

1. NAME OF THE MEDICINAL PRODUCT

Implanon®

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One implant contains 68 mg of etonogestrel; the release rate is 60-70 µg/day in week 5-6 and has decreased to approximately 35-45 µg/day at the end of the first year, to approximately 30-40 µg/day at the end of the second year and to approximately 25-30 µg/day at the end of the third year.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Implant for subdermal use.

Non-biodegradable white to off-white flexible rod.

4. CLINICAL PARTICULARS

4.1 Therapeutic indication

Contraception.

4.2 Posology and method of administration

4.2.1 How to use Implanon

Pregnancy should be excluded before insertion of Implanon.

Prior to inserting Implanon it is strongly recommended to carefully read the instructions for insertion and removal of the implant in section 4.2.2 'How to insert Implanon, and section 4.2.4 'How to remove Implanon.

Implanon is a long-acting contraceptive. One implant is inserted subdermally. The user should be informed that she can request the removal of Implanon at any time but the implant should not be left in place more than three years. Clinicians may consider earlier replacement of the implant in heavier women (see section 4.4.1). Only a physician who is familiar with the removal technique should perform, on request or at the end of the 3 years of use, the removal of Implanon. After the removal of the implant, immediate insertion of another implant will result in continued contraceptive protection.

To ensure uncomplicated removal it is necessary that Implanon is inserted correctly, directly under the skin. The risk of complications is small if the provided instructions are followed.

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Some cases have been reported in which the implant was not inserted on the correct day or was not properly inserted or was not inserted at all. Incidentally, this has resulted in unintended pregnancy. The occurrence of such incidents can be minimized when the instructions for insertion (sections 4.2.2 'How to insert Implanon' and 4.2.3 'When to insert Implanon') are strictly followed. The presence of the implant should be verified by palpation directly after insertion. In case the implant cannot be palpated or when the presence of the implant is doubtful, other methods must be applied to confirm its presence (see section 4.2.2 'How to insert Implanon'). Until the presence of Implanon has been verified a contraceptive barrier method must be used.

It is strongly recommended that physicians, prior to practicing the insertion of Implanon, participate in training sessions organized by Organon. Physicians who have little experience with subdermal insertion are advised to acquire the correct technique under supervision of a more experienced colleague. Additional information and more detailed instructions concerning the insertion and removal of Implanon[®] will be sent on request free of charge (*Local Organon affiliate, telephone: xxxxxx, or visit www.implanonlocalization.com*).

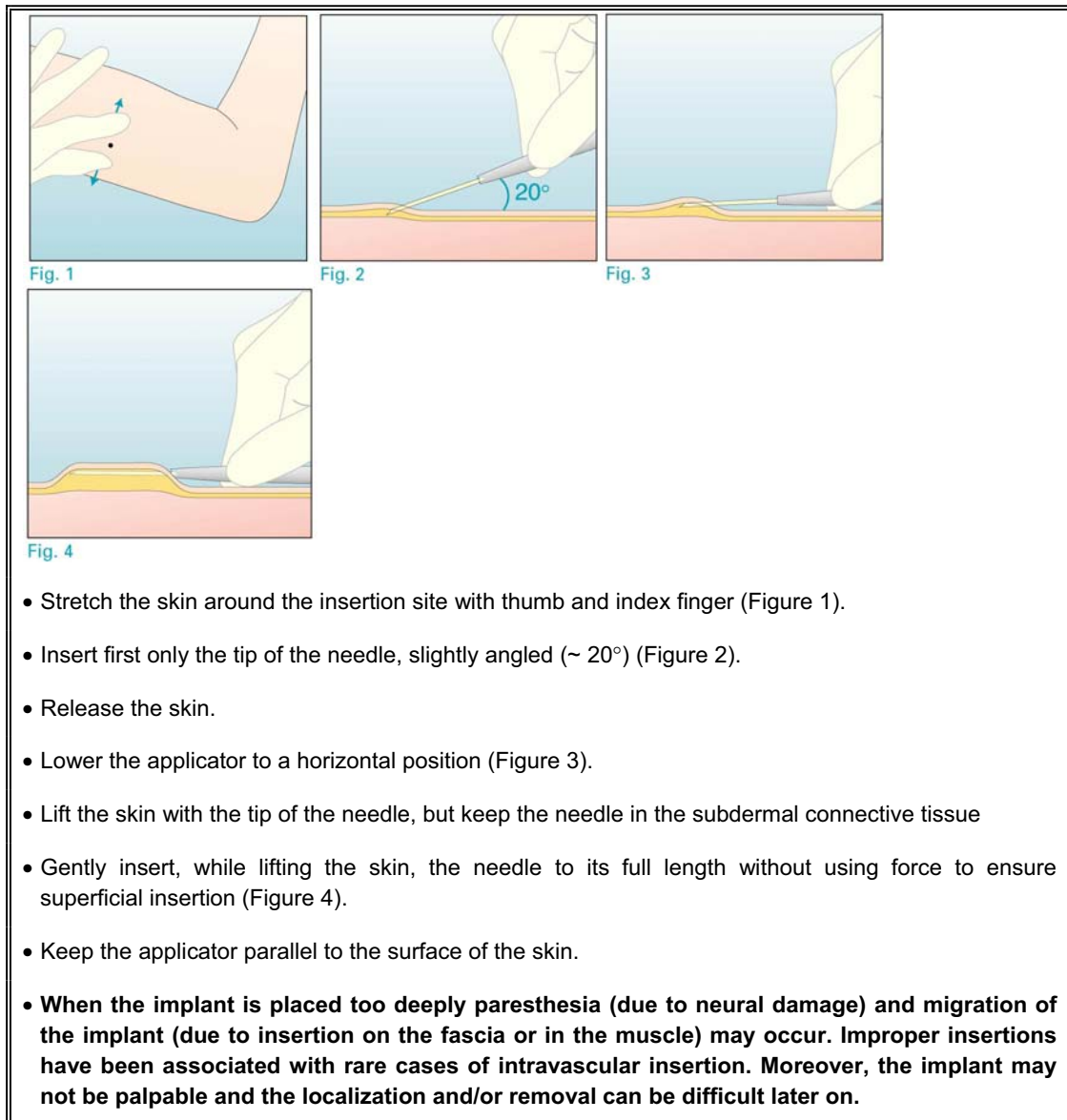
The Implanon package contains a USER CARD intended for the user, and an adhesive label intended for the physician's user record. Among others, the USER CARD records the batch number of the provided implant and helps to note the date of insertion, the arm of insertion, and the intended day of removal. The adhesive label records the batch number and the date of insertion.

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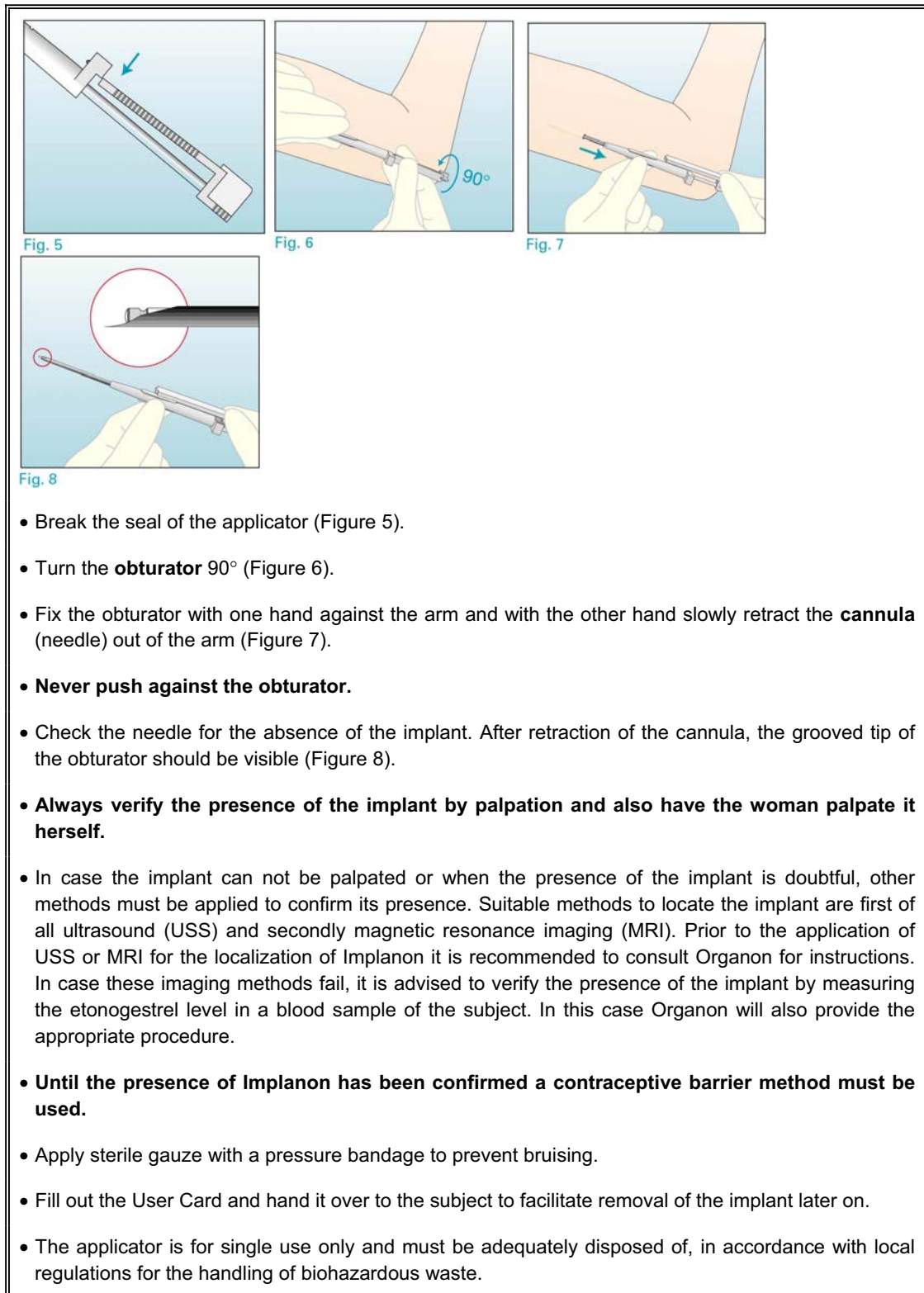
4.2.2 How to insert Implanon

- Insertion of Implanon should be performed under aseptic conditions, and only by a physician who is familiar with the procedure.
- Insertion of Implanon is performed with the specially designed applicator. The use of this applicator differs substantially from that of a classical syringe. A drawing of a dismantled applicator and its individual components (e.g. cannula, obturator and needle with double-angled bevel) is shown in this leaflet to clarify their specific functions.
- The procedure used for insertion of Implanon **is opposite to giving an injection**. When inserting Implanon the **obturator** must remain fixed while the **cannula** (needle) is retracted from the arm. For normal injections the **plunger** is pushed and the **body** of the syringe remains fixed.
- Allow the subject to lie on her back with her non-dominant arm (the arm which the woman does not use for writing) turned outwards and bent at the elbow.
- Implanon should be inserted at the inner side of the non-dominant upper arm about 8-10 cm above the medial epicondyle.
- Mark the insertion site.
- Clean the insertion site with a disinfectant.
- Anaesthetize with an anaesthetic spray, or with 2 ml of lidocaine (1%) applied just under the skin along the 'insertion canal'.
- Remove the sterile disposable applicator carrying Implanon from its blister.
- While keeping the shield on the needle, visually verify the presence of the implant, seen as a white body inside the needle-tip. If the implant is not seen, tap the top of the needle shield against a firm surface to bring the implant into the needle tip. Following visual confirmation, the implant should be lowered back into the needle by doing the opposite. The needle shield can now be removed.
- Please note that the implant can fall out of the needle prior to insertion. Therefore, always hold the applicator in the upward position (i.e. with the needle pointed upwards) until the time of insertion. This to prevent the implant from dropping out. Keep the needle and the implant sterile. If contamination occurs, a new package with a new sterile applicator must be used.

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4.2.3 When to insert Implanon

No preceding hormonal contraceptive use

Implanon should be inserted between Day 1-5, but at the latest on Day 5 of the woman's natural cycle (Day 1 is the first day of her menstrual bleeding).

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

Implanon should be inserted preferably on the day after the last active tablet (the last tablet containing the active substances) of her previous COC, but at the latest on the day following the usual tablet-free interval or following the last placebo tablet of her previous COC. In case a vaginal ring or transdermal patch has been used, Implanon should be inserted preferably on the day of removal, but at the latest when the next application would be due.

Changing from a progestagen-only-method (minipill, injectable, a different implant, or from a progestagen-releasing intrauterine system [IUS])

Implanon may be inserted any day when the woman is switching from a minipill (from another implant or an IUS on the day of its removal, from an injectable when the next injection would be due).

Following first-trimester abortion

Implanon should be inserted immediately.

Following childbirth or a second-trimester abortion

For breastfeeding women see 'Use during pregnancy and lactation'

Implanon should be inserted on day 21-28 after delivery or second-trimester abortion. When the implant is inserted later, the woman should be advised to additionally use a barrier method on the first 7 days after the insertion.

However, if intercourse has already occurred, pregnancy should be excluded or the woman's first natural period should be awaited before the actual insertion of the implant.

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4.2.4 How to remove Implanon

- Removal of Implanon should only be performed by a physician who is familiar with the removal technique.
- The precise location of the implant is indicated on the USER CARD

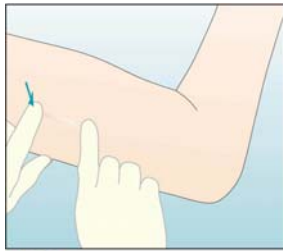


Fig. a

- Locate the implant by palpation and mark the distal end (Figure a).
- A non-palpable implant should always first be localized by either ultrasound (USS) or magnetic resonance imaging (MRI) before removal is attempted and subsequently be removed under the guidance of USS. In case of doubt, the presence of Implanon can be verified by etonogestrel determination. Please contact Organon for further guidance. Exploratory surgery without knowledge of the exact localization of the implant is strictly discouraged. Removal of deeply inserted implants should be conducted with caution in order to prevent damage to deeper neural or vascular structures in the arm and be performed by healthcare providers familiar with the anatomy of the arm.

- Wash the area and apply a disinfectant

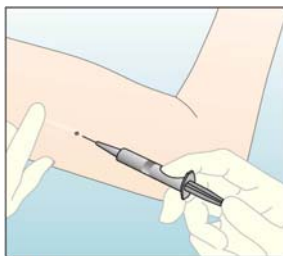


Fig. b

- Anaesthetize the arm with 0.5-1 ml lidocaine (1%) at the site of incision, which is just below the distal end of the implant. Note: Apply the anaesthetic **under** the implant. Application **above** the implant makes the skin swell, which may cause difficulties in locating the implant (Figure b).

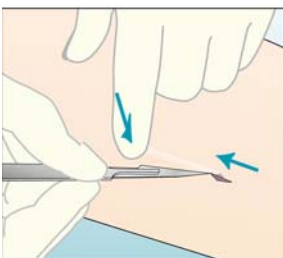


Fig. c

- Push down the proximal tip to fix the implant; a bulge may appear indicating the distal end of the implant. Starting below the distal tip of the implant, make a longitudinal incision of 2 mm towards the distal tip of the implant (Figure c).

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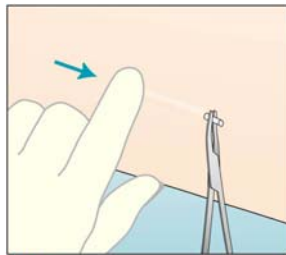


Fig. d

- Gently push the implant towards the incision until the tip is visible. Grasp the implant with forceps (preferably 'mosquito' forceps) and remove it (Figure d).

- If the tip of the implant is not visible, there might be formation of fibrotic tissue around the implant. The fibrotic tissue can be split by continuing to cut towards the distal tip, until the tip is clearly visible. Remove the implant with forceps (Figures e and f).

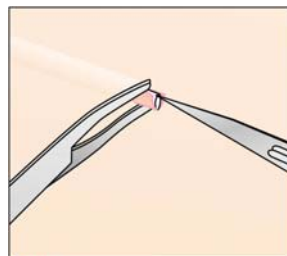


Fig. e

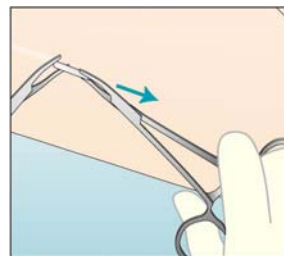


Fig. f

- If the tip of the implant is still not visible, gently insert a forceps into the incision and grasp the implant (Figures g and h). With a second forceps carefully dissect the tissue around the implant. The implant can then be removed (Figure i).

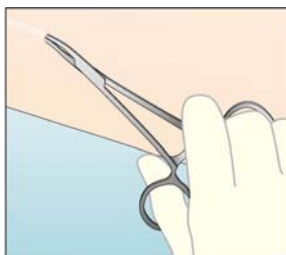


Fig. g

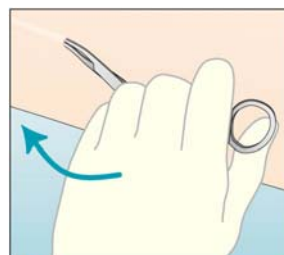


Fig. h

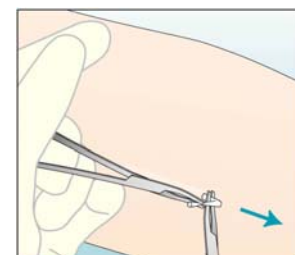


Fig. i

- Close the incision with a butterfly closure.
- Apply sterile gauze with a pressure bandage to prevent bruising.
- There have been occasional reports of displacement of the implant (see also section 4.4.1 'Warnings'); usually this involves minor movement relative to the original position. This may somewhat complicate localization of the implant by palpation, USS and/or MRI, and may require a somewhat larger incision and more time.
- If the woman would like to continue using Implanon, a new implant may be inserted immediately after the old implant is removed (see section 4.2.5 'How to replace Implanon').

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- If the woman does not wish to continue using Implanon and does not want to become pregnant, another contraceptive method should be recommended.

4.2.5 How to replace Implanon

- Replacement of Implanon should only be performed under aseptic conditions and only by a physician who is familiar with the removal and insertion procedure.
- Immediate replacement can be done after removal of the previous implant as described in section 4.2.4 'How to remove Implanon'.
- The procedure to replace Implanon is similar to the insertion procedure described in section 4.2.2 'How to insert Implanon'. The new implant can be inserted in the same arm, and frequently through the same incision from which the previous implant was removed. If the same incision is being used, the instructions below must also be taken into account.
- The small incision of the removal procedure can be used as the entrance for the needle of the new applicator.
- Anaesthetize the insertion site with 2 ml lidocaine (1%) applied just under the skin commencing at the removal incision along the 'insertion canal'.
- During replacement inserting the needle to its full length is crucial; failure to do so will result in a partly visible implant in the removal incision in the skin.
- Close the incision with a butterfly closure.
- Apply a sterile gauze with a pressure bandage to prevent bruising. Let the woman keep the bandage in place for at least 48 hours to allow the removal incision to heal.

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4.3 Contraindications

Progestagen-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 Implanon, the product should be stopped immediately.

- 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.
- Progestagen-dependent tumors.
- Undiagnosed vaginal bleeding.
- Hypersensitivity to the active substance or to any of the excipients of Implanon.

4.4 Special warnings and special precautions for use

4.4.1 Warnings

If any of the conditions / risk factors mentioned below is present, the benefits of progestagen use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start with Implanon. 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 Implanon 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 to be: 4.5/4 (16-19 years), 17.5/16 (20-24 years), 48.7/44 (25-29 years), 110/100 (30-34 years), 180/160 (35-39 years) and 260/230 (40-44 years). The risk in users of contraceptive methods, which only contain progestagens, is possibly of similar magnitude as that associated with combined OCs. However, for these methods, the evidence is less

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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 observed in OC users may be due to an earlier diagnosis, biological effects of the OC or a combination of both. Since a biological effect of hormones 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 Implanon.

- 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.
- 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 finding for etonogestrel (the biologically active metabolite of desogestrel) used as a contraceptive in the absence of an estrogenic component is unknown, Implanon should be removed in the event of a thrombosis. Removal of Implanon should also be considered in case of long-term immobilization due to surgery or illness. Women with a history of thrombo-embolic disorders should be made aware of the possibility of a recurrence.
- Although progestagens 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 progestagen-only contraceptives. However, diabetic women should be carefully observed while using progestagen-only contraceptives.
- The protection with traditional progestagen-only contraceptives against ectopic pregnancies is not as good as with combined OCs, which has been associated with the frequent occurrence of ovulations during the use of these methods. Despite the fact that Implanon consistently inhibits ovulation, ectopic pregnancy should be taken into account in the differential diagnosis if the woman gets amenorrhea or abdominal pain.
- If a sustained hypertension develops during the use of Implanon, or if a significant increase in blood pressure does not adequately respond to antihypertensive therapy, discontinuation with the use of Implanon should be considered.

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- When acute or chronic disturbances of liver function occur the woman should be referred to a specialist for examination and advice.
- 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 using Implanon.
- The contraceptive effect of Implanon is related to the plasma levels of etonogestrel, which are inversely related to body weight, and decrease with time after insertion. The clinical experience with Implanon in heavier women in the third year of use is limited. Therefore it can not be excluded that the contraceptive effect in these women during the third year of use may be lower than for women of normal weight. Clinicians may therefore consider earlier replacement of the implant in heavier women.
- The following conditions have been reported both during pregnancy and during sex steroid use, but an association with the use of progestagens has not been established: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss.
- Expulsion may occur especially if the implant is not inserted according to the instructions given in section 4.2.2 'How to insert Implanon, or as a consequence of a local inflammation.
- In rare cases, mostly related to either a too deep initial insertion (see also section 4.2.2 'How to insert Implanon') and/or to external forces (e.g. manipulation of the implant or contact sports) the implant may migrate from the insertion site. In these cases localization of the implant may be more difficult and removal may require a larger incision (see also section 4.2.4 'How to remove Implanon'). If Implanon cannot be found, contraception and the risk of progestogen-related undesirable effects may continue beyond the time desired by the woman.

4.4.2 Medical examination/consultation

Prior to the initiation or reinstatement of Implanon a complete medical history (including family medical history) should be taken and pregnancy should be excluded. Blood pressure should be measured and a physical examination should be performed, guided by the contraindications (Section 4.3) and warnings (Section 4.4.1). It is recommended that the woman returns for a medical check-up three months after insertion of Implanon. During this check-

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up, the blood pressure should be measured and an enquiry should be made after any questions, complaints or the occurrence of undesirable effects. The frequency and nature of further periodic checks should be adapted to the individual woman, guided by clinical judgement.

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

4.4.3 Reduced efficacy

The efficacy of Implanon may be reduced when concomitant medication is used (See section 4.5.1 'Interactions').

4.4.4 Changes in the vaginal bleeding pattern

During the use of Implanon, vaginal bleeding may become more frequent or of longer duration in most women. In other women bleeding may become incidental or be totally absent (approximately in 1 out of 5 women).

Information, counseling and the use of a bleeding diary can improve the woman's acceptance of a bleeding pattern. Evaluation of vaginal bleeding should be done on an ad hoc basis and may include an examination to exclude gynecological pathology 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.

4.5 Interaction with other medicinal products and other forms of interaction

4.5.1 Interactions

Interactions between hormonal contraceptives and other medicinal products may lead to breakthrough bleeding and / or contraceptive failure. No specific interaction studies have been performed with Implanon. 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, specifically cytochrome P450 enzymes, which

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can result in increased clearance of sex hormones (e.g., phenytoin, barbiturates, primidone, carbamazepine, rifampicin, and possibly also oxcarbazepine, topiramate, felbamate, ritonavir, nelfinavir, griseofulvin and the herbal remedy St. Johns wort).

Women on treatment with any of these drugs should temporarily use a barrier method in addition to Implanon. 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.

In women on long-term treatment with hepatic enzyme-inducing drugs, it is recommended to remove Implanon and to prescribe a non-hormonal method.

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

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

4.6 Pregnancy and lactation

Implanon is not indicated during pregnancy. If pregnancy occurs during use of Implanon, the implant should be removed. Animal studies have shown that very high doses of progestagenic substances may cause masculinisation of female fetuses. Extensive epidemiological studies have revealed neither an increased risk of birth defects in children born to women who used OCs prior to pregnancy, nor of a teratogenic effect when OCs were inadvertently used during pregnancy. Although this probably also applies to all OCs, it is not clear whether this is also the case for Implanon.

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Pharmacovigilance data with various desogestrel-containing combined OCs (etonogestrel is a metabolite of desogestrel) also do not indicate an increased risk.

Implanon does not influence the production or the quality (protein, lactose or fat concentrations) of breast milk. However, small amounts of etonogestrel are excreted in breast milk. Based on an average daily milk ingestion of 150 ml/kg, the mean daily infant etonogestrel dose calculated after one month of etonogestrel release is approximately 27 ng/kg/day. This corresponds to approximately 0.2% of the estimated absolute maternal daily dose (2.2% when values are normalized per kg body weight). Subsequently the milk etonogestrel concentration decreases with time during the lactation period.

Long-term data are available on 38 children, whose mothers started using Implanon during the 4th to 8th week postpartum. They were breast-fed for a mean duration of 14 months and followed-up to 36 months of age. Evaluation of growth, and physical and psychomotor development did not indicate any differences in comparison to nursing infants whose mothers used an IUD (n=33). Nevertheless, development and growth of the child should be carefully followed. Based on the available data, Implanon may be used during lactation.

4.7 Effects on ability to drive and use machines

No observed effects.

4.8 Undesirable effects

4.8.1 Serious undesirable effects

See Section 4.4.1 (Warnings)

4.8.2 Other possible undesirable effects

Possibly related undesirable effects reported in clinical trials with Implanon have been listed in the Table below. An association has been neither confirmed nor refuted.

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System Organ Class	Adverse reaction in MedDRA Term ¹		
	Very Common > 1/10	Common < 1/10, ≥ 1/100	Uncommon <1/100, ≥ 1/1000
Infections and Infestations	vaginal infection		pharyngitis, rhinitis, urinary tract infection
Immune system disorders			hypersensitivity
Metabolism and nutritional disorders		decreased appetite	
Psychiatric disorders		affect lability, depressed mood, nervousness, libido decreased	anxiety, insomnia
Nervous system disorders	headache	dizziness	migraine, somnolence
Vascular disorders		hot flush	
Gastrointestinal disorders		abdominal pain, nausea, flatulence	vomiting, constipation, diarrhoea
Skin and subcutaneous tissue disorders	acne	alopecia	hypertrichosis, rash, pruritus
Musculoskeletal and connective tissue disorders			back pain, arthralgia, myalgia, musculoskeletal pain
Renal and urinary disorders			dysuria
Reproductive system and breast disorders	breast tenderness, breast pain, menstruation irregular	dysmenorrhoea, ovarian cyst	genital discharge, vulvovaginal discomfort, galactorrhoea, hypertrophy

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System Organ Class	Adverse reaction in MedDRA Term ¹		
	Very Common > 1/10	Common < 1/10, ≥ 1/100	Uncommon <1/100, ≥ 1/1000
			breast, , pruritus genital
General disorders and administration site condition		implant site pain, implant site reaction, fatigue influenza like illness, pain	pyrexia, oedema
Investigations	weight increased	weight decreased	

¹The most appropriate MedDRA term (version 8.0) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed, but should be taken into account as well.

In rare cases, a clinically relevant rise in blood pressure has been observed during the use of Implanon. Urticaria and (aggravation of) angioedema and/or aggravation of hereditary angioedema may occur. Insertion or removal of Implanon may cause some bruising, slight local irritation, pain or itching. Occasionally fibrosis at the implant site may occur, a scar may be formed or an abscess may develop. In rare cases, paresthesia or paresthesia-like events may occur. Expulsion or migration of Implanon may be possible (see also section 4.4.1 'Warnings'). Minor surgical intervention might be necessary when removing Implanon.

4.9 Overdose

An implant should always be removed before inserting a new one. There are no data available on overdose with etonogestrel. There have been no reports of serious deleterious effects from an overdose of contraceptives in general.

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5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

(PHARMACOTHERAPEUTIC GROUP: PROGESTAGENS, ATC-classification G03AC08)

Implanon is a non-biodegradable, etonogestrel-containing implant for subdermal use. Etonogestrel is the biologically active metabolite of desogestrel, a progestagen widely used in OCs. It is structurally derived from 19-nortestosterone and binds with high affinity to progesterone receptors in the target organs. The contraceptive effect of Implanon is primarily achieved by inhibition of ovulation. Ovulations were not observed in the first two years of use and only rarely in the third year. Besides inhibition of ovulation, Implanon also causes changes in the cervical mucus, which hinders the passage of spermatozoa. Clinical trials were conducted in women between 18 and 40 years. Although no direct comparison was made, the contraceptive efficacy appeared to be at least comparable with that known for combined oral contraceptives. The high degree of protection against pregnancy is obtained among other reasons because, in contrast to OCs, the contraceptive action of Implanon is not dependent on the regular intake of tablets. The contraceptive action of Implanon is reversible, which is apparent from the rapid return of the normal menstrual cycle after removal of the implant. Although Implanon inhibits ovulation, ovarian activity is not completely suppressed. Mean estradiol concentrations remain above the level seen in the early-follicular phase. In a two-year study, in which the bone mineral density in 44 Implanon users has been compared with that in a control group of 29 IUD-users no adverse effects on bone mass have been observed. During the use of Implanon no clinically relevant effects on lipid metabolism have been observed. The use of progestagen-containing contraceptives may have an effect on insulin resistance and glucose tolerance. In clinical trials it has further been shown that Implanon users often have a less painful menstrual bleeding (dysmenorrhea).

5.2 Pharmacokinetic properties

ABSORPTION

After the insertion of Implanon, etonogestrel is rapidly absorbed into the circulation. Ovulation-inhibiting concentrations are reached within 1 day. Maximum serum concentrations (between 472 and 1270 pg/ml) are reached within 1 to 13 days. The release rate of the implant decreases with time. As a

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result serum concentrations decline rapidly over the first few months. By the end of the first year a mean concentration of approximately 200 pg/ml (range 150-261 pg/ml) is measured, which slowly decreases to 156 pg/ml (range 111-202 pg/ml) by the end of the third year. The variations observed in serum concentrations can be partly attributed to differences in body weight.

DISTRIBUTION

Etonogestrel is for 95.5-99% bound to serum proteins, predominantly to albumin and to a lesser extent to sex hormone binding globulin. The central and total volume of distribution are 27 l and 220 l, respectively, and hardly change during the use of Implanon.

METABOLISM

Etonogestrel undergoes hydroxylation and reduction. Metabolites are conjugated to sulfates and glucuronides. Animal studies show that enterohepatic circulation probably does not contribute to the progestagenic activity of etonogestrel.

ELIMINATION

After intravenous administration of etonogestrel, the mean elimination half-life is approximately 25 hours and the serum clearance is approximately 7.5 l/hour. Both clearance and elimination-half-life remain constant during the treatment period. The excretion of etonogestrel and its metabolites, either as free steroids or as conjugates, is with urine and feces (ratio 1.5:1). After insertion of Implanon in lactating women, etonogestrel is excreted in breast milk with a milk/serum ratio of 0.44-0.50 during the first four months. In lactating women using Implanon, the mean transfer of etonogestrel to the infant is approximately 0.2% of the maternal etonogestrel daily dose (2.2% when values are normalized per kg body weight). Concentrations show a gradual and statistically significant decrease over the time.

5.3 Preclinical safety data

Toxicological studies did not reveal any effects other than those, which can be explained on the basis of the hormonal properties of etonogestrel, regardless of the route of administration.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Implant

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Core: Ethylene vinylacetate copolymer (28% vinyl acetate)

Skin: Ethylene vinylacetate copolymer (14% vinyl acetate)

Applicator

Acrylonitrile-butadiene-styrene body with a stainless steel needle and a polypropylene needle shield.

6.2 Incompatibilities

No incompatibilities are known.

6.3 Shelf life

The shelf life of Implanon is 5 years when stored as indicated under Section 6.4.

Implanon should not be inserted after the expiry date as indicated on the primary package.

6.4 Special precautions for storage

Store in the original package at 2° to 30°C, protected from light and moisture.

6.5 Nature and contents of container

The pack contains one implant (4 cm in length and 2 mm in diameter) in the cannula of a disposable sterile applicator. The applicator consists of acrylonitrile-butadiene-styrene body with a stainless steel needle and a polypropylene shield. The sterile applicator containing the implant is packed in a blister pack made of transparent polyethylene terephthalate glycol sealed with coated paper. The blister pack is packed in a box together with the package leaflet.

6.6 Instructions for use and handling

See Section 4.2 ('Posology and Method of Administration').

The applicator is for single use only.

7. MARKETING AUTHORISATION HOLDER

N.V Organon, PO Box 20, 5340 BH Oss, The Netherlands.

8. MARKETING AUTHORISATION NUMBER(S)

INT00034249

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

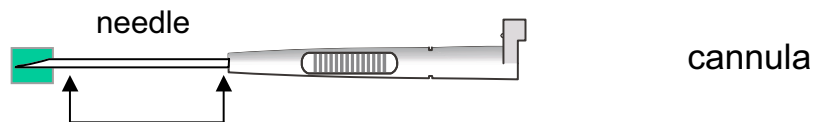
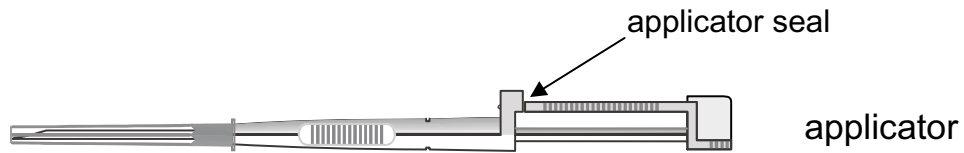
10. **DATE OF REVISION OF THE TEXT**

March 2007

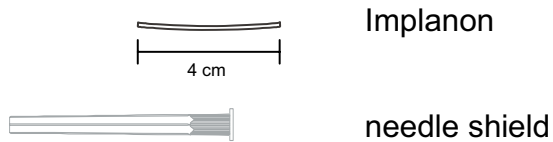
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Applicator figure to form an integral part of the SmPC text

(the precise location on the SmPC will depend on the final design of the printed SmPC).



location of Implanon



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