

AUSTRALIAN PRODUCT INFORMATION

IMPLANON NXT® (etonogestrel) Subdermal Implant

1 NAME OF THE MEDICINE

Etonogestrel

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each radiopaque implant contains 68 mg etonogestrel; the release rate is 60-70 µg/day during week 5-6 and decreases 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 the full list of excipients, see **Section 6.1 List of Excipients**.

3 PHARMACEUTICAL FORM

Implanon NXT (etonogestrel) is a subdermal contraceptive implant, consisting of a co-axial rod, preloaded in an applicator.

The radiopaque implant is a non-biodegradable, white to off-white, flexible rod with a length of 4.0 cm and a diameter of 2.0 mm and is located inside the preloaded, sterile, ready-for-use, disposable applicator.

The rod consists of a core containing a mixture of the drug substance, etonogestrel, and of barium sulfate and ethylene vinyl acetate copolymer and a skin consisting of ethylene vinyl acetate copolymer.

Applicator

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

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Contraception (removed and replaced every three years to ensure continued contraceptive efficacy).

4.2 DOSE AND METHOD OF ADMINISTRATION

Pregnancy should be excluded before insertion of Implanon NXT

Healthcare professionals (HCPs) are strongly recommended to participate in a training session to become familiar with the use of the Implanon NXT applicator and the techniques for insertion and removal of the Implanon NXT implant and where appropriate, request supervision prior to inserting or removing the implant.

Before inserting the implant, carefully read and follow the instructions for insertion and removal of the implant in the sections **How to insert Implanon NXT** and **How to remove Implanon NXT**.

Videos demonstrating insertion and removal of Implanon NXT, are available online (www.ImplanonNXTvideos.com).

Please contact your local Organon office if you have any questions:

Australia: Telephone Toll Free: 1800 023 135.

New Zealand: Telephone Toll Free: 0800 111 700.

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

How to use Implanon NXT

Implanon NXT is a long-acting hormonal contraceptive. A single implant is inserted subdermally and can be left in place for three years. Remove the implant no later than three years after the date of insertion. The user should be informed that she can request the removal of the implant at any time. Healthcare professionals may consider earlier replacement of the implant in heavier women (see **Section 4.4 Special Warnings and Precautions for Use**). 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 unintended pregnancy.** An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the localisation and/or removal can be difficult (see sections **How to remove Implanon NXT** and **Section 4.4 Special Warnings and Precautions for Use**).

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 overlaying the triceps muscle and about 8-10 cm (3-4 inches) from the medial epicondyle of the humerus and 3-5 cm (1.25-2 inches) posterior to (below) 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 Figure 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, see section **How to insert Implanon NXT**.

The Implanon NXT package contains a User Card intended for the woman which records the batch number of the implant. Healthcare professionals 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 HCP records showing the batch number.

When to insert Implanon NXT

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

No preceding hormonal contraceptive use in the past month

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

When the implant is inserted later, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

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

The implant should be inserted preferably on the next day following intake of the last active tablet (the last tablet containing the active substance) 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.

When the implant is inserted later, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

Changing from a progestagen-only contraceptive method (e.g. minipill, injectable, implant, or intrauterine system [IUS])

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.
- *Minipill:* A woman may switch to Implanon NXT on any day from the minipill. The implant should be inserted within 24 hours after taking the last tablet.
- *Implant/Intrauterine system (IUS):* Insert the implant on the day the previous implant or IUS is removed.

When the implant is inserted later, 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 may be inserted immediately following a complete first trimester abortion or miscarriage. If the implant is not inserted within five days following a first trimester abortion or miscarriage, follow the instructions under **No preceding hormonal contraceptive use in the past month.**
- *Second trimester:* Insert the implant between 21 to 28 days following second trimester abortion or miscarriage.

When the implant is inserted later, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

Postpartum

- *Not breast-feeding:* The implant should be inserted between 21 to 28 days postpartum. When the implant is inserted later, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.
- *Breast-feeding:* The implant should be inserted after the fourth postpartum week (see also **Section 4.6 Fertility, Pregnancy and Lactation, Use in 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.

Note

It is important to follow the directions above regarding the proper timing of the insertion of the Implanon NXT implant. If deviating from the above directions, pregnancy should be first ruled out and the woman should be instructed to also use a non-hormonal contraceptive method, such as condoms, until 7 days after insertion of the implant.

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 HCP 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 **Section 4.4 Special Warnings and Precautions for Use**).
- If the implant is inserted deeply, neural or vascular damage may occur. Deep or incorrect insertions have been associated with paraesthesia (due to neural damage) and migration of the implant (due to intramuscular or fascial insertion), and in rare cases with intravascular insertion.

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

Insertion Procedure

To help make sure the implant is inserted just under the skin, the HCP 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 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 muscle about 8-10 cm (3-4 inches) from the medial epicondyle of the humerus and 3-5 cm (1.25-2 inches) posterior to (below) the sulcus (groove) between the biceps and triceps muscles. (Figure 2a, 2b, and 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.

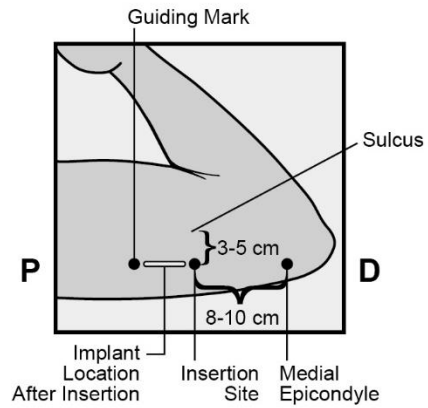


Figure 2a

P, proximal (toward the shoulder);

D, distal (toward the elbow)

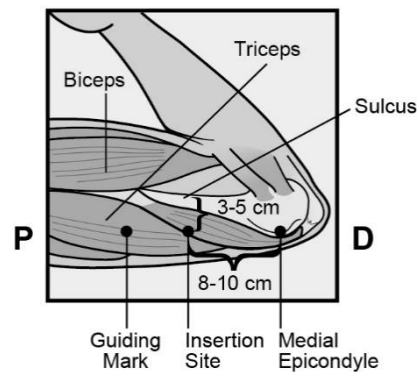
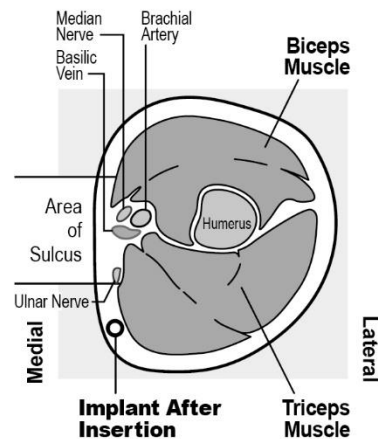


Figure 2b



Medial (inner side of the arm)

Lateral (outer side of the arm)

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 (for example, with anaesthetic spray or by injecting 2 mL of 1% lignocaine just under the skin along the planned insertion tunnel).
- Remove the sterile preloaded disposable Implanon NXT applicator carrying the implant from its blister. Visually inspect for breaches of packaging integrity prior to use for damages (e.g. torn, punctured, etc). If the packaging has any visual damage that could compromise sterility, do not use the applicator..
- 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. You should see the white coloured implant by looking into the tip of the needle. **Do not touch the purple slider until you have fully inserted the needle subdermally, as doing so will retract the needle and prematurely release the implant from the applicator.**

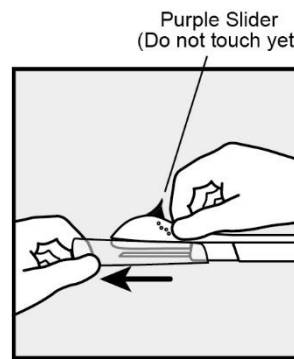


Figure 3

- If the purple slider is released prematurely, restart the procedure with a new applicator.
- With your free hand, stretch the skin around the insertion site towards the elbow (Figure 4).

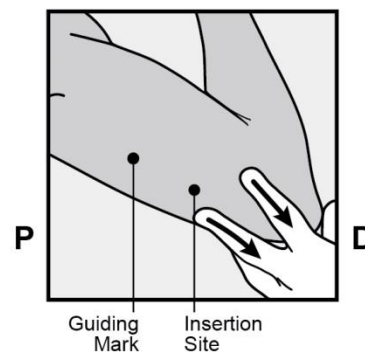


Figure 4

- **The implant should be inserted subdermally just under the skin (see Section 4.4 Special Warnings and Precautions for Use)**
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 the side view you can clearly see the insertion site and the movement of the needle just under the skin (see Figure 6).

- Puncture the skin with the tip of the needle slightly angled less than 30° (Figure 5a).

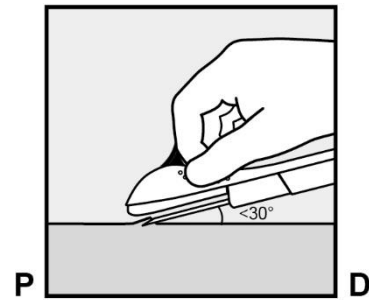


Figure 5a



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

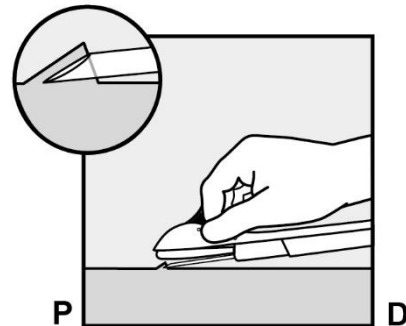


Figure 5b

- Lower the applicator 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). You may feel slight resistance but do not exert excessive force (Figure 6). **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 position before completing the insertion procedure.

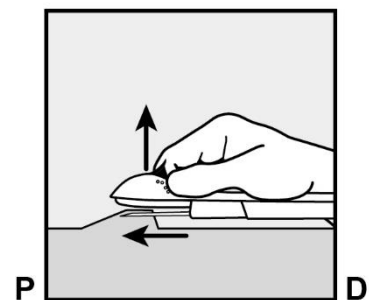


Figure 6

- Keep the applicator in the same position with the needle inserted to its full length (Figure 7). If needed, you may use your free hand to stabilise the applicator.

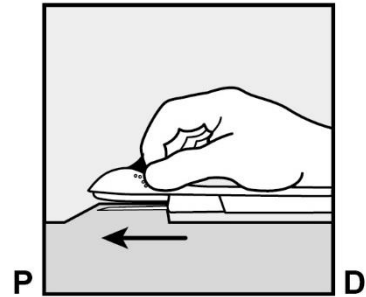


Figure 7

- Unlock the purple slider by pushing it slightly down (Figure 8a). Move the slider 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).

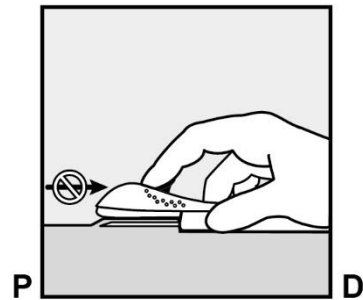


Figure 8a

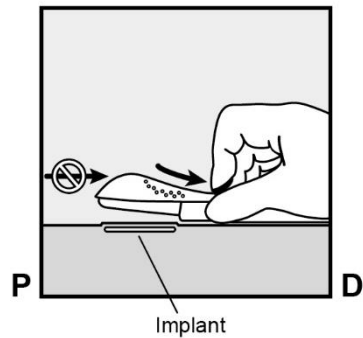


Figure 8b

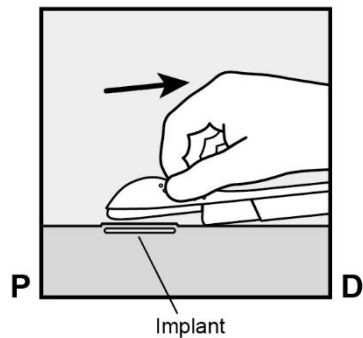


Figure 8c

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.
- **Always verify the presence of the implant in the woman's arm immediately after insertion by palpation.** By palpating both ends of the implant, you should be able to confirm the presence of the 4 cm rod (Figure 9). See section below **If the rod is not palpable after insertion.**

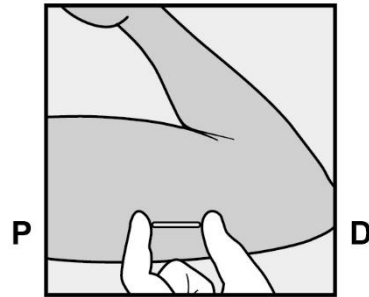


Figure 9

- Request that the woman palpate the implant.
- Apply sterile gauze with a pressure bandage to minimise bruising. The woman may remove the pressure bandage in 24 hours and the small adhesive bandage over the insertion site after 3-5 days.
- Complete the User Card and give it to the woman to keep. Also, complete the adhesive labels and affix it 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 biohazardous waste.

If the rod is not palpable after insertion

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

- Check the applicator. The needle should be fully retracted and only the purple tip of the obturator should be visible.
- Use other methods to confirm the presence of the implant. Given the radiopaque nature of the implant, suitable methods for localisation are: two-dimensional X-ray and X-ray computerised tomography (CT) scanning. 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 it is recommended to consult Organon for 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 localized and removed as soon as possible to avoid the potential for distant migration (see **Section 4.4 Special Warnings and Precautions for Use**).



How to remove Implanon NXT

Removal of the implant should only be performed under aseptic conditions by a HCP who is familiar with the removal technique. **If you are unfamiliar with the removal technique, contact Organon for further information.**

Before initiating the removal procedure, the HCP 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 HCP experienced in removing deeply placed implants and familiar with localising the implant and the anatomy of the arm. Contact Organon for further information.

See section below on **Localisation and removal of a non-palpable implant** if the implant cannot be palpated.

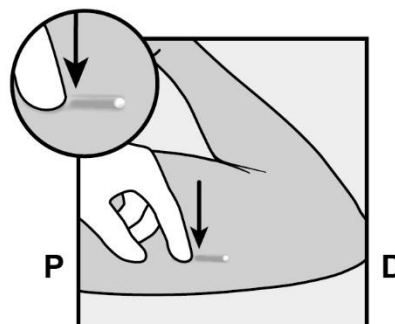
Procedure for removal of an implant that is palpable

For illustrative 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 Organon for further information.



- Mark the distal end (end closest to the elbow), for example, with a surgical marker. Figure 10

- Clean the site with an antiseptic solution.

P, proximal (toward the shoulder);
D, distal (toward the elbow)

- Anaesthetise the site, for example, with 0.5 to 1 mL 1% 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.

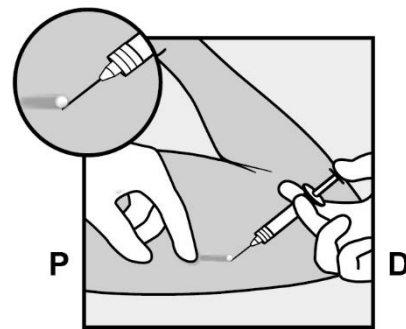


Figure 11

- 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 2 mm towards the elbow. Take care not to cut the tip of the implant.

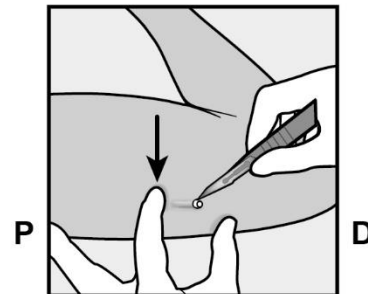


Figure 12

- 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 (Figures 14 and 15).

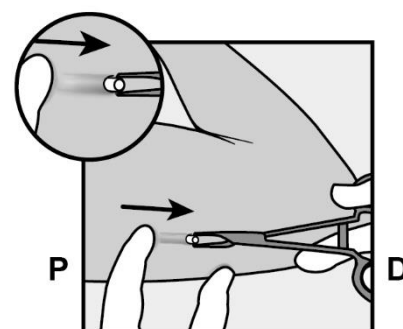


Figure 13

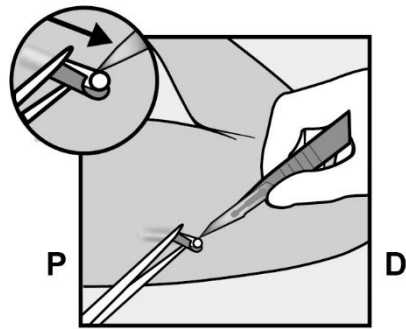


Figure 14

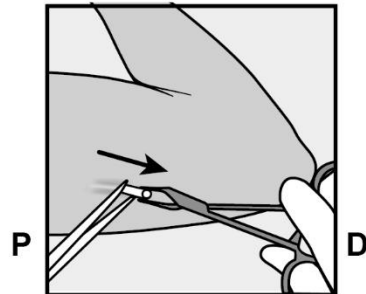


Figure 15

- If the tip of the implant does not become visible in the incision, insert 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 HCP experienced with complex removals or contact Organon.**

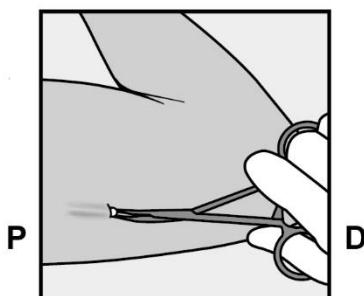


Figure 16

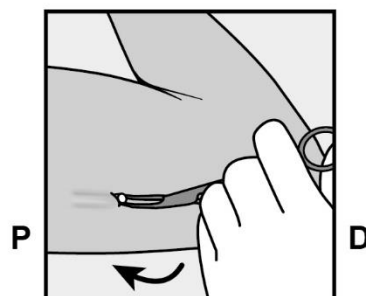


Figure 17

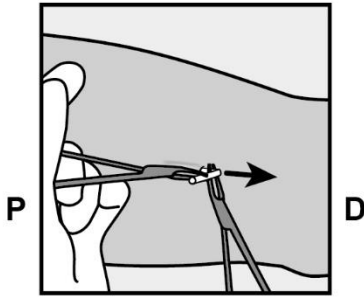


Figure 18

- Confirm that the entire implant, which is 4 cm long, has been removed by measuring its length. There have been reports of broken implants while 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.
- 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 3-5 days.

Localisation and removal of a non-palpable implant

There have been occasional reports of migration of the implant; usually this involves minor movement relative to the original position (see **Section 4.4 Special Warnings and Precautions for Use**), but may lead to the implant not being palpable at the location in which it was placed. An implant that has been 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 computer 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 HCP 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, consider applying imaging techniques to the chest as rare events of migration to the pulmonary vasculature have been reported. If the implant is located in the chest, surgical or endovascular procedures may be needed for removal; HCPs 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 Organon 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 HCPs familiar with the anatomy of the arm and removal of deeply-inserted implants.

Exploratory surgery without knowledge of the exact location of the implant is strongly discouraged.

Please contact Organon 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 **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 i.e., 8-10 cm from the medial epicondyle of the humerus and 3-5 cm posterior to (below) the sulcus (see **How to insert Implanon NXT**). If the same incision is being used to insert a new implant, anaesthetise the insertion site (e.g. 2 mL lignocaine (1%)) applied just under the skin commencing at the removal incision along the 'insertion canal' and follow the subsequent steps in the insertion instructions.

4.3 CONTRAINDICATIONS

- Known or suspected pregnancy.
- Active thromboembolic disorders.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Known or suspected sex steroid sensitive malignancies.
- Known or suspected carcinoma of the breast.
- Presence or history of liver tumours (benign or malignant).
- Undiagnosed vaginal bleeding.
- Hypersensitivity to the active substance or any of the excipients of Implanon NXT see Section 6.1 **List of excipients**.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Medical examination/consultation

Prior to the initiation or reinstatement 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, guided by **Section 4.3 Contraindications** and **Section 4.4 Special Warnings and Precautions for Use**. It is recommended that the woman returns for a medical check-up three 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, but at least once a year is advised.

Other

Women should be told that Implanon NXT does not offer protection against HIV (AIDS) and other sexually transmitted diseases.

Use with caution in the following circumstances

The user should be informed about the pros and the cons of an implant compared to other contraceptive methods before the insertion of Implanon NXT. If any of the conditions/risk factors mentioned below are present, the benefits of progestagen use should be weighed against the possible risks for each individual case and discussed with the woman before she decides to start with Implanon NXT. In the event of aggravation, exacerbation or the first appearance of any of these conditions, the woman should contact her physician. The physician should then decide whether the use of Implanon NXT should be discontinued.

Carcinoma of the breast

- The risk for breast cancer increases in general with increasing age. During the use of (combined) 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 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.

Thrombotic and other vascular events

- Epidemiological studies have associated the use of combined oral contraceptives (COCs) with an increased incidence in venous thromboembolism (VTE, deep vein 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 oestrogenic component is unknown, the implant should be removed in the event of a thrombosis. Removal of the implant should also be considered for women who are immobilised for a long time because of surgery or a disease. 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 venous thromboembolic disease should be made aware of the possibility of a recurrence.
- There have been postmarketing 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 the etonogestrel implant. Implanon NXT should be removed in the event of a thrombosis.

Other conditions

- 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; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss and (hereditary) angioedema.

Liver disease

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

Chloasma

- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to develop chloasma should avoid exposure to the sun or ultraviolet radiation whilst using Implanon NXT.

Carbohydrate and lipid metabolic effects

- 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.
- Women who are being treated for hyperlipidemia should be followed closely if they elect to use Implanon NXT. Some progestagens may elevate LDL levels and may render the control of hyperlipidemia more difficult.

Elevated blood pressure

- Implanon NXT use should be discontinued when during the use of the implant there is a constantly elevated blood pressure or when a significant increase in blood pressure does not respond to an antihypertensive therapy.

Complications of insertion

- Expulsion may occur especially if the implant is not inserted according to the instructions given in **Section 4.2 Dose and Method of Administration, How to insert Implanon NXT**, or as a consequence of a local inflammation.
- Occasionally a scar may be formed.
- There have been reports of migration of the implant within the arm from the insertion site, which may be related to a deep initial insertion (see **Section 4.2 Dose and Method of Administration, How to insert Implanon NXT**) or to external forces (e.g. manipulation of the implant or contact sports). There also have been rare postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. In cases where the implant has migrated within the arm from the insertion site, localisation may be more difficult and removal may require a minor 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 may be needed for removal (see **Section 4.2 Dose and Method of Administration, How to remove Implanon NXT**). If at any time the implant cannot be palpated, it should be localised and removal is recommended. If the implant cannot be removed, contraception and the risk of progestogen-related undesirable effects may continue beyond the time desired by the woman.

Reduced efficacy with concomitant medications

- The efficacy of Implanon NXT may be reduced when concomitant medications that decrease the plasma concentration of etonogestrel are used (see **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

Body weight

- 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. The clinical experience in heavier women in the third year of use is limited. Therefore it cannot 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.

Changes in menstrual bleeding pattern

- During the use of the implant, women are likely to have changes in their menstrual bleeding pattern. These may include changes in bleeding frequency (absent, less, more frequent or continuous), intensity (reduced or increased) or duration. Amenorrhoea was reported in about 1 of 5 women while another 1 of 5 women reported frequent and/or prolonged bleeding. Dysmenorrhoea tended to improve while using the implant. The bleeding pattern experienced during the first three months is broadly predictive of future bleeding patterns for many women. Evaluation of vaginal bleeding should be done on an ad hoc basis and may include an examination to exclude gynaecological pathology or pregnancy.

Ovarian cysts

- 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 and rarely, they require surgical intervention.

Ectopic pregnancies

- 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 NXT consistently inhibits ovulation, ectopic pregnancy should be taken into account in the differential diagnosis if the woman gets amenorrhoea or abdominal pain.

Broken or bent implant

- There have been reports of broken or bent implants, which may be related to external forces (e.g. manipulation of the implant or contact sports) while in the patient's arm. There have also been reports of migration of a broken implant fragment within the arm. There are no clinical study data on efficacy and safety with broken implants. In vitro data indicated that 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 **Section 4.2 Dose and Method of Administration, How to remove Implanon NXT**).

Use in hepatic impairment

See **Section 4.3 Contraindications** and **Section 4.4 Special warnings and precautions for use (Liver Disease)**.

Use in the elderly

- This product has not been studied in women over 65 years of age,

Paediatric use

- No well-controlled clinical studies have been conducted in women less than 18 years of age.

Effects on laboratory tests

- Data obtained with COCs have shown that contraceptive steroids may affect some laboratory parameters, 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 were generally within the normal range. To what extent this also relates to progestagen-only contraceptives is not known.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Influence of other medicinal products on Implanon NXT

Interactions between hormonal contraceptives and other medicinal products may lead to menstrual bleeding and /or contraceptive failure. The following interactions have been reported in the literature (mainly with combined contraceptives but occasionally also with progestogen-only contraceptives).

Hepatic metabolism: Interactions can occur with medicinal or herbal products that induce microsomal enzymes, specifically cytochrome P450 enzymes (CYP), which can result in increased clearance, reducing plasma concentrations of sex hormones and may decrease the effectiveness of Implanon NXT. These products include phenytoin, barbiturates, primidone, bosentan, carbamazepine, rifampicin, and possibly also oxcarbazepine, rifabutin, topiramate, felbamate, griseofulvin, some HIV protease inhibitors (e.g. ritonavir) and non-nucleoside reverse transcriptase inhibitors (e.g. efavirenz), and the herbal remedy St. John's wort.

Enzyme induction can occur after a few days of treatment. Maximum enzyme induction is generally observed within a few weeks. After drug therapy is discontinued, enzyme induction can last for about 28 days. 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 HCV medicinal products (e.g. boceprevir, telaprevir), can increase or decrease plasma concentrations of progestins, including etonogestrel. The net effect of these changes may be clinically relevant in some cases.

Women receiving any of the above mentioned hepatic enzyme-inducing drugs 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 barrier method during the time of concomitant drug administration and for 28 days after 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 medicinal products

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

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

See **Section 5.1 Pharmacodynamic Properties, Clinical trials, Return of fertility.**

Use in pregnancy: Category B3

- The use of Implanon NXT is contraindicated during pregnancy. If pregnancy occurs during use of Implanon NXT, the implant should be removed.
- Animal studies have shown that high doses of progestagens can cause masculinisation of the female foetus. However, in animal studies of etonogestrel, no embryotoxic or fetotoxic effects were seen in rats or rabbits at oral doses up to 2 mg/kg/day. Plasma drug levels were not measured in either study, but it can be estimated that systemic exposure at the high dose level in the rat study was 1.6 to 3 times higher than in women with etonogestrel implants. There are insufficient data on the use of Implanon NXT during pregnancy in humans to evaluate possible harmful effects during a possible pregnancy. So far there are no indications for an increased risk of birth defects of children born to women using COC or progestagen-only contraceptives prior to pregnancy. Neither is there any indication for teratogenic defects in cases where a progestagen-only contraceptive was used in women not knowing of their pregnancy. The relevance of this to Implanon NXT has not been confirmed yet.

Use in lactation

- In an open, non-randomised comparative study of Implanon (n=42) vs IUD (n=38) in healthy lactating women, Implanon was shown not to 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 normalised 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 had an implant inserted 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 NXT may be used during lactation.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

- No observed effects.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Serious undesirable effects

Refer to **Section 4.4 Special Warnings and Precautions for Use.**

Other possible undesirable effects

The following adverse effects have been reported during the use of Implanon. An association has been neither confirmed nor refuted. Some of these effects have also been occasionally reported with progestagen-only contraceptives.

Table 1

Percentages of subjects with at least one experience classified by body system and reported as related to the study drug pre-marketing in clinical trials performed by MSD ¹.

Body System (WHO System Organ Class)	Implanon[®] ⁽²⁾ Related AE's (> 2.5%) N= 1326 %	Norplant[®] (levonorgestrel releasing implants) Related AE's (> 5%) N= 184 %
Reproductive disorders, female		
Breast Pain	9.8	11.4
Dysmenorrhoea	4.4	3.8
Skin appendage disorders		
Acne	14.8	21.1
Alopecia	2.5	3.3
Central and peripheral system disorders		
Headache	13.3	20.1
Dizziness	3.8	7.1
Gastrointestinal system disorders		
Abdominal pain	4.7	8.2
Nausea	2.5	5.4
Flatulence	2.6	1.1
Psychiatric disorders		
Emotional lability	5.2	7.6
Depression	3.2	4.9
Nervousness	2.9	3.3
Libido decreased	3.2	5.4
Metabolic and nutritional system disorders		
Weight increase	10.4	7.1
Application site disorders		
Injection site pain	4.1	7.1
Injection site reaction	2.9	4.3

¹ Some subjects may have experienced more than one AE.

² Only AEs for Implanon with an incidence higher than 2.5% are included in the table. The data are derived from studies in the US, Europe, Singapore & Thailand.

Adverse experiences were included as drug-related when they were considered possibly, probably or definitely related to study drug administration either by the investigator or by MSD.

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 subjects. Additionally, hematoma (3.0%), bruising (2.0%), pain (1.0%) and swelling (0.7%) were reported.

Post marketing observations

Insertion or removal of the implant

Insertion or removal of the implant may cause some vasovagal reactions (for example: hypotension, dizziness or syncope), bruising, slight 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 the implant

Expulsion or migration of the implant has been reported, including rarely to the chest wall. In rare cases, implants have been found within the vasculature including the pulmonary artery. Some cases of implants found within the pulmonary artery reported chest pain and/or respiratory disorders (such as dyspnoea, cough or hemoptysis); others have been reported as asymptomatic (see **Section 4.4 Special Warnings and Precautions for Use**). Surgical intervention might be necessary when removing Implanon NXT.

Other post marketing observations

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

On rare occasions, ectopic pregnancies have been reported (see **Section 4.4 Special Warnings and Precautions for Use**).

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

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.

For information on the management of overdose, contact the Poisons Information Centre on 131126 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

Pharmacotherapeutic group: progestagens, ATC-classification G03AC08

The Implanon NXT implant is a non-biodegradable, radiopaque, etonogestrel (ENG) containing implant for subdermal use, preloaded in a sterile, disposable applicator. Etonogestrel is the biologically active metabolite of desogestrel, a progestagen widely used in oral contraceptives (OCs). It is structurally derived from 19-nortestosterone and binds with high affinity to progesterone receptors in the target organs. The contraceptive effect of ENG is achieved primarily 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 ENG also causes changes in the cervical mucus, hindering the passage of spermatozoa. The three-year Pearl Index is 0.00 (95% Confidence Interval 0.00 – 0.18). This high degree of protection against pregnancy is obtained among other reasons because, in contrast to OCs, the contraceptive action of Implanon NXT is not dependent on the regular intake of pills. The contraceptive action of ENG is reversible, which is apparent by a rapid return of a normal menstrual cycle after removal of the implant.

Although ENG inhibits ovulation, ovarian activity is not completely suppressed. Mean oestradiol concentrations remain above the level seen in the early-follicular phase. In a two-year study, in which the bone mineral density in 44 users has been compared to that in a control group of 29 IUD-users no adverse effects on bone mass have been observed. 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.

Clinical trials indicate that users of Implanon NXT often have a less painful menstrual bleeding (dysmenorrhoea).

Clinical trials

Three pivotal efficacy and safety studies were performed in healthy, fertile and sexually active women. The single primary endpoint was pregnancy and as secondary endpoints the following parameters were studied: ovulation, weight, time required for Implanon insertion and removal, and laboratory variables. Following the removal of Implanon return to normal ovulation was investigated. In these pivotal studies a total number of 1,286 subjects using Implanon were studied. Total Implanon exposure was 2,093 Women Years (27,322, 28 day cycles). Pregnancies did not occur in the pivotal or supportive studies. The Pearl Index is essentially 0.00 (0.00 – 0.18, 95% CI). Contraceptive efficacy is satisfactory for a period of three years. The data demonstrate that Implanon is a highly efficacious contraceptive product mainly by virtue of its very efficient suppression of ovulation evoked by the continuous release of the drug substance etonogestrel. The safety profile is consistent with the well-known pharmacological profile of etonogestrel.

In a 3-year double-blind, randomised, bioequivalence trial 52 women were treated with the radiopaque implant (Implanon NXT) and 56 women were treated with the non-radiopaque implant (Implanon). Based on the AUC of ENG, the two implants were shown to be bioequivalent. No in treatment pregnancies were reported during the study. Based on the results from the bioequivalence study comparing Implanon and Implanon NXT, the clinical data and contraceptive efficacy observed with Implanon is also valid for Implanon NXT.

Bone mineral density

One two year study was performed in 46 women receiving an etonogestrel implant versus 33 women with an IUD to examine the effect of etonogestrel implant use on bone mineral density parameters. The changes in bone mineral density parameters were not different from a comparator IUD group and the mean bone mineral density parameters at several sites of the body were generally higher than those reported for a standard reference population. Oestradiol levels were above the threshold level for maintaining normal bone mass.

Weight changes

A body weight increase of about 1.5% per year was found for the etonogestrel implant as well as for the IUD comparator. The increase is therefore only partly attributable to the use of Implanon NXT.

Return of fertility

In supportive studies return of ovulation after implant removal was assessed by ultrasound measurements and hormone determinations. Ovulation returns after removal of the implant shortly after etonogestrel has disappeared from the body, enabling restoration of fertility. This

conclusion is supported by the occurrence of 37 pregnancies that were reported after implant removal.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

After insertion of the implant, ENG is rapidly absorbed into the blood stream. Ovulation-inhibiting concentrations are reached within 1 day. Maximum serum concentrations (between approximately 400 and 3,000 pg/mL) are generally reached within the first 14 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 is measured, which slowly decreases to approximately 150 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 95.5-99% 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 approximately 27 l and 220 l, respectively, and hardly change during the use of the implant.

Metabolism

Etonogestrel is hydroxylated, reduced and conjugated to sulfates and glucuronides.

In vitro data provide evidence that metabolism of etonogestrel, similar to that of other contraceptive steroids, is catalysed by CYP3A4 (See **Section 4.5 Interactions with Other Medicines and Other Forms of Interactions**).

Excretion

After IV administration of ENG, 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 treatment period. The excretion of ENG and its metabolites, either as free steroids or as conjugates, is in urine and faeces (ratio 1.5:1). After insertion in lactating women, etonogestrel is excreted in breast milk with a milk/serum ratio of 0.44-0.50 during the first four months. In lactating women, the mean transfer of etonogestrel to the infant is approximately 2.2% of the maternal etonogestrel daily dose (values normalised per kg body weight). Concentrations show a gradual and statistically significant decrease from about 20 to 15 and 10 ng/kg/day at month 1, 2 and 4 respectively in a group of 41 infants.

5.3 PRECLINICAL SAFETY DATA

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

Genotoxicity

Mutagenic activity was not observed in bacterial cells (Ames assay), but mutagenic and clastogenic activities in mammalian cells have not been investigated.

Carcinogenicity

No drug-related increases in tumour incidences were observed in rats with subcutaneous implants releasing 18 or 36 µg of etonogestrel/day. Serum etonogestrel levels in the high-dose group were 3 times higher than those in women with ENG implants.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Implant

Core: Evatane 28-25RG (proprietary ingredient 139830) 43 mg, barium sulfate (15 mg), magnesium stearate (0.1 mg).

Skin: Evatane 1040VN4 (proprietary ingredient 139829) 15 mg.

6.2 INCOMPATIBILITIES

No incompatibilities are known.

6.3 SHELF LIFE

The expiry date can be found on the packaging. In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). Implanon NXT should not be inserted after the expiry date as indicated on the primary package.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C.

6.5 NATURE AND CONTENTS OF CONTAINER

The pack contains one implant (4.0 cm in length and 2.0 mm in diameter) which is preloaded in the stainless steel needle of a ready-to-use, disposable sterile applicator. The applicator containing the implant is packed in a blister pack made of transparent polyethylene terephthalate glycol (PETG) sealed with a foil lidding. The blister pack is packed in a box together with the package leaflet.

AUST R No. 358190

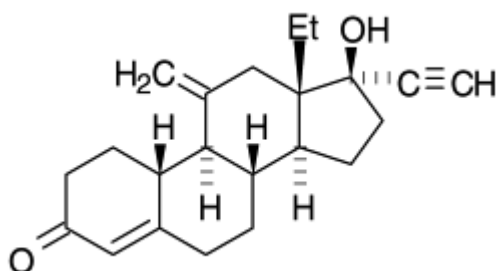
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Etonogestrel is also known as 3-ketodesogestrel or (17 α)-13-ethyl-17-hydroxy-11-methylene-18,19 dinorpregn-4-en-20-yn-3-one.

Chemical structure



Molecular formula: $C_{22}H_{28}O_2$. Molecular mass: 324.44. Etonogestrel is a white to nearly white crystalline powder.

CAS number

54048-10-1

7 MEDICINE SCHEDULE (POISONS STANDARD)

Prescription Only Medicine (S4)

8 SPONSOR

Organon Pharma Pty Ltd
Building A, 26 Talavera Rd,
Macquarie Park, NSW 2113
Australia

9 DATE OF FIRST APPROVAL

12 November 2010

10 DATE OF REVISION

18 April 2023

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
4.2	Editorial change to visual inspection
4.8	Possible vasovagal reactions side effect added

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