SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Implanon NXT, 68 mg, implant for subdermal use

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Implanon NXT is a radiopaque, non-biodegradable, progestagen-only, flexible implant preloaded in a sterile, disposable applicator.

Each radiopaque implant contains 68 mg of etonogestrel; the release rate is approximately 60-70 µg/day in week 5-6 and has decreased to approximately 35-45 µg/day at the end of the first year, to approximately 30-40 µg/day at the end of the second year and to approximately 25-30 µg/day at the end of the third year. The applicator is designed to be operated with one hand and to help facilitate correct subdermal insertion of the implant.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Implant for subdermal use.

Radiopaque, non-biodegradable, white to off-white, soft, flexible rod with a length of 4 cm and 2 mm in diameter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Contraception.

Safety and efficacy have been established in women between 18 and 40 years of age.

4.2 Posology and method of administration

Posology
1 implant, which can be left in place for three years.

Paediatric population
The safety and efficacy of Implanon NXT in adolescents under the age of 18 have not been established.

Method of administration
Pregnancy should be excluded before insertion of Implanon NXT.

It is strongly recommended that Implanon NXT be inserted and removed only by healthcare professionals (HCPs) who have completed training for the use of the Implanon NXT applicator and the techniques for insertion and removal of the Implanon NXT implant, and, where appropriate, that supervision be requested 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 section 4.2 How to insert Implanon NXT and How to remove Implanon NXT.

Videos demonstrating insertion and removal of the implant are available online, www.implanonnxtvideos.eu. Please contact your local representative of the Marketing Authorisation Holder if you have any questions, telephone: 00800-66550123.

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. HCPs may consider earlier replacement of the implant in heavier women (see section 4.4). 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 Implanon NXT package contains a Patient Alert Card intended for the woman which records the batch number of the implant. HCPs are requested to record the date of insertion, the arm of insertion and the intended date of removal on the Patient Alert Card. Patients should be instructed to keep the Patient Alert Card in a safe place and show the Card at any visits related to the use of her implant. The Patient Alert Card also contains instructions for the patient to occasionally gently palpate the implant to be sure that she knows its location. Patients should be instructed to contact their doctor as soon as possible if at any time they cannot feel the implant. The package also includes adhesive labels intended for HCP records showing the batch number. This information should be included in the electronic medical records of the patient if such are used.

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 and not on the correct day, this may result in an unintended pregnancy (see section 4.2 How to insert Implanon NXT and When to insert Implanon NXT).**
- **An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the localisation and/or removal can be difficult (see section 4.2 How to remove Implanon NXT and section 4.4).**

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 8-10 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 Figures 2a, 2b and 2c).

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 4.2 How to insert Implanon NXT subsection 'If the implant is not palpable after insertion'.

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, even if the woman is still bleeding.

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 hormonal 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 combined oral contraceptive or on the day of removal of the vaginal ring or transdermal patch. At the latest, the implant should be inserted on the day following the usual tablet-free, ring-free, patch-free or placebo tablet interval of the previous combined hormonal contraceptive when the next application would have been due. Not all contraceptive methods (transdermal patch, vaginal ring) may be available in all countries.

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.

Changing from a progestagen-only contraceptive method (e.g. progestagen-only pill, 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.
- Progestagen-only pill: A woman may switch from the 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 system (IUS): Insert the implant on the same day the previous implant or IUS 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 five 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.

Postpartum

- Not breast-feeding: The implant should be inserted between 21 to 28 days postpartum. If inserted as recommended, back-up contraception is not necessary. If the implant is inserted later than 28 days postpartum, 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 section 4.6). 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 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 (section 4.2 How to remove Implanon NXT and section 4.4).
- 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 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 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 (Figures 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.

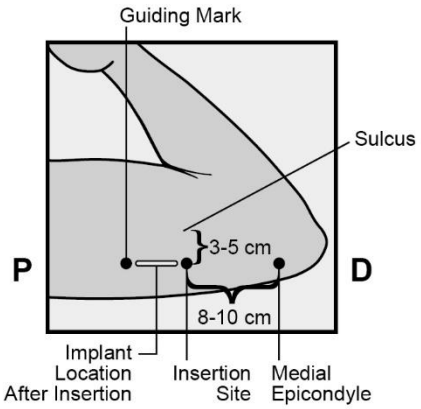

Figure 2a

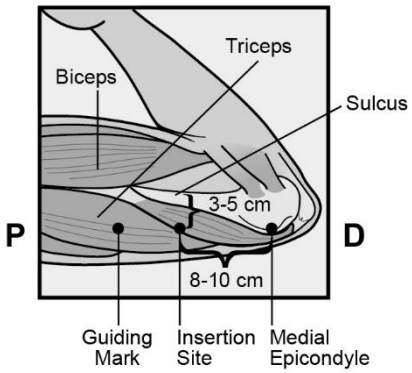

Figure 2b

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

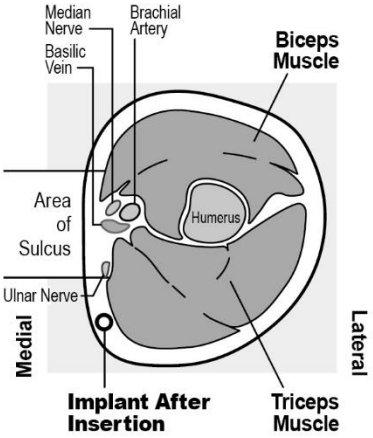

Figure 2c

Cross section of the upper left arm, as viewed from the elbow
Medial (inner side of the arm)
Lateral (outer side of the arm)

- 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 % lidocaine just under the skin along the planned insertion tunnel).
- Remove the sterile preloaded disposable Implanon NXT applicator carrying the implant from its blister. Inspect for breaches of packaging integrity prior to use by a visual check 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.**
- If the purple slider is released prematurely, restart the procedure with a new applicator.

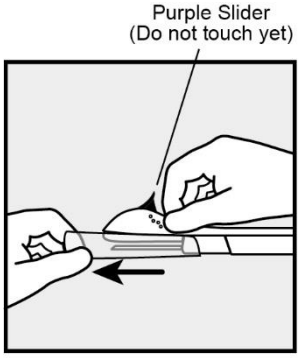

Figure 3

- With your free hand, stretch the skin around the insertion site towards the elbow (Figure 4).

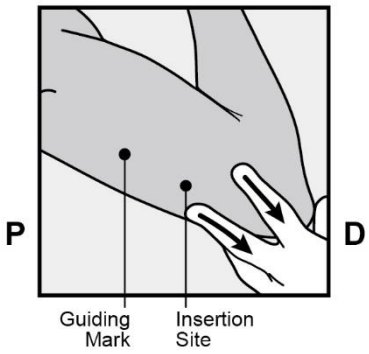

Figure 4

- **The implant should be inserted subdermally just under the skin (see section 4.4).**
  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).

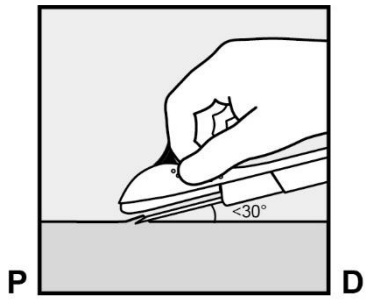

Figure 5a

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

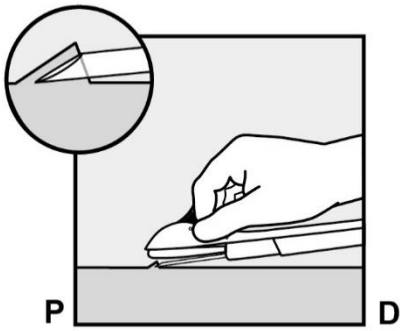

Figure 5b

- 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. **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 to further complete the insertion procedure.

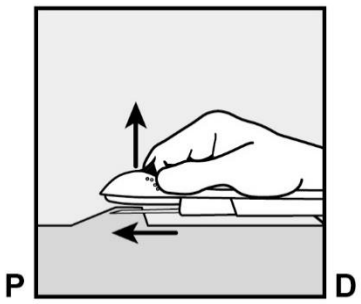

Figure 6

- 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.

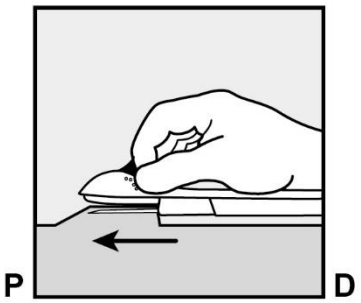

Figure 7

- 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).

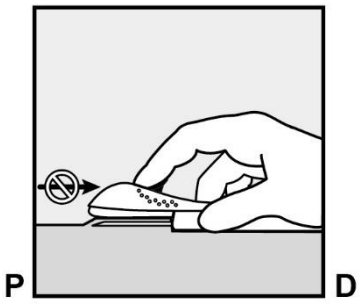

Figure 8a

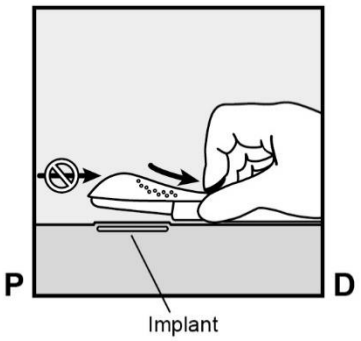

Figure 8b

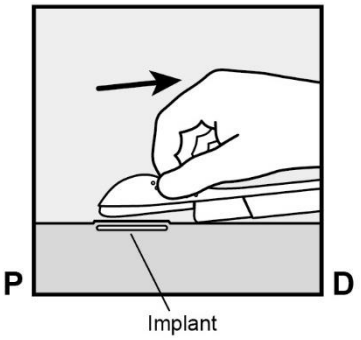

Figure 8c

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 implant is not palpable after insertion".

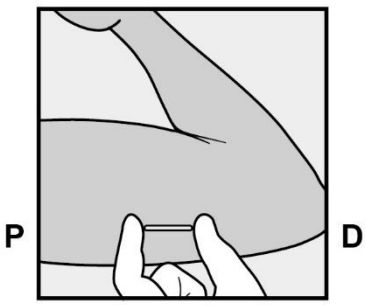

Figure 9

- 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 Patient Alert Card and give it to the woman to keep. Also, complete the adhesive labels and affix it to the woman's medical record. If electronic patient records are used, the information on the adhesive label should be recorded.
- 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 implant 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 its presence. 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 the implant cannot be found with these imaging methods, 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, contact the local representative of the Marketing Authorisation Holder who 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 section 4.4).

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 the local representative of the Marketing Authorisation Holder N.V. 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 Patient Alert 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 the local representative of the Marketing Authorisation Holder N.V. 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 10).

Figure 10

- Locate the implant by palpation. Push down the end of the implant closest to the shoulder (Figure 11) 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 difficult** and should be performed by providers experienced with removing deeper implants. Contact the local representative of the Marketing Authorisation Holder office N.V. Organon for further information.
- Mark the distal end (end closest to the elbow), for example, with a surgical marker.
- Clean the site with an antiseptic solution.

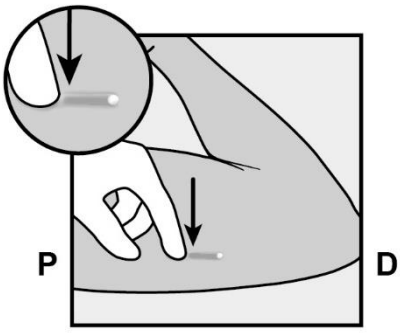

Figure 11
P, proximal (toward the shoulder);
D, distal (toward the elbow)

- Anesthetise the site, for example, with 0.5 to 1 ml 1 % lidocaine where the incision will be made (Figure 12). Be sure to inject the local anesthetic **under** the implant to keep the implant close to the skin surface. Injection of local anesthetic over the implant can make removal more difficult.

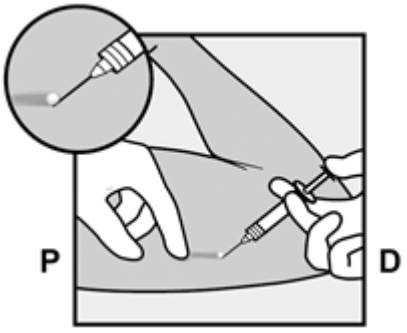

Figure 12

- Push down the end of the implant closest to the shoulder (Figure 13) 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.

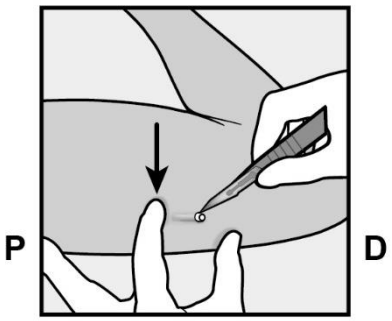

Figure 13

- 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 14). 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 15 and 16).

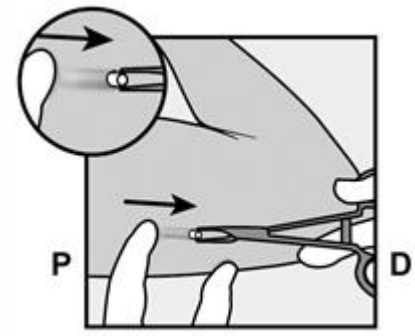

Figure 14

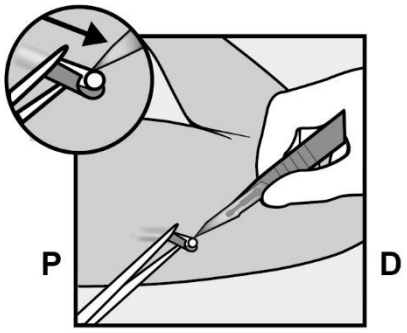

Figure 15

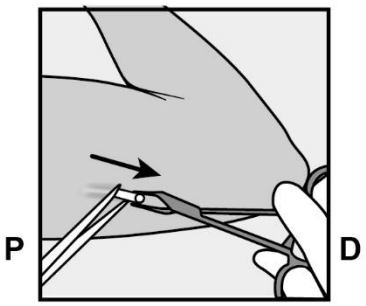

Figure 16

- If the tip of the implant does not become visible in the incision, gently insert a forceps (preferably curved mosquito forceps, with the tips pointed up) superficially into the incision (Figure 17).
- Gently grasp the implant and then flip the forceps over into your other hand (Figure 18).
- With a second pair of forceps carefully dissect the tissue around the implant and grasp the implant (Figure 19). 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 the local representative of the Marketing Authorisation Holder N.V. Organon.**

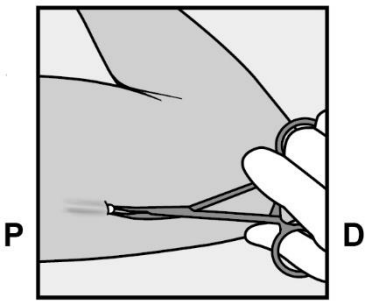

Figure 17

Figure 18

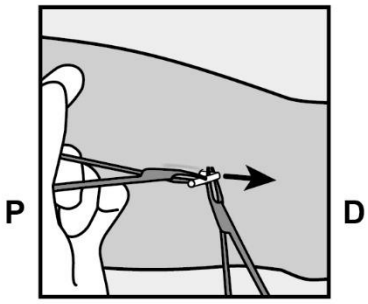

Figure 19

- Confirm that the entire rod, 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 by following the instructions in this section.
- 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 (Section 4.2 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 also section 4.4), 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 extremely rare cases 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 the local representative of the Marketing Authorisation Holder 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 the local representative of the Marketing Authorisation Holder 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 4.2 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 section 4.2 How to insert Implanon NXT). If the same incision is being used to insert a new implant, anaesthetise the insertion site by injecting an anaesthetic (e.g. 2 ml lidocaine (1 %)) 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

- Active venous thromboembolic disorder.
- Known or suspected sex steroid sensitive malignancies.
- Presence or history of liver tumours (benign or malignant).
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Undiagnosed vaginal bleeding.
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

If any of the conditions / risk factors mentioned below is present, the benefits of progestagen use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start with Implanon NXT. In the event of aggravation, exacerbation or first appearance of any of these conditions, the woman should contact her HCP. The HCP should then decide on 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) oral contraceptives (OCs) the risk of having breast cancer diagnosed is slightly increased. This increased risk disappears gradually within 10 years after discontinuation of OC use and is not related to the duration of use, but to the age of the woman when using the OC. The expected number of cases diagnosed per 10,000 women who use combined OCs (up to 10 years after stopping) relative to never users over the same period have been calculated for the respective age groups to be: 4.5/4 (16-19 years), 17.5/16 (20-24 years), 48.7/44 (25-29 years), 110/100 (30-34 years), 180/160 (35-39 years) and 260/230 (40-44 years). The risk in users of contraceptive methods, which only contain progestagens is possibly of a similar magnitude to 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.

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

Thrombotic and Other Vascular Events

Epidemiological investigations have associated the use of combined OCs (oestrogen + progestagen) with an increased incidence of venous thromboembolism (VTE, deep venous thrombosis and pulmonary embolism) and arterial thromboembolism (ATE, myocardial infarction and ischaemic stroke). The clinical relevance of these findings for etonogestrel (the biologically active metabolite of desogestrel) used as a progestagen-only contraceptive in the absence of an oestrogenic component is unknown.

Limited epidemiological data do not suggest an increased risk of VTE or ATE in women using the implant; however, there have been postmarketing reports of VTE and ATE, in women using etonogestrel implants. It is recommended to assess risk factors, which are known to increase the risk of VTE and ATE.

Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence. The implant should be removed in the event of a thrombosis. Removal of the implant should also be considered in the case of long-term immobilisation due to surgery or illness.

Elevated Blood Pressure

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, the use of Implanon NXT should be discontinued.

Carbohydrate Metabolic Effect

The use of progestagen-containing contraceptives 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.

Chloasma

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

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. HCPs may therefore consider earlier replacement of the implant in heavier women.

Complications of Insertion

There have been reports of migration of the implant within the arm from the insertion site, which may be related to a deep insertion (see section 4.2 How to insert Implanon NXT), or 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 of the implant 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 How to remove Implanon NXT). If at any time the implant cannot be palpated, it should be localised and removal is recommended as soon as medically appropriate. If the implant is not removed, contraception and the risk of progestagen-related undesirable effects may continue beyond the time desired by the woman.

Expulsion may occur especially if the implant is not inserted according to the instructions given in section 4.2 How to insert Implanon NXT, or as a consequence of local inflammation.

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. They rarely 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 will inhibit ovulation, ectopic pregnancy should be taken into account in the differential diagnosis if the woman gets amenorrhoea or abdominal pain.

Psychiatric Disorders
Depressed mood and depression are well-known undesirable effects of hormonal contraceptive use (see section 4.8). Depression can be serious and is a well-known risk factor for suicidal behaviour and suicide. Women should be advised to contact their physician in case of mood changes and depressive symptoms, including shortly after initiating the treatment.

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.

Medical examination/consultation
Prior to the initiation or reinstitution 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 the contraindications (see section 4.3) and warnings (see section 4.4). 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 the woman should be asked whether she has any questions or complaints or has experienced any undesirable effects. The frequency and nature of further periodic checks should be adapted to the individual woman, guided by clinical judgement. The implant should be palpated at each check-up visit. The woman should be instructed to contact her doctor as soon as possible if she cannot palpate her implant at any time between check-ups.

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

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).

Changes in the menstrual bleeding pattern
During the use of Implanon NXT, women are likely to have changes in their menstrual bleeding pattern which are unpredictable beforehand. These may include the occurrence of an irregular bleeding pattern (absent, less frequent, more frequent or continuous), and changes in bleeding 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. The bleeding pattern experienced during the first three months is broadly predictive of future bleeding patterns for many women. 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, which may be due to external forces applied while in the patient's arm. There have also been reports of migration of a broken implant fragment within the 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.
However, when an implant is broken, it should be removed, and it is important to remove it in its entirety. Refer to section 4.2 for the procedures of implant removal (either palpable or non-palpable).

4.5 Interaction with other medicinal products and other forms of interaction

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

Effects of other medicinal products on Implanon NXT
Interactions can occur with drugs that induce microsomal enzymes which can result in increased clearance of sex hormones and which may lead to menstrual bleeding and / or contraceptive failure.

Management
Enzyme induction can already be observed after a few days of treatment. Maximum enzyme induction is generally observed within a few weeks. After the cessation of drug therapy, enzyme induction may be sustained for about 4 weeks.

Women receiving hepatic enzyme-inducing drugs or herbal products should be advised that the efficacy of Implanon NXT may be reduced. Removal of the implant is not needed, but women are advised to use an additional non-hormonal contraceptive method during the time of concomitant drug administration and for 28 days after their discontinuation in order to obtain maximum protection.

The following interactions have been reported in the literature (mainly with combined contraceptives but occasionally also with progestagen-only contraceptives including Implanon NXT):

Substances increasing the clearance of hormonal contraceptives (diminished efficacy of hormonal contraceptives by enzyme-induction), e.g.:
Barbiturates, bosentan, carbamazepine, phenytoin, primidone, rifampicin, and HIV/HCV medication like ritonavir, efavirenz, boceprevir, nevirapine and possibly also felbamate, griseofulvin, oxcarbazepine, topiramate and products containing the herbal remedy St. John's Wort (*hypericum perforatum*).

Substances with variable effects on the clearance of hormonal contraceptives
When co-administered with hormonal contraceptives, many combinations of HIV protease inhibitors and non-nucleoside reverse transcriptase inhibitors, including combinations with HCV inhibitors, can increase or decrease plasma concentrations of progestins, including etonogestrel. The net effect of these changes may be clinically relevant in some cases.

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

Substances decreasing the clearance of hormonal contraceptives (enzyme inhibitors)
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.

Effects of Implanon NXT on other medicinal products
Hormonal contraceptives may affect metabolism of certain other active substances. Accordingly, plasma and tissue concentrations may either increase (e.g., ciclosporin) or decrease (e.g., lamotrigine).

Laboratory parameters
Data obtained with combined OCs 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 generally remain within the normal range. To what extent this also applies to progestagen-only contraceptives is not known.

4.6 Fertility, pregnancy and lactation

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

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

Breast-feeding
Clinical data indicate that Implanon NXT does not influence the production or the quality (protein, lactose or fat concentrations) of breast milk. However, small amounts of etonogestrel are excreted in breast milk. Based on an average daily milk ingestion of 150 ml/kg, the mean daily infant etonogestrel dose calculated after one month of etonogestrel release is approximately 27 ng/kg/day. This corresponds to approximately 2.2 % of the weight-adjusted maternal daily dose and to approximately 0.2 % of the estimated absolute maternal daily dose. Subsequently the milk etonogestrel concentration decreases with time during the lactation period.
Limited 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 and should be inserted after the 4th postpartum week.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

During the use of Implanon NXT, women are likely to have changes in their menstrual bleeding pattern which are unpredictable beforehand. These may include the occurrence of an irregular bleeding pattern (absent, less frequent, more frequent or continuous), and changes in bleeding 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. Occasionally, heavy bleeding has been reported. In clinical trials, bleeding changes were the most common reason for stopping treatment (about 11 %). The bleeding pattern experienced during the first three months is broadly predictive of future bleeding patterns for many women.

Possibly related 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 (≥1/100 to <1/10)**	**Uncommon (≥ 1/1,000 to <1/100)**
Infections and Infestations	vaginal infection;		pharyngitis, rhinitis; urinary tract infection;
Immune system disorders			Hypersensitivity;
Metabolism and nutrition disorders		increased appetite;	
Psychiatric disorders		affect lability; depressed mood; nervousness; libido decreased;	Anxiety; insomnia;
Nervous system disorders	Headache;	Dizziness;	Migraine; somnolence;
Vascular disorders		hot flush;	
Gastrointestinal disorders		abdominal pain; nausea; flatulence;	Vomiting; constipation; diarrhoea;
Skin and subcutaneous tissue disorders	Acne;	Alopecia;	hypertrichosis, rash; pruritus;
Musculoskeletal and connective tissue disorders			back pain; arthralgia; myalgia, musculoskeletal pain;
Renal and urinary disorders			Dysuria;
Reproductive system and breast disorders	breast tenderness; breast pain; menstruation irregular;	Dysmenorrhoea; ovarian cyst;	genital discharge; vulvovaginal discomfort; galactorrhoea; breast

System Organ Class	Adverse reaction in MedDRA Term[1]		
	Very Common (≥ 1/10)	**Common (≥1/100 to <1/10)**	**Uncommon (≥ 1/1,000 to <1/100)**
			enlargement; pruritus genital;
General disorders and administration site condition		implant site pain; implant site reaction; fatigue; influenza like illness; pain;	Pyrexia; oedema;
Investigations	weight increased;	weight decreased;	

[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.

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.

The following undesirable effects have been reported in connection with the insertion or removal procedure of the implant:
Insertion or removal of the implant may cause some bruising, including haematoma in some cases, slight local irritation, pain or itching.
Insertion of the implant may cause vasovagal reactions (such as hypotension, dizziness, or syncope).

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 have 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, haemoptysis); others have been reported as asymptomatic (see section 4.4). If instructions are not followed (see section 4.2), incorrect insertions, difficult localisations and difficult removals of the implant may occur. Surgical intervention might be necessary when removing the implant.

On rare occasions, ectopic pregnancies have been reported (see section 4.4).

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 Special Precautions for Use".

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via het Nederlands Bijwerkingen Centrum Lareb, website: www.lareb.nl.

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.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Hormonal Contraceptives for Systemic Use, progestagens, ATC code: G03AC08

Mechanism of action
The Implanon NXT 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 widely used in OCs. It is structurally derived from 19-nortestosterone and binds with high affinity to progesterone receptors in the target organs. The contraceptive effect of etonogestrel is primarily achieved by inhibition of ovulation. Ovulations were not observed in the first two years of use of the implant and only rarely in the third year. Besides inhibition of ovulation, etonogestrel also causes changes in the cervical mucus, which hinders the passage of spermatozoa.

Clinical efficacy and safety
Clinical trials were conducted in women between 18 and 40 years. Although no direct comparison was made, the contraceptive efficacy appeared to be at least comparable to that known for combined OCs. During the clinical studies no pregnancies were observed during 35,057 cycles of exposure; the Pearl Index observed is 0.00 (95 % confidence limits: 0.00-0.14). However, it must be realised that in practice no method can be considered 100 % effective. The high degree of protection against pregnancy is obtained, amongst other reasons, because the contraceptive action of Implanon NXT is not dependent on adherence to a dosing regimen by the woman herself. The contraceptive action of etonogestrel is reversible, which is apparent from the rapid return of the normal menstrual cycle after removal of the implant. Although etonogestrel 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 further indicate that users of Implanon NXT often have a less painful menstrual bleeding (dysmenorrhoea).

5.2 Pharmacokinetic properties

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 150-261 pg/ml) is measured, which slowly decreases to 156 pg/ml (range 111-202 pg/ml) by the end of the third year. The variations observed in serum concentrations can be partly attributed to differences in body weight.

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

Biotransformation
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 0.44-0.50 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 and statistically significant decrease over time.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Implant
Core: Ethylene vinyl acetate copolymer (28 % vinyl acetate, 43 mg)
barium sulphate (15 mg)
magnesium stearate (0.1 mg).
Skin: Ethylene vinyl acetate copolymer (15 % vinyl acetate, 15 mg).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

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

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.
Store in the original blister package.

6.5 Nature and contents of container

The blister pack contains one implant (4 cm in length and 2 mm in diameter) 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 polyethyleneterephthalate glycol (PETG) sealed with a lidding made of high density poly ethylene (HDPE). The content of the blister pack is sterile unless the package is damaged or opened.

Pack sizes: Carton box with 1 blister pack, carton box with 5 blister packs.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

See section 4.2.
The applicator is for single use only.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

N.V. Organon
Kloosterstraat 6
5349 AB Oss
Nederland

8. MARKETING AUTHORISATION NUMBER(S)

RVG 21168

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of the first authorisation: 25 August 1998
Date of the lastest renewal: 28 August 2013

10. DATE OF REVISION OF THE TEXT

Last partial revision concerned section 4.2: 23-04-2023