SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Desolett 28 tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each large active tablet contains:
Desogestrel 150 µg
Ethinylestradiol 30 µg.
The small tablets do not contain active substances (placebo tablets).

Excipient with known effect: lactose monohydrate 67 mg (active tablets) and 40 mg (placebo tablets)
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablet

The active tablets are round, biconvex and 6 mm in diameter. The tablets are coded TR5 on one side and ORGANON and a five pointed star on the other side.
The placebo tablets are smaller (4.5 mm), white and are coded with KH2 on one side and a small square on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception.

The decision to prescribe Desolett 28 should take into consideration the individual woman's current risk factors, particularly those for venous thromboembolism (VTE), and how the risk of VTE with Desolett 28 compares with other CHCs (see sections 4.3 and 4.4).

4.2 Posology and method of administration

Posology

How to take Desolett 28

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 during 28 days, starting with the large, white, active tablets followed by the 7 small placebo tablets.
Each subsequent pack is started immediately following the last placebo tablet with no tablet-free interval. During the placebo days a withdrawal bleed usually occurs. This usually starts on day 2-3 after the last active tablet and may not have finished before the next pack is started.

How to start taking Desolett 28

No hormonal method has been used in the previous cycle

Desolett 28 should be started on the first day of the woman's menstruation (i.e. the first bleeding day). Desolett 28 will then give full contraceptive efficacy from the first treatment day. It is also possible to start on day 2-5, but then it is recommended to use a barrier method as extra precaution during the first 7 days of the first treatment cycle.

Changing from another combined hormonal contraceptive method (combined oral contraceptive, vaginal ring, or transdermal patch)

The woman should start with Desolett 28 preferably on the day after the last active tablet of her previous combined oral contraceptive, but at the latest on the day following the usual tablet free interval or the day following the last placebo tablet. In case a vaginal ring or transdermal patch has been used, the woman should start taking Desolett 28 preferably on the day of removal, but at the latest when the next ring or a new patch would have been due.

If the woman has been using her previous method consistently and correctly and if it is reasonably certain that she is not pregnant she may also switch from her previous combined hormonal contraceptive on any day of the cycle.
The hormone-free interval of the previous method should never be extended beyond its recommended length.

Changing from a progestogen-only-method (minipill, injection, implant or from a progestogen-releasing intrauterine system (IUS))
The woman may switch from progestogen tablets to Desolett 28 on any day without any tablet free interval. When switching from an implant or hormone releasing IUS, Desolett 28 should be started the same day as the implant/IUS is removed. When switching from injections Desolett 28 should be started on the same day as next injection should have been given. In all these cases the woman should be advised to additionally use a barrier method, for example condom, for the following 7 days.

Following first-trimester abortion
The woman may start with Desolett 28 immediately, i.e. the same day as the abortion. When doing so there is no need to take additional contraceptive measures.

Following delivery or second-trimester abortion
For breastfeeding women see Section 4.6.
The woman should be advised to start with Desolett 28 at day 21 to 28 after delivery or second-trimester abortion. When starting later, the woman should be advised to additionally use a barrier method for the first 7 days of tablet-taking. However, if intercourse has already occurred after delivery/abortion, pregnancy should be excluded before she starts with Desolett 28 or she has to wait for her first menstrual period.

Management of missed tablets

If *less than 12 hours* has passed since the tablet should have been taken the contraceptive protection is not reduced. The tablet should be taken as soon as possible and the next tablet at the usual time.

If *more than 12 hours* has passed since the tablet should have been taken, the contraceptive protection may be reduced. The management of missed tablets can be guided by the following two basic rules:
1. No tablet free interval may ever exceed 7 days.
2. 7 days of uninterrupted tablet intake are required to attain adequate suppression of the ovulation.

Accordingly the following advice can be given in daily practice:

- Week 1
The last missed tablet should be taken as soon as she remembers, even if this means taking two tablets at the same time. She then continues to take tablets at her usual time. In addition, a barrier method such as a

condom should be used for the next 7 days. If intercourse took place in the preceding 7 days, the possibility of a pregnancy should be considered. The more tablets that are missed and the closer they are to the tablet free interval, the higher the risk is of a pregnancy.

- Week 2
The last missed tablet should be taken as soon as possible, even if this means taking two tablets at the same time. Thereafter the tablets are taken at the usual time. Provided that the tablets have been taken correctly in the preceding 7 days, there is no need to use extra contraceptive precautions. However, if this is not the case, or if she missed more than 1 tablet, the woman should be advised to use extra precautions for 7 days.

- Week 3
The risk of reduced reliability is imminent because of the forthcoming tablet free interval. However, by adjusting the tablet-intake schedule, reduced contraceptive protection can still be prevented. By adhering to either of the following two options, there is therefore no need to use extra contraceptive precautions, provided that in the 7 days preceding the first missed tablet the woman has taken all tablets correctly. If this is not the case, the first of these two options should be followed and the use of extra precautions for the next 7 days as well.

1. The last missed tablet should be taken as soon as possible, even if this means taking two tablets at the same time. Thereafter the tablets should be taken at the usual time until the active tablets in the current pack are finished. The 7 tablets from the last row (placebo tablets) should be discarded. The next pack must be started immediately. The woman is unlikely to have a withdrawal bleeding until the second pack is finished, but irregular bleedings such as spotting or breakthrough bleeding may occur on active tablet-taking days.
2. The woman may also be advised to discontinue tablet-taking from the current pack. She should then immediately continue with the placebo tablets. The total number of missed tablets and placebo tablets must never exceed seven. Subsequently she should continue with the next pack.

- Week 4
Contraceptive protection is not reduced; the woman should take further tablets at the usual time.

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

Advice in case of gastro-intestinal disturbances
In case of vomiting and gastro-intestinal disturbance with diarrhea, the absorption of the steroids may decrease and thereby also the contraceptive protection. If vomiting occurs within 3-4 hours after tablet taking, the advice concerning missed tablets, as given in *Management of missed tablets*, is applicable. If the woman does not want to change her normal tablet-taking schedule, she has to take extra tablet(s) needed from another pack.

How to change or postpone withdrawal bleeding (menstruation)
Delaying a period is not an indication for the product. However, if in exceptional cases a period needs to be delayed, the woman should continue with another pack of Desolett 28 without having a placebo tablet interval. The extension can be carried on for as long as wished until the end of the second pack. During the extension the woman may experience breakthrough bleeding or spotting. Regular intake of Desolett 28 is then resumed after the usual 7-day placebo tablet interval.

To shift her period to another day of the week than the woman is used to with her current scheme, she can be advised to shorten her forthcoming placebo tablet interval by as many days as she likes. The shorter the interval, the higher the risk that she does not have a withdrawal bleed and will experience breakthrough bleeding and spotting during the second pack (just as when delaying a period).

Paediatric population
The safety and efficacy of Desolett 28 in adolescents under the age of 18 years have not been studied.

Method of administration
Oral use.

4.3 Contraindications

Combined hormonal contraceptives (CHCs) should not be used in the following conditions. Should any of these conditions appear for the first time during use of Desolett 28, the treatment should be stopped immediately.

- Presence or risk of venous thromboembolism (VTE)
  - Venous thromboembolism – current VTE (on anticoagulants) or history of (e.g. 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 (see section 4.4)
  - A high risk of venous thromboembolism due to the presence of multiple risk factors (see section 4.4)
- Presence or risk of arterial thromboembolism (ATE)
  - Arterial thromboembolism – current arterial thromboembolism, history of arterial thromboembolism (e.g. myocardial infarction) or prodromal condition (e.g. angina pectoris)
  - Cerebrovascular disease – current stroke, history of stroke or prodromal condition (e.g. transient ischaemic attack, TIA)
  - Known hereditary or acquired predisposition for arterial thromboembolism, such as hyperhomocysteinaemia and antiphospholipid-antibodies (anticardiolipin-antibodies, lupus anticoagulant).
  - History of migraine with focal neurological symptoms.
  - A high risk of arterial thromboembolism due to multiple risk factors (see section 4.4) or to the presence of one serious risk factor such as:
    - diabetes mellitus with vascular symptoms
    - severe hypertension
    - severe dyslipoproteinaemia
- Presence of pancreatitis or history of pancreatitis associated with severe hypertriglyceridaemia.
- 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 or pre-malignant disease (e.g. of the genital organs or the breasts).
- Endometrial hyperplasia.
- Undiagnosed vaginal bleeding.
- Hypersensitivity to the active substances or to any of the excipients, listed in section 6.1.
- Desolett 28 is contraindicated for concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir or medicinal products containing glecaprevir / pibrentasvir (see sections 4.4 and section 4.5).

4.4 Special warnings and precautions

Warnings
If any of the conditions or risk factors mentioned below are present, the suitability of Desolett 28 should be discussed with the woman. In the event of aggravation, or first appearance of any of these

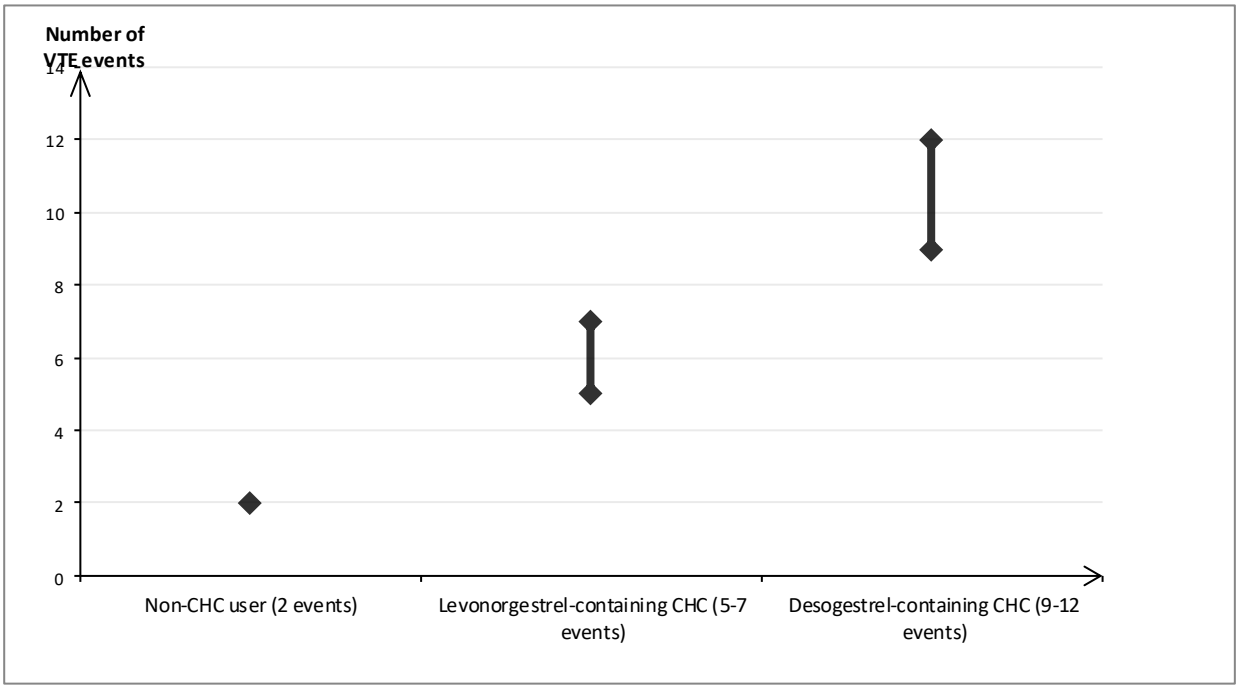
conditions or risk factors, the woman should be advised to contact her physician/midwife. The physician/midwife should then decide on whether the treatment should be discontinued.

1. Circulatory disease

Risk of venous thromboembolism (VTE)

- The use of any combined hormonal contraceptive (CHC) increases risk of venous thromboembolism (VTE) compared with no use. **Products that contain levonorgestrel, norgestimate or norethisterone are associated with the lowest risk of VTE. Other products such as Desolett 28 may have up to twice this level of risk. 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 Desolett 28, how her current risk factors influence this risk, and that her VTE risk is highest in the first ever year of use. There is also some evidence that the risk is increased when a CHC is re-started after a break in use of 4 weeks or more.**
- In women who do not use CHC and are not pregnant about 2 out of 10,000 will develop a VTE over the period of one year. However, in any individual woman the risk may be far higher, depending on her underlying risk factors (see below).
- It is estimated[1] that out of 10,000 women who use a CHC containing desogestrel between 9 and 12 women will develop a VTE in one year; this compares with about 6[2] in women who use a levonorgestrel-containing CHC.
- In both cases, the number of VTEs per year is fewer than the number expected during pregnancy or in the postpartum period.
- VTE may be fatal in 1-2 % of cases.

Number of VTE events per 10,000 women in one year



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

[1] These incidences were estimated from the totality of the epidemiological study data, using relative risks for the different products compared with levonorgestrel-containing CHCs.
[2] Mid-point of range of 5-7 per 10,000 WY, based on a relative risk for CHCs containing levonorgestrel versus non-use of approximately 2.3 to 3.6

Risk factors for VTE

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

Desolett 28 is contraindicated if a woman has multiple risk factors that put her at high risk of venous thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors – in this case her total risk of VTE should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for VTE

Risk factor	Comment
Obesity (body mass index over 30 kg/m²)	Risk increases substantially as BMI rises. Particularly important to consider if other risk factors also present.
Prolonged immobilisation, major surgery, any surgery to the legs or pelvis, neurosurgery, or major trauma Note: temporary immobilisation including air travel >4 hours can also be a risk factor for VTE, particularly in women with other risk factors	In these situations it is advisable to discontinue use of the patch/pill/ring (in the case of elective surgery at least four weeks in advance) and not resume until two weeks after complete remobilisation. Another method of contraception should be used to avoid unintentional pregnancy. Antithrombotic treatment should be considered if Desolett 28 has not been discontinued in advance.
Positive family history (venous thromboembolism ever in a sibling or parent especially at a relatively early age e.g. before 50).	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use
Other medical conditions associated with VTE	Cancer, systemic lupus erythematosus, haemolytic uraemic syndrome, chronic inflammatory bowel disease (Crohn's disease or ulcerative colitis) and sickle cell disease
Increasing age	Particularly above 35 years

There is no consensus about the possible role of varicose veins and superficial thrombophlebitis in the onset or progression of venous thrombosis.
The increased risk of thromboembolism in pregnancy, and particularly the 6 week period of the puerperium, must be considered (for information on "Pregnancy and lactation" see section 4.6).

Symptoms of VTE (deep vein thrombosis and pulmonary embolism)
In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of deep vein thrombosis (DVT) can include:
- unilateral swelling of the leg and/or foot or along a vein in the leg;
- pain or tenderness in the leg which may be felt only when standing or walking,
- increased warmth in the affected leg; red or discoloured skin on the leg.

Symptoms of pulmonary embolism (PE) can include:
- sudden onset of unexplained shortness of breath or rapid breathing;
- sudden coughing which may be associated with haemoptysis;
- sharp chest pain;
- severe light headedness or dizziness;
- rapid or irregular heartbeat.

Some of these symptoms (e.g. "shortness of breath", "coughing") are non-specific and might be misinterpreted as more common or less severe events (e.g. respiratory tract infections).

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

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

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

Risk factors for ATE
The risk of arterial thromboembolic complications or of a cerebrovascular accident in CHC users increases in women with risk factors (see table). Desolett 28 is contraindicated if a woman has one serious or multiple risk factors for ATE that puts her at high risk of arterial thrombosis (see section 4.3). If a woman has more than one risk factor, it is possible that the increase in risk is greater than the sum of the individual factors - in this case her total risk should be considered. If the balance of benefits and risks is considered to be negative a CHC should not be prescribed (see section 4.3).

Table: Risk factors for ATE

Risk factor	**Comment**
Increasing age	Particularly above 35 years
Smoking	Women over 35 years should be advised not to smoke if they wish to use a CHC. Women over 35 who continue to smoke should be strongly advised to use a different method of contraception.
Hypertension	
Obesity (body mass index over 30 kg/m^2)	Risk increases substantially as BMI increases. Particularly important in women with additional risk factors
Positive family history (arterial thromboembolism ever in a sibling or parent	If a hereditary predisposition is suspected, the woman should be referred to a specialist for advice before deciding about any CHC use

especially at relatively early age e.g. below 50).	
Migraine	An increase in frequency or severity of migraine during CHC use (which may be prodromal of a cerebrovascular event) may be a reason for immediate discontinuation
Other medical conditions associated with adverse vascular events	Diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinaemia and systemic lupus erythematosus.

Symptoms of ATE

In the event of symptoms women should be advised to seek urgent medical attention and to inform the healthcare professional that she is taking a CHC.

Symptoms of a cerebrovascular accident 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;
- sudden, severe or prolonged headache with no known cause;
- loss of consciousness or fainting with or without seizure.

Temporary symptoms suggesting 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.

2. Tumours

- Some epidemiological studies indicate that the long-term use of oral contraceptives displays a risk factor for the development of cervical cancer in women infected with human papillomavirus (HPV). However, there is still uncertainty about the extent to which this finding is influenced by confounding effects (e.g. differences in number of sexual partners or in use of barrier contraceptives).
- A meta-analysis from 54 epidemiological studies reported that there is a slightly increased relative risk (RR = 1.24) of having breast cancer diagnosed in women who are currently using oral contraceptives. The excess risk gradually disappears during the course of the 10 years after cessation of oral contraceptive use. Because breast cancer is rare in women under 40 years of age, the excess number of breast cancer diagnoses in current and recent users of oral contraceptives 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 users of oral contraceptives, the biological effects of oral contraceptives or a combination of both. The breast cancers diagnosed in ever-users tend to be less advanced clinically than the cancers diagnosed in never-users.
- In rare cases, benign liver tumours, and even more rarely, malignant liver tumours have been reported in users of oral contraceptives. In isolated cases, these tumours have led to life-threatening intra-abdominal haemorrhages. Therefore, 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 using combined oral contraceptives.

3. ALT elevations
- During clinical trials with patients treated for hepatitis C virus infections (HCV) with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, transaminase (ALT) elevations higher than 5 times the upper limit of normal (ULN) occurred significantly more frequently in women using ethinylestradiol-containing medications such as combined hormonal contraceptives (CHCs). Additionally, in patients treated with glecaprevir / pibrentasvir, elevated ALT was observed in women using ethinylestradiol-containing medications such as CHCs (see sections 4.3 and 4.5).

4. Other conditions
- Women with hypertriglyceridaemia, or a family history thereof, may be at an increased risk of pancreatitis when using hormonal contraception.
- Exogenous estrogens may induce or exacerbate symptoms of hereditary and acquired angioedema.
- Although small increases in blood pressure have been reported in many women using hormonal contraception, clinically relevant increases are rare. A relationship between combined oral contraceptive use and clinical hypertension has not been established. If a sustained clinically significant hypertension develops during the use of Desolett 28 then it is advisable for the physician/midwife to stop the treatment and treat the hypertension. Where considered appropriate, Desolett 28 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 hormonal contraception, but the evidence of an association is inconclusive: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uremic syndrome; chorea minor; herpes gestationis; otosclerosis-related hearing loss.
- Acute or chronic disturbances of liver function may necessitate the discontinuation of Desolett 28 use until the liver values return to normal. Recurrence of cholestatic jaundice which occurred first during pregnancy or previous use of sex steroids necessitates the discontinuation of combined oral contraceptives.
- Although combined oral contraceptives 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 combined oral contraceptives. However, diabetic women should be carefully observed while taking combined oral contraceptives.
- Crohn's disease and ulcerative colitis has been associated with combined oral contraception use.
- Chloasma may occasionally occur, especially in women with a history of chloasma during pregnancy. Women with a tendency to get chloasma should avoid exposure to the sun or ultraviolet radiation whilst taking combined oral contraceptives.
- Amenorrhea for longer or shorter periods may occur after stopping the treatment.
- Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.
- Desolett 28 tablets contain lactose monohydrate. Patients with any of the following rare, hereditary conditions should not use this drug: galactose intolerance, total deficiency of lactase or glucose-galactose malabsorption

When counseling the choice of contraceptive method(s), all the above information should be taken into account.

Medical Examination/Consultation

Prior to the initiation or reinstitution of Desolett 28 a complete medical history (including family history) should be taken and pregnancy must be ruled out. Blood pressure should be measured and a

physical examination should be performed, guided by the contra-indications (see section 4.3) and warnings (see section 4.4). It is important to draw a woman's attention to the information on venous and arterial thrombosis, including the risk of Desolett 28 compared with other CHCs, the symptoms of VTE and ATE, the known risk factors and what to do in the event of a suspected thrombosis. Menstruation disturbances like oligomenorrhoea, amenorrhea and irregular bleedings should be investigated prior to prescription. If Desolett 28 use might affect any latent or manifested disease, the date for the control checkup must be chosen with regard to this.

The woman should also be instructed to carefully read the user leaflet and to adhere to the advice given. The frequency and nature of further periodic checks should be based on established practice guidelines and be adapted to the individual woman.

Women should be advised that hormonal contraceptives do not protect against HIV infections (AIDS) and other sexually transmissible diseases.

Reduced efficacy

The efficacy of Desolett 28 may be reduced in the event of e.g., missed tablets (see section 4.2), gastro-intestinal disturbances (see section 4.2) or concomitant medications that decrease the plasma concentration of ethinylestradiol and/or etonogestrel, the active metabolite of desogestrel (see section 4.5).

Herbal preparations containing St. John's wort (*Hypericum perforatum*) should not be used while taking Desolett 28 due to the risk of decreased plasma concentrations and reduced clinical effects of Desolett 28 (see section 4.5)

Reduced cycle control

With all combined oral contraceptives, irregular bleeding (spotting or breakthrough bleeding) may occur, especially during the first months of use. Therefore, the evaluation of any irregular bleeding is only meaningful after an adaptation interval of about three cycles.
If bleeding irregularities persist or occur after previously regular cycles, then non-hormonal causes should be considered and adequate diagnostic measures are indicated to exclude malignancy or pregnancy. These may include curettage.
In some women withdrawal bleeding may not occur during the placebo tablet interval. If the combined oral contraceptive has been taken according to the directions described in section 4.2, it is unlikely that the woman is pregnant. However, if the combined oral contraceptive has not been taken according to these directions prior to the first missed withdrawal bleed or if two withdrawal bleeds are missed, pregnancy must be ruled out before combined oral contraceptive use is continued.

4.5 Interactions with other medicinal products and other forms of interaction

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

- ***Effect of other medicinal products on Desolett 28***

Interactions can occur with medicinal or herbal products that induce microsomal enzymes, specifically cytochrome P450 enzymes (CYP), which can result in increased clearance of sex hormones and which may lead to breakthrough bleeding and/or contraceptive failure.

<u>Management</u>
Enzyme induction can already be observed after a few days of treatment. Maximal enzyme induction is generally seen within a few weeks. After the cessation of drug therapy, enzyme induction may be

sustained for about 4 weeks.

Short-term treatment
Women on treatment with enzyme-inducing medicinal or herbal products should temporarily use a barrier method or another method of contraception in addition to the Desolett 28. The barrier method must be used during the whole time of concomitant drug therapy and for 28 days after its discontinuation.

Long-term treatment
In women on long-term therapy with enzyme-inducing active substances, another reliable, non-hormonal method of contraception unaffected by enzyme inducing medicinal products is recommended.

The following interactions have been reported in literature.
Substances increasing the clearance of Desolett 28 (enzyme induction) e.g.
Phenytoin, phenobarbital, primidone, bosentan, carbamazepine, rifampicin, some HIV protease inhibitors (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz, nevirapine), and possibly also oxcarbazepine, topiramate, rifabutin, felbamate, griseofulvin and products containing the herbal remedy St. John's wort.

Substances with variable effects on the clearance of Desolett 28
When co-administered with hormonal contraceptives, many combinations of HIV protease inhibitors (e.g. nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and/or combinations with Hepatitis C virus (HCV) medicinal products (e.g. boceprevir, telaprevir), can increase or decrease plasma concentrations of progestagens, including etonogestrel, or estrogens. The net effect of these changes may be clinically relevant in some cases.

Therefore, the prescribing information of concomitant HIV/HCV medications should be consulted to identify potential interactions and any related recommendations. In case of any doubt, and additional barrier contraceptive method should be used by women on protease inhibitor or non-nucleoside reverse transcriptase inhibitor therapy.

Substances decreasing the clearance of Desolett 28 (enzyme inhibitors)
The clinical relevance of potential interactions with enzyme inhibitors remains unknown. Concomitant administration of strong (e.g. ketoconazole, itraconazole, clarithromycin) or moderate (e.g. fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of estrogens or progestagens, including etonogestrel.

Etoricoxib doses of 60 to 120 mg/day have been shown to increase plasma concentrations of ethinylestradiol 1.4 to 1.6-fold, respectively when taken concomitantly with a combined hormonal contraceptive containing 0.035 mg ethinylestradiol.

- ***Effects of Desolett 28 on other medicinal products***

Combined oral contraceptives may interfere with the metabolism of other drugs. Accordingly, plasma and tissue concentrations may either increase (e.g. ciclosporin) or decrease (e.g. lamotrogine).

Clinical data suggests that ethinylestradiol is inhibiting the clearance of CYP1A2 substrates leading to a weak (e.g. theophylline) or moderate (e.g. tizanidine) increase in their plasma concentration.

Pharmacodynamic interactions
Concomitant use with medicinal products containing ombitasvir/paritaprevir/ritonavir and dasabuvir, with or without ribavirin, or glecaprevir/pibrentasvir may increase the risk of ALT elevations (see sections 4.3 and 4.4). Therefore, Desolett 28 users must switch to an alternative method of contraception (e.g., progestagen-only contraception or non-hormonal methods) prior to starting therapy with this combination drug regimen. Desolett 28 can be restarted 2 weeks following completion of treatment with this combination drug regimen.

Laboratory tests
The use of contraceptive steroids may influence the results of certain laboratory tests, including biochemical parameters of liver, thyroid, adrenal and renal function, plasma levels of carrier proteins, e.g., corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. The changes generally remain within the normal laboratory range. When treated together with concomitant medication, the product information for the concomitant drugs should be consulted to identify possible interactions.

4.6 Fertility, pregnancy and lactation

Pregnancy
Desolett 28 should not be used during pregnancy. If pregnancy occurs during treatment with Desolett 28, the intake should be stopped immediately.
Most epidemiological studies have up to now not shown any negative effects or defects on the foetuses when women have taken combined oral contraception prior to pregnancy, nor a teratogenic effect when combined oral contraceptives were taken inadvertently during early pregnancy.

The increased risk of VTE during the postpartum period should be considered when re-starting Desolett 28 (see section 4.2 and 4.4).

Breastfeeding
Lactation may be influenced by combined oral contraceptives as they may reduce the quantity and also change the composition of breast milk. Therefore, the use of combined oral contraceptives should generally not be recommended until the nursing mother has completely weaned her child. Small amounts of steroids and/or their metabolites may be excreted with the milk but there is no evidence that this adversely affects infant health.

4.7 Effects on ability to drive and use machines

Desolett 28 has no or negligible influence on ability to drive and use machines.

4.8 Undesirable effects

As with all combined oral contraceptives, changes in vaginal bleeding patterns may occur, especially during the first months of use. These may include changes in bleeding frequency (absent, less, more frequent or continuous), intensity (reduced or increased) or duration.

During the first treatment cycles, among 10-30 % of the women may experience some kind of side effect, i.e. breast tenderness, nausea or spotting. These initial side effects are often mild and usually disappear within 2 to 4 months of treatment. The side effects that might be related to Desolett 28 and that have been reported in women using Desolett 28, or other combined oral contraceptives, are listed in the table below.

Description of selected adverse reactions
An increased risk of arterial and venous thrombotic and thrombo-embolic events, including myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism has been observed in women using CHCs, which are discussed in more detail in section 4.4.

Possibly related undesirable effects that have been reported in users of Desolett 28 or combined oral contraceptive users in general are listed in the table below. All adverse drug reactions are listed by system organ class and frequency; common (≥1/100, <1/10), uncommon (≥1/1,000, <1/100), rare (≥1/10,000, <1/1,000) and not known (cannot be estimated from the available data).

Classification of body system	Common (≥1/100, <1/10)	Uncommon (≥1/1 000, <1/100)	Rare (≥1/10 000, <1/1 000)	Not known
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			Liver adenoma, focal nodular dysplasia in the liver	
Immune system disorder			Hypersensitivity	Exacerbation of symptoms of hereditary and acquired angioedema
Metabolism and nutrition disorders		Fluid retention	Increased demand for insulin	
Psychiatric disorders	Depressed mood, mood changes	Decreased libido	Increased libido	
Nervous system disorders	Headache	Migraine		
Eye disorders			Difficulties to wear contact lenses Decreased tear flow	
Cardiac disorders			Myocardial infarction	
Vascular disorders			Venous thromboembolism Arterial thromboembolism	
Respiratory, thoracic and mediastinal disorders			Pulmonary embolism	
Gastrointestinal disorders	Nausea Abdominal pain	Vomiting, diarrhoea		
Hepatobiliary disorders			Jaundice stasis Cholelithiasis Changes in liver function values	
Skin and subcutaneous tissue disorder		Redness, rash, urticaria	Erythema nodosum, erythema multiforme Chloasma Itching	
Reproductive system and breast disorders	Breast pain Breast tenderness Vaginal bleeding	Breast enlargement Absent withdrawal bleeding	Vaginal discharge, breast discharge	
Investigations	Weight increase	Elevation in blood pressure	Weight decrease Impaired glucose tolerance	

			Elevated blood glucose	

There is an increased risk for myocardial infarction for smoking women that use combined oral contraceptives from the age 35-40. The risk for cardiovascular disease increases with age, especially in combination with other risk factors such as smoking, severe overweight, hyperlipidemia, and hypertension.
The influence on liver function is reversible. A very rare complication, which has been associated with use of the type of hormones in Desolett 28, is benign liver adenoma and focal nodular hyperplasia in the liver, a condition that may give severe abdominal pain and intra-abdominal bleeding.

Interactions
Breakthrough bleeding and/or contraceptive failure may result from interactions of other drugs (enzyme inducers) with oral contraceptives (see section 4.5).

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V*.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: hormonal contraceptives for systemic use, progestogens and estrogens, ATC code: G03AA09

The contraceptive effect of combined oral contraceptives is based on various factors, of which the most important is the inhibition of ovulation. In addition there are changes in endometrium and the cervical secretion. Besides protection against pregnancy, combined oral contraceptives have several positive properties which, next to the negative properties (see sections 4.4 and 4.8), should be considered in deciding on the method of birth control. The cycle is more regular and the menstruation is often less painful and bleeding is lighter. The latter may result in a decrease in the occurrence of iron deficiency anemia. Apart from this, there are older studies with high dosed combined oral contraceptives (≥50 µg ethinylestradiol) that show a reduced risk of benign breast disease, ovarian cysts, pelvic inflammatory disease, ectopic pregnancy, endometrial cancer and ovarian cancer. Whether this also applies to lower-dosed combined oral contraceptives remains to be confirmed.

Paediatric population
No clinical data on efficacy and safety are available in adolescents below 18 years.

5.2 Pharmacokinetic properties

Desogestrel

Absorption

Orally administered desogestrel is rapidly and completely absorbed and converted to the active metabolite etonogestrel. Peak serum concentrations are reached at about 1.5 hour. The bioavailability is 62 - 81 %.

Distribution
Etonogestrel is bound to serum albumin and to sex hormone binding globulin (SHBG). Only 2 - 4 % of the total serum drug concentrations of etonogestrel are present as free steroid. 40 -70 % are specifically bound to SHBG. The ethinylestradiol-induced increase in SHBG influences the distribution over the serum proteins, causing an increase of the SHBG-bound fraction and a decrease of the albumin-bound fraction. The apparent volume of distribution of desogestrel is 1.5 l/kg.

Biotransformation
Etonogestrel is completely metabolized by the known pathways of steroid metabolism. The metabolism is complete. The metabolic clearance rate from serum is about 2 ml/min/kg. No interaction was found with the co-administered ethinylestradiol

Elimination

Etonogestrel serum levels decrease in two phases. The terminal disposition phase is characterized by a half-life of approximately 30 hours. Desogestrel and its metabolites are excreted at a urinary to biliary ratio of about 6:4.

Steady-state conditions
Etonogestrel pharmacokinetics is influenced by SHBG levels, which are increased threefold by ethinylestradiol. Following daily ingestion, drug serum levels increase about two- to threefold, reaching steady state conditions during the second half of the treatment cycle.

Ethinylestradiol

Absorption
Orally administered ethinylestradiol is rapidly and completely absorbed. Peak serum concentrations are reached within 1-2 hours. The absolute bioavailability, with large inter individual variability, as a result of pre-systemic conjugation and first-pass metabolism is approximately 60%.

Distribution
Ethinylestradiol is highly but non-specifically bound to serum albumin (approximately 98.5%) and induces an increase in the serum concentrations of SHBG. An apparent volume of distribution of about 5 l/kg was determined.

Biotransformation

Ethinylestradiol is subject to presystemic conjugation in both small bowel mucosa and the liver. Ethinylestradiol is primarily metabolized by aromatic hydroxylation but a wide variety of hydroxylated and methylated metabolites are formed. These are present as free metabolites and as conjugates with glucuronides and sulphate. The metabolic clearance rate is about 5 ml/min/kg.

In vitro, ethinylestradiol is a reversible inhibitor of CYP2C19, CYP1A1 and CYP1A2 as well as a mechanism based inhibitor of CYP3A4/5, CYP2C8, and CYP2J2.

Elimination

Ethinylestradiol serum levels decrease in two disposition phases. The terminal disposition phase is characterized by a half-life of approximately 24 hours. Unchanged drug is not excreted. Ethinylestradiol metabolites are excreted at a urinary to biliary ratio of 4:6. The half-life of metabolite excretion is about 1 day.

Steady-state conditions

Steady state concentrations are reached after 3-4 days when serum drug levels are higher by 30 - 40% as compared to single dose

5.3 Preclinical safety data

Current studies of general toxicity, reproduction effects, genotoxicity and carcinogenicity showed no special risks to humans. However, it must be borne in mind that sex steroids can promote the growth of certain hormone-dependent tissue and tumours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Active tablets
α-tocopherol
anhydrous colloidal silicon dioxide
lactose monohydrate
potato starch
povidone
stearic acid

Placebo tablets
lactose monohydrate
magnesium stearate
potato starch

6.2 Incompatibilities

Not relevant.

6.3 Shelf life

3 years.

6.4 Special instructions for storage

No special instructions for storage.

6.5 Nature and contents of the container

Push-through pack PVC/aluminium foil: 1 x 28 or 3 x 28 tablets.
Each card is packed in an aluminium bag with printing.

6.6 Special instructions for disposal

No special instructions.

7. MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
5349 AB Oss
The Netherlands

8. MARKETING AUTHORISATION NUMBER

11489

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

1992-01-24/2006-07-01

10. DATE OF REVISION OF THE TEXT

2022-09-15