

**1. NAME OF THE MEDICINAL PRODUCT**

Cerazette®

**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**

Each tablet contains 75 microgram desogestrel.  
For a full list of excipients, see section 6.1.

**3. PHARMACEUTICAL FORM**

Film-coated tablet.

The tablet is white, round, biconvex and 5 mm in diameter. On one side it is coded KV above 2 and on the reverse side Organon \*.

**4. CLINICAL PARTICULARS**

**4.1 Therapeutic indications**

Contraception.

**4.2 Posology and method of administration**

**4.2.1 How to take Cerazette**

Tablets must be taken in the order directed on the package every day at about the same time with some liquid as needed. One tablet is to be taken daily for 28 consecutive days. Each subsequent pack is started immediately after finishing the previous pack.

**4.2.2 How to start Cerazette**

- *No preceding hormonal contraceptive use [in the past month].*  
Tablet-taking has to start on day 1 of the woman's natural cycle (day 1 is the first day of her menstrual bleeding). Starting on days 2-5 is allowed, but during the first cycle a barrier method is recommended 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 Cerazette preferably on the day after the last active tablet (the last tablet containing the active substances), or on the day of

INT00008128

removal of her vaginal ring or patch. In these cases, the use of an additional contraceptive is not necessary.

The women may also start at the latest on the day following the usual tablet-free, patch-free, ring-free, or placebo tablet interval of her previous combined hormonal contraceptive, but during the first 7 days of tablet-taking an additional barrier method is recommended.

- *Changing from a progestogen-only-method (minipill, injection, implant or from a progestogen-releasing intrauterine system [IUS]).*  
The woman may switch any day from the minipill (from an implant or the IUS on the day of its removal, from an injectable when the next injection would be due); an additional contraceptive method is not necessary.
- *Following first-trimester abortion.*  
The woman may start immediately; an additional contraceptive method is not necessary.
- *Following delivery or second-trimester abortion.*  
For breastfeeding women see Section 4.6.

The woman should be advised to start at day 21 to 28 after delivery or second-trimester abortion. When starting later, she 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 Cerazette use or the woman has to wait for her first menstrual period.

#### **4.2.3 Management of missed tablets**

Contraceptive protection may be reduced if more than 36 hours have elapsed between two tablets. If the user is less than 12 hours late in taking any tablet, the missed tablet should be taken as soon as it is remembered and the next tablet should be taken at the usual time. If she is more than 12 hours late, she should follow the same advice but also use an additional method of contraception for the next 7 days. If tablets were missed in the very first week of use and intercourse took place in the week before the tablets were missed, the possibility of a pregnancy should be considered.

#### **4.2.4 Advice in case of gastrointestinal disturbances**

In case of severe gastro-intestinal disturbance, absorption may not be complete and additional contraceptive measures should be taken.

INT00008128

If vomiting occurs within 3-4 hours after tablet-taking, absorption may not be complete. In such an event, the advice concerning missed tablets, as given in Section 4.2.3 is applicable.

### 4.3 Contraindications

Progestogen-only contraceptives 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 the use of Cerazette, the product should be stopped immediately.

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

### 4.4 Special warnings and precautions for use

#### 4.4.1 Warnings

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 Cerazette. 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 Cerazette should be discontinued.

- The risk for breast cancer increases in general with increasing age. During the use of oral contraceptives (OCs) the risk of having breast cancer diagnosed is slightly increased. This increased risk disappears gradually within 10 years after discontinuation of OC use and is not related to the duration of use, but to the age of the woman when using the OC. The expected number of cases diagnosed per 10 000 women who use combined OCs (up to 10 years after stopping) relative to never users over the same period have been calculated for the respective age groups and are presented in the table below

INT00008128

<i>age group</i>	<i>expected cases combined OC-users</i>	<i>expected cases non-users</i>
16-19 years	4.5	4
20-24 years	17.5	16
25-29 years	48.7	44
30-34 years	110	100
35-39 years	180	160
40-44 years	260	230

The risk in POP users is possibly of similar magnitude as that associated with combined OCs. However, for POPs the evidence is less conclusive.

Compared to the risk of getting breast cancer ever in life, the increased risk associated with OCs is low. The cases of breast cancer diagnosed in OC users tend to be less advanced than in those who have not used OCs. The increased risk in OC users may be due to an earlier diagnosis, biological effects of the pill or a combination of both. Since a biological effect cannot be excluded, an individual benefit/risk assessment should be made in women with pre-existing breast cancer and in women in whom breast cancer is diagnosed while using Cerazette.

- 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.
- If a sustained hypertension develops during the use of Cerazette, or if a significant increase in blood pressure does not adequately respond to antihypertensive therapy, discontinuation with the use of Cerazette should be considered.
- Epidemiological investigations have associated the use of combined OCs with an increased incidence of venous thromboembolism (VTE, deep venous thrombosis and pulmonary embolism). Although the clinical relevance of this

INT00008128

finding for desogestrel used as a contraceptive in the absence of an estrogenic component is unknown, Cerazette should be discontinued in the event of a thrombosis. Discontinuation of Cerazette 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 while taking progestogen-only pills.
- Treatment with Cerazette 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 Cerazette 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 Cerazette.
- 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.
- Cerazette 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.

#### 4.4.2 Medical examination/consultation

Before prescription, a thorough case history should be taken and a thorough gynaecological examination is recommended to exclude pregnancy. Bleeding

INT00008128

disturbances, such as oligomenorrhoea and amenorrhoea should be investigated before prescription. The interval between check-ups depends on the circumstances in each individual case. If the prescribed product may conceivably influence latent or manifest disease (see Section 4.4), the control examinations should be timed accordingly. Despite the fact that Cerazette is taken regularly, bleeding disturbances may occur. If bleeding is very frequent and irregular, another contraceptive method should be considered. If the symptoms persist, an organic cause should be ruled out. Management of amenorrhoea during treatment depends on whether or not the tablets have been taken in accordance with the instructions and may include a pregnancy test. The treatment should be stopped if a pregnancy occurs.

Women should be advised that Cerazette® does not protect against HIV (AIDS) and other sexually transmitted diseases.

#### **4.4.3 Reduced efficacy**

The efficacy of progestogen-only pills may be reduced in the event of missed tablets (Section 4.2.3), gastro-intestinal disturbances (Section 4.2.4), or concomitant medication (Section 4.5).

#### **4.4.4 Changes in vaginal bleeding pattern**

During the use of a progestogen-only contraceptive, vaginal bleeding may become more frequent or of longer duration in some women, whereas in others bleeding may become incidental or be totally absent. These changes are often a reason for the woman to reject the method or to be non-compliant. Acceptance of bleeding pattern can be improved by offering women who have chosen to use Cerazette careful counselling on this point. Evaluation of vaginal bleeding should be done on an ad hoc basis and may include examination to exclude malignancy or pregnancy.

#### **4.4.5 Follicular development**

With all low-dose hormonal contraceptives, follicular development occurs and occasionally the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally, these enlarged follicles disappear spontaneously. Often, they are asymptomatic; in some cases they are associated with mild abdominal pain. They rarely require surgical intervention.

INT00008128

## 4.5 Interaction with other medicinal products and other forms of interaction

### 4.5.1 Interactions

Interactions between oral contraceptives and other drugs may lead to breakthrough bleeding and/or contraceptive failure. No specific interaction studies have been performed with Cerazette. 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 oxcarbazepine, rifabutin, topiramate, felbamate, ritonavir, nelfinavir, griseofulvin and products containing St. John's wort (*Hypericum perforatum*)). Women on treatment with any of these drugs should temporarily use a barrier method in addition to Cerazette or choose another method of contraception. The barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

During treatment with medical charcoal, the absorption of the steroid in the tablet may be reduced and thereby the contraceptive efficacy. In such an event, the advice concerning missed tablets, as given in Section 4.2.3 is applicable.

Hormonal contraceptives may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may be affected (e.g., cyclosporine).

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

### 4.5.2 Laboratory tests

Data obtained with combined OCs 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

INT00008128

range. To what extent this also applies to progestogen-only contraceptives is not known.

#### **4.6 Pregnancy and lactation**

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 OCs prior to pregnancy, nor a teratogenic effect when OCs were taken inadvertently during early pregnancy. Pharmacovigilance data collected with various desogestrel-containing combined OCs also do not indicate an increased risk.

Similar to other progestogen-only contraceptives, Cerazette does not influence the production or the quality (protein, lactose, or fat concentrations) of breast milk, but a small amount of etonogestrel is 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 Cerazette during the 4<sup>th</sup> to 8<sup>th</sup> week post-partum. They were breast-fed for 7 months and followed up to 2.5 years of age. Evaluation of growth and physical and psychomotor development did not indicate any differences in comparison to nursing infants, whose mother used an IUD. Nevertheless, development and growth of the child should be carefully observed. Based on the available data Cerazette may be used during lactation.

#### **4.7 Effects on ability to drive and use machines**

On the basis of the pharmacodynamic profile, Cerazette is expected to have no or negligible influence on the ability to drive and use machines.

#### **4.8 Undesirable effects**

The most commonly reported undesirable effects in the clinical trials with Cerazette (> 2.5%) were Menstruation irregular, acne, mood alterations, breast pain, nausea and weight increase. The undesirable effects mentioned in the table below have been judged, by the investigators, as having an established, probable, or possible link to the treatment.

INT00008128

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

\* MedDRA version 9.0;

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., breast cancer), and chloasma, some of which are discussed in more detail in Section 4.4 Special warnings and precautions for use.

#### 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.

INT00008128

## 5. PHARMACOLOGICAL PROPERTIES

### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: hormonal contraceptives for systemic use, ATC code: G03A C09.

Cerazette is a progestogen-only pill, which contains the progestogen desogestrel. Like other progestogen-only pills, Cerazette is best suited for use during breast-feeding and for women who may not or do not want to use estrogens. In contrast to traditional progestogen-only pills, the contraceptive effect of Cerazette is achieved primarily by inhibition of ovulation. Other effects include increased viscosity of the cervical mucus.

When studied for 2 cycles, using a definition of ovulation as a progesterone level greater than 16 nmol/L for 5 consecutive days, the ovulation incidence was found to be 1% (1/103) with a 95% confidence interval of 0.02% - 5.29% in the ITT group (user and method failures). Ovulation inhibition was achieved from the first cycle of use. In this study, when Cerazette was discontinued after 2 cycles (56 continuous days), ovulation occurred on average after 17 days (range 7-30 days).

In a comparative efficacy trial (which allowed a maximum time of 3 hours for missed pills) the overall ITT Pearl-Index found for Cerazette was 0.4 (95% confidence interval 0.09 - 1.20), compared to 1.6 (95% confidence interval 0.42 - 3.96) for 30 µg levonorgestrel.

The Pearl-Index for Cerazette is comparable to the one historically found for combined OCs in the general OC-using population. Treatment with Cerazette leads to decreased estradiol levels, to a level corresponding to the early follicular phase. No clinically relevant effects on carbohydrate metabolism, lipid metabolism, and haemostasis have been observed.

### 5.2 Pharmacokinetic properties

#### ABSORPTION

After oral dosing of Cerazette desogestrel (DSG) is rapidly absorbed and converted into its biologically active metabolite etonogestrel (ENG). Under steady-state conditions, peak serum levels are reached 1.8 hours after tablet-intake and the absolute bioavailability of ENG is approximately 70%.

INT00008128

#### DISTRIBUTION

ENG is 95.5-99% bound to serum proteins, predominantly to albumin and to a lesser extent to SHBG.

#### METABOLISM

DSG is metabolised via hydroxylation and dehydrogenation to the active metabolite ENG. ENG is metabolised via sulphate and glucuronide conjugation.

#### ELIMINATION

ENG is eliminated with a mean half-life of approximately 30 hours, with no difference between single and multiple dosing. Steady-state levels in plasma are reached after 4-5 days. The serum clearance after i.v. administration of ENG is approximately 10 l per hour. Excretion of ENG and its metabolites either as free steroid or as conjugates is with urine and faeces (ratio 1.5:1). In lactating women, ENG is excreted in breast milk with a milk/serum ratio of 0.37-0.55. Based on these data and an estimated milk intake of 150 ml/kg/day, 0.01 - 0.05 microgram etonogestrel per kg body weight per day may be ingested by the infant.

### 5.3 Preclinical safety data

Toxicological studies did not reveal any effects other than those, which can be explained from the hormonal properties of desogestrel.

## 6. PHARMACEUTICAL PARTICULARS

### 6.1 List of excipients

#### TABLET CORE

Silica, colloidal anhydrous; all-*rac*- $\alpha$ -tocopherol; lactose monohydrate; maize starch; povidone; stearic acid.

#### FILM COATING

Hypromellose; macrogol 400; talc; titanium dioxide (E 171).

### 6.2 Incompatibilities

Not applicable

INT00008128

**6.3 Shelf life**

3 years.

**6.4 Special precautions for storage**

2 °C to 30 °C, protected from light and moisture.

**6.5 Nature and contents of container**

Blister of 28 tablets each. PVC/Aluminium foil push-through blister (1, 3 or 6 strips per box). Each blister is enveloped in aluminium laminate sachet, packed in a printed cardboard box. Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

No special requirements.

**7. MARKETING AUTHORISATION HOLDER**

*[Market specific information must be included in this section where applicable]*

**8. MARKETING AUTHORISATION NUMBER(S)**

*[Market specific information must be included in this section where applicable]*

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

*[Market specific information must be included in this section where applicable]*

**10. DATE OF REVISION OF THE TEXT**

July 2006

INT00008128