablet

24 light pink round tablets marked on one side with the letters "DS" in a regular hexagon, each containing ethinyloestradiol 20 µg and drospirenone 3 mg.

YAZ placebo tablet

4 white round tablets marked on one side with the letters "DP" in a regular hexagon.

YAZ tablets are contained in blister packs. Each blister contains 24 light pink tablets followed by 4 white placebo tablets.

Carton containing memo packs of 1 x 28, 2 x 28, 3 x 28, 4 x 28 or 6 x 28 tablets. 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 AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (ARTG)

4 August 2014

DATE OF MOST RECENT AMENDMENT

30 January 2018

® Registered trademark of the Bayer group, Germany

REFERENCES

1. Dinger JC, Heinemann LA, Kuhl-Habich D. The safety of a drospirenone-containing oral contraceptive: final results from the European Active Surveillance Study on oral contraceptives based on 142,475 women-years of observation. Contraception 2007; 75:344-54
2. Long-term Active Surveillance Study for oral contraceptives (LASS), 2nd update report based on study status May 2009
3. Seeger JD, Loughlin J, Eng PM, Clifford CR, Cutone J, Walker AM. Risk of thromboembolism in women taking ethinyloestradiol/drospirenone and other oral contraceptives. Obstet Gynecol 2007; 100:587–593
4. Heit JA, Kobbervig CE, James AH Petterson TM, Bailey KR, Melton LJ. Trends in the incidence of venous thromboembolism during pregnancy or postpartum: a 30 year population based study. Ann Intern Med 2005; 143:697–706
5. Lidegaard Ø, Løkkegaard E, Svendsen AL, Agger C. Hormonal contraception and risk of venous thromboembolism: national follow up. BMJ 2009; 339:b2890
6. Van Hylckama Vlieg A, Helmerhorst FM, Vandenbroucke JP, Doggen CJM, Rosendaal FR. Effects of oestrogen dose and progestogen type on venous thrombotic risk associated with oral contraceptives: results of the MEGA case-control study. BMJ 2009; 339:b2921
7. Parkin L, Sharples K, Hernandez RK, Jick SS. Risk of venous thromboembolism in users of oral contraceptives containing drospirenone or levonorgestrel nested case-control study based on UK General Practice Research Database. BMJ 2011; 340:d2139
8. Jick SS, Hernandez RK. Risk of non-fatal venous thromboembolism in women using oral contraceptives containing drospirenone compared with women using oral contraceptives containing levonorgestrel: case-control study using United States claims data. BMJ 2011; 340:d2151
9. Lidegaard O, Nielsen LH, Skovlund CW, Skjeldestad FE, Lokkegaard, E. Risk of venous thromboembolism from use of oral contraceptives containing different progestogens and oestrogen doses: Danish cohort study, 2001-9. BMJ 2011; 343:d6423
10. FDA 2011 Ouellet-Hellstrom R, Graham DJ, Staffa JA, Sidney S, Cheetham TC, Cooper WO, Connell, F. Combined hormonal contraceptives (CHCs) and the risk of cardiovascular disease endpoints. CHC-CVD Final Report 111022v2 (available at http://www.fda.gov/downloads/drugs/drugsafety/ucm277384.pdf, addendum available at http://www.fda.gov/downloads/drugs/drugsafety/ucm287762.pdf)
11. Dinger J, Bardenheuer K, Heinemann K. Cardiovascular and general safety of a 24-day regimen of drospirenone-containing combined oral contraceptives: Final results from the international active surveillance study of women taking oral contraceptives. Contraception 2014; 89(4):253–63