PRODUCT INFORMATION

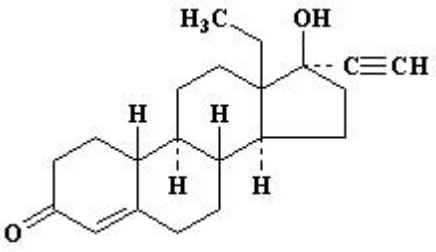
Seasonique® (levonorgestrel and ethinyloestradiol)

NAME OF THE MEDICINE

Levonorgestrel and Ethinyloestradiol.

Seasonique is a 91-day extended-regimen oral contraceptive (OC) tablet containing a combination of 150 µg of levonorgestrel and 30 µg ethinyloestradiol for 84 days followed by 10 µg ethinyloestradiol tablets for 7 days.

The structural formula of levonorgestrel is shown below:



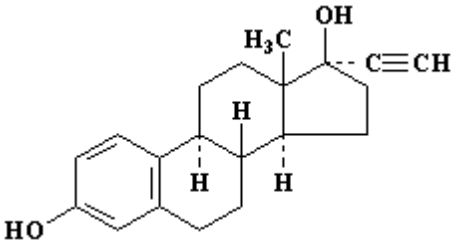
Chemical name: (-)-13-Ethyl-17-hydroxy-18, 19-dinor-17 α-pregn-4-en-20-yn-3-one

Molecular formula: $C_{21}H_{28}O_2$

Molecular weight: 312.45

CAS number: 797-63-7

The structural formula of ethinyloestradiol is shown below:



Chemical name: 19-Nor-17 α- pregna-1,3,5 (10)-trien-20-yne-3,17 diol

Molecular formula: $C_{20}H_{24}O_2$

Molecular weight: 296.4

CAS number: 57-63-6

DESCRIPTION

Levonorgestrel is a white crystalline powder. It is practically insoluble in water, soluble in chloroform, sparingly soluble in ethanol and methylene chloride.

Ethinyloestradiol is a white to cream crystalline powder. It is insoluble in water, soluble in alcohol, ethanol, chloroform, ether, vegetable oil, and solutions of fixed alkali hydroxides.

Each Seasonique package contains 84 combination tablets of 150 µg levonorgestrel and 30 µg ethinyloestradiol and 7 tablets of 10 µg ethinyloestradiol.

Each pink film-coated levonorgestrel and ethinyloestradiol tablet contains lactose anhydrous, hypromellose, microcrystalline cellulose, magnesium stearate, titanium dioxide (E171), macrogol 400, Allura Red AC (E129), Polysorbate 80, Brilliant Blue FCF (E133).

Each white ethinyloestradiol tablet contains lactose anhydrous, polacrilin potassium, microcrystalline cellulose, magnesium stearate, titanium dioxide (E171), polydextrose, hypromellose, glycerol triacetate, Macrogol 8000.

PHARMACOLOGY

Pharmacodynamic properties

Levonorgestrel is a synthetic progestogen and ethinyloestradiol is a synthetic oestrogen. These hormonal components act to inhibit ovulation by supressing gonadotrophin release from the pituitary gland. This results in suppressed levels of follicle stimulating hormone (FSH) and luteinizing hormone (LH) with consequent inhibition of follicle development and ovulation. In addition, there are also other factors, such as changes in the endometrium, implantation, cervical mucus and ovum transport that can contribute to the efficacy of oral contraceptives in preventing pregnancy. While each hormonal component alone can be shown to exert these effects in certain circumstances, the combination synergistically decreases plasma gonadotrophin levels and suppresses ovulation more consistently than each substance alone.

Pharmacokinetics

Absorption

Ethinyloestradiol and levonorgestrel are absorbed with maximum plasma concentrations occurring within 2 hours after oral administration. Levonorgestrel is completely absorbed after oral administration (bioavailability nearly 100%) and is not subject to first-pass metabolism. Ethinyloestradiol is absorbed from the gastrointestinal tract but, due to first-pass metabolism in gut mucosa and liver, its bioavailability is approximately 43%.

The mean plasma pharmacokinetic parameters, including area under the curve (AUC), maximum plasma concentration (C_{max}), time to maximum plasma concentration (T_{max}), and half-life ($T_{1/2}$), of Seasonique following a single dose of two levonorgestrel/ethinyloestradiol combination tablets used in Seasonique clinical studies in healthy women under fasting conditions are presented in Table 1.

Table 1: Mean pharmacokinetic parameters for Seasonique® after a single two-tablet dose

Analyte	AUC_{0-t} (mean)	C_{max} (mean)	t_{max} (mean)	$t_{1/2}$ (mean)
Levonorgestrel	75.79 ng•hr/mL	6.01 ng/mL	1.38 hours	34.85 hours
Ethinyloestradiol	1453.14 pg•hr/mL	158.06 pg/mL	1.52 hours	18.10 hours

Steady-state

During the continuous use of Seasonique serum levonorgestrel levels increase about 3-fold and ethinyloestradiol levels about 1.6-fold at Day 21 compared to Day 1 of the treatment.
The daily exposure to levonorgestrel and ethinyloestradiol on Day 21, corresponding to the end of a typical 3-week contraceptive regimen, and on Day 84, at the end of an extended-regimen, were similar without any further accumulation of drug.

Distribution

Levonorgestrel is highly protein-bound, principally to sex hormone binding globulin (SHBG) and serum albumin. Only 1.3% or the total serum drug concentration is present as free steroid, approximately 64% is specifically bound to SHBG and about 35% is non-specifically bound to albumin. Ethinyloestradiol is highly (about 95%-98.5%), but non-specifically bound to serum albumin. Ethinyloestradiol does not bind to SHBG, but induces an increase in the serum concentrations of SHBG, influencing the relative distribution of levonorgestrel into different protein fractions (increase in SHBG-bound fraction and decrease in albumin-bound fraction).

Metabolism

Following absorption, levonorgestrel is conjugated at the 17β-OH position to form sulfate and to a lesser extent, glucuronide conjugates in plasma.

First-pass metabolism of ethinyloestradiol involves formation of ethinyl estradiol-3-sulfate in the gut wall, followed by 2-hydroxylation of a portion of the remaining untransformed ethinyloestradiol by hepatic cytochrome P-450 3A4. The various hydroxylated metabolites are subject to further methylation and/or conjugation.

Excretion

About 45% of levonorgestrel and its metabolites are excreted in the urine and about 32% are excreted in faeces, mostly as glucuronide conjugates. The terminal elimination half-life for levonorgestrel after a single dose of Seasonique was about 34 hours.

Ethinyloestradiol is excreted in the urine and faeces as glucuronide and sulfate conjugates, and it undergoes enterohepatic recirculation. The terminal elimination half-life of ethinyloestradiol after a single dose of Seasonique was found to be about 18 hours.

Special Populations

Effect of hepatic impairment
No formal studies to evaluate the effect of hepatic disease on the disposition of Seasonique have been conducted. However, steroid hormones may be poorly metabolized in patients with impaired liver function.

Effect of renal impairment
No formal studies to evaluate the effect of renal disease on the disposition of Seasonique have been conducted. However, renal excretion is the principal route of elimination for ethinyloestradiol, and ethinyloestradiol clearance in renal failure patients was found to be decreased relative to normal healthy women.

Elderly
Combined oral contraceptives are not indicated for use in postmenopausal women.

Gender
Seasonique is an oral contraceptive and therefore is for use in women only.

Race
Population pharmacokinetic analyses (including Caucasians, African-American, Asian, Hispanic and other) showed no effect of race on the pharmacokinetics of levonoregstrel or ethinyloestradiol.

Body weight
There has been some concern that some hormonal contraceptives are not as effective in obese women, possibly due to an enhanced metabolic rate in obese women leading to more rapid drug metabolism and subsequent insufficient hormone levels. There were no pregnancies in women who weighed ≥ 90kg and the efficacy of Seasonique does not appear to be reduced in obese women.

CLINICAL TRIALS

The clinical efficacy and safety of Seasonique® (84-day 150 µg Levonorgestrel/30 µg Ethinyloestradiol + 7-day 10 µg Ethinyloestradiol (DP3-84/10)) was examined in two multi-center open trials, PSE-301 and PSE-302 and one long tern extension study (DR-PSE-304) for safety monitoring.

The contraceptive reliability was analysed in both studies using the Pearl Index (PI) and a life table analysis. Pearl Index (PI) calculations (for Study PSE-301) using both 91-day and 28-day cycle equivalents were performed to retain relevant data and for comparison of Seasonique with currently available 28-day oral contraceptive regimens.

PSE-301

The pivotal study, PSE-301 was a Phase III, 12-month, multi-center, randomised, open-label clinical trial conducted to evaluate the efficacy and safety of two 91-day extended regimens, Seasonique and DP3-84/30, (84-day 150 µg Levonorgestrel/30 µg Ethinyloestradiol + 7-day 30 µg Ethinyloestradiol). The mean age of the subjects was 27.4 years, mean weight was 69.6 kg and mean body mass index (BMI) 26.0 kg/m^2. At enrolment in the study, most subjects (63.1%) were taking another oral contraceptive regimen and were then switched to the extended-regimen. The racial demographic of those enrolled was: Caucasian (80%), African-American (11%), Hispanic (5%), Asian (2%), and Other (2%). Almost 80% of the patients were non-smokers.

Out of the 1,006 women, who received Seasonique, 799 had completed at least one complete cycle and 500 completed the study.

In the efficacy analysis, 1,578 91-day cycles (621 women), in which no other back-up contraceptive method was used, were included yielding a PI of 0.76 (95 % CI; 0.00 – 1.76), based on 3 pregnancies. When calculated on 6,814 28-day cycles (841 women), in which no other back-up contraceptive method was used, a PI of 0.57 was calculated (95% CI 0.00 – 1.33), based on 3 pregnancies.

In addition to the Pearl Index calculation, a life table approach was used to estimate the cumulative pregnancy rate on a cycle-by-cycle basis. The life-table results for patients between the ages of 18 and 35 years who completed one cycle of treatment was calculated. The cumulative failure rate at the end of one year of treatment, estimated by the life-table method was 0.61% (95% C.I.: 0.19% - 1.90%) for Seasonique. Life table estimates of the cumulative pregnancy confirm that Seasonique is >99% effective in preventing pregnancy and are comparable to the PI calculations.

As seen in PSE-301 and also confirmed by the formal ovarian inhibition studies (DR-PSE-310 and DR-PSE-312) the addition of EE 10 µg during the standard hormone free interval (HFI) appears to better suppress ovarian function. Estradiol, FSH, and LH levels were lower during the Seasonique EE 10 µg monotherapy interval compared with the HFIs of the 21/7 OC and the 84/7-day cycle OC. Seasonique suppresses ovarian function as assessed both by ovarian hormone levels and follicular growth. **).**

PSE-302

The second study PSE-302 was an open label, randomised clinical trial designed to assess endometrial biopsy results and included a limited number of cycles of exposure available for the PI evaluation. In addition to three test products, including Seasonique, a standard 28-day LNG/EE comparator was included. The majority of treated patients (n=95) were Caucasian (60%), 20% African-American, and 12% Hispanic. Almost 80% of the patients were non-smokers, and 60% were continuous users of oral contraceptives (28% prior users and 11% fresh starts). The median age was about 26 years, median weight was 66.2 kg, and the median BMI was 24.1 kg/m^2. 95 subjects received Seasonique and 80 completed at least one complete cycle. Study participants completed 166 91-day cycles or 539.50 28-day patient cycles. The results show similar contraceptive efficacy as observed in the pivotal PSE-301 study.

Endometrial biopsy results showed no evidence of any pathologic changes; hyperplasia was not observed in any of the end of treatment biopsy samples. Other safety results for Seasonique® were comparable to those for the 28-day comparator, including the incidence of serious adverse events, changes in vital signs, and changes in laboratory values from baseline to end of treatment; none were of any clinical significance.

Cycle control

In study PSE-301, the median number of scheduled bleeding/spotting was 3 days for all 4 cycles. The number of scheduled bleeding only days decreased from a median of 3 days during the first cycle to 2 days during the 3 subsequent cycles.

A reduction in the number of unscheduled bleeding/spotting days and unscheduled bleeding only days was observed from the beginning at the second 91-day cycle of treatment, see Table 1.

Table 1: Total number of days of unscheduled bleeding and/or spotting per cycle (completed cycles only) – Intent-to-Treat (Study PSE-301)

	Cycle	N	Mean (SD)	Min	Q1	Median	Q3	Max	Median Per Patient-Month
Seasonique	1	758	14.3 (13.60)	0	3	11	22	73	2.8
	2	625	9.5 (10.48)	0	2	5	14	63	1.3
	3	533	7.2 (9.04)	0	1	4	10	50	1.0
	4	446	7.6 (9.37)	0	1	4	10	58	1.0

The decrease in the unscheduled bleeding/spotting over treatment cycles was confirmed in the comparative PSE-302 study. After one year of treatment, the total number of days of bleeding/spotting was similar for Seasonique and the 28-day comparator.

Observations from a cross study analysis of clinical trials for the 84/7 EE Seasonique and 84/7-placebo regimen showed statistically significant reductions in bleeding and/or spotting at all four cycles during the 7 days of low-dose EE (in the 84/7-EE Seasonique regimen) compared to the 7 days of placebo (in the 84/7-placebo regimen). The duration of the scheduled withdrawal bleeding episodes appeared to be shorter with the 84/7-EE Seasonique regimen than with 84/7-placebo (median of 3 days compared to a median of 4 days)

DR-PSE-304

Study DR-PSE-304 was an open label, non randomized extension study of both PSE-301 and PSE-302, designed to evaluate Seasonique's safety profile when taken for up to an additional 5 consecutive years in a subset of patients who had successfully completed one year of therapy in either the pivotal PSE-301 study (either the Seasonique or the DP3 84/30 arm) or the endometrial biopsy study PSE-302.

The study demographic for DR-PSE-304 was 82% Caucasian; about 12.5% African-American; Asian, Hispanic the remainder were other ethnicities. About 84% of the patients were non-smokers and about 70% were continuous users of OCs (21% prior user and 9% fresh starts). The median age of all treated patients was 27.5 years, median weight was 65.3 kg, and the median BMI was approximately 24.1 kg/m2.

The DR-PSE-304 study included exposure for a total of 1,302 complete 91-day Seasonique cycles, corresponding to 4,411 28-day cycles. These cycles combined with the exposure observed in studies PSE-301 and PSE-302 result in over 25,000 28-day cycles of exposure among patients in the Seasonique clinical development program.

Overall rates of study discontinuation, the incidence of adverse events (including serious adverse events and adverse events leading to study discontinuation) are consistent with those observed in study PSE-301 and PSE-302 and support the long-term safety of the Seasonique-84/10 extended regimen oral contraceptive, (refer **ADVERSE EVENTS**).

INDICATIONS

Seasonique is indicated for use as an oral contraceptive.

CONTRAINDICATIONS

Seasonique 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 Seasonique 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 severe or 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
- 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
- In association with herbal remedy St. John's Wort (hypericum perforatum)
- Hypersensitivity to any of the ingredients contained in Seasonique.

PRECAUTIONS

If any of the conditions/risk factors mentioned below are present, the benefits of Seasonique use 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 on whether Seasonique should be discontinued. In the case of suspected or confirmed thrombosis, combined oral contraceptives (COC) use 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

The use of any COC increases the risk of VTE compared with no use. The women considering using Seasonique 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 COC is re-started after a break in use of 4 weeks or more.

The risk of VTE with the COC is greatest for products containing over 50 micrograms of ethinyloestradiol. There is less risk for products such as Seasonique containing less than 35 micrograms ethinyloestradiol. It is not known how Seasonique, with its 91-day regimen, influences the occurrence of such events in comparison to other levonorgestrel containing COCs, which have a 28-day regimen.

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 COCs, and how her current risk factors influence this risk.

Risk[1] of developing a blood clot (VTE) in a year

Women not using a combined hormonal contraceptive (CHC) and not pregnant	About 2 out of 10,000 women
Women using a CHC containing levonorgestrel, norethisterone or norgestimate	About 5-7 out of 10,000 women
Women using a CHC containing etonogestrel or norelgestromin	About 6-12 out of 10,000 women
Women using a CHC containing drospirenone, gestodene, desogestrel or cyproterone[2]	About 9-12 out of 10,000 women
Women using a CHC containing chlormadinone, dienogest or nomegestrol	Not yet known[3]

[1] In any individual woman the risk may be far higher, depending on her underlying risk factors (see below).

[2] While cyproterone is indicated for the treatment of moderate to severe acne related to androgen sensitivity and/or hirsutism, it is known to have efficacy as a contraceptive. The risk of VTE associated with cyproterone use is considered to be 1.5 to 2 times higher than for CHCs containing levonorgestrel and may be similar to the risk with contraceptives containing gestodene, desogestrel or drospirenone.

[3] Further studies are ongoing or planned to collect sufficient data to estimate the risk for these products. Where the risk for a particular progestogen is uncertain, the risk of the class should be used in determining the risk for the individual patient.

It is important that women understand that VTE associated with COC use is rare. 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 COC use.

However VTE is a serious condition and may be fatal in 1-2% of cases. Extremely rarely, thrombosis has been reported to occur in COC users in other blood vessels, e.g. hepatic, mesenteric, renal, cerebral or retinal veins and arteries.

Risk factors for VTE

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

Seasonique 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 COC should not be prescribed.

List of 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 Activated Protein C (APC) resistance (including Factor V Leiden), antithrombin-III deficiency, protein C deficiency, protein S deficiency.
- Other medical conditions associated with VTE
    - 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 Seasonique (in the case of elective surgery at least six 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 Seasonique 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 COC use.

The possibility of anticoagulant therapy should also be taken into account. Adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

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

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 COC.

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;
- 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 or an ‘acute’ abdomen.
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 (partial or complete) can occur almost immediately.

Risk of arterial thromboembolism (ATE)

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

Risk factors for ATE

The risk of arterial thromboembolic complications in COC users increases in women with risk factors. Seasonique 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 COC should not be prescribed.

List of risk factors for ATE

- Increasing age, particularly above 35 years
- Smoking
- Hypertension
- Obesity (body mass index over 30 kg/m²)
- Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age e.g. below 50).
- Biochemical factors: 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 strongly advised not to smoke if they wish to use a COC. 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 COC use.

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.

The possibility of anticoagulant therapy should also be taken into account. Adequate alternative contraception should be initiated because of the teratogenicity of anticoagulant therapy (coumarins).

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

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

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 COC.

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, trouble speaking or understanding;

- sudden trouble seeing in one or both eyes, including 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.

Carcinogenicity

Sex steroids can promote the growth of certain hormone-dependent tissues and tumours. Long-term continuous administration of natural and synthetic oestrogens in certain animal species increases the frequency of carcinomas of the breast, uterus, cervix, vagina, testis and liver. A long-term study with levonorgestrel in dogs showed an increased incidence of mammary tumours, although a similar effect was not apparent in studies in mice, rats or monkeys. The occurrence of these mammary tumours in dogs may be due in part to a hormonal feedback mechanism.

Combined oestrogen-progestogen oral contraceptives are classified as Group 1 carcinogens by the International Agency for Research on Cancer (IARC) reflecting sufficient evidence of carcinogenicity in humans based on findings of increased risk for cancer of the breast among current and recent user only, for cancer of the cervix and for cancer of the liver in populations that are at low risk of hepatitis B viral infection - See Tumours. However, there is also convincing evidence in humans that these agents confer a protective effect against cancer of the endometrium and ovary and that the protection lasts for up to 2 decades after stopping use.

Genotoxicity

Oestrogenic and progestogenic hormones have been tested for genotoxicity in a number of *in vitro* and *in vivo* test systems with mixed results. The genotoxicity of levonorgestrel has not been fully investigated, although limited data available to date suggest that it does not appear to be gentoxic. In mutagenicity studies performed in different strains of *Salmonella typhimurium* with and without metabolic activation no mutagenic potential of levonorgestrel was detected.

There is limited evidence available in the literature suggesting that oestrogens may be weakly genotoxic at high doses. Ethinyloestradiol did not induce mutations in bacterial, yeast or mammalian cells or unscheduled DNA synthesis in rat hepatocytes or DNA-adduct formation in cultured human liver slices *in vitro*. It also did not induce sex linked recessive lethal mutations in *Drosophila*. Ethinyloestradiol gave equivocal results in assays for chromosomal damage (clastogenic effects were not consistently seen and occurred at high doses).

Tumours

Cervical Cancer

An increased risk of cervical cancer in long-term users of COCs (> 5 years) has been reported in some epidemiological studies, but there continues to be controversy about the extent to which this finding is attributable to the confounding effects of sexual behaviour and other factors such as human

papilloma virus (HPV).

Breast Cancer

A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using COCs. The excess risk gradually disappears during the course of the 10 years after cessation of COC use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent COC users is small in relation to the overall risk of breast cancer. These studies do not provide evidence for causation. The observed pattern of increased risk may be due to an earlier diagnosis of breast cancer in COC users, the biological effects of COCs or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.

Hepatocellular carcinoma

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 hepatic tumour should be considered in the differential diagnosis when severe upper abdominal pain, liver enlargement or signs of intra-abdominal haemorrhage occur in women taking COCs.

With the use of the higher-dosed COCs (50 µg ethinyloestradiol) the risk of endometrial and ovarian cancer is reduced. Whether this also applies to lower-dosed COCs remains to be confirmed.

Other conditions

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

Although small increases in blood pressure have been reported in many women taking COCs, clinically relevant increases are rare. Only in these rare cases an immediate discontinuation of COC use is justified. If, during the use of a COC in preexisting hypertension, constantly elevated blood pressure values or a significant increase in blood pressure do not respond adequately to antihypertensive treatment, the COC must be withdrawn. 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; gallstones; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.

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

Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal. Recurrence of cholestatic jaundice and/or cholestasis-related pruritus which previously occurred during pregnancy or during previous use of sex steroids necessitates the discontinuation of COCs.

Although COCs may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using low-dose COCs (containing < 50µg ethinyloestradiol). However, diabetic women should be carefully observed, particularly in the

early stage of COC use.

Worsening of endogenous depression, of epilepsy, of Crohn's disease and of ulcerative colitis has been reported during COC use.

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

Medical examination/consultation

A complete medical history and physical examination should be taken prior to the initiation or reinstitution of COC use, guided by the contraindications and precautions, and should be repeated periodically during the use of COCs. In general an annual examination is recommended. Pregnancy should be ruled out before the start of therapy. 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 COC use. The frequency and nature of examinations 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.

The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given.

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 transmitted 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 active tablets, gastro-intestinal disturbances or concomitant medication (see **DOSAGE AND ADMINISTRATION** and **INTERACTIONS WITH OTHER MEDICINES**).

Reduced cycle control

With all COCs, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first 3 months of use. The evaluation of any irregular bleeding should be conducted if the bleeding persists.

In the Seasonique clinical trials scheduled (withdrawal) bleeding and/or spotting remained fairly constant over time, with an average of 3 days of bleeding and/or spotting per each 91-day cycle. Unscheduled bleeding and unscheduled spotting decreased over successive 91-day cycles.

If unscheduled spotting or bleeding occurs, the woman should be instructed to continue on the same regimen. If the bleeding is persistent or prolonged, the woman should be advised to consult her doctor.

Information for the Patient

A Consumer Medicine Information leaflet is available. Please advise your patient to read this information carefully. Seasonique tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.
Seasonique pink tablets contain the azo colouring agents Allura red AC Aluminium Lake (E129) and Brilliant Blue FCF (E133) that can cause allergic reactions.

Effects on Fertility

In studies PSE-301 and PSE-302 post-study follow-up was planned for all patients after study completion or withdrawal for occurrence of pregnancy and/or until the menstrual cycle return to normal; subjects were followed for three months for return to fertility. Among the patients who reported pregnancies rapid return to fertility was noted with 9 of 18 reported pregnancies (on-treatment or off-treatment) occurred within three weeks of discontinuing or completing treatment with Seasonique and 15 out of 18 occurred within three months of the last dose. Overall, there was no suggestion of any impairment of fertility following cessation of the Seasonique in its clinical programme.

Use in Pregnancy

Pregnancy Category B3

Seasonique is contraindicated during pregnancy.

If pregnancy occurs during use of Seasonique, the treatment should be withdrawn immediately. Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used COCs prior to pregnancy, nor a teratogenic effect when COCs were taken inadvertently during pregnancy.

Animal studies have shown adverse effects during pregnancy and lactation. Based on these animal data, adverse effects due to hormonal action of the active compounds cannot be excluded.

Use in Lactation

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

Children and Adolescents

The efficacy and safety of Seasonique in women of reproductive age under 18 years have not been established.

Effects on Ability to Drive and Use Machines

No studies on the effects on the ability to drive and use machines have been performed. No effects on ability to drive and use machines have been observed in users of COCs.

INTERACTIONS WITH OTHER MEDICINES

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

Influence of other medicinal products on Seasonique

Interactions between oral contraceptives and other medicinal products may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature:

Hepatic metabolism
Interactions can occur with drugs that induce hepatic enzymes which can result in increased clearance of sex hormones (e.g. phenytoin, barbiturates, primidone, carbamazepine, rifampicin, bosentan, vemurafenib and HIV-medication (e.g. ritonavir, nevirapine) and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and products containing the herbal remedy St. John's Wort (hypericum perforatum)). Maximal enzyme induction is generally seen in about 10 days but may then be sustained for at least 4 weeks after the cessation of drug therapy.

Management
Women on short-term treatment with any of the above-mentioned classes of medicinal products or individual active substances (hepatic enzyme-inducing medicine) besides rifampicin should temporarily use a barrier method in addition to the COC, i.e. during the time of concomitant medicinal product administration and for 7 days after their discontinuation. For women on rifampicin a barrier method should be used in addition to the COC during the time of rifampicin administration and for 28 days after its discontinuation.

In women on long-term treatment with hepatic enzyme-inducing active substances, another reliable, non-hormonal, method of contraception is recommended.

Influence of Seasonique on other medicinal products

The concomitant use of COCs and lamotrigine has been shown to reduce lamotrigine levels by about 50%. This interaction may be due to the estrogen component since it does not occur with progestogens given alone. In a patient already treated with lamotrigine, close clinical monitoring and a possible dosage adjustment at the beginning and the end of the contraceptive may be necessary. Conversely, starting oral contraception during lamotrigine titration should be avoided.

Laboratory tests

The use of COCs may change the results of some 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. The changes generally remain within the normal laboratory range.

Women on thyroid hormone replacement therapy may need increased doses of thyroid hormone because serum concentrations of thyroid binding globulin increase with use of COCs.

ADVERSE EFFECTS

The pivotal clinical trial that evaluated the safety and efficacy of Seasonique was a 12-month, randomized, multicenter, open-label study, which enrolled women aged 18-40, of whom 1,006 took at least one dose of Seasonique. The most commonly reported treatment-emergent adverse reactions were irregular and/or heavy uterine bleeding, weight gain and acne.

Table 2: Incidence of Treatment- Emergent Adverse Events Occurring in 5% or More of Treated Patients (Study PSE-301)

	DP3-84/30 (N=1013)		DP3-84/10 (N=1006)		Total (N=2019)	
MedDRA System Organ Class and Preferred Term	**N**	**%**	**N**	**%**	**N**	**%**
REPRODUCTIVE SYSTEM AND BREAST DISORDERS						
Intermenstrual bleeding	123	12.14	116	11.53	239	11.84
Menorrhagia	78	7.70	58	5.77	136	6.74
INFECTIONS AND INFESTATIONS						
Nasopharyngitis	85	8.39	72	7.16	157	7.78
Sinusitis NOS	63	6.22	65	6.46	128	6.34
INVESTIGATIONS						
Weight increased	39	3.85	53	5.27	92	4.56
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
Acne NOS	40	3.95	52	5.17	92	4.56

The adverse events associated with bleeding were consistently slightly higher for DP3-84/30 compared to Seasonique. Intermenstrual bleeding was reported in 12.1% of the DP3-84/30 patients compared to 11.5% of the DP3-84/10 patients and menorrhagia was reported in 7.7% of patients on DP3-84/30 compared to 5.8% on DP3-84/10.

Table 3: Incidence of Treatment- Emergent Adverse Events Occurring in 5% or More of Treated Patients (Study PSE-302)

	DP3-84/30 (N=95)		DP3-84/10 (N=95)		DP3-25/30 (N=89)		Nordette (N=93)		Total (N=372)	
MedDRA System Organ Class and Preferred Term	N	%	N	%	N	%	N	%	N	%
REPRODUCTIVE SYSTEM AND BREAST DISORDERS										
Intermenstrual bleeding	14	14.74	10	10.53	9	10.11	2	2.15	35	9.41
Menorrhagia	7	7.37	4	4.21	2	2.25	2	2.15	15	4.03
INFECTIONS AND INFESTATIONS										
Nasopharyngitis	12	12.63	8	8.42	12	13.48	12	12.90	44	11.83
Sinusitis NOS	1	1.05	7	7.37	4	4.49	3	3.23	15	4.03
Pharyngitis streptococcal	5	5.26	5	5.26	1	1.12	2	2.15	13	3.49
Urinary tract infection NOS	2	2.11	4	4.21	5	5.62	7	7.53	18	4.84
SKIN AND SUBCUTANEOUS TISSUE DISORDERS										
Acne NOS	3	3.16	8	8.42	2	2.25	1	1.08	14	3.76
GASTROINTESTINAL DISORDERS										
Nausea	5	5.26	3	3.16	2	2.25	7	7.53	17	4.57
NERVOUS SYSTEM DISORDERS										
Headache NOS	7	7.37	3	3.16	7	7.87	3	3.23	20	5.38
INVESTIGATIONS										
Weight increased	5	5.26	0	0.00	2	2.25	1	1.08	8	2.15

Table 4: Incidence of Treatment- Emergent Adverse Events Occurring in 5% or More of Treated Patients (Study DR-PSE-304)

	DP3-84/30 (N=147)		DP3-84/10 (N=173)		Total (N=320)	
MedDRA System Organ Class and Preferred Term	N	%	N	%	N	%
NERVOUS SYSTEM DISORDERS						
HEADACHE	32	21.77	38	21.97	70	21.88
MIGRAINE	9	6.12	8	4.62	17	5.31
INFECTIONS AND INFESTATIONS						
UPPER RESPIRATORY TRACT INFECTION	25	17.01	34	19.65	59	18.44
NASOPHARYNGITIS	22	14.97	26	15.03	48	15.00
VAGINITIS BACTERIAL	8	5.44	19	10.98	27	8.44
INFLUENZA	12	8.16	18	10.40	30	9.38
SINUSITIS	21	14.29	18	10.40	39	12.19
URINARY TRACT INFECTION	12	8.16	16	9.25	28	8.75
BRONCHITIS	11	7.48	13	7.51	24	7.50
VULVOVAGINAL MYCOTIC INFECTION	9	6.12	13	7.51	22	6.88
FUNGAL INFECTION	9	6.12	7	4.05	16	5.00
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
BACK PAIN	16	10.88	21	12.14	37	11.56
INVESTIGATIONS						
WEIGHT INCREASED	13	8.84	16	9.25	29	9.06
REPRODUCTIVE SYSTEM AND BREAST DISORDERS						
METRORRHAGIA	13	8.84	16	9.25	29	9.06
DYSMENORRHOEA	8	5.44	15	8.67	23	7.19
CERVICAL DYSPLASIA	8	5.44	11	6.36	19	5.94
PSYCHIATRIC DISORDERS						
INSOMNIA	8	5.44	13	7.51	21	6.56
ANXIETY	6	4.08	10	5.78	16	5.00
DEPRESSION	7	4.76	10	5.78	17	5.31
INJURY, POISONING AND PROCEDURAL COMPLICATIONS						
PROCEDURAL PAIN	11	7.48	5	2.89	16	5.00
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
FATIGUE	8	5.44	4	2.31	12	3.75

The following serious adverse events have been reported in women using COCs, which are discussed in **CONTRAINDICATIONS** and **PRECAUTIONS**:

- Venous thromboembolic disorders
- Arterial thromboembolic disorders
- Hypertension
- Liver tumours
- Occurrence or deterioration of conditions for which association with COC use is not conclusive: Crohn's disease, ulcerative colitis, epilepsy, migraine, uterine myoma, porphyria,

systemic lupus erythematosus, herpes gestationis, Sydenham's chorea, haemolytic uremic syndrome, cholestatic jaundice

- Chloasma
- Acute or chronic disturbances of liver function may necessitate the discontinuation of COC use until markers of liver function return to normal
- In women with hereditary angioedema exogenous estrogens may induce or exacerbate symptoms of angioedema.

Post-Marketing Adverse Reactions:

The most commonly reported adverse events were in the category of reproductive system and breast disorders, most commonly metrorrhagia (n=159), vaginal haemorrhage (n=58) and menorrhagia (n=18).

Additional adverse reactions that have been identified during post-marketing experience with Seasonique include hypersensitivity reaction, loss of consciousness, thrombosis, pulmonary embolism, pulmonary thrombosis, alopecia and pain in extremity.

DOSAGE AND ADMINISTRATION

Seasonique is an extended-regimen oral contraceptive where tablets are taken continuously for 91 days. Each subsequent 91-day pack is started the day after the last tablet of the previous pack. Seasonique pack consists of 84 combination tablets of 150 µg levonorgestrel and 30 µg ethinyloestradiol and 7 tablets of 10 µg ethinyloestradiol.

How to use Seasonique

Tablet taking is continuous for 91 days. One tablet is to be taken by mouth at the same time every day in the order shown at the blister pack.

One pink tablet containing levonorgestrel and ethinyloestradiol is taken daily for 84 consecutive days, followed by one white ethinyloestradiol tablet for 7 days, during which time withdrawal bleeding usually occurs.

How to start Seasonique

The daily dosing regime should start with the first tablet (#1) of *Month 1* blister, consistent with the packaging presentation.The tablets must be taken every day at about the same time, if necessary with a little liquid, in the order shown on the blister pack. One tablet is to be taken daily for 91 consecutive days. One pink tablet should be taken daily for 84 consecutive days, followed by one white tablet for 7 consecutive days. A scheduled withdrawal bleeding should occur during the 7 days that the white tablets are taken.

Each subsequent 91-day cycle is started without interruption on the same day of the week on which the patient began her first dose of Seasonique, following the same schedule.

- **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 may start Seasonique later (i.e. days 2-5 of the cycle), but should in this case be advised to additionally use a barrier method for the first 7 days of tablet-taking.

- **Changing from a combined hormonal contraceptive (combined oral contraceptive (COC), vaginal ring, or transdermal patch**

The woman should start with Seasonique on the day after the last active tablet (the last tablet containing the active substances) of her previous COC. In case a vaginal ring or transdermal patch has been used, the woman should start using Seasonique on the day of removal but at the latest when the next application would have been due.

- **Changing from a progestogen-only method (progestogen-only pill, injection, implant) or from a progestogen-releasing intrauterine system (IUS)**

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

- **Following first-trimester abortion**

The woman may start immediately. When doing so, she 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. 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**

Contraceptive reliability may be reduced if taking the pink tablets is forgotten and particularly if one forgets to take the first tablets from the blister pack.

If it is found within 12 hours of the usual time of taking that one pink tablet has been forgotten, the tablet that was forgotten should be taken immediately, and the treatment should be continued normally by taking the next tablet at the usual time.

If it is found more than 12 hours after the normal time of taking that one or several pink tablets have been forgotten, contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:

1. tablet-taking must never be discontinued for longer than 7 days
2. 7 days of uninterrupted tablet-taking are required to attain adequate suppression of the hypothalamic-pituitary-ovarian-axis.

Accordingly the following advice can be given in daily practice:

<u>Missed pink levonorgestrel/ethinyloestradiol tablets</u>

- **During Day 1 – Day 7 (week 1)**

If one or more tablets are missed during week 1, there is a higher risk of pregnancy because 7 days of uninterrupted tablet-taking are required to attain suppression of the hypothalamic-pituitary-ovarian-

axis. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the white tablet phase, the higher the risk of a pregnancy.

A single delayed pink tablet should be taken as soon as possible even if this means taking two tablets at the same time. Further tablets should be taken at the usual time.

If two pink tablets are missed, two tablets should be taken on the day woman remembers missing tablets and additional two on the next day. Further tablets should be taken at the usual time.

If three or more pink tablets are missed, the missed tablets should be omitted and further tablets continued at the usual time as indicated on the pack. Woman may experience bleeding during the week following the missed tablets.

In any case, back-up contraception should be used for the next 7 days.

- **During Day 8 – Day 84 (week 2 to week 12)**

A single delayed pink tablet should be taken as soon as possible even if this means taking two tablets at the same time. Further tablets should be taken at the usual time. No additional contraception precautions are required.

If two pink tablets are missed, two tablets should be taken on the day woman remembers missing tablets and additional two on the next day. Further tablets should be taken at the usual time. Additional non-hormonal methods of contraception should be used for the next 7 days after restarting tablets.

If three or more pink tablets are missed, the missed tablets should be omitted and further tablets continued at the usual time as indicated on the pack. Woman may experience bleeding during the week following the missed tablets. Additional non-hormonal methods of contraception should be used for the next 7 days after restarting tablets. If intercourse took place during the days of missed tablets, the possibility of a pregnancy should be considered. The more tablets are missed and the closer they are to the white tablet phase, the higher the risk of a pregnancy.

Missed white ethinyloestradiol tablets (week 13)

The missed tablets should be omitted and further tablets continued at the usual time until the pack is finished. No additional contraception precautions are required.

If the woman has no withdrawal bleeding during the week 13 (while taking the white ethinyloestradiol tablets), the possibility of pregnancy must be ruled out before a new 91-day cycle is started.

Advice in case of gastro-intestinal disturbances

In case of severe gastro-intestinal disturbances (e.g. vomiting or diarrhoea), absorption may not be complete and additional contraceptive measures should be taken. If vomiting occurs within 3-4 hours after tablet-taking, the women should apply the advice given for missed tablets. If the woman does not want to change her normal tablet-taking schedule, she can take the extra pink tablet(s) from the he last row (week 12).

Disposal
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

OVERDOSAGE

There have been no reports of serious adverse effects from overdose of oral contraceptives. On the basis of general experience with combined oral contraceptives, symptoms that may possibly occur in this case are: nausea, vomiting and, in young girls, slight vaginal bleeding. There are no antidotes and treatment should be symptomatic.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

PRESENTATION AND STORAGE CONDITIONS

Each composite pack contains 84 round pink tablets each containing levonorgestrel 150 µg/ethinyloestradiol 30 µg tablets embossed "172" on one side and "T" on the other side and 7 round white film-coated tablets, each containing ethinyloestradiol 10 µg embossed "173" on one side and "T" on the other side.
The carton contains three monthly blisters packaged inside an inner carton folder inside a non-resealable foil pouch:

Month 1 and Month 2 blisters contain 28 pink film-coated levonorgestrel 150 µg/ethinyloestradiol 30 µg tablets;
Month 3 blister contains 28 pink film-coated levonorgestrel 150µg/ethinyoestradiol 30 µg tablets + 7 white film-coated ethinyloestradiol 10 µg tablets

Storage

Store below 25°C. Keep in original container in order to protect from light and humidity.
Once opened, the product should be stored in the original packaging inside the inner carton.

NAME AND ADDRESS OF THE SPONSOR

Teva Pharma Australia Pty Ltd
Level 2, 37 Epping Road
Macquarie Park NSW 2113
Australia.

POISON SCHEDULE OF THE MEDICINE

Prescription Only Medicine - S4.

DATE OF FIRST INCLUSION IN THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS

24 May 2016 (AUST R 238384).

DATE OF MOST RECENT AMENDMENT

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