SCHEDULING STATUS

S4

PROPRIETARY NAME AND DOSAGE FORM

Implanon NXT® 68 mg Implant

COMPOSITION

Each radiopaque implant contains 68 mg of etonogestrel.

Inactive ingredients:

Core: ethylene vinyl acetate copolymer (28 % vinyl acetate), barium sulphate.

Skin: ethylene vinyl acetate copolymer (15 % vinyl acetate, 15 mg).

PHARMACOLOGICAL CLASSIFICATION

A.18.8 Ovulation controlling agents

PHARMACOLOGICAL ACTION

Pharmacodynamic properties

The implant is a non-biodegradable, radiopaque, etonogestrel-containing implant for subdermal use, preloaded in a sterile, disposable applicator. Etonogestrel is the biologically active metabolite of desogestrel, a progestagen. It is structurally derived from 19-nortestosterone and binds with high affinity to progesterone receptors in the target organs. The contraceptive effect of etonogestrel is primarily achieved by inhibition of ovulation and changes in the cervical mucus, which hinders the passage of spermatozoa.

The contraceptive action of etonogestrel is reversible. Although etonogestrel inhibits ovulation, ovarian activity is not completely suppressed. Mean estradiol concentrations

remain above the level seen in the early-follicular phase. The use of progestagen-containing contraceptives may have an effect on insulin resistance and glucose tolerance.

Pharmacokinetic properties

The release rate is approximately 60 to 70 µg/day in week 5 to 6 and decreases to approximately 35 to 45 µg/day at the end of the first year, to approximately 30 to 40 µg/day at the end of the second year, and to approximately 25 to 30 µg/day at the end of the third year.

Absorption

After the insertion of the implant, etonogestrel is rapidly absorbed into the circulation. Ovulation-inhibiting concentrations are reached within 1 day. Maximum serum concentrations (between 472 and 1 270 pg/mL) are reached within 1 to 13 days. The release rate of the implant decreases with time. As a 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 to 261 pg/mL), is measured, which slowly decreases to 156 pg/mL (range 111 to 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 95,5 to 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 is 27 L and 220 L, respectively, and hardly change during the use of Implanon NXT.

Metabolism

Etonogestrel undergoes hydroxylation and reduction. Metabolites are conjugated to sulphates 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 faeces (ratio 1,5:1). After insertion in lactating women, etonogestrel is excreted in breast milk with a milk/serum ratio of 0,44 to 0,50 during the first four months. In lactating women the mean transfer of etonogestrel to the infant is approximately 0,2 % of the estimated absolute maternal etonogestrel daily dose (2,2 % when values are normalised per kg body weight). Concentrations show a gradual decrease over the time.

INDICATIONS

Implanon NXT is indicated for contraception.

CONTRAINDICATIONS

Implanon NXT 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 NXT, the product should be removed immediately.

- Hypersensitivity to the active substance or to any of the inactive ingredients of Implanon NXT.
- Active venous or arterial thromboembolic disorders or history thereof (see **WARNINGS AND SPECIAL PRECAUTIONS**).
- Known or suspected sex-steroid sensitive malignancies such as breast and ovarian cancers.
- Presence or history of liver tumours (benign or malignant).

- Presence or history of any hepatic disease for as long as liver function values have not returned to normal.
- Known or suspected pregnancy.
- Undiagnosed vaginal bleeding.

WARNINGS AND SPECIAL PRECAUTIONS

If any of the conditions or risk factors mentioned below are present, the potential risk should be discussed with the woman before the decision to implement treatment with Implanon NXT is made. In the event of aggravation, exacerbation or first appearance of any of these conditions, the woman should contact her medical practitioner. The medical practitioner should then decide on whether Implanon NXT should be removed.

Pregnancy should be excluded before insertion of Implanon NXT.

Carcinoma of the Breast

- The risk for breast cancer increases in general with increasing age. During the use of (combined) oral contraceptives the risk of having breast cancer diagnosed is slightly increased. This increased risk disappears gradually within 10 years after discontinuation of oral contraceptive use and is not related to the duration of use, but to the age of the woman when using the oral contraceptive. The risk in users of contraceptive methods which only contain progestagens, such as Implanon NXT, is possibly of similar magnitude as that associated with combined oral contraceptives. However, for these methods, the evidence is less conclusive.

Venous and arterial thromboembolism

- Epidemiological investigations have associated the use of combined oral contraceptives

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 metabolites of desogestrel in Implanon NXT) used as a contraceptive in the absence of an estrogenic component is unknown, Implanon NXT should be removed in the event of a confirmed thrombosis. Removal of Implanon NXT should also be considered in case of long-term immobilisation due to surgery or illness. Although Implanon NXT is a progestagen only contraceptive, it is recommended to assess risk factors, which are known to increase the risk of venous and arterial thromboembolism. Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence (see **CONTRAINDICATIONS**).

- There have been post-marketing reports of serious arterial and venous thromboembolic events, including cases of pulmonary emboli (some fatal), deep vein thrombosis, myocardial infarction and strokes, in women using etonogestrel implants such as Implanon NXT. Implanon NXT should be removed in the event of any venous or arterial thrombotic event.

Carbohydrate and Lipid Metabolic Effects and body weight

- The use of progestagen-containing contraceptives such as Implanon NXT may have an effect on peripheral insulin resistance and glucose tolerance. Therefore, diabetic women should be carefully monitored during the first months of Implanon NXT use.
- Women who are being treated for hyperlipidaemia should be monitored closely if they elect to use Implanon NXT. Progestogens such as Implanon NXT may elevate LDL cholesterol levels and may render the control of hyperlipidaemia more difficult.
- The contraceptive effect of Implanon NXT is related to the plasma levels of etonogestrel, which are inversely related to body weight, and decrease with time after insertion. More frequent replacement of Implanon NXT may be required in women with higher body weight.

Ectopic Pregnancies

- Ectopic pregnancy should be taken into account in the differential diagnosis, if the woman gets amenorrhoea or abdominal pain.

Hypertension

- If a sustained hypertension develops during the use of Implanon NXT, or if a significant increase in blood pressure does not adequately respond to antihypertensive therapy, Implanon NXT should be removed.

Liver Disease

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

Chloasma

- Chloasma may 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 while using Implanon NXT.

Other Conditions

- Insertion or removal of Implanon NXT may cause bruising. Scar formation has been reported.
- Itching, pain and infection at the implantation site may occur.
- The following conditions have been reported both during pregnancy and during sex steroid use, but an association with the use of Implanon NXT 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 and (hereditary) angioedema.

Complications of Insertion

- Expulsion may occur if the implant is inserted not according to the instructions given in **DOSAGE AND DIRECTIONS FOR USE, How to insert Implanon NXT**, or as a consequence of a local inflammation.
- There have been rare post-marketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. There have also been reports of migration of the implant within the arm from the insertion site, which may be related to an incorrect insertion technique and placement (see **DOSAGE AND DIRECTIONS FOR USE, How to insert Implanon NXT**) or external forces (e.g. manipulation of the implant or contact sport activities).

In cases where the implant has migrated within the arm from the insertion site, localisation may be more difficult, and removal may require a surgical procedure with a larger incision or a surgical procedure in an operating room. In cases where the implant has migrated to the pulmonary artery, endovascular or surgical procedures including thoracotomy may be needed for removal (see **DOSAGE AND DIRECTIONS FOR USE, How to remove Implanon NXT**). If at any time the implant cannot be palpated, it should be localised and removal is recommended. If Implanon NXT is not removed, contraception and the risk of progestagen-related undesirable effects may continue beyond the time desired by the woman.

Ovarian Cysts

- Follicular development occurs with Implanon NXT and 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 may require surgical intervention.

Reduced Efficacy with concomitant medicines

The efficacy of Implanon NXT may be reduced when used concomitantly with medicines that decrease the plasma concentration of etonogestrel (see **INTERACTIONS**).

Changes in the Menstrual Bleeding Pattern

During the use of Implanon NXT, women are likely to have changes in their menstrual bleeding pattern. These may include the occurrence of an irregular pattern (absent, less, more frequent or continuous), and changes in bleeding intensity (reduced or increased) or duration. Amenorrhoea was reported in about 20 % of women while another 20 % reported frequent and/or prolonged bleeding.

Information, counselling 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 gynaecological pathology or pregnancy.

***In situ* broken or bent implant**

There have been reports of broken or bent implants while in the patient's arm. Based on *in vitro* data, when the implant is broken or bent, the release rate of etonogestrel may be slightly increased. This change is not expected to have clinically meaningful effects.

When an implant is removed, it is important to remove it in its entirety (see **How to Remove Implanon NXT**)

Ability to drive and use machines

No effects have been observed.

INTERACTIONS

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

Influence of other medicinal products on Implanon NXT

Interactions between Implanon NXT and other medicines may lead to menstrual bleeding and/or contraceptive failure. The following interactions have been reported in the literature, mainly with combined contraceptives, but also with progestagen-only contraceptives, such as Implanon NXT.

Hepatic metabolism: Interactions can occur with medicinal or herbal products that induce hepatic enzymes, specifically cytochrome P450 enzymes (CYP), which can result in increased clearance, reducing plasma concentrations of etonogestrel as in Implanon NXT, and may decrease the effectiveness of Implanon NXT. These products include (phenytoin, barbiturates, primidone, bosentan, carbamazepine, rifampicin; HIV medication (e.g. ritonavir, nelfinavir, nevirapine, efavirenz); and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and the herbal remedy St John’s wort).

Enzyme induction can occur within a few days of treatment. Maximum enzyme induction is generally observed within a few weeks. After medicine therapy is discontinued, enzyme induction can last for about 28 days.

When co-administered with Implanon NXT, many combinations of HIV protease inhibitors (e.g. nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine), and/or combinations with medicines used to treat HCV (e.g. boceprevir, telaprevir), can increase or decrease plasma concentrations of etonogestrel as in Implanon NXT, as the net effect of these changes cannot be predicted and may result in decreased efficacy of IMPLANON NXT.

Management

Women receiving any of these above mentioned hepatic enzyme-inducing medicines or herbal products should be advised that the efficacy of Implanon NXT may be reduced. If it is decided to continue using Implanon NXT, women should be advised to also use a non-hormonal contraceptive method during the time of concomitant medication administration and for 28 days after their discontinuation.

Concomitant administration of strong (e.g. ketoconazole, itraconazole, clarithromycin) or moderate (e.g. fluconazole, diltiazem, erythromycin) CYP3A4 inhibitors may increase the serum concentrations of progestins, including etonogestrel.

Influence of Implanon NXT on other medicines

Implanon NXT may interfere with the metabolism of other medicines. Accordingly, plasma and tissue concentrations of these medicines may either increase (e.g. ciclosporin) or decrease (e.g. lamotrigine).

Laboratory investigations

Data obtained with combined oral contraceptives have shown that contraceptive steroids may affect some laboratory investigations, 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 Implanon NXT is not known.

PREGNANCY AND LACTATION

Implanon NXT is contraindicated during pregnancy. If pregnancy occurs during use of Implanon NXT, the implant should be removed. Animal studies have shown that progestagenic substances may cause masculinisation of female foetuses.

Implanon NXT does not influence the production or the quality (protein, lactose or fat concentrations) of breast milk. Etonogestrel is excreted in breast milk.

Based on limited available data, Implanon NXT may be used during lactation and should be inserted after the 4th post-partum week.

Medical Examination/Consultation

Prior to the insertion of Implanon NXT, 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 (see **CONTRAINDICATIONS** and **WARNINGS AND SPECIAL PRECAUTIONS**). It is recommended that the woman returns for a medical check-up 3 months after insertion of Implanon NXT. During this check-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 NXT does not protect against HIV (AIDS) and other sexually transmitted diseases.

DOSAGE AND DIRECTIONS FOR USE

Pregnancy should be excluded before insertion of Implanon NXT.

Medical practitioners should be trained to become familiar with the use of the Implanon NXT applicator, and techniques for insertion and removal of the Implanon NXT implant.

Before inserting the implant, the instructions for insertion and removal of the implant under **How to insert Implanon NXT** and **How to remove Implanon NXT** should be carefully read and followed.

Video demonstrating insertion and removal of the implant are available online (https://bcove.video/3tyM4Cb and https://bcove.video/382u8Yt). Please contact your local Organon office (Organon South Africa (Pty) Ltd, Tel No. +27(0)87 106 9655).

If you are unsure of the necessary steps safely insert and/or remove Implanon NXT, do not attempt the procedure.

How to use Implanon NXT

The applicator is designed to be operated with one hand and to help facilitate correct subdermal insertion of the implant.

A single implant is inserted subdermally and can be left in place for 3 years. Remove the implant no later than 3 years after the date of insertion. The user should be informed that she can request the removal of the implant at any time. Medical practitioners may consider earlier replacement of the implant in women with higher body weight (see **WARNINGS AND SPECIAL PRECAUTIONS**). After the removal of the implant, immediate insertion of another implant will result in continued contraceptive protection. If the woman does not wish to continue using Implanon NXT, but wants to continue preventing pregnancy, another contraceptive method should be recommended.

The basis for successful use and subsequent removal of the Implanon NXT implant, is a correct and carefully performed subdermal insertion of the implant, in accordance with the instructions.

If the implant is not inserted in accordance with the instructions (see How to insert Implanon NXT) and on the correct day (see When to insert Implanon NXT), this may result in pregnancy. An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the localisation and/or removal can be difficult (see **How to remove Implanon NXT** and **WARNINGS AND SPECIAL PRECAUTIONS**).

The Implanon NXT implant should be inserted subdermally just under the skin at the inner side of the non-dominant upper arm. The insertion site is overlying the triceps muscle about 8 to 10 cm (3 to 4 inches) from the medial epicondyle of the humerus and 3 to 5 cm (1,25 to 2 inches) posterior to the sulcus (groove) between the biceps and triceps muscles. This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus (see **Figures 2a and 2b**).

Immediately after insertion, the presence of the implant should be verified by palpation. 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 **How to insert Implanon NXT**). Until the presence of the implant has been verified, the woman should be advised to use a non-hormonal contraceptive method.

The Implanon NXT package contains a User Card intended for the woman which records the batch number of the implant. Medical practitioners are requested to record the date of insertion, the arm of insertion and the intended day of removal on the User Card. The package also includes adhesive labels intended for medical practitioner records showing the batch number.

When to insert Implanon NXT

Important: Rule out pregnancy before inserting the implant.

Timing of insertion depends on the woman's recent contraceptive history, as follows:

No preceding hormonal contraceptive use in the past month.

The implant should be inserted between Day 1 (first day of menstrual bleeding) and Day 5 of the menstrual cycle.

If inserted as recommended, back-up contraception is not necessary. If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

Switching contraceptive method to Implanon NXT

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

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

- **Changing from a progestagen-only contraceptive method (e.g. progestagen-only pill, injectable, implant or intrauterine contraceptive device [IUCD])**

  As there are several types of progestagen-only methods, the insertion of the implant must be performed as follows:

  - Injectable contraceptives: Insert the implant on the day the next injection is due.
  - Progestagen-only pill: A woman may switch from progestagen-only pill to Implanon NXT on any day of the month. The implant should be inserted within 24 hours after taking the last tablet.

- Implant/Intrauterine conceptive device (IUCD): Insert the implant on the day the current implant or IUCD is removed. If inserted as recommended, back-up contraception is not necessary. If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded

Following abortion or miscarriage

- First trimester: The implant should be inserted within 5 days following a first trimester abortion or miscarriage.
- Second trimester: Insert the implant between 21 to 28 days following second trimester abortion or miscarriage.

If inserted as recommended, back-up contraception is not necessary. If deviating from the recommended timing of insertion, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

Post-partum

- **Breastfeeding: The implant should be inserted after the 4th post-partum week (see PREGNANCY AND LACTATION).** The woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.
- **Not breastfeeding:** The implant should be inserted between 21 to 28 days post-partum. If inserted as recommended, back-up contraception is not necessary. If the implant is inserted later than 28 days post-partum, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

How to insert Implanon NXT

The basis for successful use and subsequent removal of Implanon NXT is a correct and carefully performed subdermal insertion of the implant in the non-dominant arm in accordance with the instructions. Both the medical practitioner and the woman should be able to feel the implant under the woman's skin after placement.

The implant should be inserted subdermally just under the skin at the inner side of the non-dominant upper arm.

- An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the localisation and/or removal can be difficult (see **How to remove Implanon NXT** and **WARNINGS AND SPECIAL PRECAUTIONS**).
- If the implant is inserted too deep, neural or vascular damage may occur. Too deep or incorrect insertions have been associated with paraesthesia (due to neural damage) and local migration of the implant due to intramuscular or fascial insertion, and in cases with intravascular (arterial and venous) insertion.

Insertion of Implanon NXT should be performed under aseptic conditions and only by a qualified medical practitioner who received training and is familiar with the procedure. Insertion of the implant should only be performed with the preloaded applicator.

To help make sure the implant is inserted just under the skin, the medical practitioner should be positioned to see the advancement of the needle by viewing the applicator from the side and not from above the arm. From the side view, the insertion site and the movement of the needle just under the skin can be clearly visualised.

For illustrative purposes, Figures depict the left inner arm.

- Have the woman lie on her back on the examination table, with her non-dominant arm flexed at the elbow and externally rotated, so that her hand is underneath her head (or as close as possible (**Figure 1**).



Figure 1

Identify the insertion site, which is at the inner side of the non-dominant upper arm. The insertion site is overlying the triceps muscles about 8 to10 cm (3 to 4 inches) from the medial epicondyle of the humerus and 3 to 5 cm (1,25 to 2 inches) posterior to the sulcus (groove) between the biceps and triceps muscles, (**Figure 2a, 2b, 2c**). This location is intended to avoid the large blood vessels and nerves lying within and surrounding the sulcus. If it is not possible to insert the implant in this location (e.g. in women with thin arms), it should be inserted as far posterior from the sulcus as possible.

- Make two marks with a surgical marker: First, mark the spot where the implant will be inserted, and second, mark a spot at 5 centimetres (2 inches) proximal (toward the shoulder) to the first mark (**Figure 2a and 2b**). This second mark (guiding mark) will later serve as a direction guide during insertion (guiding mark).

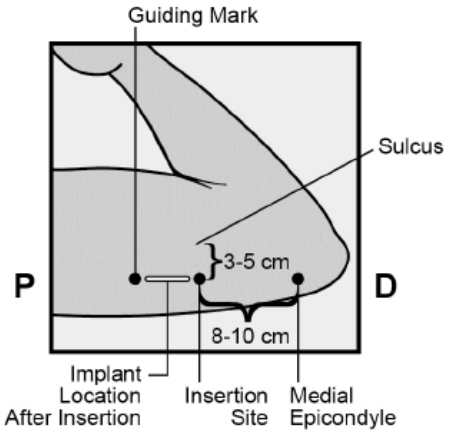


Figure 2a

P, proximal (toward the shoulder);

D, distal (toward the elbow)

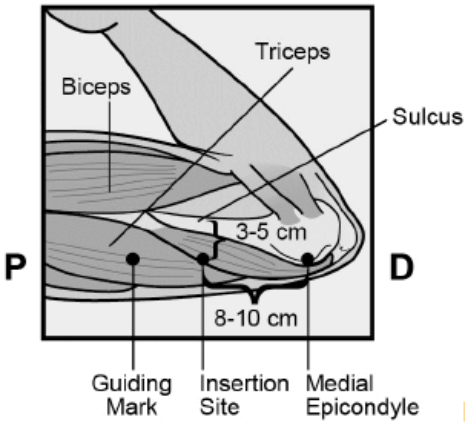


Figure 2b

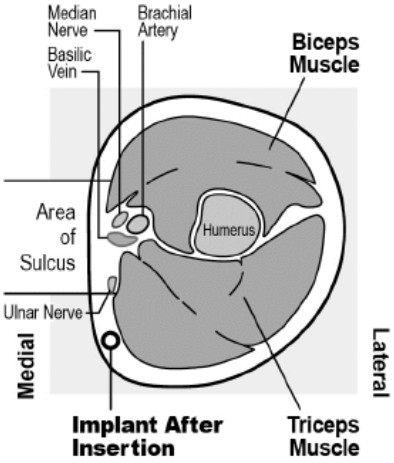


Figure 2c

Cross section of the upper left arm, as viewed from the elbow

- After marking the arm, confirm the site is in the correct location on the inner side of the arm.
- Clean the skin from the insertion site to the guiding mark with an antiseptic solution.
- Anaesthetise the insertion area (e.g. with anaesthetic spray or by injecting 2 ml of 1 % lidocaine (or lignocaine) just under the skin along the planned insertion tunnel).
- Remove the sterile preloaded disposable Implanon NXT applicator carrying the implant from its blister. The applicator should not be used if sterility is in question.

- Hold the applicator just above the needle at the textured surface area. Remove the transparent protection cap by sliding it horizontally in the direction of the arrow away from the needle (**Figure 3**). If the cap does not come off easily the applicator should not be used. The white coloured implant should be visible when looking into the tip of the needle. **The purple slider should not be touched until the needle has been fully inserted subdermally, as doing so will retract the needle and prematurely release the implant from the applicator.**

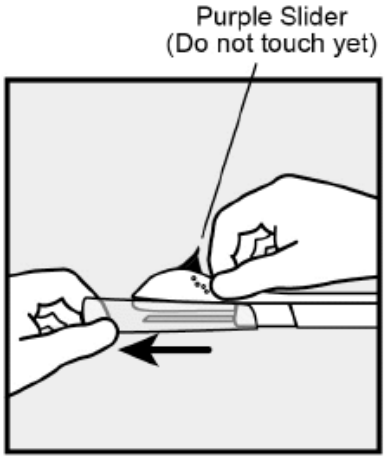


Figure 3

- With the free hand, the skin around the insertion site should be stretched towards the elbow (**Figure 4**).

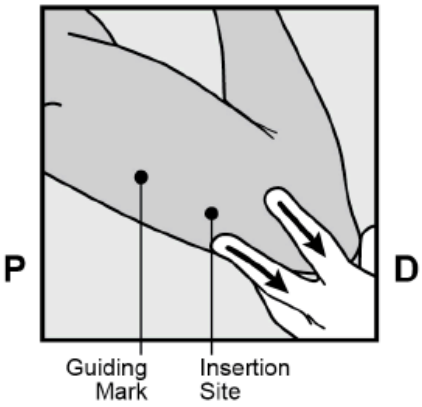


Figure 4

- **The implant should be inserted subdermally just under the skin** (see **WARNINGS AND SPECIAL RECAUTIONS**).

  To help make sure the implant is inserted just under the skin, you should position yourself to see the advancement of the needle by viewing the applicator from the side and not from above the arm. From side view you can

clearly see the insertion site and the movement of the needle just under the skin (see Figure 6).

- The skin should be punctured with the tip of the needle slightly angled less than 30 degrees (**Figure 5a)**).

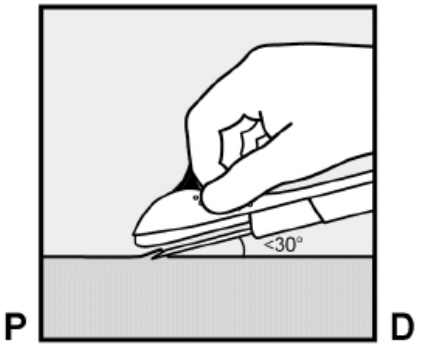


Figure 5a

- Insert the needle until the bevel (slanted opening of the tip) is just under the skin (and no further) (**Figure 5b**). If you insert the needle past the bevel, withdraw it until only the bevel is beneath the skin.

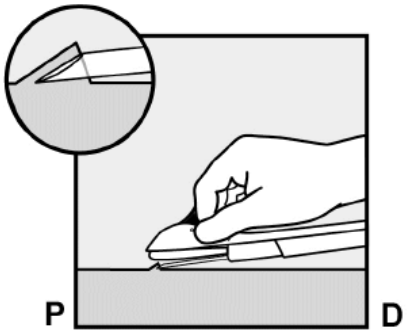


Figure 5b

- The applicator should be lowered to a nearly horizontal position. To facilitate subdermal placement, lift the skin with the needle, while sliding the needle to its full length (**Figure 6**). A slight resistance may be felt but excessive force should not be exerted. **If the needle is not inserted to its full length, the implant will not be inserted properly. If the needle tip emerges from the skin before needle insertion is complete, the needle should be pulled back and be readjusted to subdermal**

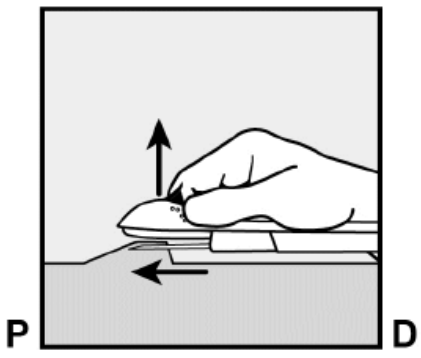


Figure 6

position before completing the insertion procedure.

- The applicator should be kept in the same position with the needle inserted to its full length **(Figure 7)**. If needed, the free hand may be used to stabilise the applicator.



Figure 7

- The purple slider should be unlocked by pushing it slightly down (**Figure 8a**). The slider should be moved fully back until it stops. **Do not move the applicator while moving the purple slider (Figure 8b).** The implant is now in its final subdermal position, and the needle is locked inside the body of the applicator. The applicator can now be removed (**Figure 8c**).

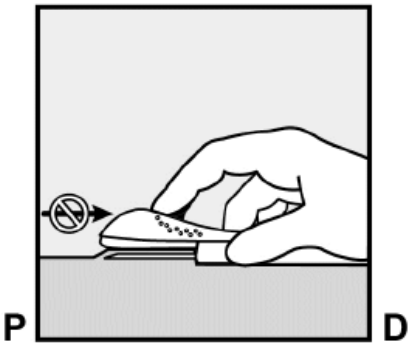


Figure 8a

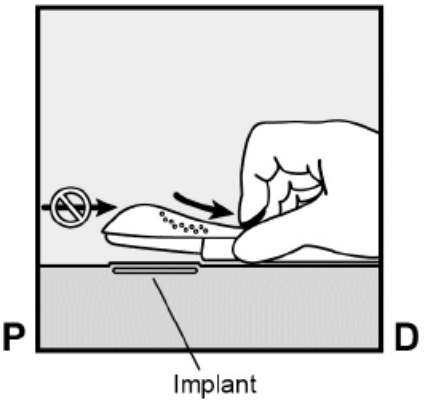


Figure 8b

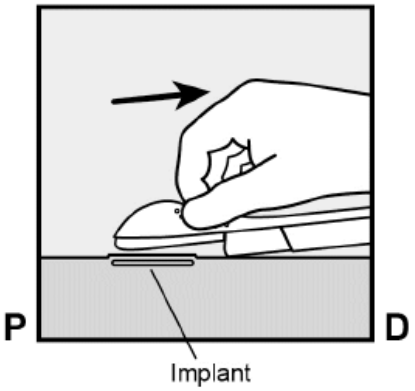


Figure 8c

If the applicator is not kept in the same position during this procedure or if the purple slider is not moved fully back until it stops, the implant will not be inserted properly and may protrude from the insertion site.

If the implant is protruding from the insertion site, remove the implant and perform a new procedure at the same insertion site using a new applicator. **Do not push the protruding implant back into the incision.**

- Apply a small adhesive bandage over the insertion site.
- **The presence of the implant in the woman's arm should always be verified immediately after insertion by palpation.** By palpating both ends of the implant, it should be able to confirm the presence of the 4 cm rod (**Figure 9**). See If rod is not palpable after insertion.

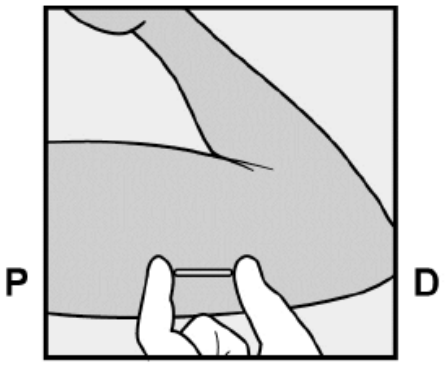


Figure 9

- The woman should be requested to palpate the implant.
- Sterile gauze with a pressure bandage should be applied to minimise bruising. The woman may remove the pressure bandage in 24 hours and the small adhesive bandage over the insertion site after 3 to 5 days.

- The User Card should be completed and given to the woman to keep. Also, the adhesive labels should be completed and affixed to the woman's medical record.
- The applicator is for single use only and must be adequately disposed of, in accordance with local regulations for the handling of bio-hazardous waste.

If the rod is not palpable after insertion:

If you cannot feel the implant or are in doubt of its presence, the implant may not have been inserted or it may have been inserted too deeply:

- Check the applicator. The needle should be fully retracted and only the purple tip of the obturator should be visible.
- Other methods to confirm the presence of the implant may be used. Given the radiopaque nature of the implant, suitable methods for localisation are two-dimensional x-ray and x-ray computerised tomography (CT scan), ultrasound scanning (USS) with a high-frequency linear array transducer (10 MHz or greater) or magnetic resonance imaging (MRI) may be used. In case these imaging methods fail, it is advised to verify the presence of the implant by measuring the etonogestrel level in a blood sample from the woman. In this case the local Organon office (Telephone: +27(0)87 106 9655) will provide the appropriate protocol.
- **Until you have verified the presence of the implant, the woman must use a non-hormonal contraceptive method.**
- Deeply-placed implants should be localised and removed as soon as possible to avoid the potential for distant migration (see **WARNINGS AND SPECIAL PRECAUTIONS**).

How to remove Implanon NXT


Removal of the implant should only be performed under aseptic conditions by a medical practitioner who is familiar with the removal technique. **If you are unfamiliar with**

the removal technique, contact the local Organon office (Telephone: +27(0)87 106 9655) for further information.

Before initiating the removal procedure, the medical practitioner should assess the location of the implant. Verify the exact location of the implant in the arm by palpation.

If the implant is not palpable, consult the User Card or medical record to verify the arm which contains the implant. If the implant cannot be palpated, it may be deeply located or have migrated. Consider that it may lie close to vessels and nerves. Removal of non-palpable implants should only be performed by a medical practitioner experienced in removing deeply placed implants and familiar with localising the implant and the anatomy of the arm. Contact the local Organon office (Telephone: +27(0)87 106 9655) for further information.

See, Localisation and removal of a non-palpable implant, if the implant cannot be palpated.

Procedure for removal of an implant that is palpable

For illustration purposes, Figures depict the left inner arm

- Have the woman lie on her back on the table. The arm should be positioned with the elbow flexed and the hand underneath the head (or as close as possible) (see **Figure 1**)

- Locate the implant by palpation. Push down the end of the implant closest to the shoulder (**Figure 10**) to stabilise it; a bulge should appear indicating the tip of the implant that is closest to the elbow. **If the tip does not pop up, removal of the implant may be more challenging** and should be performed by providers experienced with removing deeper implants. Contact the local Organon office (Telephone: +27(0)87 106 9655) for further information.
- Mark the distal end (end closest to the elbow) e.g. with a surgical marker.
- Clean the site with an antiseptic solution.

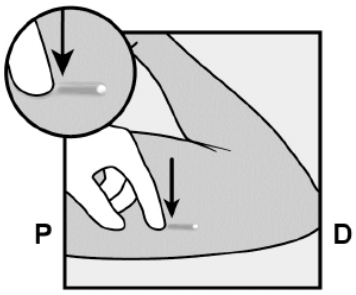


Figure 10

P, proximal (toward the shoulder);

D, distal (toward the elbow)

- Anaesthetise the site e.g. with 0,5 to 1 ml of 1 % lidocaine or lignocaine where the incision will be made (**Figure 11**). Be sure to inject the local anaesthetic **under** the implant to keep the implant close to the skin surface. Injection of local anaesthetic over the implant can make removal more difficult.

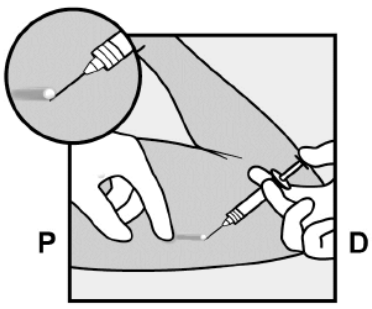


Figure 11

- Push down the end of the implant closest to the shoulder (**Figure 12**) to stabilise it throughout the procedure. Starting over the tip of the implant closest to the elbow, make a longitudinal (parallel to the implant) incision of approximately 2 mm towards the elbow. Take care not to cut the tip of the implant.

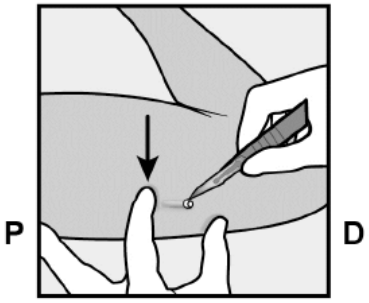


Figure 12

- The tip of the implant should pop out of the incision. If it does not, gently push the implant towards the incision until the tip is visible. Grasp the implant with forceps and if possible remove the implant (**Figure 13**). If needed, gently remove adherent tissue from the tip of the implant using blunt dissection. If the implant tip is not exposed following blunt dissection, make an incision into the tissue sheath and then remove the implant with the forceps (**Figure 14** and **15**).

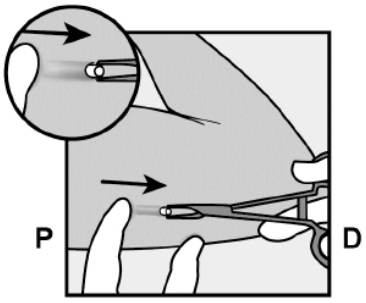


Figure 13

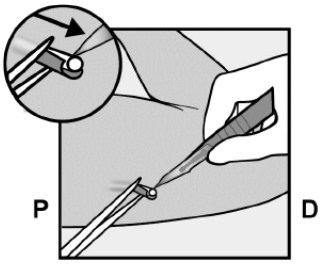


Figure 14

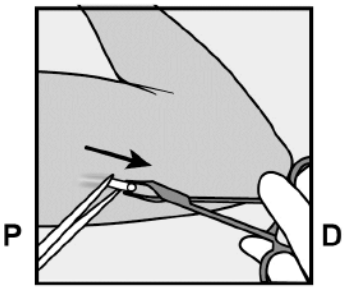


Figure 15

If the tip of the implant does not become visible in the incision, insert a forceps (preferably curved mosquito forceps, with the tips pointed up) superficially into the incision (**Figure 16**). Gently grasp the implant and then flip the forceps over

into your other hand (**Figure 17**). With a second pair of forceps carefully dissect the tissue around the implant and grasp the implant (**Figure 18**). The implant can then be removed. **If the implant cannot be grasped, stop the procedure and refer the woman to a medical practitioner experienced with complex removals or contact the local Organon office (Telephone: +27(0)87 106 9655).**

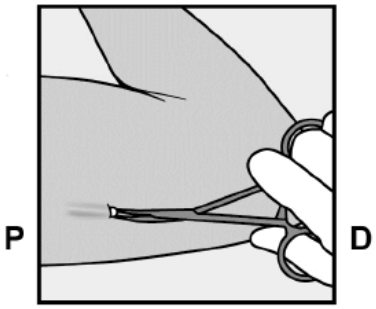


Figure 16

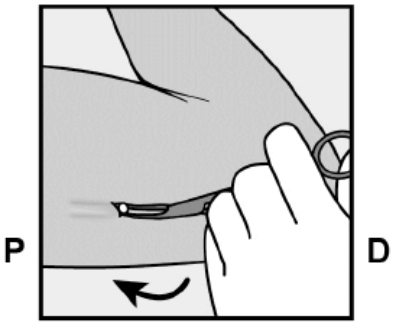


Figure 17

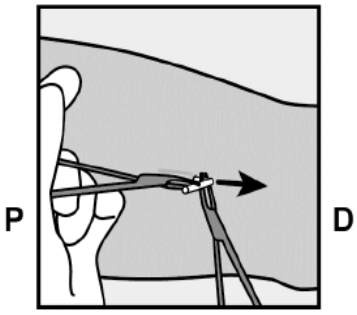


Figure 18

- Confirm that the entire implant, which is 4 cm long, has been removed by measuring its length. There have been reports of broken implants in the patient's arm. In some cases, difficult removal of the broken implant has been reported. If a partial implant (less than 4 cm) is removed, the remaining piece should be removed by following the instructions in **How to remove Implanon NXT.**
- If the woman would like to continue using Implanon NXT, a new implant may be inserted immediately after the old implant is removed using the same incision as long as the site is in the correct location (see **How to replace Implanon NXT**).
- After removing the implant, close the incision with a sterile adhesive wound closure.
- Apply sterile gauze with a pressure bandage to minimise bruising. The woman may remove the pressure bandage after 24 hours and the sterile adhesive wound closure after 3 to 5 days.

Localisation and removal of a non-palpable implant

There have been reports of migration of the implant; usually this involves movement in the region of the original position (see **WARNINGS AND SPECIAL PRECAUTIONS**) but may lead to the implant not being palpable at the location in which it was placed. An implant that has been too deeply inserted or has migrated may not be palpable and therefore imaging procedures, as described below, may be required for localisation.

A non-palpable implant should always be located prior to attempting removal. Given the radiopaque nature of the implant, suitable methods for localisation include two-dimensional x-ray and x-ray computed tomography (CT). Ultrasound scanning (USS) with a high-frequency linear array transducer (10 MHZ or greater) or magnetic resonance imaging (MRI) may be used. Once the implant has been localised in the arm, the implant should be removed by a medical practitioner experienced in removing deeply placed implants and familiar with the anatomy of the arm. The use of ultrasound guidance during the removal should be considered.

If the implant cannot be found in the arm after comprehensive localisation attempts, imaging techniques to the chest should be considered as migration to the pulmonary vasculature has been reported. If the implant is located in the chest, surgical or endovascular procedures may be needed for removal; a medical practitioner who has been trained and is familiar with the anatomy of the chest should be consulted.

If at any time these imaging methods fail to locate the implant, etonogestrel blood level determination can be used for verification of the presence of the implant. Please contact your local Organon office (Telephone: +27(0)87 106 9655) for further guidance.

If the implant migrates within the arm, removal may require a minor surgical procedure with a larger incision or a surgical procedure in an operating room. Removal of deeply inserted implants should be conducted with caution in order to help prevent damage to deeper neural

or vascular structures in the arm. Non-palpable and deeply inserted implants should be removed by a medical practitioner who has been trained and is familiar with the anatomy of the arm and removal of deeply-inserted implants.

Exploratory surgery without knowledge of the exact location of the implant should not be attempted.

Please contact your local Organon office (Telephone: +27(0)87 106 9655) for further guidance.

How to replace Implanon NXT

Immediate replacement can be done after removal of the previous implant and is similar to the insertion procedure described in section **How to insert Implanon NXT**.

The new implant may be inserted in the same arm, and through the same incision from which the previous implant was removed, as long as the site is in the correct location (see **How to insert Implanon NXT**). If the same incision is used to insert a new implant, anaesthetise the insertion site (e.g. with 2 ml of 1 % lidocaine or lignocaine) applied just under the skin commencing at the removal incision along the ‘insertion canal’ and follow the subsequent steps in the insertion instructions.

SIDE EFFECTS

Serious undesirable effects see **WARNINGS AND SPECIAL PRECAUTIONS.**

After insertion of Implanon NXT, women are likely to have changes in their menstrual bleeding pattern which are unpredictable beforehand. These may include occurrence of an irregular bleeding pattern (absent, less, more frequent or continuous), and changes in bleeding intensity (reduced or increased) or duration. Amenorrhoea was reported in about 20 % of women while another 20 % of women reported frequent and/or prolonged bleeding.

Occasionally, heavy bleeding has been reported. In clinical trials, Bleeding changes were the most common reason for stopping treatment (about 11 %).

Undesirable effects reported in clinical trials have been listed in the Table below.

System Organ Class	**Adverse reaction in MedDRA Term[1]**		
	Very Common **> 1/10**	**Common** **< 1/10 to ≥ 1/ 100**	**Uncommon** **< 1/100 to ≥ 1/1 000**
Infections and Infestations	Vaginal infections	-	Pharyngitis, rhinitis, urinary tract infection
Immune system disorders	-	-	Hypersensitivity
Metabolism and nutritional disorders	-	Increased appetite	-
Psychiatric disorders	-	Affect lability, depressed mood, nervousness, libido decreased	Anxiety, insomnia
Nervous system disorders	Headache	Dizziness	Migraine, somnolence
Vascular disorders	-	Hot flushes	-
Gastrointestinal disorders	-	Abdominal pain, nausea, flatulence	Vomiting, constipation, diarrhoea
Skin and subcutaneous tissue disorders	Acne	Alopecia	Hypertrichosis, rash, pruritus
Musculoskeletal and	-	-	Back pain, arthralgia,

connective tissue disorders			myalgia, musculoskeletal pain
Renal and urinary disorders	-	-	Dysuria
Reproductive system and breast disorders	Breast tenderness, breast pain, irregular menstruation	Dysmenorrhoea, ovarian cyst	Genital discharge, vulvovaginal discomfort, galactorrhoea, breast enlargement, genital pruritus
General disorders and administration site condition	-	Implant site pain, implant site reaction, fatigue, influenza like illness, pain	Pyrexia, oedema
Investigations	Increased weight	Decreased weight	-

[1] The most appropriate MedDRA term (version 10.1) to describe a certain adverse reaction is listed. Synonyms or related conditions are not listed but should be taken into account as well.

In a clinical trial of Implanon NXT, in which investigators were asked to examine the implant site after insertion, implant site reactions were reported in 8,6 % of women. Erythema was the most frequent implant site complication, reported during and/or shortly after insertion, occurring in 3,3 % of patients. Additionally, haematoma (3,0 %), bruising (2,0 %), pain (1,0 %) and swelling (0,7 %) were reported.

During post-marketing surveillance:

- A clinically relevant rise in blood pressure has been observed in rare cases. Seborrhoea has also been reported.
- Anaphylactic reactions, urticaria, angioedema, aggravation of angioedema and/or aggravation of hereditary angioedema may occur.

Insertion or removal of Implanon NXT may cause bruising, local irritation, pain or itching. Fibrosis at the implant site may occur, a scar may be formed or an abscess may develop. Paraesthesia or paraesthesia-like events may occur. Expulsion or migration of Implanon NXT have been reported, including to the chest wall. Implants have also been found within the vasculature including the pulmonary artery. Some cases of implants found within the pulmonary artery reported chest pain and/or dyspnoea. Implanon NXT that has migrated to the pulmonary artery may be asymptomatic or may lead to clinical symptoms such as chest pain and/or dyspnoea (see **WARNINGS AND SPECIAL PRECAUTIONS**). Surgical intervention may be necessary when removing Implanon NXT.

Ectopic pregnancies have been reported (see **WARNINGS AND SPECIAL PRECAUTIONS**).

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT

An implant should always be removed before inserting a new one. There is no data available on overdose with etonogestrel.

IDENTIFICATION

The pack contains a smooth and flexible rod of a white to slightly yellow or slightly brown colour, 4 cm in length and 2 mm in diameter, in the stainless steel needle of a ready-for-use, disposable sterile applicator.

PRESENTATION

One pack contains one implant, which is preloaded in the stainless steel needle of a ready-for-use, disposable sterile applicator. The applicator containing the implant is packed in a blister pack, made of transparent polyethyleneterephtalate glycol (PETG), sealed with a lidding made of high density polyethylene (HDPE).

STORAGE INSTRUCTIONS

Store at or below 30 °C.

Contents are sterile unless package is damaged or opened.

For single use only.

Keep out of reach of children.

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

REGISTRATION NUMBER

34/18.8/0448

NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION

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