Desolon®

DESOGESTREL 0.15MG + ETHINYLESTRADIOL 0.03MG

Product Description
6.0 mm, White, Round Biconvex tablet, One side having logo "D" and other side is plain.

Pharmacodynamics
Mode of Action: Combination hormonal contraceptives inhibit ovulation via a negative feedback mechanism on the hypothalamus, which alters the normal pattern of gonadotropin secretion of a follicle-stimulating hormone (FSH) and luteinizing hormone by the anterior pituitary. The follicular phase FSH and midcycle surge of gonadotropins are inhibited. In addition, combination hormonal contraceptives produce alterations in the genital tract, including changes in the cervical mucus, rendering it unfavorable for sperm penetration even if ovulation occurs. Changes in the endometrium may also occur, producing an unfavorable environment for nidation. Combination hormonal contraceptive drugs may alter the tubal transport of the ova through the fallopian tubes. Progestational agents may also alter sperm fertility.

Pharmacokinetics
Ethinyloestradiol
Absorption: Ethinyloestradiol (EE) is rapidly and completely absorbed from the intestine with an absorption half-life of 0.2-0.4 hours. After oral administration of 50 mcg EE, the plasma peak time was approximately 1-2 hours, whereas plasma peak height amounted to 0.12 ± 0.03 mcg/l and the area under curve to 1048 ± 247 pg/ml/h. With EE, a great inter- and intra-population variability of plasma levels has been reported. As a result of gut wall metabolism during absorption and the effect of first-pass metabolism, the absolute bioavailability of EE after single-dose administration is approx. 45%. The absolute bioavailability of EE calculated on the basis of repeated measurements after administration of DSG (desogestrel)/EE 150/30 mcg/d for 21 days is 74 ± 25%. The reason for this figure being higher than the average figure of 45% mentioned above, probably has to do with the fact that the former figure is based on single-dose administration and single measurements. A possible explanation for the higher absolute bioavailability of EE upon repeated measurements could be an influence on hepatic enzyme systems.

Distribution: After absorption there is a rapid distribution of EE over the body, with a volume of distribution of 3.8 l/kg, whereas the distribution half-life amounts to 0.5-2.5 hrs. Plasma protein binding with EE and its metabolites is almost completely (± 95%), mainly to albumin.

Metabolism: EE is subject to a significant degree of presystemic conjugation in both the small bowel mucosa (the major metabolite being EE-3-sulphate) and the liver. EE escaping gut wall conjugation undergoes hepatic conjugation and phase I metabolism (oxidation, reduction or hydrolysis). Sulphate and glucuronide conjugates of both EE (direct conjugates) and phase I metabolites, which are excreted in bile, can undergo hydrolysis by gut flora. Hydrolysis of the direct conjugates yields EE which can be reabsorbed, thus producing an enterohepatic circulation. Whether the enterohepatic circulation of EE contributes significantly to plasma concentration and hence to therapeutic effect in most women is not known. The metabolic pathways of EE are of two general types, hydroxylation, being the principal route, and in addition, although to a very minor extent, modification of the ethinylgroup. The principal hydroxylated metabolites of EE are, in order of importance respectively, the catechol oestrogen 2-hydroxy(OH)-EE and the catechol 2-methoxy-EE, whereas in addition small amounts of both 6alpha-OH-EE and 16B-OH-EE have been identified. 2-OH-EE is further metabolised to chemically reactive metabolites, probably o-quinone/o-semi-quinones, which can bind irreversibly to protein.

Elimination: EE disappears from the plasma in an elimination phase with a half-life of 13-27 hours. The excretion of conjugates of EE and its metabolites is via the urine and with the faeces (ratio 1:1.5). Reports on the time after which steady state conditions are reached reflect great differences: 3-4 days (no specific preparation mentioned); 7 days triphasic LNG (levonorgestrel)/EE; 10-13 days (DSG/EE 150/30 mcg/d).

Desogestrel
Absorption: After oral administration, desogestrel (DSG) is rapidly and almost completely absorbed (most probably from the duodenum), with an absorption half-life of 0.2 hours (range 0.1-0.4 h). During phase I metabolism DSG is almost completely converted in the body, mainly into the pharmacologically active metabolite 3-ketodesogestrel (3K-DSG). After oral administration of 150 mcg DSG + 30 mcg EE the plasma peak time of 3K-DSG was 1.8 ± 0.8 h whereas peak height amounted to 6.4 ± 3.7 mcg/l. The mean serum level of 3K-DSG 12 hours after dosing was 1.4 ± 0.5 mcg/l and the mean area under curve was 45.5 ± 24.4 mcg/h/l. There was, however, a great inter-individual variability of the plasma levels, a well-known phenomenon with progestagens.

Abovementioned parameters point to a high first pass metabolism of DSG and indicate that the relative bioavailability of the agent is comparable to that of 3K-DSG. The absolute bioavailability of 3K-DSG after single dose administration is about 76 ± 23% and during steady-state conditions 81 ± 27%.

Distribution: The distribution half-life of 3K-DSG in women is ± 1.4 hours (range 1.1-1.8 hrs). Plasma protein binding of 3K-DSG and its metabolites in clinical and experimental studies is almost complete (98%), mainly to albumin.

Metabolism: Studies in female volunteers with radioactive-labelled desogestrel show that the compound is completely metabolized. Phase I metabolism (biotransformation), which is rapid, includes hydroxylation of the C3-atom, whereby 3-alpha and 3-beta hydroxy-DSG are formed, which are subsequently dehydrogenized into 3K-DSG. There is no indication for the biotransformation of the 11-methylene-group. Hydroxylation and dehydrogenation are normal metabolic processes in the liver. The rapid biotransformation indicates that this process does not constitute a burden to the liver. The active metabolite 3K-DSG is further reduced to 3-alpha-OH-5-alpha-H-DSG via 3K-5-alpha-H-DSG. Subsequently, these degradation products are partly converted into polar metabolites by conjugation into sulphates and glucuronides. Enterohepatic circulation is not of importance for the progestagenic activity of desogestrel, since only some inactive metabolites undergo this pathway.

Elimination: 3K-DSG disappears from the plasma in an elimination phase with a half-life of 21 hrs (range 16-29 hrs). The excretion of DSG and its metabolites is via the urine and with the faeces, the ratio being 1.5:1. As a result of the pharmacokinetic properties of desogestrel, steady-state conditions (no further increase in plasma concentration) are reached within 10 days of daily administration. Based on both steady state and excretion data, it can be assumed that there is no accumulation of the drug in the body.

Indication
Oral contraception
Recommended Dose
The first tablet of the first pack is taken on the first day of menstruation. This also applied when changing over from another brand of oral contraceptive. One tablet is taken daily at the same time, without interruption for 21 days, followed by a 7-day tablet-free period. Each subsequent pack is started after the 7-day tablet-free period has elapsed. After delivery administration can be started on the first day of the first spontaneous menstruation. If it is necessary to start earlier, eg. immediately after delivery, additional contraceptive precautions are necessary for the first 14 days of tablet intake. After a miscarriage or abortion administration should start immediately. In this way no additional contraceptive precautions are required.

Mode of Administration
Route: Oral

Contraindication
Hypersensitivity to ethinyl estradiol, etonogestrel, desogestrel, or any component of the formulation; history of or current thrombophlebitis or venous thromboembolic disorders (including DVT, PE); active or recent (within 1 year) arterial thromboembolic disease (eg, stroke, MI); cerebral vascular disease, coronary artery disease, valvular heart disease with complications, severe hypertension; diabetes mellitus with vascular involvement; severe headache with focal neurological symptoms; known or suspected breast carcinoma, endometrial cancer, estrogen-dependent neoplasms, undiagnosed abnormal genital bleeding; hepatic dysfunction or tumor, cholestatic jaundice of pregnancy, jaundice with prior combination hormonal contraceptive use; major surgery with prolonged immobilization; heavy smoking (15 cigarettes/day) in patients >35 years of age; pregnancy.

Desolon is contraindicated for concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir (See Section Warnings and Precautions and Section Interactions with Other Medicaments).

Warning and Precautions
- If any signs of thromboembolic processes occur, treatment should be discontinued immediately
- Smoking increase the risk of contracting vascular diseases, a risk increasing with age. In addition, this risk is probably slightly greater in users of estrogen containing oral contraceptives than in non-users. Women over approximately 35 years of age should therefore be advised to stop smoking if they want to use this preparation.
- In patients using estrogen-containing preparations, the risk of deep-vein thrombosis may be temporarily increased when undergoing major surgery or prolonged immobilization
- In the presence of severe varicose veins, the benefits of estrogen-containing preparations must be weighed against the possible risks
- Treatment shoud be discontinued if the results of liver function tests become abnormal
- Hepatic cell adenomas have been reported very rarely in women using oral contraceptives. The adenoma may paresent itself as an abdominal mass and/or with the signs and symptoms of acute abdominal pain. A bleeding hepatic cell adenoma should be considered if the patient has abdominal pain or signs of intra-abdominal bleeding.
- Chloasma is occasionally seen during the use of estrogen and/or progestagen-containing preparations, especially in women with a history of chloasma gravidarum. Women with a tendency to chloasma should avoid exposure to the sun while taking this preparation
- During the use of estrogen-containing oral contraceptives, depression may occasionally occur. If this is accompanied by a disturbance in tryptophan metabolism, administration of vitamin B6 might be therapeutic value
- The use of steroids may influence the results of certain laboratory tests.
- During prolonged treatment with estrogen and/or progestagen-containing preparations periodic medical examination is advisable.
- Patients with any of the following conditions should be monitored:

- latent or overt cardiac failure, renal dysfunction, hypertension, epilepsy or migraine (or a history of these conditions) , since aggravation or recurrence may occasionally be induced during infections or anoxia, estrogen-containing preparations may induce thromboembolic processes in patients with this condition
- estrogen-sensitive gynaecological disorders, egL uterine fibromyomata which may increase in size, and endometriosis which may become aggravated during estrogen treatment.
- ALT elevations During clinical trials with patients treated for hepatitis C virus infections (HCV) with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir with/without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequent in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Patients who are taking ethinylestradiol-containing medicinal products must switch to an alternative method of contraception (e.g. progestin only contraception or non-hormonal methods) prior to initiating ombitasvir / paritaprevir / ritonavir and dasabuvir therapy (See Section Contraindications and Section Interactions with Other Medicaments).

Interactions With Other Medicaments

Ethinyl estradiol: Substrate of CYP2C8/9 (minor), 3A4 (major), 3A5-7 (minor); Inhibits CYP1A2 (weak), 2B6 (weak), 2C19 (weak), 3A4 (weak)

Desogestrel: Substrate of CYP2C19 (major)

Acetaminophen: May increase plasma concentration of synthetic estrogens, possibly by inhibiting conjugation. Combination hormonal contraceptives may also decrease the plasma concentration of acetaminophen.

Acitretin: Interferes with the contraceptive effect of microdosed progestin-containing 'minipill' preparations. The effect on other progestational contraceptives (eg, implants, injectables) is unknown.

Aminoglutethimide: May increase CYP metabolism of progestins leading to possible decrease in contraceptive effectiveness. Use of a nonhormonal contraceptive product is recommended.

Antibiotics (ampicillin, tetracycline): Pregnancy has been reported following concomitant use, however, pharmacokinetic studies have not shown consistent effects with these antibiotics on plasma concentrations of synthetic steroids. Use of a nonhormonal contraceptive product is recommended.

Anticoagulants: Combination hormonal contraceptives may increase or decrease the effects of coumarin derivatives. Combination hormonal contraceptives may also increase risk of thromboembolic disorders

Anticonvulsants (carbamazepine, felbamate, phenobarbital, phenytoin, topiramate): Increase the metabolism of ethinyl estradiol and/or some progestins, leading to possible decrease in contraceptive effectiveness. Use of a nonhormonal contraceptive product is recommended.

Ascorbic acid: Doses of ascorbic acid (vitamin C) 1 g/day have been reported to increase plasma concentration of synthetic estrogens by ~47%, possibly by inhibiting conjugation; clinical implications are unclear.

Atorvastatin: Atorvastatin increases the AUC for norethindrone and ethinyl estradiol.

Benzodiazepines: Combination hormonal contraceptives may decrease the clearance of some benzodiazepines (alprazolam, chlordiazepoxide, diazepam) and increase the clearance of others (lorazepam, oxazepam, temazepam)

Clofibric acid: Combination hormonal contraceptives may increase the clearance of clofibric acid.

Cyclosporine: Combination hormonal contraceptives may inhibit the metabolism of cyclosporine, leading to increased plasma concentrations; monitor cyclosporine.

CYP2C19 inducers: May decrease the levels/effects of desogestrel. Example inducers include aminoglutethimide, carbamazepine, phenytoin, and rifampin.

CYP3A4 inducers: CYP3A4 inducers may decrease the levels/effects of ethinyl estradiol. Example inducers include aminoglutethimide, carbamazepine, nafcillin, nevirapine, phenobarbital, phenytoin, and rifamycins.

Griseofulvin: Griseofulvin may induce the metabolism of combination hormonal contraceptives causing menstrual changes; pregnancies have been reported. Use of barrier form of contraception is suggested while on griseofulvin therapy.

Morphine: Combination hormonal contraceptives may increase the clearance of morphine.

Non-nucleoside reverse transcriptase inhibitors (NNRTIs): Nevirapine may decrease plasma levels of combination hormonal contraceptives; use of a nonhormonal contraceptive product is recommended. No data for delavirdine; incomplete data for efavirenz.

Prednisolone: Ethinyl estradiol may inhibit the metabolism of prednisolone, leading to increased plasma concentrations.

Protease inhibitors: Amprenavir, lopinavir, nelfinavir, and ritonavir have been shown to decrease plasma levels of combination hormonal contraceptives; use of a nonhormonal contraceptive product is recommended. Indinavir has been shown to increase plasma levels of combination hormonal contraceptives. No data for saquinavir.

Repaglinide: Increased level of ethinyl estradiol when combined with levonorgestrel.

Rifampin: Rifampin increases the metabolism of ethinyl estradiol and some progestins (norethindrone) resulting in decreased contraceptive effectiveness and increased menstrual irregularities. Use of a nonhormonal contraceptive product is recommended.

Salicylic acid: Combination hormonal contraceptives may increase the clearance of salicylic acid.

Selegiline: Combination hormonal contraceptives may increase the serum concentration of selegiline.

Theophylline: Ethinyl estradiol may inhibit the metabolism of theophylline, leading to increased plasma concentrations.

Tricyclic antidepressants (amitriptyline, imipramine, nortriptyline): Metabolism may be inhibited by combination hormonal contraceptives, increasing plasma levels of antidepressant; use caution.

Troglitazone: Troglitazone decreases the serum concentration of ethinyl estradiol and norethindrone by ~30%, leading to possible reduction in contraceptive effectiveness.

Ethanol/Nutrition/Herb Interactions

Food: CNS effects of caffeine may be enhanced if combination hormonal contraceptives are used concurrently with caffeine. Grapefruit juice increases ethinyl estradiol concentrations and would be expected to increase progesterone serum levels as well; clinical implications are unclear.

Herb/Nutraceutical: St John's wort may decrease the effectiveness of combination hormonal contraceptives by inducing hepatic enzymes. Avoid dong quai and black cohosh (have estrogen activity). Avoid saw palmetto, red clover, and ginseng.

Concomitant use with the medicinal products containing ombitasvir / paritaprevir / ritonavir and dasabuvir, with or without ribavirin may increase the risk of ALT elevations (See Section Contraindications and Section Warnings and Precautions). Therefore, users must switch to an alternative method of contraception (e.g., progestogen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. Desolon can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Pregnancy and Lactation

Use in Pregnancy

Pregnancy should be ruled out prior to treatment and discontinued if pregnancy occurs. In general, the use of combination hormonal contraceptives when inadvertently taken early in pregnancy have not been associated with teratogenic effects. Due to increased risk of thromboembolism postpartum, combination hormonal contraceptives should not be started earlier than 4-6 weeks following delivery. Hormonal contraceptives may be less effective in obese patients. An increase in oral contraceptive failure was noted in women with a BMI >27.3. Similar findings were noted in patients weighing 90 kg (198 lb) using the contraceptive patch.

Use in Lactation

Estrogen/progestagen-containing oral contraceptives may affect the quality and reduce the quality of milk produced. A small proportion of the active substances may be excreted in the milk.

Side Effects

Frequency not defined.

Cardiovascular: Arterial thromboembolism, cerebral hemorrhage, cerebral thrombosis, edema, hypertension, mesenteric thrombosis, MI

Central nervous system: Depression, dizziness, headache, migraine, nervousness, premenstrual syndrome, stroke

Dermatologic: Acne, erythema multiforme, erythema nodosum, hirsutism, loss of scalp hair, melasma (may persist), rash (allergic)

Endocrine & metabolic: Amenorrhea, breakthrough bleeding, breast enlargement, breast secretion, breast tenderness, carbohydrate intolerance, lactation decreased (postpartum), glucose tolerance decreased, libido changes, menstrual flow changes, sex hormone-binding globulins (SHBG) increased, spotting, temporary infertility (following discontinuation), thyroid-binding globulin increased, triglycerides increased

Gastrointestinal: Abdominal cramps, appetite changes, bloating, cholestasis, colitis, gallbladder disease, jaundice, nausea, vomiting, weight gain/loss

Genitourinary: Cervical erosion changes, cervical secretion changes, cystitis-like syndrome, vaginal candidiasis, vaginitis

Hematologic: Antithrombin III decreased, folate levels decreased, hemolytic uremic syndrome, norepinephrine induced platelet aggregability increased, porphyria, prothrombin increased; factors VII, VIII, IX, and X increased.

Hepatic: Benign liver tumors, Budd-Chiari syndrome, cholestatic jaundice, hepatic adenomas

Local: Thrombophlebitis

Ocular: Cataracts, change in corneal curvature (steepening), contact lens intolerance, optic neuritis, retinal thrombosis

Renal: Impaired renal function

Respiratory: Pulmonary thromboembolism

Miscellaneous: Hemorrhagic eruption

Symptoms and Treatment of Overdose

Symptoms that may occur in this case are nausea, vomiting and, in young girls, slight vaginal bleeding. There have been no reports of serious deleterious effects from overdose. There are no antidotes and further treatment should be symptomatic.

Storage Condition

Store in a cool place (below 30°C), protected from light and children.

Packs and Tablets

Desolon is presented in strips of 21 tablets packed in a ply carton.

Manufactured by :
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