Desogestrel

Core Safety Profile

4.3 CONTRAINDICATIONS

- Active venous thromboembolic disorder.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Known or suspected sex-steroid sensitive malignancies.
- Undiagnosed vaginal bleeding.
- Hypersensitivity to the active substance or to any of the excipients.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

If any of the conditions/risk factors mentioned below is present, the benefits of progestogen use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start with <Product name>. In the event of aggravation, exacerbation, or first appearance of any of these conditions, the woman should contact her physician. The physician should then decide on whether the use of <Product name> should be discontinued.
The risk for breast cancer increases in general with increasing age. During use of combined oral contraceptives (COCs) the risk of having breast cancer diagnosed is slightly increased. This increased risk disappears gradually within 10 years after discontinuation of COC use and is not related to the duration of use, but to the age of the woman when using the COC. The expected number of cases diagnosed per 10 000 women who use COCs (up to 10 years after stopping) relative to never users over the same period has been calculated for the respective age groups and is presented in the table below.

age group	*expected cases COC-users*	*expected cases non-users*
16-19years	4.5	4
20-24years	17.5	16
25-29years	48.7	44
30-34years	110	100
35-39years	180	160
40-44years	260	230

The risk in users of progestogen-only contraceptives (POCs), such as <Product name>, is possibly of similar magnitude as that associated with COCs. However, for POCs the evidence is less conclusive. Compared to the risk of getting breast cancer ever in life, the increased risk associated with COCs is low. The cases of breast cancer diagnosed in COC users tend to be less advanced than in those who have not used COCs. The increased risk in COC users may be due to an earlier diagnosis, biological effects of the pill or a combination of both.

Since a biological effect of progestogens on liver cancer cannot be excluded an individual benefit/risk assessment should be made in women with liver cancer.

When acute or chronic disturbances of liver function occur the woman should be referred to a specialist for examination and advice.

Epidemiological investigations have associated the use of COCs with an increased incidence of venous thromboembolism (VTE, deep venous thrombosis and pulmonary embolism). Although the clinical relevance of this finding for desogestrel used as a contraceptive in the absence of an oestrogenic component is unknown, <Product name> should be discontinued in the event of a thrombosis. Discontinuation of <Product name> should also be considered in case of long-term immobilisation due to surgery or illness. Women with a history of thrombo-embolic disorders should be made aware of the possibility of a recurrence.

Although progestogens 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 progestogen-only pills. However, diabetic patients should be carefully observed during the first months of use.

If a sustained hypertension develops during the use of <Product name>, or if a significant increase in blood pressure does not adequately respond to antihypertensive therapy, the discontinuation of <Product name> should be considered.

Treatment with <Product name> leads to decreased estradiol serum levels, to a level corresponding with the early follicular phase. It is as yet unknown whether the decrease has any clinically relevant effect on bone mineral density.

The protection with traditional progestogen-only pills against ectopic pregnancies is not as good as with combined oral contraceptives, which has been associated with the frequent occurrence of ovulations during the use of progestogen-only pills. Despite the fact that <Product name> consistently inhibits ovulation, ectopic pregnancy should be taken into account in the differential diagnosis if the woman gets amenorrhoea or abdominal pain.

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 <Product name>.

The following conditions have been reported both during pregnancy and during sex steroid use, but an association with the use of progestogens has not been established: 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; (hereditary) angioedema.
<Product name> contains less than 65 mg lactose and therefore should not be administered to patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency, or glucose-galactose malabsorption.

4.5 INTERACTION WITH OTHER MEDICINAL PRODUCTS AND OTHER FORMS OF INTERACTION

INTERACTIONS
Interactions between hormonal contraceptives and other medicinal products may lead to breakthrough bleeding and/or contraceptive failure. The following interactions have been reported in the literature (mainly with combined contraceptives but occasionally also with progestogen-only contraceptives).
Hepatic metabolism: Interactions can occur with medicinal products that induce microsomal enzymes, which can result in increased clearance of sex hormones (such as, hydantoins (e.g. phenytoin), barbiturates (e.g. phenobarbital), primidone, carbamazepine, rifampicin, and possibly also for oxcarbazepine, topiramate, rifabutin, felbamate, ritonavir, nelfinavir, griseofulvin and products containing St. John's wort *(Hypericum perforatum)*).
Maximal enzyme induction is not seen for 2-3 weeks, but may then be sustained for at least 4 weeks after the cessation of drug therapy. Women on treatment with any of these medicinal products should temporarily use a barrier method in addition to <Product name>. With microsomal enzyme-inducing drugs, the barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation. For women on long-term therapy with hepatic enzyme inducers a non-hormonal method of contraception should be considered.
During treatment with medical charcoal, the absorption of the steroid in the tablet may be reduced and thereby the contraceptive efficacy. Under these circumstances, the advice as given for missed tablets in Section 4.2 is applicable.
Hormonal contraceptives may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. cyclosporine) or decrease.
Note: The prescribing information of concomitant medications should be consulted to identify potential interactions.

LABORATORY TESTS
Data obtained with COCs have shown that contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, serum 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 range. To what extent this also applies to progestogen-only contraceptives is not known.

4.6 PREGNANCY AND LACTATION

<Product name> is not indicated during pregnancy. If pregnancy occurs during treatment with < Product name>, further intake should be stopped.
Animal studies have shown that very high doses of progestogenic substances may cause masculinisation of female foetuses.
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 early pregnancy. Pharmacovigilance data collected with various desogestrel-containing COCs also do not indicate an increased risk.
<Product name> does not influence the production or the quality (protein, lactose, or fat concentrations) of breast milk. However, small amounts of etonogestrel are excreted in the breast milk. As a result, 0.01 - 0.05 microgram etonogestrel per kg body weight per day may be ingested by the child (based on an estimated milk ingestion of 150 ml/kg/day).
Limited long-term follow-up data are available on children, whose mothers started using <Product name> during the 4^{th} to 8^{th} week post-partum. They were breast-fed for 7 months and followed up to 1.5 years (n=32) or to 2.5 years (n= 14) of age. Evaluation of growth and physical and psychomotor development did not indicate any differences in comparison to nursing infants, whose mother used a copper-IUD. Based on the available data <Product name> may be used during lactation. The development and growth of a nursing infant, whose mother uses <Product name>, should, however, be carefully observed.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

<Product name> has no or negligible influence on the ability to drive and use machines.

4.8 UNDESIRABLE EFFECTS

The most commonly reported undesirable effect in the clinical trials is bleeding irregularity. Some kind of bleeding irregularity has been reported in up to 50% of women using <Product name>. Since <Product name> causes ovulation inhibition close to 100%, in contrast to other progestogen-only pills, irregular bleeding is more common than with other progestogen-only pills. In 20 - 30% of the women, bleeding may become more frequent, whereas in another 20% bleeding may become less frequent or totally absent. Vaginal bleeding may also be of longer duration. After a couple of months of treatment, bleedings tend to become less frequent. Information, counselling, and a bleeding diary can improve the woman's acceptance of the bleeding pattern.

The most commonly reported other undesirable effects in the clinical trials with <Product name> (> 2.5%) were acne, mood changes, breast pain, nausea and weight increase. The undesirable effects are mentioned in the table below

All ADRs are listed by system organ class and frequency; common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100) and rare (≥1/10,000 to <1/1,000).

System Organ Class (MedDRA)*	**Frequency of adverse reactions**		
	Common ≥ 1/100	**Uncommon < 1/100, ≥ 1/1000**	**Rare (<1/1000)**
Infections and infestations		Vaginal infection	
Psychiatric disorders	Mood altered, Libido decreased Depressed mood		
Nervous system disorders	Headache		
Eye disorders		Contact lens intolerance	
Gastrointestinal disorders	Nausea	Vomiting	
Skin and subcutaneous tissue disorders	Acne	Alopecia	Rash, Urticaria, Erythema nodosum
Reproductive	Breast pain,	Dysmenorrhoe	

system and breast disorders	Menstruation irregular, Amenorrhoea	a, Ovarian cyst	
General disorders and administration site condition		Fatigue	
Investigations	Weight increased		

* MedDRA version 9.0

Breast discharge may occur during use of <Product name>. On rare occasions, ectopic pregnancies have been reported (see Section 4.4). **In addition, (aggravation of) angioedema and/or aggravation of hereditary angioedema may occur (see Section 4.4).**"

In women using (combined) oral contraceptives a number of (serious) undesirable effects have been reported. These include venous thromboembolic disorders, arterial thromboembolic disorders, hormone-dependent tumours (e.g. liver tumours, breast cancer) and chloasma, some of which are discussed in more detail in Section 4.4.

4.9 OVERDOSE

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