Product Monograph

Including Patient Medication Information

[PR]NEXPLANON®

etonogestrel extended release subdermal implant

Extended release implant

For subdermal use

68 mg per implant (to deliver up to 70 mcg etonogestrel per day)

Hormonal Contraceptive

Organon Canada Inc.

16766 route Transcanadienne

Kirkland QC Canada, H9H 4M7

www.organon.ca

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Recent Major Label Changes

4 Dosage and Administration, 4.4 Administration	02/2026
7 Warnings and Precautions, Cardiovascular	02/2026

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Certain sections (as indicated in section 2.1. of the PM Guidance) or subsections that are not applicable at the time of the preparation of the most recent authorized product monograph are not listed.

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Part 1: Healthcare Professional Information

1. Indications

NEXPLANON® (etonogestrel) is indicated for:

- Prevention of pregnancy for up to 3 years.

1.1. Pediatrics

Pediatrics (< 18 years of age): Safety and efficacy have been studied in women between 18 and 40 years. NEXPLANON is not indicated for use before menarche. No clinical studies have been conducted in women less than 18 years of age; therefore, Health Canada has not authorized an indication for pediatric use.

1.2. Geriatrics

Geriatrics (> 65 years of age): This product has not been studied in women over 65 years of age and is not indicated in postmenopausal women. No data are available to Health Canada; therefore, Health Canada has not authorized an indication for geriatric use.

Overweight women

NEXPLANON may become less effective in overweight women over time, especially in the presence of other factors that decrease etonogestrel concentrations, such as concomitant use of hepatic enzyme inducers. (see 7 Warnings and Precautions, 7.1 Special Populations, Overweight Women).

2. Contraindications

NEXPLANON is contraindicated in patients who are hypersensitive to this drug or to any ingredient in the formulation, including any non-medicinal ingredient, or component of the container. For a complete listing, see 6 Dosage Forms, Strengths, Composition and Packaging.

Progestin-only contraceptives should not be used in the presence of any of the conditions listed below. Should any of the conditions appear for the first time during the use of NEXPLANON, the product should be stopped immediately.

NEXPLANON should not be used in women with:

- Known or suspected pregnancy;
- Current or past history of thrombosis or thromboembolic disorders;
- Liver tumours, benign or malignant, or active liver disease;
- Undiagnosed abnormal genital bleeding;
- Known or suspected breast cancer, personal history of breast cancer, or other progestin sensitive cancer, now or in the past.

3. Serious Warnings and Precautions Box

- NEXPLANON should be inserted and/or removed by a Healthcare Professional familiar with use of the implant. All Healthcare Professionals should receive instruction and training prior to performing insertion and/or removal of NEXPLANON, and, where appropriate, request supervision prior to inserting or removing the implant.
- If at any time the implant is not palpable by the Healthcare Professional or the patient, NEXPLANON should be localized as soon as possible and removed as soon as medically

appropriate to manage the risks of migration. There have been post-marketing reports of implants located within the vessels of the arm and the pulmonary artery which may be related to deep insertions or intravascular insertion.

- Women should be counselled that NEXPLANON DOES NOT PROTECT against sexually transmitted infections (STIs) including Human Immunodeficiency Virus (HIV)/ Acquired immunodeficiency syndrome (AIDS). For protection against STIs, it is advisable to use latex or polyurethane condoms IN COMBINATION WITH NEXPLANON.

4. Dosage and Administration

4.1. Dosing Considerations

- **Pregnancy should be excluded before insertion of NEXPLANON.**
- **NEXPLANON should be inserted and/or removed by a Healthcare Professional familiar with use of the implant. All Healthcare Professionals should receive instruction and training prior to performing insertion and/or removal of NEXPLANON, 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 (see 4.4 Administration, "How to insert NEXPLANON" and "How to remove NEXPLANON").
- Videos demonstrating insertion and removal of the implant are available online. Please refer to www.nexplanonvideos.com. Healthcare Professionals may obtain more information about available training by visiting www.etonogestrel-implant-training.ca. Please contact Organon Canada at 1 -844 -820 -5468 if you have any questions.
- The implant should not be inserted after the expiry date as indicated on the primary package.
- **If you are unsure of the necessary steps to safely insert and/or remove NEXPLANON, do not attempt the procedure.**

4.2. Recommended Dose and Dosage Adjustment

NEXPLANON is a long-acting reversible 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 overweight women (see 7 Warnings and Precautions, Endocrine and Metabolism, Weight Gain and 7.1 Special Populations, Overweight Women). 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 NEXPLANON, but wants to continue preventing pregnancy, another contraceptive method should be recommended.

4.4. Administration

The basis for successful use and subsequent removal of the NEXPLANON 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 specified below in "How to insert NEXPLANON", and on the correct day in "When to insert Nexplanon", unintended pregnancy may occur.** An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the

localization and/or removal can be difficult (see **"**How to remove NEXPLANON" below and 7 Warnings and Precautions).

The NEXPLANON 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 and 2b).

Immediately after insertion, the presence of the implant should be verified by palpation. Both the Healthcare Professional and the woman should be able to feel the implant under the skin after placement. In case the implant cannot be palpated or when the presence of the implant is doubtful, see "How to insert NEXPLANON". The Healthcare Professional should instruct the woman on how to continue to verify the presence of the implant by having her gently palpate the site occasionally.

The NEXPLANON package contains a Patient Alert 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 Patient Alert Card. The card provides a warning for the woman to contact her Healthcare Professional as soon as possible if she is unable to feel the implant. The package also includes adhesive labels intended for Healthcare Professional records showing the batch number.

When to insert NEXPLANON

IMPORTANT: Pregnancy should be ruled out 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 contraceptive method to NEXPLANON

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

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

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 progestin-only contraceptive method (progestin-only pill, injectable, implant or intrauterine system (IUS))

As there are several types of progestin-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.

- Progestin-only pill: A woman may switch from the progestin-only pill to NEXPLANON 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 5 days following a first trimester abortion or miscarriage.

- Second trimester: Insert the implant between 21 to 28 days following second trimester abortion or miscarriage.

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

Postpartum:

- Breast-feeding: The implant should be inserted after the fourth postpartum week (see 7 Warnings and Precautions, 7.1 Special Populations, 7.1.1 Pregnancy and 7.1.2 Breastfeeding). The woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded.

- Not 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.

Women at high risk of immediate unintended pregnancy and loss to follow-up:

The implant can be inserted immediately following second trimester abortion or miscarriage and postpartum in both breastfeeding and non-breastfeeding women. If inserted after 21 days, the woman should be advised to use a barrier method until 7 days after insertion. If intercourse has already occurred, pregnancy should be excluded before insertion**.**

How to insert NEXPLANON

The basis for successful use and subsequent removal of the NEXPLANON implant is a correct and carefully performed subdermal insertion of the implant in the non-dominant arm in accordance with the instructions. Both the Healthcare Professional 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 localization and/or removal can be difficult (see "How to remove NEXPLANON" and 7 Warnings and Precautions).

- If the implant is inserted deeply, neural or vascular damage may occur. Deep or incorrect insertions have been associated with paresthesia (due to neural damage) and migration of the implant (due to intramuscular or fascial insertion), and in rare cases with intravascular insertion.

Insertion of NEXPLANON should be performed under aseptic conditions and only by a qualified Healthcare Professional who is familiar with the procedure. Insertion of the implant should only be performed with the preloaded applicator.

Insertion Procedure
Insert NEXPLANON under aseptic conditions.

The following equipment is needed for the implant insertion:
- An examination table for the woman to lie on
- Sterile surgical drapes, sterile gloves, antiseptic solution, surgical marker
- Local anesthetic, needles, and syringe
- Sterile gauze, adhesive bandage, pressure bandage

To help make sure the implant is inserted just under the skin, the Healthcare Professional 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 visualized.

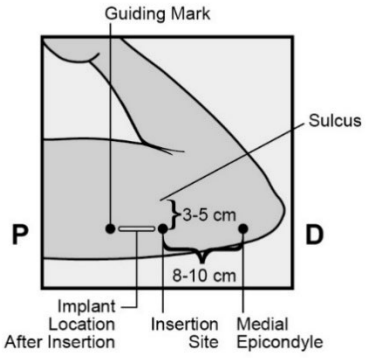
For illustrative purposes, figures depict the left inner arm.

Step 1. 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). This position deflects the ulnar nerve away from the insertion site.

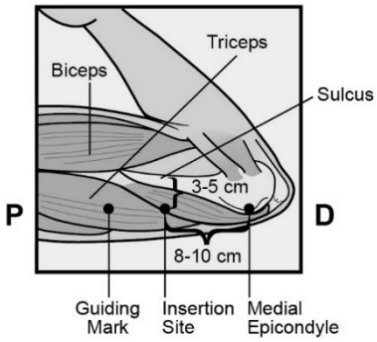
[Figure 1]

Step 2. 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 muscle (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.

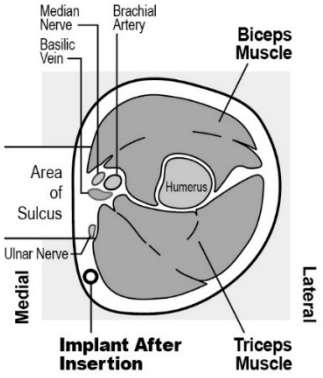
Step 3. Make two marks with a surgical marker: first, mark the spot where the implant will be inserted, and second, mark a spot at 5 centimeters (2 inches) proximal (toward the shoulder) to the first mark (Figure 2a and 2b). This second mark (guiding mark) will later serve as a direction guide during insertion.



[Figure 2a]



[Figure 2b]



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

[Figure 2c]

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

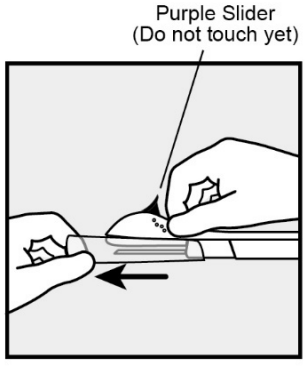
Step 4. After marking the arm, confirm the site is in the correct location on the inner side of the arm.

Step 5. Clean the skin from insertion site to the guiding mark with an antiseptic solution.

Step 6. Anesthetize the insertion area (for example, with anesthetic spray or by injecting 2 mL of 1% lidocaine just under the skin along the planned insertion tunnel).

Step 7. Remove the sterile preloaded disposable NEXPLANON 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.

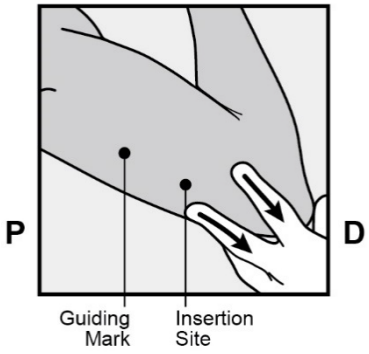
Step 8. Hold the applicator just above the needle at the textured surface area. Remove the transparent protection cap by sliding it horizontally in the direction of the arrow away from the needle (Figure 3). If the cap does not come off easily, the applicator should not be used. You should see the white colored 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 release the implant from the applicator**.



[Figure 3]

Step 9. If the purple slider is released prematurely, restart the procedure with a new applicator.

Step 10. With your free hand, stretch the skin around the insertion site towards the elbow (Figure 4).

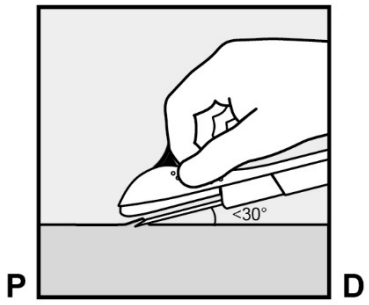


[Figure 4]

Step 11. **The implant should be inserted subdermally just under the skin** (see **7 Warnings and Precautions**).

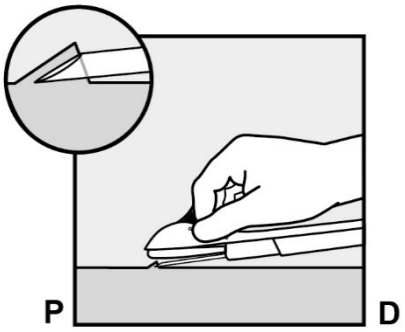
To help make sure the implant is inserted just under the skin, you should position yourself to see the advancement of the needle by viewing the applicator from the side and not from above the arm. From the side view you can clearly see the insertion site and the movement of the needle just under the skin (see Figure 6).

Step 12. Puncture the skin with the tip of the needle slightly angled less than 30° (Figure 5a).



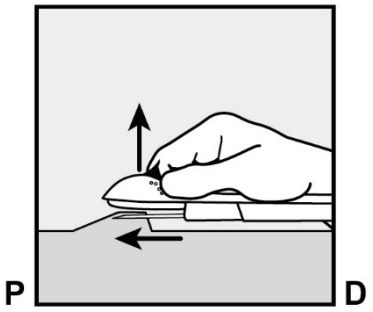
[Figure 5a]

Step 13. 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]

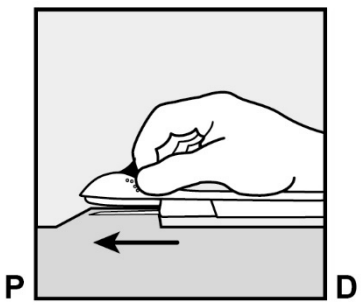
Step 14. Lower the applicator to a nearly horizontal position. To facilitate subdermal placement, lift the skin with the needle while sliding the needle to its full length (Figure 6). You may feel slight resistance but do not exert excessive force**. If the needle is not inserted to its full length, the implant will not be inserted properly.**



[Figure 6]

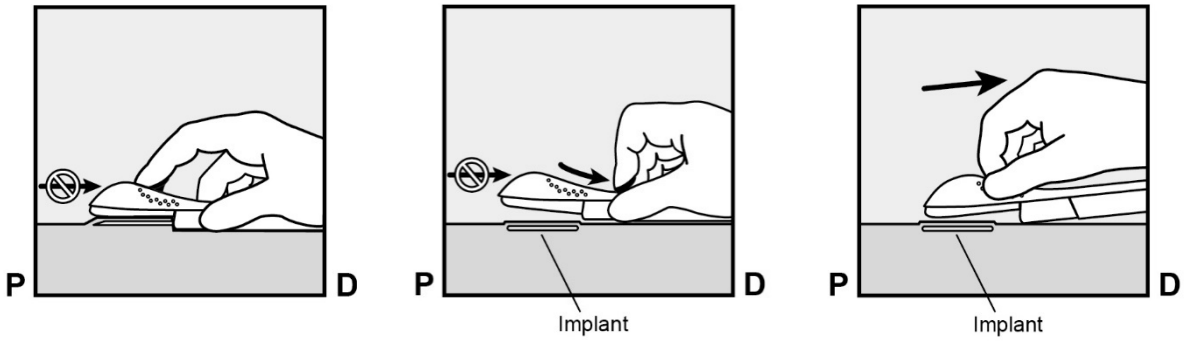
If the needle tip emerges from the skin before needle insertion is complete, the needle should be pulled back and be readjusted to subdermal position before completing the insertion procedure.

Step 15. 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 stabilize 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).



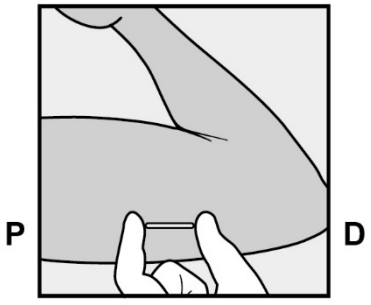
[Figure 8a] **[Figure 8b]** **[Figure 8c]**

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.**

Step 16. Apply a small adhesive bandage over the insertion site.

Step 17. **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]

Step 18. Request that the woman palpate the implant.

Step 19. Apply sterile gauze with a pressure bandage to minimize bruising. The woman may remove the pressure bandage in 24 hours and the small adhesive bandage over the insertion site after 3-5 days.

Step 20. 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.

Step 21. 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 localization are: two-dimensional X-ray, X-ray computerized 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 (see 7 Warnings and Precautions, Monitoring and Laboratory Tests). 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 women. In this case the Organon Canada office (which can be reached at 1-844-820-5468) 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 localized and removed as soon as possible to avoid the potential for distant migration.

How to remove NEXPLANON

Removal of the implant should only be performed under aseptic conditions by a Healthcare Professional who is familiar with the removal technique. **If you are unfamiliar with the removal technique, contact Organon Canada at 1-844-820-5468 for further information.**

Before initiating the removal procedure, the Healthcare Professional 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 Healthcare Professional experienced in removing deeply placed implants and familiar with localizing the implant and the anatomy of the arm. Contact Organon Canada at 1-844-820-5468 for further information.

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

Procedure for removal of an implant that is palpable

Before removal of the implant, the healthcare provider should confirm that:

- The woman does not have allergies to the antiseptic or anesthetic to be used.

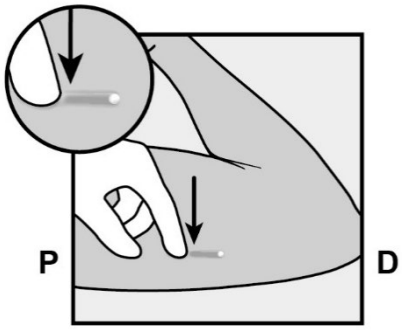
The following equipment is needed for removal of the implant:

- An examination table for the woman to lie on
- Sterile surgical drapes, sterile gloves, antiseptic solution, surgical marker
- Local anesthetic, needles, and syringe
- Sterile scalpel, forceps (straight and curved mosquito)

For illustrative purposes, figures depict the left inner arm

Step 1. 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) This position deflects the ulnar nerve away from the removal site.

Step 2. Locate the implant by palpation. Push down the end of the implant closest to the shoulder (Figure 10) to stabilize 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 Canada at 1-844-820-5468 for further information.



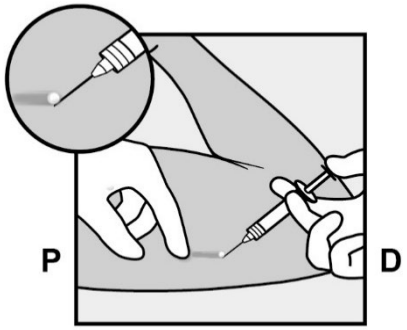
[Figure 10]

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

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

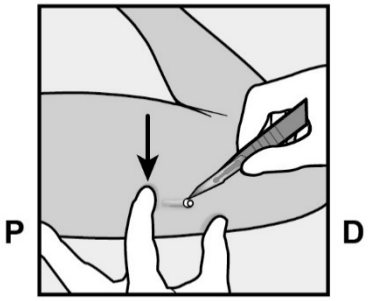
Step 3. Clean the site with an antiseptic solution.

Step 4. Anesthetize the site, for example, with 0.5 to 1 mL 1% lidocaine where the incision will be made (Figure 11). 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.



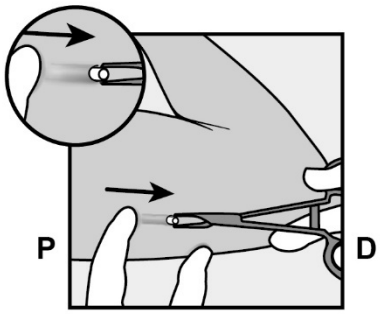
[Figure 11]

Step 5. Push down the end of the implant closest to the shoulder (Figure 12) to stabilize 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.

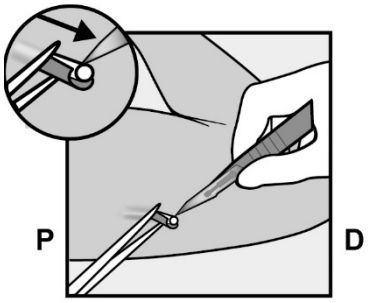


[Figure 12]

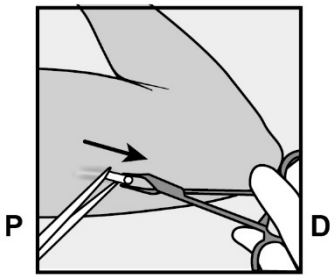
Step 6. The tip of the implant should pop out of the incision. If it does not, gently push the implant towards the incision until the tip is visible. Grasp the implant with forceps and if possible, remove the implant (Figure 13). If needed, gently remove adherent tissue from the tip of the implant using 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]

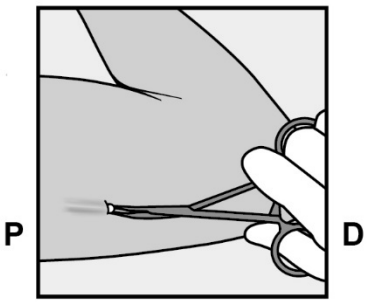


[Figure 14]



[Figure 15]

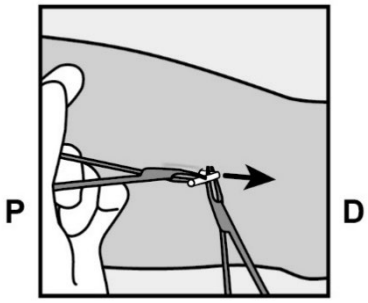
Step 7. If the tip of the implant does not become visible in the incision, insert forceps (preferably curved mosquito forceps, with the tips pointed up) superficially into the incision (Figure 16). Gently grasp the implant and then flip the forceps over into your other hand (Figure 17).



[Figure 16]

[Figure 17]

Step 8. 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 Healthcare Professional experienced with complex removals or contact Organon Canada at 1-844-820-5468.**



[Figure 18]

Step 9. 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 by following the instructions in "How to remove NEXPLANON". If the woman would like to continue using NEXPLANON, 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 NEXPLANON").

Step 10. After removing the implant, close the incision with a sterile adhesive wound closure.

Step 11. Apply sterile gauze with a pressure bandage to minimize bruising. The woman may remove the pressure bandage after 24 hours and the sterile adhesive wound closure after 3-5 days.

Localization 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, but it may lead to the implant not being palpable at the location in which it was placed (see 7 Warnings and Precautions). 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 localization.

A non-palpable implant should always be located prior to attempting removal. Given the radiopaque nature of the implant, suitable methods for localization include two-dimensional X-ray and X-ray CT scan. USS with a high-frequency linear array transducer (10 MHZ or greater) or MRI may be used (see 7 Warnings and Precautions, Monitoring and Laboratory Tests). Once the implant has been localized in the arm, the implant should be removed by a Healthcare Professional 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 localization 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; Healthcare Professionals 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 Canada at 1-844-820-5468 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 Healthcare Professionals 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 not recommended.

Please contact Organon Canada at 1-844-820-5468 for further guidance.

How to replace NEXPLANON

Immediate replacement can be done after removal of the previous implant and is similar to the insertion procedure described in "How to insert NEXPLANON" (See 4 Dosage and Administration).

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 NEXPLANON"). If the same incision is being used to insert a new implant, anaesthetize the insertion site (e.g., 2 mL lidocaine (1%)) applied just under the skin commencing at the removal incision along the 'insertion canal' and follow the subsequent steps in the insertion instructions.

5. 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 the most recent information in the management of a suspected drug overdose, contact your regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669).

6. Dosage Forms, Strengths, Composition, and Packaging

Table 1 – Dosage Forms, Strengths, and Composition

Route of Administration	Dosage Form/ Strength/Composition	Non-Medicinal Ingredients
subdermal	Implant / 68 mg / radiopaque, non-biodegradable, white to off-white, soft, progestin-only flexible implant rod preloaded in a sterile, disposable applicator with a length of 4 cm and 2 mm in diameter	Implant core Barium sulfate (15 mg), ethylene vinyl acetate copolymer (28% vinyl acetate, 43 mg), magnesium stearate (0.1 mg). Implant skin Ethylene vinyl acetate copolymer (15% vinyl acetate, 15 mg)

Description

NEXPLANON (etonogestrel extended release subdermal implant) is a non-uterine, long-acting reversible contraceptive. NEXPLANON consists of a radiopaque, non-biodegradable, soft, progestin-only flexible implant rod. Each radiopaque implant contains 68 mg of etonogestrel. After insertion into the arm, NEXPLANON releases etonogestrel continuously for up to 3 years. NEXPLANON does not contain estrogen. The release rate is approximately 60-70 mcg/day in week 5-6 and decreases to approximately 35-45 mcg/day at the end of the first year, to approximately 30-40 mcg/day at the end of the second

year and to approximately 25-30 mcg/day at the end of the third year. The innovative applicator is designed to be operated with one hand and to help facilitate correct subdermal insertion of the implant.

Packaging

The 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 polyethyleneterephtalate glycol sealed with an EVA coated spunbonded High Density Polyethylene lidding film. The blister pack is packed in a box together with the package leaflet.

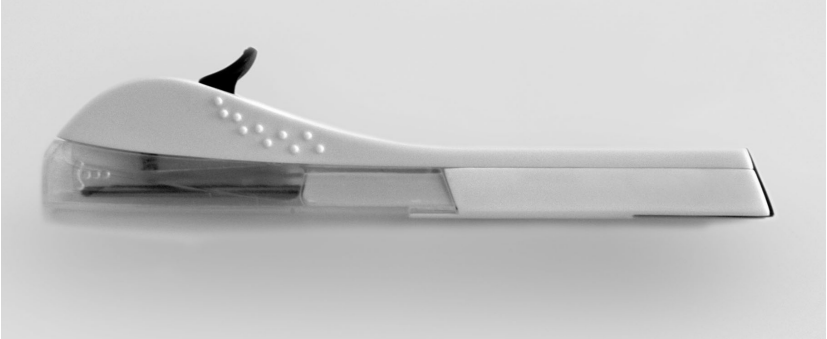


Figure 19: NEXPLANON applicator

7. Warnings and Precautions

See 3 Serious Warnings and Precautions Box.

General

If any of the conditions / risk factors described below are present, the benefits of progestin use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start with NEXPLANON. In the event of aggravation, exacerbation or first appearance of any of these conditions, the woman should contact her Healthcare Professional. The Healthcare Professional should then decide if use of NEXPLANON should be discontinued.

Complications of Insertion and Removal

NEXPLANON should be inserted subdermally so that it will be palpable after insertion, and this should be confirmed by palpation immediately after insertion. Failure to insert NEXPLANON properly may go unnoticed unless it is palpated immediately after insertion. Undetected failure to insert the implant may lead to an unintended pregnancy. Complications related to insertion and removal procedures, such as pain, paresthesias, bleeding, hematoma, scarring or infection, may occur.

If NEXPLANON is inserted deeply (intramuscular or in the fascia), neural or vascular injury may occur. To help reduce the risk of neural or vascular injury, NEXPLANON should be inserted subdermally just under the skin at the inner side of the non-dominant upper arm 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 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. Deep insertions of NEXPLANON have been associated with paraesthesia (due to neural injury), migration of the implant (due to intramuscular or fascial insertion), and intravascular insertion. If infection develops at the insertion site, start suitable treatment. If the infection persists, the implant should be removed. Incomplete insertions or infections may lead to expulsion.

Implant removal may be difficult or impossible if the implant is not inserted correctly, is inserted too deeply, not palpable, encased in fibrous tissue, or has migrated.

There have been reports of migration of the implant within the arm from the insertion site, which may be related to deep insertion. There also have been 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 to the pulmonary artery, endovascular or surgical procedures may be needed for removal. Some cases of implants found within the pulmonary artery were associated with chest pain and/or respiratory disorders (such as dyspnea, cough, or hemoptysis); others were asymptomatic.

If at any time the implant cannot be palpated, it should be localized and removal is recommended.

Exploratory surgery without knowledge of the exact location of the implant is strongly discouraged. Removal of deeply inserted implants should be conducted with caution in order to prevent injury to deeper neural or vascular structures in the arm and be performed by healthcare providers familiar with the anatomy of the arm. If the implant is located in the chest, healthcare providers familiar with the anatomy of the chest should be consulted. Failure to remove the implant may result in continued effects of etonogestrel, such as compromised fertility, ectopic pregnancy, or persistence or occurrence of a drug-related adverse event.

Changes in the menstrual bleeding pattern

After starting NEXPLANON, women are likely to have a change from their normal menstrual bleeding pattern. These may include changes in bleeding frequency (absent, less, more frequent or continuous), intensity (reduced or increased) or duration. In clinical trials of the non-radiopaque etonogestrel implant (IMPLANON), bleeding patterns ranged from amenorrhea (1 in 5 women) to frequent and/or prolonged bleeding (1 in 5 women). The bleeding pattern experienced during the first three months of NEXPLANON use is broadly predictive of future bleeding pattern for many women. Women should be counseled regarding the bleeding pattern changes they may experience so that they know what to expect. Abnormal bleeding should be evaluated as needed to exclude pathologic conditions or pregnancy. Also see 8.2 Clinical Trial Adverse Reactions.

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, tourniquet use at the implant site or trauma to the implant site during contact sports) 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, which is not expected to have clinically meaningful effects. When an implant is removed, it is important to remove it in its entirety.

Medical examination/consultation

Prior to the initiation or reinstitution of NEXPLANON 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 2

Contraindications) and warnings (see 7 Warnings and Precautions). It is recommended that the woman returns for a medical check-up three months after insertion of NEXPLANON. During this check-up, the blood pressure should be measured and an enquiry should be made after any questions, complaints or the occurrence of undesirable effects. The frequency and nature of further periodic checks should be adapted to the individual woman, guided by clinical judgement. Women should be advised that NEXPLANON does not protect against HIV (AIDS) and other sexually transmitted diseases.

Other Conditions

The following other conditions not described below have been reported both during pregnancy and during sex steroid use, but an association with the use of progestins has not been established: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; hemolytic uremic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss and (hereditary) angioedema.

Reduced efficacy with concomitant medications

The efficacy of NEXPLANON may be reduced when concomitant medications that decrease the plasma concentration of etonogestrel are used (see 9 Drug Interactions).

Carcinogenesis and Genotoxicity

Carcinoma of the Breast and Reproductive Organs

Women who currently have or have had breast cancer should not use hormonal contraception because breast cancer may be hormonally sensitive (see 2 Contraindications). Some studies suggest that the use of combination hormonal contraceptives might increase the incidence of breast cancer; however, other studies have not confirmed such findings.

Some studies suggest that the use of combination hormonal contraceptives is associated with an increase in the risk of cervical cancer or intraepithelial neoplasia. However, there is controversy about the extent to which these findings are due to differences in sexual behavior and other factors.

Women with a family history of breast cancer or who develop breast nodules should be carefully monitored.

Cardiovascular

Elevated Blood Pressure

Women with a history of hypertension-related diseases or renal disease should be discouraged from using hormonal contraception. For women with well-controlled hypertension, use of NEXPLANON can be considered. Women with hypertension using NEXPLANON should be closely monitored. If a sustained hypertension develops during the use of NEXPLANON, or if a significant increase in blood pressure does not adequately respond to antihypertensive therapy, NEXPLANON should be removed.

Thrombotic and Other Vascular Events

The use of combination hormonal contraceptives (progestin plus estrogen) increases the risk of vascular events, including arterial events (strokes and myocardial infarctions) or deep venous thrombotic events (venous thromboembolism, deep venous thrombosis, retinal vein thrombosis, and pulmonary embolism). NEXPLANON is a progestin-only contraceptive. It is unknown whether this increased risk is applicable to etonogestrel alone. It is recommended, however, that women with risk factors known to increase the risk of venous and arterial thromboembolism be carefully assessed.

There have been postmarketing reports of serious arterial thrombotic and venous thromboembolic events, including cases of pulmonary emboli (some fatal), deep vein thrombosis, myocardial infarction, and strokes, in women using etonogestrel implants. NEXPLANON should be removed in the event of a thrombosis.

Due to the risk of thromboembolism associated with pregnancy and immediately following delivery, NEXPLANON should not be used prior to 21 days postpartum with the exception of women at greater risk of short interval repeat pregnancy and loss to follow-up (see 4.4 Administration).

Evaluate for retinal vein thrombosis immediately if there is unexplained loss of vision, proptosis, diplopia, papilledema, or retinal vascular lesions.

Driving and Operating Machinery

No observed effects.

Endocrine and Metabolism

Carbohydrate and Lipid Metabolic Effects

Use of NEXPLANON may induce mild insulin resistance and small changes in glucose concentrations of unknown clinical significance. Carefully monitor prediabetic and diabetic women using NEXPLANON.

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

Weight Gain

In clinical studies, mean weight gain in U.S. non-radiopaque etonogestrel implant (IMPLANON) users was 2.8 pounds after one year and 3.7 pounds after two years. How much of the weight gain was related to the non-radiopaque etonogestrel implant is unknown. In studies, 2.3% of the users reported weight gain as the reason for having the non-radiopaque etonogestrel implant removed.

Fluid Retention

Hormonal contraceptives (HCs) may cause some degree of fluid retention. They should be prescribed with caution, and only with careful monitoring, in patients with conditions which might be aggravated by fluid retention. It is unknown if NEXPLANON causes fluid retention.

Genitourinary

Ectopic Pregnancy

As with all progestin-only contraceptive products, be alert to the possibility of an ectopic pregnancy among women using NEXPLANON who become pregnant or complain of lower abdominal pain. Although ectopic pregnancies are uncommon among women using NEXPLANON, a pregnancy that occurs in a woman using NEXPLANON may be more likely to be ectopic than a pregnancy occurring in a woman using no contraception.

Ovarian Cysts

With all low-dose HCs, follicular development may occur 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.

Hepatic/Biliary/Pancreatic

Liver Disease

Disturbances of liver function may necessitate the discontinuation of hormonal contraceptive use until markers of liver function return to normal. Remove NEXPLANON if jaundice develops.

Hepatic adenomas are associated with combination hormonal contraceptives use. An estimate of the attributable risk is 3.3 cases per 100,000 for combination hormonal contraceptives users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON.

The progestin in NEXPLANON may be poorly metabolized in women with liver impairment. Use of NEXPLANON in women with active liver disease or liver cancer is contraindicated (see 2 Contraindications).

Gallbladder Disease

Studies suggest a small increased relative risk of developing gallbladder disease among combination hormonal contraceptive users. It is not known whether a similar risk exists with progestin-only methods like NEXPLANON.

Monitoring and Laboratory Tests

Laboratory parameters

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 generally remain within the normal range. To what extent this also applies to progestin-only contraceptives is unknown.

Sex hormone-binding globulin concentrations may be decreased for the first six months after NEXPLANON insertion followed by gradual recovery. Thyroxine concentrations may initially be slightly decreased followed by gradual recovery to baseline.

Magnetic Resonance Imaging (MRI)

NEXPLANON is Magnetic Resonance (MR) safe.

Ophthalmologic

Contact Lenses

Contact lens wearers who develop visual changes or changes in lens tolerance should be assessed by an ophthalmologist.

Perioperative Considerations

Removal of the implant should also be considered in case of long-term immobilization due to surgery or illness (see 7 Warnings and Precautions, Cardiovascular).

Psychiatric

Depressed Mood

Women with a history of depressed mood should be carefully observed. Consideration should be given to removing NEXPLANON in patients who become significantly depressed.

Reproductive Health

NEXPLANON is contraindicated during pregnancy (See 2 Contraindications, 7.1.1 Pregnancy).

Return to Ovulation

In clinical trials with the non-radiopaque etonogestrel implant (IMPLANON), the etonogestrel levels in blood decreased below sensitivity of the assay by one week after removal of the implant. In addition, pregnancies were observed to occur as early as 7 to 14 days after removal. Therefore, a woman should re-start contraception immediately after removal of the implant if continued contraceptive protection is desired.

Skin

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 NEXPLANON.

7.1. Special Populations

7.1.1. Pregnancy

NEXPLANON is contraindicated during pregnancy because there is no need for pregnancy prevention in a woman who is already pregnant (see Contraindications). Epidemiologic studies and meta-analyses have not shown an increased risk of genital or non-genital birth defects (including cardiac anomalies and limb-reduction defects) following maternal exposure to low dose combined hormonal contraceptives (CHCs) prior to conception or during early pregnancy. NEXPLANON should be removed if maintaining a pregnancy. Also see 16 Non-Clinical Toxicology.

7.1.2. Breastfeeding

NEXPLANON may be used while breastfeeding after the fourth postpartum week. In women at greater risk for immediate unintended pregnancy or loss to follow-up NEXPLANON may be used immediately post partum.

Small amounts of contraceptive steroids and/or metabolites, including etonogestrel are present in human milk. No significant adverse effects have been observed in the production or quality of breast milk, or on the physical and psychomotor development of breastfed infants. The amount of etonogestrel contained within breast milk was measured in 38 lactating women who began using IMPLANON during the fourth to eighth week postpartum. The study evaluated IMPLANON versus another contraceptive, was not randomized and data were considered observational and exploratory; therefore, comparisons could not be made. Based on the findings of this study, during the first months after insertion of IMPLANON, when maternal blood levels of etonogestrel are highest, about 100 ng of etonogestrel may be ingested by the child per day based on an average daily milk ingestion of 658 mL.

Based on daily milk ingestion of 150 mL/kg, the mean daily infant etonogestrel dose one month after insertion of IMPLANON is about 2.2% of the weight-adjusted maternal daily dose, or about 0.2% of the estimated absolute maternal daily dose. Adverse reactions were not observed in breastfed infants exposed to etonogestrel through breast milk. No adverse effects on the production or quality of breast milk were detected.

HCs, including etonogestrel, can reduce milk production in breastfeeding mothers. This is less likely to occur once breastfeeding is well-established; however, it can occur at any time in some women. When possible, advise the nursing mother about both hormonal and non-hormonal contraceptive options, as steroids may not be the initial choice for these patients. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for NEXPLANON and any potential adverse effects on the breastfed child from NEXPLANON or from the underlying maternal condition.

7.1.3. Pediatrics

Safety and efficacy of NEXPLANON have been established in women of reproductive age and are expected to be the same for post pubertal adolescents. However, no clinical studies have been conducted in women less than 18 years of age. Use of this product before menarche is not indicated.

7.1.4. Geriatrics

NEXPLANON is not indicated for postmenopausal women. This product has not been studied in women over 65 years of age and is not indicated in this population.

Overweight Women

The effectiveness of the etonogestrel implant in women who weighed more than 130% of their ideal body weight has not been defined because such women were not studied in clinical trials. Serum concentrations of etonogestrel are inversely related to body weight and decrease with time after implant insertion. It is therefore possible that NEXPLANON may be less effective in overweight women, especially in the presence of other factors that decrease serum etonogestrel concentrations such as concomitant use of hepatic enzyme inducers.

8. Adverse Reactions

8.1. Adverse Reaction Overview

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 (see 7 Warnings and Precautions).

The adverse reactions reported with the use of implants are discussed elsewhere in the Product Monograph:

- Ectopic Pregnancies (see 7 Warnings and Precautions)
- Thrombotic and Other Vascular Events (see 7 Warnings and Precautions)
- Complications of Insertion and Removal (see 7 Warnings and Precautions)
- *In situ* Broken or Bent Implant (see 7 Warnings and Precautions)

8.2. Clinical Trial Adverse Reactions

Clinical trials are conducted under very specific conditions. Therefore, the frequencies of adverse reactions observed in the clinical trials may not reflect frequencies observed in clinical practice and should not be compared to frequencies reported in clinical trials of another drug. Adverse reaction information from clinical trials is useful in identifying drug-related adverse events and for approximating rates.

The safety assessment of the clinical studies was performed using a non-radiopaque implant on a total of 942 subjects. Data was accumulated from 11 clinical trials which are detailed in PART II (see 14 Clinical Trials).

During the use of NEXPLANON, 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. Amenorrhea 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 %). Dysmenorrhea tended to improve while using NEXPLANON. The bleeding pattern experienced during the first three months is broadly predictive of future bleeding patterns for many women.

In these studies, women had an average of 17.7 days of bleeding or spotting every 90 days (based on 3,315 intervals of 90 days recorded by 780 patients). The percentages of patients having 0, 1-7, 8-21, or >21 days of spotting or bleeding over a 90-day interval while using the nonradiopaque etonogestrel implant are shown in Table 2.

Table 2 – Percentages of Patients With 0, 1-7, 8-21, or >21 Days of Spotting or Bleeding Over a 90-Day Interval While Using the Non-Radiopaque Etonogestrel Implant (IMPLANON)

Total Days of Spotting or Bleeding	Percentage of Patients		
	Treatment Days 91-180 (N = 745)	Treatment Days 271-360 (N = 657)	Treatment Days 631-720 (N = 547)
0 Days	19%	24%	17%
1-7 Days	15%	13%	12%
8-21 Days	30%	30%	37%
>21 Days	35%	33%	35%

Bleeding patterns observed with use of the non-radiopaque etonogestrel implant for up to 2 years, and the proportion of 90-day intervals with these bleeding patterns, are summarized in Table 3.

Table 3 – Bleeding Patterns Using the Non-Radiopaque Etonogestrel Implant (IMPLANON) During the First 2 Years of Use*

BLEEDING PATTERNS	DEFINITIONS	%†
Infrequent	Less than three bleeding and/or spotting episodes in 90 days (excluding amenorrhea)	33.6
Amenorrhea	No bleeding and/or spotting in 90 days	22.2
Prolonged	Any bleeding and/or spotting episode lasting more than 14 days in 90 days	17.7
Frequent	More than 5 bleeding and/or spotting episodes in 90 days	6.7

* Based on 3315 recording periods of 90 days duration in 780 women, excluding the first 90 days after implant insertion
%[†] = Percentage of 90-day intervals with this pattern

In case of undiagnosed, persistent, or recurrent abnormal vaginal bleeding, appropriate measures should be conducted to rule out malignancy.

Adverse reactions that resulted in a rate of discontinuation of ≥1% are shown in Table 4.

Table 4 – Adverse Reactions Leading to Discontinuation of Treatment in 1% or More of Subjects in Clinical Trials of the Non-Radiopaque Etonogestrel Implant (IMPLANON)

Adverse Reactions	All Studies N = 942
Bleeding Irregularities[*]	11.1%
Emotional Lability[†]	2.3%
Weight Increase	2.3%
Headache	1.6%
Acne	1.3%
Depression[‡]	1.0%

*Includes "frequent", "heavy", "prolonged", "spotting", and other patterns of bleeding irregularity.
[†]Among US subjects (N=330), 6.1% experienced emotional lability that led to discontinuation.
[‡]Among US subjects (N=330), 2.4% experienced depression that led to discontinuation.

The most frequently occurring treatment related individual Adverse Events were headache (15.5%), weight increase (12.0%), acne (11.8%), breast pain (10.2%), emotional lability (5.8%) and abdominal pain (5.2%).

Table 5 – Drug-related Adverse Events with a causal relation to study medication (defined as possibly, probably, or definitely related to study drug according to the investigator) with an incidence of ≥1% in subjects treated with the non-radiopaque etonogestrel implant*

	Number of Subjects (n=942)	
	n	%
Gastro-intestinal disorders		
abdominal pain	49	5.2
flatulence	29	3.1
nausea	24	2.5
General disorders and administration site conditions		
insertion site pain	45	4.8
insertion site reaction	33	3.5
fatigue	15	1.6
influenza-like symptoms	10	1.1
pyrexia	17	1.8
pain	23	2.4
edema	16	1.7
Infections and Infestations		

vaginitis	13	1.4
Investigations		
weight decrease	24	2.5
weight increase	113	12
Metabolism & nutritional disorders		
appetite increased	13	1.4
Musculoskeletal and connective tissue disorders		
back pain	10	1.1
Nervous system disorders		
headache	146	15.5
dizziness	46	4.9
Psychiatric disorders		
depression	33	3.5
emotional Lability	55	5.8
libido decreased	23	2.4
anxiety	12	1.3
nervousness	33	3.5
Reproductive system and breast disorders		
breast pain	96	10.2
dysmenorrhea	41	4.4
abnormal sexual function	16	1.7
leukorrhea	10	1.1
ovarian cyst	24	2.5
Skin and subcutaneous disorders		
acne	111	11.8
rash	9	1.0
alopecia	22	2.3
Vascular disorders		
hot flush	15	1.6

In a clinical trial of NEXPLANON, 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.

8.3. Less Common Clinical Trial Adverse Reactions

Gastrointestinal disorders: vomiting, constipation, diarrhea
Immune System disorders: hypersensitivity
Infections and Infestations: pharyngitis, rhinitis, urinary tract infection
Musculoskeletal and connective tissue disorders: arthralgia, myalgia, musculoskeletal pain
Nervous System disorders: migraine, somnolence
Psychiatric disorders: insomnia
Renal and urinary disorders: dysuria
Reproductive system and breast disorders: vulvovaginal discomfort, galactorrhea, breast enlargement, pruritis genital
Skin and subcutaneous disorders: hypertrichosis, pruritus

8.4. Abnormal Laboratory Findings: Hematologic, Clinical Chemistry, and Other Quantitative Data

Changes in laboratory values have not been studied during clinical trials with NEXPLANON (see 7 Warnings and Precautions, Monitoring and Laboratory Tests).

8.5. Post-Market Adverse Reactions

During post-marketing surveillance, a clinically relevant rise in blood pressure has been observed in rare cases. Additionally, idiopathic intracranial hypertension has been reported. Seborrhoea has also been reported. Anaphylactic reactions, urticaria, angioedema, aggravation of angioedema and/or aggravation of hereditary angioedema may occur.

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. Paresthesia or paresthesia-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 dyspnea, cough or hemoptysis); others have been reported as asymptomatic (see 7 Warnings and Precautions). Surgical intervention might be necessary when removing the implant.**

On rare occasions, ectopic pregnancies have been reported (see 7 Warnings and Precautions).

The following additional adverse reactions have been identified during post-approval use of IMPLANON and NEXPLANON. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Gastrointestinal disorders: constipation, diarrhea, flatulence, vomiting.

General disorders and administration site conditions: edema, fatigue, implant site reaction, pyrexia.

Immune system disorders: anaphylactic reactions.

Infections and infestations: rhinitis, urinary tract infection.

Investigations: clinically relevant rise in blood pressure, weight decreased.

Metabolism and nutrition disorders: increased appetite.

Musculoskeletal and connective tissue disorders: arthralgia, musculoskeletal pain, myalgia.

Nervous system disorders: convulsions, migraine, somnolence.

Pregnancy, puerperium and perinatal conditions: ectopic pregnancy.

Psychiatric disorders: anxiety, insomnia, libido decreased.

Renal and urinary disorders: dysuria.

Reproductive system and breast disorders: breast discharge, breast enlargement, ovarian cyst, pruritus genital, vulvovaginal discomfort.

Skin and subcutaneous tissue disorders: angioedema, aggravation of angioedema and/or aggravation of hereditary angioedema, alopecia, chloasma, hypertrichosis, pruritus, rash, seborrhea, urticaria.

Vascular disorders: hot flush.

9. Drug Interactions

9.2. Drug Interactions Overview

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

9.4. Drug-Drug Interactions

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

The drugs listed in this table are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 6 – Established or Potential Drug-Drug Interactions

[Non-proprietary name(s) of the drug product(s)]	Effect	Clinical comment
- Aprepitant - Barbiturates - Bosentan - Carbamazepine - Efavirenz - Felbamate - Griseofulvin - Oxcarbazepine - Rifampicin - Phenytoin - Rifabutin - Rufinamide - Topiramate	Substances decreasing the plasma concentrations of HCs and potentially diminishing the efficacy of HCs	Drugs that induce certain enzymes, including cytochrome P450 3A4 (CYP3A4), may decrease the plasma concentrations of HCs and potentially diminish the effectiveness of HCs or increase breakthrough bleeding. Interactions between HCs and other drugs may lead to breakthrough bleeding and/or contraceptive failure. Counsel women to use an alternative non-hormonal method of contraception or a back-up method when enzyme inducers are used with HCs, and to continue back-up non-hormonal contraception for 28 days after discontinuing the enzyme inducer to ensure contraceptive reliability.
Strong or moderate CYP3A4 inhibitors: - Itraconazole - Voriconazole - Fluconazole Ketoconazole	Substances increasing the plasma concentrations of HCs	Co-administration of certain HCs and strong or moderate CYP3A4 inhibitors may increase the serum concentrations of progestins, including etonogestrel.

HIV protease inhibitors: - Nelfinavir	Significant decreases in the plasma concentrations of progestin	Significant decrease in the plasma concentrations of progestin have been noted in cases of co-administration with HIV protease inhibitors. These changes may be clinically relevant in some cases. Consult the prescribing information of anti-viral and anti-retroviral concomitant medications to identify potential interactions.
HIV protease inhibitors: - Indinavir - Ritonavir and Ritonavir-boosted protease inhibitors	Significant increases in the plasma concentrations of progestin	Significant increase in the plasma concentrations of progestin have been noted in cases of co-administration with HIV protease inhibitors. These changes may be clinically relevant in some cases. Consult the prescribing information of anti-viral and anti-retroviral concomitant medications to identify potential interactions.
Hepatitis C Virus (HCV) protease inhibitors: - Boceprevir - Telaprevir	Significant decreases in the plasma concentrations of progestin	Significant decrease in the plasma concentrations of progestin have been noted in cases of co-administration with HCV protease inhibitors. These changes may be clinically relevant in some cases. Consult the prescribing information of anti-viral concomitant medications to identify potential interactions.
Non-nucleoside reverse transcriptase inhibitors: - Nevirapine Efavirenz	Significant decreases in the plasma concentrations of progestin	Significant decrease in the plasma concentrations of progestin have been noted in cases of co-administration with non-nucleoside reverse transcriptase inhibitors. These changes may be clinically relevant in some cases. Consult the prescribing information of anti-viral concomitant medications to identify potential interactions.
Non-nucleoside reverse transcriptase inhibitors: - Etravirine	Significant increases in the plasma concentrations of progestin	Significant increase in the plasma concentrations of progestin have been noted in cases of co-administration with non-nucleoside reverse transcriptase inhibitors. These changes may be clinically relevant in some cases. Consult the prescribing information of anti-viral concomitant medications to identify potential interactions.

Effects of NEXPLANON on other medicinal products

HCs may affect the metabolism of other drugs. Consequently, plasma concentrations may either

increase (e.g., cyclosporine) or decrease (e.g., lamotrigine). Consult the labeling of all concurrently-used drugs to obtain further information about interactions with HCs or the potential for enzyme alterations.

9.5. Drug-Food Interactions

Grapefruit or its juice are known to inhibit CYP3A4 and may increase the serum concentrations of progestins, including etonogestrel. See 9.4 Drug-Drug Interactions.

9.6. Drug-Herb Interactions

Herbal products (including St. Johns wort) that induce certain enzymes, including cytochrome P450 3A4, may decrease the plasma concentrations of HCs and potentially diminish the effectiveness of HCs or increase breakthrough bleeding. See 9.4 Drug-Drug Interactions.

9.7. Drug-Laboratory Test Interactions

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 generally remain within the normal range. To what extent this also applies to progestin-only contraceptives is not known.

10. Clinical Pharmacology

10.1. Mechanism of Action

Etonogestrel is the biologically active metabolite of desogestrel, a progestin widely used in oral contraceptives. 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.

10.2. Pharmacodynamics

Exposure-response relationships of NEXPLANON are unknown.

10.3. Pharmacokinetics

Absorption

After subdermal insertion of the etonogestrel implant, etonogestrel is released into the circulation and is approximately 100% bioavailable.

In a three-year clinical trial, NEXPLANON and the non-radiopaque etonogestrel implant (IMPLANON) yielded comparable systemic exposure to etonogestrel. For NEXPLANON, the mean (± SD) maximum serum etonogestrel concentrations were 1200 (± 604) pg/mL and were reached within the first two weeks after insertion (n=50). The mean (± SD) serum etonogestrel concentration decreased gradually over time, declining to 202 (± 55) pg/mL at 12 months (n=41), 164 (± 58) pg/mL at 24 months (n=37), and 138 (± 43) pg/mL at 36 months (n=32). For the non-radiopaque etonogestrel implant (IMPLANON), the mean (± SD) maximum serum etonogestrel concentrations were 1145 (± 577) pg/mL and were reached

within the first two weeks after insertion (n=53). The mean (± SD) serum etonogestrel concentration decreased gradually over time, declining to 223 (± 73) pg/mL at 12 months (n=40), 172 (± 77) pg/mL at 24 months (n=32), and 153 (± 52) pg/mL at 36 months (n=30).

The pharmacokinetic profile of NEXPLANON is shown in Figure 20.

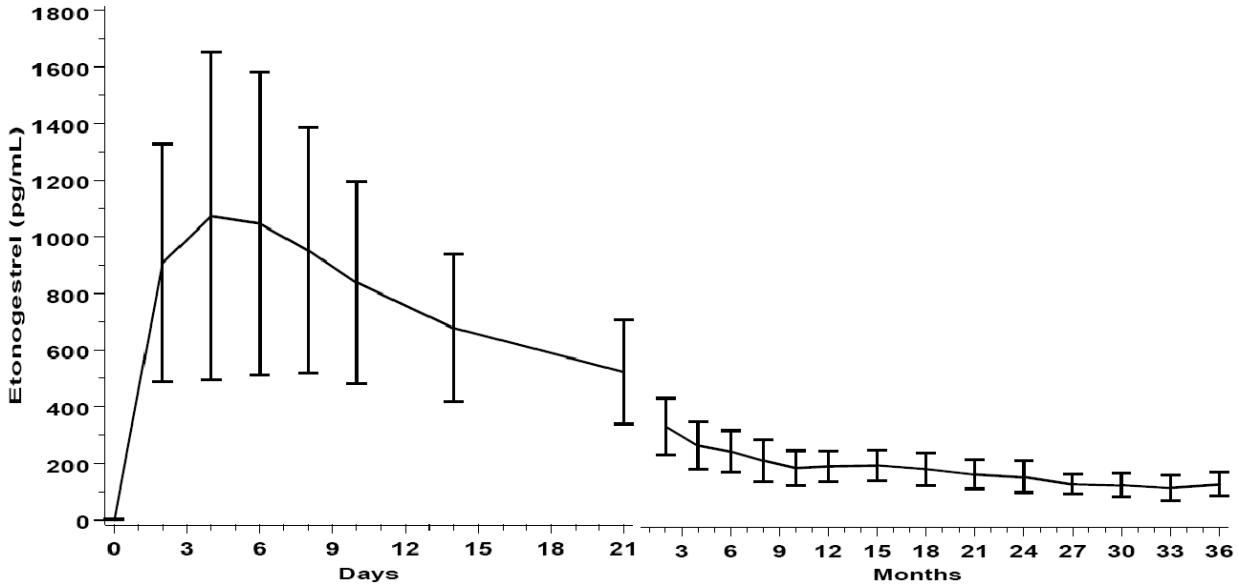


Figure 20: Mean (± SD) Serum Concentration-Time Profile of Etonogestrel After Insertion of NEXPLANON® During 3 Years of Use

Distribution

The apparent volume of distribution averages about 201 L. Etonogestrel is approximately 32% bound to sex hormone binding globulin (SHBG) and 66% bound to albumin in blood.

Metabolism

In vitro data shows that etonogestrel is metabolized in liver microsomes by the cytochrome P450 3A4 isoenzyme. The biological activity of etonogestrel metabolites is unknown.

Elimination

The elimination half-life of etonogestrel is approximately 25 hours. Excretion of etonogestrel and its metabolites, either as free steroid or as conjugates, is mainly in urine and to a lesser extent in feces. After removal of the implant, etonogestrel concentrations decreased below sensitivity of the assay by one week.

Special populations and conditions

- **Pediatrics:** Safety and efficacy of NEXPLANON have been established in women of reproductive age and are expected to be the same for post pubertal adolescents. However, no clinical studies have been conducted in women less than 18 years of age. Use of this product before menarche is not indicated (see 1 Indications).
- **Geriatrics:** NEXPLANON is not indicated for postmenopausal women (see 1 Indications)
- **Sex:** NEXPLANON is indicated for prevention of pregnancy in women aged 18 years or older (see

1 Indications).

- **Pregnancy and breastfeeding:**

Pregnancy

NEXPLANON is not indicated during pregnancy (see 2 Contraindications and 7 Warnings and Precautions, 7.1 Special Populations, 7.1.1 Pregnancy).

Breastfeeding

Clinical data indicate that NEXPLANON 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 (see 7 Warnings and Precautions, 7.1 Special Populations, 7.1.2 Breastfeeding).

- **Hepatic Insufficiency:** No formal studies were conducted to evaluate the effect of hepatic disease on the pharmacokinetics of NEXPLANON. However, steroid hormones may be poorly metabolized in women with impaired liver function. The use of NEXPLANON in women with active liver disease is contraindicated (see 2 Contraindications).
- **Renal Insufficiency:** No formal studies were conducted to evaluate the effect of renal impairment on the pharmacokinetics of NEXPLANON.
- **Obesity:** The effectiveness of the etonogestrel implant in overweight women has not been defined because women who weighed more than 130% of their ideal body weight were not studied (see 7 Warnings and Precautions, 7.1 Special Populations, Overweight Women).

11. Storage, Stability, and Disposal

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

NEXPLANON should be stored at 2°-30°C.

12. Special Handling Instructions

See 4 Dosage and Administration for detailed handling instructions.

The applicator is for single use only.

Part 2: Scientific Information

13. Pharmaceutical Information

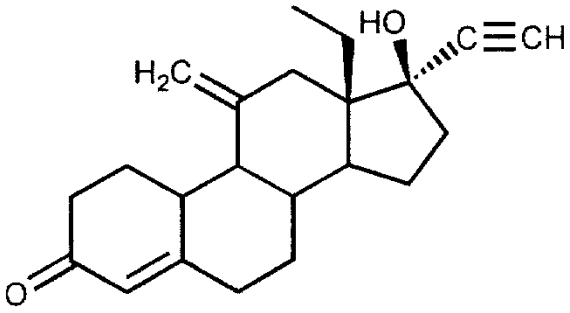
Drug Substance

Non-proprietary name of the drug substance(s): etonogestrel

Chemical name: (17α)-13-Ethyl-17-hydroxy-11-methylene-18,19-dinorpregn-4-en-20-yn-3-one

Molecular formula and molecular mass: $C_{22}H_{28}O_2$ / 324.46

Structural formula:



Physicochemical properties: White to practically white powder.

Solubility	at 22°C: n-Hexane – 2 mg/mL Ethanol (96%) – 60 mg/mL Ethyl acetate – 60 mg/mL Water – practically insoluble
Melting Point:	196.5 – 199.5°C

14. Clinical Trials

14.1. Clinical Trials by Indication

Prevention of pregnancy

The overall contraceptive efficacy database provides data from 923 non-breastfeeding subjects from 11 studies, who were treated with a non-radiopaque etonogestrel subdermal implant for 1-5 years.

Table 7 – Summary of patient demographics (safety population) for clinical trials to determine safety and efficacy of etonogestrel subdermal implant (non-radiopaque)

Study #	Study design	Duration	Study subjects (n) / cycles of exposure	Mean age (Range) / Mean BMI (kg/m2)
069001	open label, multicenter safety & efficacy	2 years	330 / 6186	26.1 (18-40) / 23.6
34502	open label, single-center PK&PD	5 years	15 / 755	26.0 (20-37) / 22.3
34505	open label, single-center safety & efficacy	4 years	100 / 3863	26.3 (18-39) / 21.7
34507	open label, Multicenter efficacy & safety	2 -3 years	267 / 7879	28.2 (18-40) / 22.7
34510	open label, bi-center randomized, comparative≠ safety & efficacy	2 years	15 / 358	28.5 (19-36) / 21.9
34511	open label, single-center, randomized, comparative≠	2 years	40 / 1028	29.1 (19-39) / 23.3
34512	open label, bi-center, randomized, comparative≠	2 years	20 / 376	31.8 (19-40) / 22.2
34515	open label, single-center	2 years	10 / 253	32.3 (27-39) / 23.3
34522	open label, 3-center, non-randomized	2 years	46 / 1054	30.8 (18-39) / 23.3
34525	bi-center	1 year	30 / 356	30.1 (21-39) / 22.2
E1729	open label, Multicenter	2-3 years	69 / 1775	29.7 (19-38) / 23.6

≠ Norplant: 6 subdermal implants with initial release rate of 85 mcg/l d-levonorgestrel

Table 8 – Summary of patient demographics for clinical trial to determine safety and efficacy of etonogestrel subdermal implant (radiopaque)

Study #	Study design	Duration	Study subjects (n) / cycles of exposure	Mean age (Range) / Mean BMI (kg/m2)
34530	open label, multicenter	3 years	301 / 8544	28.2 (18-40) 23.8
34528	bioequivalence	3 years	108/3159	27.1 (18-43) 22.4

Study Results

Studies using non-radiopaque implant

In clinical trials of up to 3 years duration that involved 923 subjects, 18-40 years of age at entry, and 1756 women-years of use with the non-radiopaque etonogestrel implant (IMPLANON), the total exposures expressed as 28-day cycle equivalents by study year were:

Year 1: 10,866 cycles
Year 2: 8,581 cycles
Year 3: 3,442 cycles

The clinical trials excluded women who:

- Weighed more than 130% of their ideal body weight
- Were chronically taking medications that induce liver enzymes

In the subgroup of women, 18-35 years of age at entry, 6 pregnancies during 20,648 cycles of use were reported. Two pregnancies occurred in each of Years 1, 2, and 3. Each conception was likely to have occurred shortly before or within 2 weeks after removal of the non-radiopaque etonogestrel implant. With these 6 pregnancies, the cumulative Pearl Index was 0.38 pregnancies per 100 women-years of use.

Table 9 – Overall, Annual and Cumulative Pearl Indices for etonogestrel subdermal implant*

OVERALL			
Parameter			
Number of subjects (N)	923		
Pregnancies (n)	0		
Exposure Woman Years	1832		
(28-day cycle equivalents)	23 883		
Pearl index	0		
Pearl index (95% CI)	0, 0.20		
ANNUAL			
Parameter	Year 1 (Day 1 – 365)	Year 2 (Day 366 – 730)	Year 3 (Day 731 – 1095)
Number of subjects (N)	923	743	533
Pregnancies (n)	0	0	0
Exposure Woman Years	834	658	264
(28-day cycle equivalents)	10 866	8 581	3 441
Pearl index	0	0	0

Pearl index (95% CI)	0, 0.49	0, 0.62	0, 1.57
CUMULATIVE			
Parameter	923	923	923
Pregnancies (n)	0	0	0
Exposure Woman Years	834	1492	1755
(28-day cycle equivalents)	10 866	19 447	22 888
Pearl index	0	0	0
Pearl index (95% CI)	0, 0.44	0, 0.25	0, 0.21

* results presented in this table were acquired using a non-radiopaque implant.

Return to Ovulation

In clinical trials with the non-radiopaque etonogestrel implant (IMPLANON), the etonogestrel levels in blood decreased below sensitivity of the assay by one week after removal of the implant. In addition, pregnancies were observed to occur as early as 7 to 14 days after removal. Therefore, a woman should re-start contraception immediately after removal of the implant if continued contraceptive protection is desired.

Studies using radiopaque implant

Out of 301 insertions of the NEXPLANON implant in a clinical trial, the mean insertion time (from the removal of the protection cap of the applicator until retraction of the needle from the arm) was 27.9 ± 29.3 seconds. After insertion, 300 out of 301 (99.7%) NEXPLANON implants were palpable. The single, non-palpable implant was not inserted according to the instructions.

For 112 out of 114 (98.2%) subjects in 2 clinical trials for whom insertion and removal data were available, NEXPLANON implants were clearly visible with use of two-dimensional x-ray after insertion. The two implants that were not clearly visible after insertion were clearly visible with two-dimensional x-ray before removal.

14.2. Comparative Bioavailability Studies

A multicenter, randomized, double-blind, parallel group bioequivalence study comparing the radiopaque NEXPLANON to the non-radiopaque etonogestrel subdermal implant was conducted in healthy female volunteers. The design of the study was adequate to determine the Cmax and AUC parameters from 2 days through 3 years after subdermal insertion of the implants. Data from this study demonstrate that NEXPLANON and the non-radiopaque etonogestrel subdermal implant meet comparative bioavailability standards with respect to rate and extent of absorption of etonogestrel.

16. Non-Clinical Toxicology

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.

Acute Toxicity Studies:

Acute toxicity studies were conducted in rats and in mice using the oral and intraperitoneal route. Etonogestrel was dosed orally by gavage (2000 mg/kg) or intraperitoneally by injection (500 mg/kg). No mortalities occurred at the dose levels used. This is in agreement with published data indicating that natural and synthetic sex steroids, in general, exert low toxic activity in animals.

Chronic Toxicity Studies:

The chronic toxicity studies comprised of exposure to etonogestrel by oral administration in rats (52 weeks) and dogs (26 weeks). In rats, oral dosages of up to ~70 times and in dogs up to ~160 times the anticipated average human daily dose were administered. In general, etonogestrel induced a pattern of endocrinological changes, in particular in the genital organs and the accessory glands in rats as well as in dogs. These changes were dose-related, generally reversible and they were to be expected on the basis of the hormonal activity of etonogestrel. Studies in rats for up to 2 years and in dogs for up to 5.8 years using etonogestrel-containing implants also revealed no systemic or local abnormalities considered to be related to etonogestrel or the implant. These chronic toxicity studies showed that etonogestrel lacks intrinsic toxic properties. This is consistent with the observation that etonogestrel is the biologically active metabolite of desogestrel (DSG).

Special toxicity studies were performed in monkeys for up to 3 months using either suppositories, vaginal rings, or oral formulations containing etonogestrel and ethinyl estradiol (EE). The results showed that treatment with etonogestrel and EE at intravaginal dose levels up to about 25 times and oral dose levels up to 100 times the anticipated human vaginal dose did not induce overt signs of toxicity.

Reproductive Toxicity Studies:

Teratology studies have been performed in rats and rabbits, using oral administration up to 315 and 781 times the human etonogestrel dose (based upon body surface) and revealed no evidence of fetal harm due to etonogestrel exposure. Etonogestrel was neither embryotoxic nor teratogenic. Previous data reported using DSG support this conclusion. Thus, based on historical data on desogestrel and etonogestrel, it was concluded that etonogestrel is devoid of reproductive toxicological hazards. Fertility in rats returned after withdrawal from treatment.

Carcinogenesis, Mutagenesis:

Studies with etonogestrel also found no genotoxicity in the in vitro Ames/Salmonella reverse mutation assay, the chromosomal aberration assay in Chinese hamster ovary cells or in the in vivo mouse micronucleus test.

Since etonogestrel is the biologically active metabolite of desogestrel and since the metabolic profiles of the two compounds are very similar supportive evidence can be obtained from carcinogenicity studies previously performed with desogestrel. In these studies, desogestrel was orally administered for 81 weeks either to mice at dose levels of 2x, 20x and 200x the human desogestrel dose or to rats for 104 weeks. In neither study were neoplastic changes observed.

The conclusion that desogestrel and therefore etonogestrel was non-carcinogenic can also be derived from studies previously performed in rats, dogs and monkeys using oral administration of the combination of desogestrel and ethinyl estradiol. In these studies mice and rats were treated for 80 weeks and 104 weeks, respectively at dose levels 2x, 20x and 200x the human dose. Pituitary tumour and mammary tumour induction observed in mice and rats in those studies was fully ascribed to the estrogenic component. Dogs were treated for 3 years at dose levels 2x, 10x and 25x the anticipated human dose and monkeys for 3 years at dose levels 2x, 10x and 50x the human dose. In these species only, the expected non-neoplastic changes were observed and no tumorigenic effects were seen.

In a 24-month carcinogenicity study in rats with subdermal implants releasing 10 and 20 mcg etonogestrel per day (equal to approximately 1.8-3.6 times the systemic steady state exposure in women using NEXPLANON), no drug-related carcinogenic potential was observed.

In conclusion, chronic toxicity and tumorigenicity studies demonstrated that there is no evidence of carcinogenicity of etonogestrel.

Product ingredients

Ethylene vinyl acetate (EVA)

Extracts of EVA material caused neither sensitization nor irritation upon direct contact with tissues of mice and guinea pigs in vivo. Implantation of the EVA material (with or without etonogestrel) caused no toxic, irritation or sensitizing effects in rabbit, rat and dog. Potentially leachable components of the EVA copolymer, when extracted in conformity with ISO guidelines were not cytotoxic under in vitro conditions. No local toxicity has been observed in mice, rats, guinea pigs, rabbits, and monkeys after subcutaneous, intramuscular, intradermal, or vaginal administration. The EVA copolymer was shown to be devoid of clastogenic and carcinogenic properties.

Barium sulfate

The incorporation of barium sulfate (3% v/v; 15 mg) per implant is not expected to cause safety concerns in view of the (i) very low solubility of barium sulfate in water (approximately 0.3mcg/mL at 30°C); (ii) the extremely low (< 0.1 mcg) daily release of Ba++ ions from the intact or damaged implant and (iii) the maximal total release of barium sulfate particles from the open ends of the implant (< 11 mcg over approximately 2 years) will be phagocytosed at the application site by macrophages. These amounts are toxicologically insignificant considering that Ba++ ions are natural constituents of the human body and daily dietary and inhalatory exposure of the general population is > 1 mg. The normal body content of barium is about 22 mg and a normal blood value is 1.2 mcg/L. Moreover, there is a long established clinical experience without barium sulfate-related safety problems with radiopaque products, e.g.: stents and IUDs and large oral doses (grams) of barium sulfate are used on a routine basis for the purpose of radiologic diagnosis of GI tract disease.

Patient Medication Information

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE

PR **NEXPLANON®**

etonogestrel extended release subdermal implant

This patient medication information is written for the person who will be taking **NEXPLANON®**. This may be you or a person you are caring for. Read this information carefully. Keep it as you may need to read it again.

This patient medication information is a summary. It will not tell you everything about this medication. If you have more questions about this medication or want more information about **NEXPLANON**, talk to a healthcare professional.

Serious warnings and precautions box

- NEXPLANON will be inserted and removed by a healthcare professional who is familiar with this implant. They should be trained in how to perform the procedure.
- If, at any time, you cannot feel the implant, contact your healthcare professional as soon as possible. The implant may have moved from the place it was inserted and may need to be removed.
- NEXPLANON will NOT protect you against sexually transmitted infections (STIs), including Human Immunodeficiency Virus (HIV)/ Acquired immunodeficiency syndrome (AIDS). To protect yourself against STIs, use latex or polyurethane condoms while you are using NEXPLANON.

What NEXPLANON is used for:

NEXPLANON is used to prevent pregnancy in adult women for up to 3 years.

How NEXPLANON works:

NEXPLANON is a birth control implant that contains a hormone called etonogestrel. It does not contain estrogen. This implant is a small, soft, flexible plastic rod that is about the size of a matchstick (Figure 1). It is contained in an applicator. This applicator allows the healthcare professional to insert (place) the implant just below the skin on the inside of your upper arm.

Figure 1

NEXPLANON will continuously release a small amount of etonogestrel into your blood. The etonogestrel works in two ways to prevent pregnancy:

- It stops the release of egg cells from your ovaries.
- It causes changes in your cervical mucus to make it hard for sperm to enter your uterus.

NEXPLANON is a long-acting reversible contraceptive. This means that it can provide birth control over a long period of time. In fact, NEXPLANON can be left in place for up to 3 years. It is also reversible. This means that, if you want to stop using NEXPLANON before 3 years, the implant can be removed at any time. You may be able to get pregnant as early as 1 week after the implant is removed. If you wish to continue to prevent pregnancy, start a different type of birth control right away.

Long-acting reversible contraceptives are highly effective in preventing pregnancy.

Other Ways to Prevent Pregnancy

Other methods of birth control are available to you, including the birth control pill. When used properly, other methods of birth control are effective enough for many women.

The following table lists pregnancy rates for different types of birth control. It also shows the pregnancy rate when no birth control is used. A pregnancy rate is the number of women out of 100 who would become pregnant in one year.

Reported Pregnancies per 100 Women per Year:

Subdermal implant	less than 0.05
Combination pill	less than 1 to 2
Contraceptive vaginal ring	between 1 and 2
Intrauterine device (IUD)	less than 1 to 6
Condom with spermicidal foam or gel	1 to 6
Mini-pill	3 to 6
Condom	2 to 12
Diaphragm with spermicidal foam or gel	3 to 18
Spermicide	3 to 21
Sponge with spermicide	3 to 28
Cervical cap with spermicide	5 to 18
Periodic abstinence (rhythm), all types (example natural family planning)	2 to 20
No birth control	60 to 85

There are differences in these pregnancy rates. This is because not all women use their birth control as carefully or as regularly as they should. This does not apply to intra-uterine devices (IUD) or implants (like NEXPLANON) as these are placed into the body. If other types of birth control are used carefully and regularly, pregnancy rates should be lower. Talk to your healthcare professional about the different types of birth control available to you and any associated risks.

The ingredients in NEXPLANON are:

Medicinal ingredients: etonogestrel

Non-medicinal ingredients: barium sulfate, ethylene vinyl acetate copolymer, magnesium stearate.

The implant itself is made of a plastic that will not dissolve in your body. It also contains a small amount of barium sulfate. This ensures that the implant can be seen on an x-ray.

NEXPLANON comes in the following dosage form(s):

Subdermal implant, 68 mg

Once inserted, NEXPLANON will release up to 70 mcg etonogestrel per day. More etonogestrel will be released during the first few weeks after insertion. The amount released will slowly decrease over time.

Do not use NEXPLANON if:

- you are allergic to etonogestrel or any of the other ingredients in this medicine.
- you are pregnant or think you might be pregnant.
    - Before NEXPLANON is inserted, a pregnancy test should be done to confirm that you are not pregnant.
    - If you do become pregnant while using NEXPLANON, tell your healthcare professional right away.
- you have a clotting disorder or have had blood clots in veins (venous thrombosis) or arteries (arterial thrombosis) of the:
    - leg. This is called deep vein thrombosis;
    - lungs. This is called pulmonary embolism;
    - eyes. This is called retinal vascular occlusion;
    - heart. This is called a heart attack; or
    - brain. This is called a stroke.
- you have, think you have, or have previously had breast cancer or any cancer that is sensitive to the female hormone, progestin.
- you have liver disease or liver tumours that may be either cancerous or not.
- you have any unexplained bleeding from the vagina.

If any of the above conditions appear for the first time while using NEXPLANON, contact your healthcare professional right away.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you use NEXPLANON. Talk about any health conditions or problems you may have, including if you:

- have had a liver disease;
- have diabetes. This is a disease that occurs when your blood sugar is too high;
- are overweight. This is because your implant may need to be replaced earlier;
- have high cholesterol or a high level of fat called triglyceride in your blood;
- have high blood pressure;
- have kidney problems;
- have a condition that causes you to retain fluid;
- wear contact lenses;
- are going to have surgery or if you have mobility issues;
- suffer from depression;

- suffer from epilepsy (uncontrolled seizures) or tuberculosis (a bacterial infection of the lungs). This is because NEXPLANON may interact with drugs used to treat these conditions.

If you use NEXPLANON and have any of these conditions, you may need to be kept under close observation. Your healthcare professional will explain what to do. **If the condition develops or gets worse while you are using NEXPLANON, tell your healthcare professional right away.**

Other warnings you should know about:

Breast cancer

Breast cancer has been found more often in women who use birth control pills ("the Pill"). It is not known if the increased risk in these women is caused by the treatment.

It may be that tumours are found more in these women because they are examined more often by a healthcare professional. The risk for breast cancer in these women slowly lessens after stopping the Pill.

It is not known if this same risk applies to women who use birth control implants. **While you are using NEXPLANON, check your breasts regularly.** See your healthcare professional if you notice any lump in your breast. Be sure to tell your healthcare professional if a close relative has or ever had breast cancer.

Liver tumours

In rare cases, benign and even more rarely malignant (cancerous) liver tumours have been reported in women using the Pill. Contact your healthcare professional if you experience severe abdominal pain or if you are jaundiced. This is when your skin or the whites of your eyes turn yellow. These may be signs that you have a problem with your liver.

Gallbladder disease

The risk for gallbladder disease is higher in women who use birth control pills that contain hormones. It is not known if this risk is also associated with the use of NEXPLANON.

Thrombosis

Combined hormonal birth control contains two hormones, progestin and estrogen. Using this type of birth control increases a woman's risk of developing blood clots. It is not known if this risk is the same for birth control methods like NEXPLANON that only contain etonogestrel (a progestin hormone). There have been reports of blood clots in women using etonogestrel implants. Seek medical help right away if you develop any signs or symptoms of a blood clot including:

- swelling, pain, tenderness or discolouration in the leg or arms
- chest pain, shortness of breath
- slurred speech, face drooping to one side
- loss of vision, double vision, bulging eyeball
- dizziness, headache

If you are to be immobilized or are to have surgery, tell your healthcare professional that you are using NEXPLANON. It may need to be removed.

Menstrual bleeding pattern changes

Your period bleeding pattern may change while you are using NEXPLANON including changes in:

- frequency. This means that your periods may be absent, happen less often, happen more often or may not stop.
- intensity. This means that your periods may be lighter or heavier than normal.
- duration. This means that your periods may be shorter or longer than normal.

About 1 in 5 women have reported that their periods stopped. Another 1 in 5 women reported more frequent and / or prolonged period bleeding.

The bleeding pattern that you experience in the first three months should generally continue during your treatment with NEXPLANON.

A changing bleeding pattern does not mean that NEXPLANON does not suit you or is not working. In general, you do not need to take any action unless your period bleeding is heavy or does not stop. If this happens, contact your healthcare professional.

Ectopic Pregnancy

If you become pregnant while using NEXPLANON, you have a slightly higher chance that the pregnancy will be ectopic than women who do not use birth control. Ectopic pregnancy happens when a fertilized egg attaches into tissue outside of the uterus. Unusual vaginal bleeding or lower abdominal pain may be signs of ectopic pregnancy. Ectopic pregnancy is a medical emergency that often requires surgery. It can cause serious internal bleeding, infertility, and even death. Call your healthcare professional right away if you think you are pregnant or have unexplained lower abdominal pain.

Ovarian cysts

While using birth control that contains low levels of hormones, small fluid-filled sacs may form in the ovaries. These are called ovarian cysts. Sometimes, these cause mild abdominal pain. Ovarian cysts usually disappear on their own. In rare cases, these may lead to more serious problems.

Breastfeeding

A small amount of the medicinal ingredient in NEXPLANON, etonogestrel, will pass into your breast milk. You may use NEXPLANON while breastfeeding, four weeks after the baby is born, or as directed by your healthcare professional. However, using NEXPLANON while you are breastfeeding may lower the amount of milk you make.

Skin conditions

Tell your healthcare professional if you have or have had chloasma. This skin condition appears as yellowish-brown patches on the skin particularly on the face. Chloasma may develop while you are using NEXPLANON. It is more likely to happen if you had chloasma gravidarum. This is when these patches appear during pregnancy (often known as “the mask of pregnancy”). If you have or had chloasma, avoid exposure to the sun while using NEXPLANON. The sun contains invisible rays that can burn the skin. These rays are called ultraviolet radiation.

Complications of insertion and removal

NEXPLANON should be inserted directly under the skin. You should be able to feel it after it is inserted. You may experience pain, numbness, bleeding, infection or scarring at the site after insertion and removal.

It is possible that the NEXPLANON implant could move from the original insertion site in your arm. This might happen if it is not inserted correctly or as a result of force like during contact sports.

If the implant moves, finding it may be difficult. You may need a bigger incision (a cut into your skin) or surgery to remove it. If the implant cannot be found and there are no signs it has come out, the prevention of pregnancy and the risk for side effects may last longer than you want. If you have questions about this, talk to your healthcare professional.

In rare cases, implants have been found in the pulmonary artery. This is a blood vessel in the lung. If the implant cannot be found in the arm, your healthcare professional may use x-rays or other imaging methods to find it. In some cases where NEXPLANON has been found in the pulmonary artery, chest pain and breathing problems (such as shortness of breath, cough and coughing up blood) were reported. Contact your healthcare professional immediately if you have any of these symptoms. If the implant is found in your chest, you may need surgery to remove it.

While you are using NEXPLANON, feel for the implant occasionally. If, at any time, you cannot feel it, contact your healthcare professional as soon as possible.

Broken or bent implant

The implant could break or bend while in your arm. This should not affect how the implant works. Breakage or bending may occur due to external forces (e.g., manipulation of the implant, using a tourniquet at the implant site or trauma to the implant site during contact sports). The broken implant may move from the insertion site.

Magnetic Resonance Imaging (MRI)

NEXPLANON is Magnetic Resonance (MR) safe.

Regular check-ups

Before NEXPLANON is inserted, you will need to have examinations and tests. Your healthcare professional will conduct a physical exam. They will also ask you some questions about your personal health history and that of your close relatives. Your blood pressure will be measured and a pregnancy test may be conducted.

While you are using NEXPLANON, you will need to have regular check-ups. Your first check-up should be about three months after NEXPLANON is inserted. Additional check-ups will be scheduled periodically thereafter. Your healthcare professional will measure your blood pressure at these visits. You may also need to have other tests done. Your healthcare professional should feel for the implant at each of these visits.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

If you see a different doctor or a dentist who prescribes another medication to you, be sure to tell them that you use NEXPLANON. You should also tell the pharmacist. These healthcare professionals can tell you if your other medications will affect how NEXPLANON works. This means you might experience some vaginal bleeding or that you may not be fully protected from getting pregnant.

Your healthcare professionals may suggest that you use an extra birth control method that doesn't contain hormones, while you are using another medication. Continue to use this birth control 28 days after your last dose of the other medication. This is because the effect of another medication on NEXPLANON may last for that long.

The following may interact with NEXPLANON:

Some medications can affect how NEXPLANON works. These may include:

- medicines for epilepsy (such as phenytoin, barbiturates, carbamazepine, oxcarbazepine, topiramate, felbamate, rufinamide),
- medicines for tuberculosis (such as rifampicin),
- medicines for HIV infection (such as ritonavir, nelfinavir, nevirapine, efavirenz, etravirine, indinavir),
- medicines for Hepatitis C Virus infection (such as boceprevir, telaprevir),
- medicines for other infectious diseases (such as griseofulvin, rifabutin, itraconazole, voriconazole, fluconazole, ketoconazole),
- medicines for high blood pressure in the blood vessels of the lungs (such as bosentan),
- medicines to prevent nausea and vomiting that may be caused by chemotherapy (such as aprepitant),
- an herbal remedy for depressive moods (St. John's wort),
- grapefruit juice.

NEXPLANON may affect how other medicines work. These include:

- medicines for organ transplantation (such as cyclosporine),
- medicines for seizures or mood disorders (such as lamotrigine).

How to use NEXPLANON:

NEXPLANON will be placed and removed by your healthcare professional, who will be familiar with how to do this. The insertion of NEXPLANON will require a small surgical procedure in their office. The implant is inserted under the skin on the inside of your non-dominant upper arm. This is the arm that you do not write with.

Before insertion, tell your healthcare professional if you are pregnant or think you might be pregnant (e.g., if you had unprotected sex during the current menstrual cycle).

The timing of the insertion is important. You and your healthcare professional will decide when to have the implant placed. It will depend your personal situation including:

- your menstrual cycle,
- whether you are using other types of birth control, and
- if you have recently had a baby, miscarriage or abortion.

Unless you are switching from another type of birth control, NEXPLANON is usually placed between day 1 and 5 of your cycle. This is to avoid the chance that you will be pregnant. If it cannot be inserted until after the 5th day of your cycle, use another form of birth control for the first seven days of NEXPLANON use.

NEXPLANON will be inserted according to the following steps:
Step 1. Lie on your back, with your arm bent at the elbow. Put your hand underneath your head, or as close as possible. This position will help with the insertion of the implant (Figure 2).

Figure 2

Step 2. Your healthcare professional will find the correct spot on your arm for the insertion. They will mark your arm in two spots using a marker. These spots will help to make sure the implant is placed in the correct spot.

Step 3. Your healthcare professional will clean the area and give you a medication to numb your arm. This is called an anesthetic. This medication may be sprayed onto your arm or given with a needle.

Step 4. Your healthcare professional will stretch the skin of your upper arm and use the applicator to place the implant. The applicator has a small needle, which will puncture your skin. This allows the implant (rod) to be inserted under the skin.

Step 5. Your healthcare professional will remove the applicator and apply a small bandage over the insertion site.

Step 6. Your healthcare professional will feel for the implant. They will also ask you to feel it. You should be able to feel both ends between your thumb and finger (Figure 3).

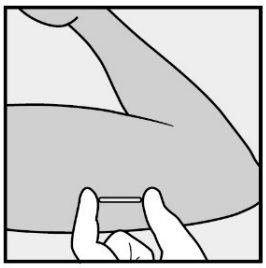


Figure 3

Step 7. The insertion site will then be covered with some gauze. A second bandage, called a pressure bandage, will also be applied. This will help to reduce bruising. You may remove the pressure bandage after 24 hours. The other bandage should stay in place for 3 to 5 days.

Step 8. Your healthcare professional will give you a **Patient Alert Card**. This card shows when and where NEXPLANON was inserted, and when it must be removed. Your healthcare professional will also show you how to feel for the implant. **Occasionally feel for the implant. If, at any time, you cannot feel it, contact your healthcare professional as soon as possible.** The Patient Alert card will also remind you about this. Store the card in a safe place.

If your healthcare professional is not sure the implant was inserted properly:

- you may need to have blood tests and an x-ray, ultrasound or MRI. These will help to confirm if NEXPLANON was inserted.
- you will need to use other methods of birth control until your healthcare professional is certain that NEXPLANON was inserted correctly. This is because you may not be protected against pregnancy during this time. Continue to use this form of birth control until your healthcare professional confirms that the implant was placed correctly. Talk to your healthcare professional about types of birth control to use.
- in the event the implant cannot be found in your arm, you may need an x-ray or other scan of your chest.
- once your healthcare professional finds the implant that they were not initially able to feel, it should be removed.

Removing NEXPLANON:

The implant can be removed at your request or, at the latest, 3 years after it was inserted.

A new implant may be inserted immediately after the old implant is removed. In some cases, the same incision can be used. However, this will only be possible if the insertion site was correct.

You may be able to get pregnant as early as 1 week after your implant is removed. If you do not want to become pregnant after NEXPLANON is removed, ask your healthcare professional about other ways to prevent pregnancy.

If you wish to stop using NEXPLANON because you want to get pregnant, wait until you have had a period before trying to conceive. This will help you to determine when the baby will be due.

NEXPLANON will be removed according to the following steps:

Step 1. Lie on your back, with your arm bent at the elbow. Put your hand underneath your head, or as close as possible (Figure 2).

Step 2. Your healthcare professional will find the implant. If it cannot be found, your healthcare professional may have to use X-ray, CT, ultrasound or MRI techniques to find it.

Step 3. Your healthcare professional will mark a spot on your arm at the end of the implant. This mark will help to ensure the implant is removed correctly.

Step 4. Your healthcare professional will clean your arm and then give you an anesthetic to numb your arm.

Step 5. Your healthcare professional will make a small incision in your arm, just below the tip of the implant. They will gently push the implant towards this incision and pull the implant out using forceps.

Sometimes, the implant is surrounded by hard tissue. This will make it more difficult to remove. If this is the case, your healthcare professional will make a small incision into this tissue.

Step 6. The incision site will be closed using a sterile adhesive wound closure.

A pressure bandage will be placed on top to minimize bruising. You may remove the pressure bandage in 24 hours. The sterile adhesive wound closure should remain in place for 3 to 5 days.

Usual dose:

68 mg

One implant is inserted at a time. The implant can stay in place for up to three years. However, you can ask your healthcare professional to remove it at any time.

If you are overweight, your healthcare professional may suggest replacing your implant earlier.

Overdose:

An implant should always be removed before another is inserted or an overdose could happen.

If you think you, or a person you are caring for, are overdosing, contact a healthcare professional, hospital emergency department, regional poison control centre or Health Canada's toll-free number, 1-844 POISON-X (1-844-764-7669) immediately, even if there are no signs or symptoms.

Possible side effects from using NEXPLANON:

These are not all the possible side effects you may have when taking NEXPLANON. If you experience any side effects not listed here, tell your healthcare professional.

- period bleeding that is not regular (lighter or heavier bleeding, more or less frequent periods, continuous bleeding, longer or shorter periods, no period at all)
- painful period
- ovarian cyst
- vaginal infection or abnormal discharge
- decreased sex drive
- breast pain or tenderness
- inflammation of the vagina
- vaginal pain
- milky discharge from the breast
- breast enlargement
- pain or reaction (including redness, swelling, bruising, numbness) at the insertion site
- fatigue
- drowsiness or trouble sleeping
- flu-like symptoms, fever, pain
- back pain
- abdominal pain, joint, muscle or bone pain
- headache, migraine, dizziness
- depression, anxiety, nervousness
- mood swings (uncontrollable laughing or crying)
- nausea, gas
- weight gain or weight loss
- increased appetite
- diarrhea, constipation, vomiting
- acne, rash, hair loss
- hot flushes
- excessive hair growth
- skin itching
- oily skin
- yellowish-brown patches on the skin particularly on the face
- hives
- dandruff

- fluid retention
- sore throat
- stuffy or runny nose
- urinary tract infection
- painful or difficult urination
- increased blood pressure

If your period bleeding is heavy or does not stop, contact your healthcare professional.

During the insertion or removal of NEXPLANON, drop in blood pressure, dizziness, or fainting, some bruising, pain, swelling, or itching may occur and, in rare cases, infection. A scar may form or an abscess (blister) may develop at the site. This site may also be numb. It is possible that the implant could move or come out. This is especially true if it has not been inserted properly. Surgery might be necessary when removing the implant. In rare cases, implants have been reported to be found in a blood vessel, including those in the lung. This can cause shortness of breath, cough, coughing up blood or blood-stained mucus.

NEXPLANON may cause abnormal blood test results. Your healthcare professional will decide when to perform blood tests and will interpret the results.

Serious side effects and what to do about them

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
Uncommon			
Abnormal vaginal bleeding		√	
Allergic reaction: difficulty swallowing or breathing, wheezing, nausea, vomiting, swollen face, lips, tongue or throat, hives			√
Breast Cancer: breast lumps or tumours that you can see or feel			√
Deep vein thrombosis (blood clot in the leg): pain or swelling in the leg, may be warm to the touch			√
Jaundice (build-up of bilirubin in the blood): yellowing of the skin and eyes, dark urine, light coloured stool			√
Liver tumour: Abnormal liver test and/or yellowing of the skin or eyes, dark urine, nausea, vomiting, severe pain or lump in the abdomen			√
Myocardial infarction (heart attack): crushing chest pain, pressure or heaviness			√
Peripheral edema: unusual swelling of the extremities		√	
Pulmonary embolism (blood clot in the lung): sharp pain in the chest, coughing blood, or sudden shortness of breath			√
Retinal vascular occlusion (blood clot in the eye): sudden partial or complete loss of vision, double vision			√
Stroke: sudden severe or worsening headache, vomiting, dizziness or fainting, disturbance of vision or speech, weakness or numbness in the arm or leg			√
Unknown			
Angioedema (swelling of the tissue under the skin): difficulty breathing; swelling of the face,			√

Frequency/Side Effect/Symptom	Talk to your healthcare professional		Get immediate medical help
	Only if severe	In all cases	
hands, feet, genitals, tongue, throat; diarrhea, nausea, vomiting			
Ectopic pregnancy (when a fertilized egg attaches to tissue outside of the uterus): abdominal or pelvic pain, bleeding from the vagina, lightheadedness, fainting, shoulder pain			√
Idiopathic intracranial hypertension (IIH) (increased pressure inside your skull): severe or recurrent headaches, eyesight problems/ visual changes, tinnitus (ringing/ buzzing in the ear)			√

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, tell your healthcare professional.

Reporting side effects

You can report any suspected side effects associated with the use of health products to Health Canada by:

- Visiting the Web page on Adverse Reaction Reporting (canada.ca/drug-device-reporting) for information on how to report online, by mail or by fax; or
- Calling toll-free at 1-866-234-2345.

NOTE: Contact your healthcare professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.

Storage:

Store NEXPLANON at 2-30°C.

Keep out of reach and sight of children.

If you want more information about NEXPLANON:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes the Patient Medication Information by visiting the Health Canada Drug Product Database website (https://www.canada.ca/en/health-canada/services/drugs-health-products/drug-products/drug-product-database.html); the manufacturer's website (www.organon.ca); or by calling 1-844-820-5468.

This leaflet was prepared by Organon Canada Inc.

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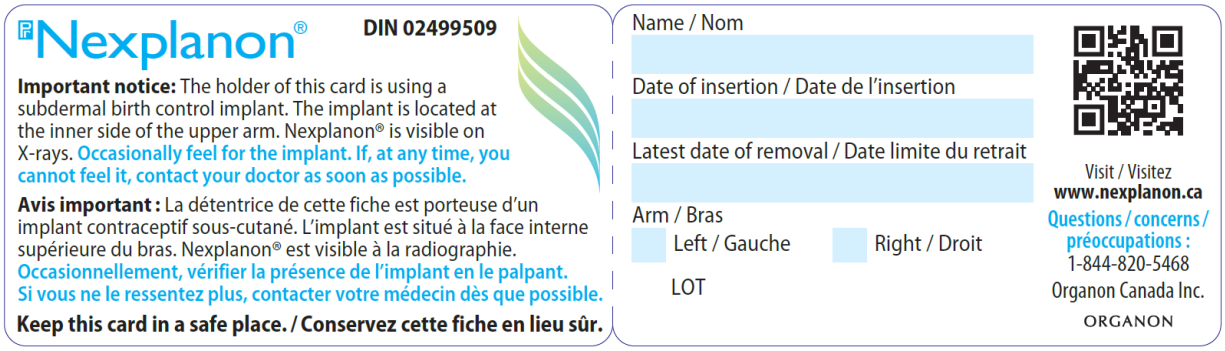
A copy of the Patient Alert Card included with the NEXPLANON® carton is shown below.