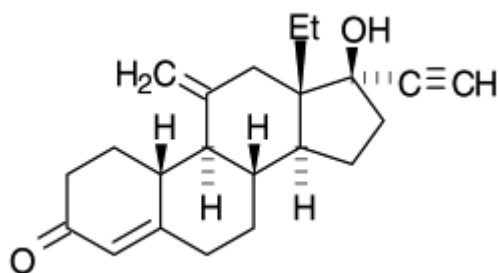


Implanon NXT[®]

NAME OF THE MEDICINE

Etonogestrel subdermal implants.

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



Molecular formula $C_{22}H_{28}O_2$

Molecular mass 324.44

CAS No. 54048-10-1

DESCRIPTION

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

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

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

Implant

Core: Ethylene vinylacetate copolymer (28% vinyl acetate) 43 mg - proprietary ingredient, barium sulfate (15 mg), magnesium stearate (0.1 mg)

Skin: Ethylene vinylacetate copolymer (15% vinyl acetate) 15 mg - proprietary ingredient

Applicator

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

Qualitative and Quantitative Composition

Each radiopaque implant contains 68 mg etonogestrel; the release rate is 60-70 $\mu\text{g}/\text{day}$ during week 5-6, and decreases to approximately 35-45 $\mu\text{g}/\text{day}$ at the end of the first year, to approximately 30-40 $\mu\text{g}/\text{day}$ at the end of the second year, and to approximately 25-30 $\mu\text{g}/\text{day}$ at the end of the third year.

Pharmacotherapeutic group: progestagens, ATC-classification G03AC08

PHARMACOLOGY

Pharmacodynamic properties

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

Although ENG inhibits ovulation, ovarian activity is not completely suppressed. Mean oestradiol concentrations remain above the level seen in the early-follicular phase. In a two-year study, in which the bone mineral density in 44 users has been compared to that in a control group of 29 IUD-users no adverse effects on bone mass have been observed. No clinically relevant effects on lipid metabolism have been observed. The use of progestagen-containing contraceptives may have an effect on insulin resistance and glucose tolerance.

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

Pharmacokinetic properties

Absorption

After insertion of the implant, ENG is rapidly absorbed into the blood stream. Ovulation-inhibiting concentrations are reached within 1 day. Maximum serum concentrations (between approximately 400 and 3,000 pg/mL) are generally reached within the first 14 days. The release rate of the implant decreases with time. As a result serum concentrations decline rapidly over the first few months. By the end of the first year a mean concentration of approximately 200 pg/mL is measured, which slowly decreases to approximately 150 pg/mL by the end of the third year. The variations observed in serum concentrations can be partly attributed to differences in body weight.

Distribution

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

Metabolism

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

In vitro data provide evidence that metabolism of etonogestrel, similar to that of other contraceptive steroids, is catalysed by CYP3A4 (See **Interaction with other medicines**).

Elimination

After IV administration of ENG, the mean elimination half-life is approximately 25 hours and the serum clearance is approximately 7.5 l/hour. Both clearance and elimination half-life remain constant during treatment period. The excretion of ENG and its metabolites, either as free steroids or as conjugates, is in urine and faeces (ratio 1.5:1). After insertion in lactating women, etonogestrel is excreted in breast milk with a milk/serum ratio of 0.44-0.50 during the first four months. In lactating women, the mean transfer of etonogestrel to the infant is approximately 2.2% of the maternal etonogestrel daily dose (values normalised per kg body weight). Concentrations show a gradual and statistically significant decrease from about 20 to 15 and 10 ng/kg/day at month 1, 2 and 4 respectively in a group of 41 infants.

Preclinical safety data

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

CLINICAL TRIALS

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

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

Bone mineral density

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

Weight changes

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

Return of fertility

In supportive studies return of ovulation after implant removal was assessed by ultrasound measurements and hormone determinations. Ovulation returns after removal of the implant shortly after etonogestrel has disappeared from the body, enabling restoration of fertility. This conclusion is supported by the occurrence of 37 pregnancies that were reported after implant removal.

INDICATIONS

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

CONTRAINDICATIONS

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

PRECAUTIONS

Medical Examination and Follow Up

Prior to the initiation or reinstatement of Implanon NXT a complete medical history (including family medical history) should be taken and pregnancy should be excluded. Blood pressure should be measured and a physical examination should be performed, guided by the **CONTRAINDICATIONS** and **PRECAUTIONS**. It is recommended that the woman returns for a medical check-up three months after insertion of Implanon NXT. During this check-up, the blood pressure should be measured and an enquiry should be made after any questions, complaints or the occurrence of undesirable effects. The frequency and nature of further periodic checks should be adapted to the individual woman, guided by clinical judgement, but at least once a year is advised.

Other

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

Use with caution in the following circumstances

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

- The risk for breast cancer increases in general with increasing age. During the use of (combined) OCs the risk of having breast cancer diagnosed is slightly increased. This increased risk disappears gradually within 10 years after discontinuation of OC use and is not related to the duration of use, but to the age of the woman when using the OC. The expected number of cases diagnosed per 10,000 women who use combined OCs (up to 10 years after stopping) relative to never users over the same period have been calculated for the respective age groups to be: 4.5/4 (16-19 years), 17.5/16 (20-24 years), 48.7/44 (25-29 years), 110/100 (30-34 years), 180/160 (35-39 years) and 260/230 (40-44 years). The risk in users of contraceptive methods which only contain progestagens is possibly of similar magnitude as that associated with combined OCs. However, for these methods, the evidence is less conclusive. Compared to the risk of getting breast cancer ever in life, the increased risk associated with OCs is low. The cases of breast cancer diagnosed in OC users tend to be less advanced than in those who have not used OCs. The increased risk observed in OC users may be due to an earlier diagnosis, biological effects of the OC or a combination of both.
- Epidemiological studies have associated the use of combined oral contraceptives (COCs) with an increased incidence in venous thromboembolism (VTE, deep vein thrombosis and pulmonary embolism). Although the clinical relevance of this finding for etonogestrel (the biologically active metabolite of desogestrel) used as a contraceptive in the absence of an oestrogenic component is unknown, the implant should be removed in the event of a thrombosis. Removal of the implant should also be considered for women who are immobilised for a long time because of surgery or a disease. Although Implanon NXT is a progestagen-only contraceptive, it is recommended to assess risk factors which are known to increase the risk of venous and arterial thromboembolism. Women with venous thromboembolic disease should be made aware of the possibility of a recurrence.

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

- The following conditions have been reported both during pregnancy and during sex steroid use, but an association with the use of progestagens has not been established: jaundice and/or pruritus related to cholestasis; gallstone formation; porphyria; systemic lupus erythematosus; haemolytic uraemic syndrome; Sydenham's chorea; herpes gestationis; otosclerosis-related hearing loss and (hereditary) angioedema.
- When acute or chronic disturbances of liver function occur, the woman should be referred to a specialist for examination and/or advice.
- Chloasma may occasionally occur, especially in women with a history of chloasma gravidarum. Women with a tendency to develop chloasma should avoid exposure to the sun or ultraviolet radiation whilst using Implanon NXT.
- Although progestagens may have an effect on peripheral insulin resistance and glucose tolerance, there is no evidence for a need to alter the therapeutic regimen in diabetics using progestagen-only contraceptives. However, diabetic women should be carefully observed while using progestagen-only contraceptives.
- Women who are being treated for hyperlipidemia should be followed closely if they elect to use Implanon NXT. Some progestagens may elevate LDL levels and may render the control of hyperlipidemia more difficult.
- Implanon NXT use should be discontinued when during the use of the implant there is a constantly elevated blood pressure or when a significant increase in blood pressure does not respond to an antihypertensive therapy.
- Expulsion may occur especially if the implant is not inserted according to the instructions given in the section **How to insert Implanon NXT**, or as a consequence of a local inflammation.
- Occasionally a scar may be formed.
- There have been reports of migration of the implant within the arm from the insertion site, which may be related to a deep initial insertion (see **How to insert Implanon NXT**) or to external forces (e.g. manipulation of the implant or contact sports). There also have been rare postmarketing reports of implants located within the vessels of the arm and the pulmonary artery, which may be related to deep insertions or intravascular insertion. In cases where the implant has migrated within the arm from the insertion site, localisation may be more difficult and removal may require a minor surgical procedure with a larger incision or a surgical procedure in an operating room. In cases where the implant has migrated to the pulmonary artery, endovascular or surgical procedures may be needed for removal (see **How to remove Implanon NXT**). If at any time the implant cannot be palpated, it should be localized and removal is recommended. If the implant cannot be removed, contraception and the risk of progestogen-related undesirable effects may continue beyond the time desired by the woman.
- The efficacy of Implanon NXT may be reduced when concomitant medication is used (see **Interactions with other medicines**).
- The contraceptive effect of Implanon NXT is related to the plasma levels of etonogestrel, which are inversely related to body weight and decrease with time after insertion. The clinical experience in heavier women in the third year of use is limited. Therefore it cannot be excluded that the contraceptive effect in these women during the third year of use may be lower than for women of normal weight. Clinicians may therefore consider earlier replacement of the implant in heavier women.

Changes in menstrual bleeding pattern

During the use of the implant, women are likely to have changes in their menstrual bleeding pattern. These may include changes in bleeding frequency (absent, less, more frequent or continuous), intensity (reduced or increased) or duration. Amenorrhoea was reported in about 1 of 5 women while

another 1 of 5 women reported frequent and/or prolonged bleeding. Dysmenorrhoea tended to improve while using the implant. The bleeding pattern experienced during the first three months is broadly predictive of future bleeding patterns for many women. Evaluation of vaginal bleeding should be done on an ad hoc basis and may include an examination to exclude gynaecological pathology or pregnancy.

Follicular development

With all low-dose hormonal contraceptives, follicular development occurs and occasionally the follicle may continue to grow beyond the size it would attain in a normal cycle. Generally, these enlarged follicles disappear spontaneously. Often, they are asymptomatic; in some cases they are associated with mild abdominal pain and rarely, they require surgical intervention.

Ectopic pregnancy

The protection with traditional progestagen-only contraceptives against ectopic pregnancies is not as good as with combined OCs, which has been associated with the frequent occurrence of ovulations during the use of these methods. Despite the fact that Implanon NXT consistently inhibits ovulation, ectopic pregnancy should be taken into account in the differential diagnosis if the woman gets amenorrhoea or abdominal pain.

Carcinogenicity and Mutagenicity

No drug-related increases in tumour incidences were observed in rats with subcutaneous implants releasing 18 or 36 µg of etonogestrel/day. Serum etonogestrel levels in the high-dose group were 3 times higher than those in women with ENG implants. Mutagenic activity was not observed in bacterial cells (Ames assay), but mutagenic and clastogenic activities in mammalian cells have not been investigated.

Pregnancy: Category B3

The use of Implanon NXT is contraindicated during pregnancy. If pregnancy occurs during use of Implanon NXT, the implant should be removed.

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

Lactation

In an open, non-randomised comparative study of Implanon (n=42) vs IUD (n=38) in healthy lactating women, Implanon was shown not to influence the production or the quality (protein, lactose or fat concentrations) of breast milk. However, small amounts of etonogestrel are excreted in breast milk. Based on an average daily milk ingestion of 150 ml/kg, the mean daily infant etonogestrel dose calculated after one month of etonogestrel release is approximately 27 ng/kg/day. This corresponds to approximately 0.2% of the estimated absolute maternal daily dose (2.2% when values are normalised per kg body weight). Subsequently the milk etonogestrel concentration decreases with time during the lactation period. Long-term data are available on 38 children, whose mothers had an implant inserted during the 4th to 8th week postpartum. They were breast-fed for a mean duration of 14 months and followed up to 36 months of age. Evaluation of growth, and physical and psychomotor development did not indicate any differences in comparison to nursing infants whose mothers used an IUD (n=33). Nevertheless, development and growth of the child should be carefully followed. Based on the available data, Implanon NXT may be used during lactation.

Effects on laboratory tests

Data obtained with COCs have shown that contraceptive steroids may affect some laboratory parameters, including biochemical parameters of liver, thyroid, adrenal and renal function, serum levels of (carrier) proteins, e.g., corticosteroid binding globulin and lipid/lipoprotein fractions, parameters of carbohydrate metabolism and parameters of coagulation and fibrinolysis. The changes were generally within the normal range. To what extent this also relates to progestagen-only contraceptives is not known.

Effects on ability to drive and use machines

No observed effects.

In situ broken or bent implant

There have been reports of broken or bent implants while in the patient's arm. There are no clinical study data on efficacy and safety with broken implants. In vitro data indicated that when the implant is broken or bent, the release rate of etonogestrel may be slightly increased. This change is not expected to have clinically meaningful effects.

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

INTERACTIONS WITH OTHER MEDICINES

Interactions between hormonal contraceptives and other medicinal products may lead to menstrual bleeding and / or contraceptive failure. No specific interaction studies have been performed with Implanon NXT. The following interactions have been reported in the literature (mainly with combined contraceptives but occasionally also with progestogen-only contraceptives).

Hepatic metabolism: Interactions can occur with medicinal products that induce microsomal enzymes, specifically cytochrome P450 enzymes, which can result in increased clearance of sex hormones (e.g. phenytoin, barbiturates, primidone, bosentan, carbamazepine, rifampicin, and possibly also oxcarbazepine, rifabutin, topiramate, felbamate, griseofulvin and the herbal remedy St. John's wort).

Also HIV protease (e.g. ritonavir, nelfinavir) and non-nucleoside reverse transcriptase inhibitors (e.g. nevirapine, efavirenz), and combinations of them, have been reported to potentially affect hepatic metabolism.

Women on treatment with any of the above mentioned drugs should temporarily use a barrier method in addition to Implanon NXT. With microsomal enzyme-inducing drugs, the barrier method should be used during the time of concomitant drug administration and for 28 days after their discontinuation.

In women on long-term treatment with hepatic enzyme-inducing drugs, it is recommended to remove Implanon NXT and to advise a contraceptive method that is unaffected by the interacting drug.

Increase in plasma hormone levels associated with co-administered drugs: Drugs (e.g., ketoconazole) that inhibit microsomal enzymes, such as CYP3A4, may increase plasma hormone levels.

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

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

ADVERSE EFFECTS

Serious undesirable effects

Refer to **PRECAUTIONS**

Other possible undesirable effects

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

Table: Percentages of subjects with at least one experience classified by body system and reported as related to the study drug pre-marketing in clinical trials performed by MSD¹.

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

¹ Some subjects may have experienced more than one AE.

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

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

In a clinical trial of Implanon NXT, in which investigators were asked to examine the implant site after insertion, implant site reactions were reported in 8.6% of women. Erythema was the most frequent implant site complication, reported during and / or shortly after insertion, occurring in 3.3% of subjects. Additionally, hematoma (3.0%), bruising (2.0%), pain (1.0%) and swelling (0.7%) were reported.

During post marketing surveillance, a clinically relevant rise in blood pressure has been observed in rare cases. Seborrhoea has also been reported. Anaphylactic reactions, urticaria and (aggravation of) angioedema and/or aggravation of hereditary angioedema may occur. Insertion or removal of the implant may cause some bruising, slight local irritation, pain or itching. Fibrosis at the implant site may occur, a scar may be formed or an abscess may develop. Paraesthesia or paraesthesia-like events may occur. Expulsion or migration of the implant has been reported, including rarely to the chest wall. In rare cases, implants have been found within the vasculature including the pulmonary artery. Some cases of implants found within the pulmonary artery reported chest pain and/or dyspnea; others have

been reported as asymptomatic (see **PRECAUTIONS**). Surgical intervention might be necessary when removing Implanon NXT.

On rare occasions, ectopic pregnancies have been reported (see **PRECAUTIONS**).

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

DOSAGE AND ADMINISTRATION

Pregnancy should be excluded before insertion of Implanon NXT

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

Additional information and more detailed instructions concerning the insertion and removal of the implant will be sent on request free of charge:

Australia: Telephone Toll Free: 1800 818 553.

New Zealand: Telephone Toll Free: 0800 500 673

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

How to use Implanon NXT

Implanon NXT is a long-acting hormonal contraceptive. A single implant is inserted subdermally and can be left in place for three years. Remove the implant no later than three years after the date of insertion. The user should be informed that she can request the removal of the implant at any time. Healthcare professionals may consider earlier replacement of the implant in heavier women (see **PRECAUTIONS**). After the removal of the implant, immediate insertion of another implant will result in continued contraceptive protection. If the woman does not wish to continue using Implanon NXT, but wants to continue preventing pregnancy, another contraceptive method should be recommended.

The basis for successful use and subsequent removal of the Implanon NXT implant is a correct and carefully performed subdermal insertion of the implant in accordance with the instructions. An implant inserted more deeply than subdermally (deep insertion) may not be palpable and the localization and/or removal can be difficult (see sections "**How to remove Implanon NXT**" and "**Warnings**"). **If the implant is not inserted in accordance with the instructions (see When to insert Implanon NXT and How to insert Implanon NXT) and on the correct day, this may result in unintended pregnancy.**

The Implanon NXT implant should be inserted subdermally just under the skin at the inner side of the upper non-dominant arm avoiding the sulcus (groove) between the biceps and triceps muscles and the large blood vessels and nerves that lie there in the neurovascular bundle deeper in the subcutaneous tissue.

Immediately after insertion, the presence of the implant should be verified by palpation. In case the implant cannot be palpated or when the presence of the implant is doubtful, see section **How to insert Implanon NXT**.

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

When to insert Implanon NXT

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

No preceding hormonal contraceptive use in the past month

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

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

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

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

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

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

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

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

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

Following abortion or miscarriage

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

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

Postpartum

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

Note

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

How to insert Implanon NXT

The basis for successful use and subsequent removal of Implanon NXT is a correct and carefully performed subdermal insertion of the implant in the non-dominant arm in accordance with the

instructions. Both the HCP and the woman should be able to feel the implant under the woman's skin after placement.

The implant should be inserted subdermally just under the skin. 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 Implanon NXT** and **PRECAUTIONS**). If the implant is inserted deeply, neural or vascular damage may occur. Deep or incorrect insertions have been associated with paraesthesia (due to neural damage) and migration of the implant (due to intramuscular or fascial insertion), and in rare cases with intravascular insertion.

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

It is recommended that the HCP is in a seated position during the entire insertion procedure so that the insertion site and the movement of the needle just under the skin can be clearly seen from the side.

- 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 wrist is parallel to her ear or her hand is positioned next to her head (Figure 1).

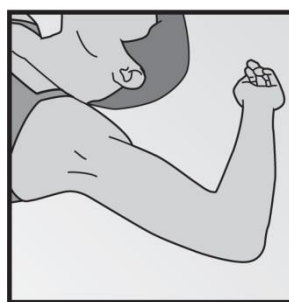


Figure 1

- Identify the insertion site, which is at the inner side of the non-dominant upper arm about 8-10 cm (3-4 inches) above the medial epicondyle of the humerus, avoiding the sulcus (groove) between the biceps and triceps muscle and the large blood vessels and nerves that lie there in the neurovascular bundle deeper in the subcutaneous tissue. (Figure 2). **The implant should be inserted subdermally just under the skin (see PRECAUTIONS).**

- Make two marks with a sterile marker: first, mark the spot where the implant will be inserted, and second, mark a spot a few centimetres proximal to the first mark (Figure 2). This second mark will later serve as a direction guide during insertion.

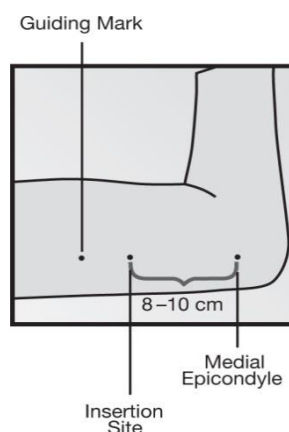


Figure 2

- Clean the insertion site with an antiseptic solution.
- Anaesthetise the insertion area (for example, with anaesthetic spray or by injecting 2 mL of 1% lignocaine just under the skin along the planned insertion tunnel).
- Remove the sterile preloaded disposable Implanon NXT applicator carrying the implant from its blister. The applicator should not be used if sterility is in question.

- Hold the applicator just above the needle at the textured surface area. Remove the transparent protection cap by sliding it horizontally in the direction of the arrow away from the needle (Figure 3). If the cap does not come off easily the applicator should not be used. You may see the white coloured implant by looking into the tip of the needle. **Do not touch the purple slider until you have fully inserted the needle subdermally, as it will retract the needle and prematurely release the implant from the applicator.**

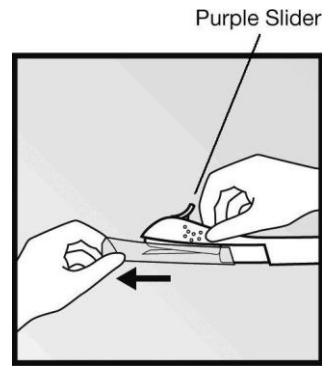


Figure 3

- With your free hand, stretch the skin around the insertion site with thumb and index finger (Figure 4).

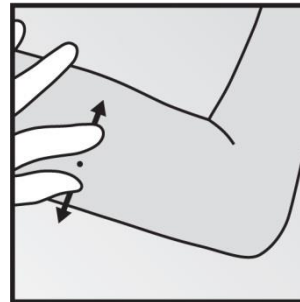


Figure 4

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

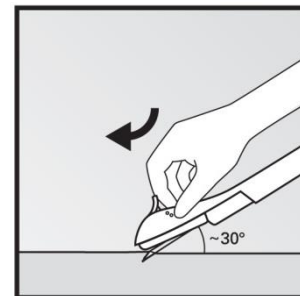


Figure 5

- Lower the applicator to a horizontal position. While lifting the skin with the tip of the needle (figure 6), slide the needle to its full length. You may feel slight resistance but do not exert excessive force (Figure 6). If the needle is not inserted to its full length, the implant will not be inserted properly. **You can best see movement of the needle and that it is inserted just under the skin if you are seated and are looking at the applicator from the side and NOT from above. In this position, you can clearly see the insertion site and the movement of the needle just under the skin.**

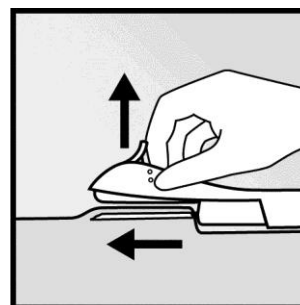


Figure 6

- Keep the applicator in the same position with the needle inserted to its full length. If needed, you may use your free hand to keep the applicator in the same position during the following procedure. Unlock the purple slider by pushing it slightly down. Move the slider fully back until it stops (figure 7). 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. If the applicator is not kept in the same position during this procedure or if the purple slider is not completely moved to the back, the implant will not be inserted properly

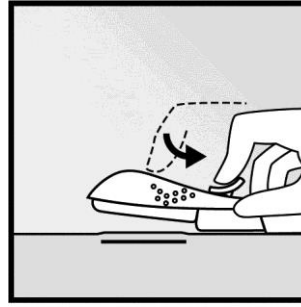


Figure 7

- **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 8). See section below "**If the rod is not palpable**".

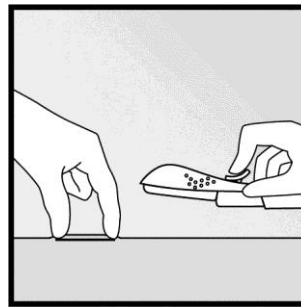


Figure 8

- Apply a small adhesive bandage over the insertion site. Request that the woman palpate the implant.
- Apply sterile gauze with a pressure bandage to minimise bruising. The woman may remove the pressure bandage in 24 hours and the small bandage over the insertion site after 3-5 days.
- Complete the User Card and give it to the woman to keep. Also, complete the adhesive labels and affix it to the woman's medical record.
- The applicator is for single use only and must be adequately disposed of, in accordance with local regulations for the handling of biohazardous waste.

If the rod is not palpable:

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

- Check the applicator. The needle should be fully retracted and only the purple tip of the obturator should be visible.
- Use other methods to confirm the presence of the implant. Given the radiopaque nature of the implant, suitable methods for localisation are: two-dimensional X-ray and X-ray

computerised tomography (CT) scanning. Ultrasound scanning (USS) with a high-frequency linear array transducer (10 MHz or greater) or magnetic resonance imaging (MRI) may be used. Prior to the application of any of these methods for the localisation of the implant, it is recommended to consult MSD for instructions. 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 of the subject. In this case it is recommended to consult MSD for the appropriate procedure. **Until you have verified the presence of the implant, a non-hormonal contraceptive method must be used.**

- Once the non-palpable implant has been located, removal is recommended (see **PRECAUTIONS**)

How to remove Implanon NXT

Before initiating the removal procedure, the HCP should consult the User Card for the location of the Implanon NXT implant. Verify the exact location of the implant in the arm by palpation. See section below on “*Localisation and removal of a non-palpable implant*” if the implant cannot be palpated.

Procedure for removal of an implant that is palpable

Removal of the implant should only be performed under aseptic conditions by a HCP who is familiar with the removal technique.

- Clean the site where the incision will be made and apply an antiseptic. Locate the implant by palpation and mark the distal end (end closest to the elbow), for example, with a sterile marker (Figure 9).

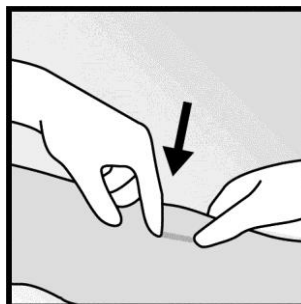


Figure 9

- Anaesthetise the arm, for example, with 0.5 to 1 mL 1% lignocaine at the marked site where the incision will be made (Figure 10). Be sure to inject the local anaesthetic under the implant to keep it close to the skin surface.

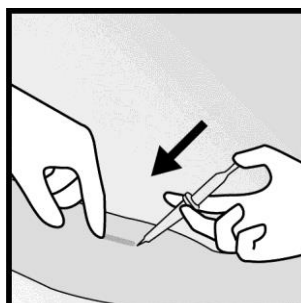


Figure 10

- Push down the proximal end of the implant (Figure 11) to stabilise it; a bulge may appear indicating the distal end of implant. Starting at the distal tip of the implant, make a longitudinal incision of 2 mm towards the elbow.

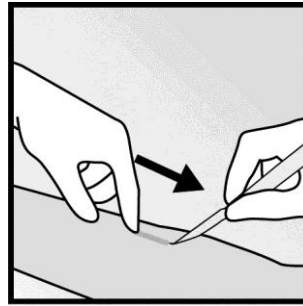


Figure 11

- Gently push the implant towards the incision until the tip is visible. Grasp the implant with forceps (preferably curved mosquito forceps) and remove the implant (Figure 12).

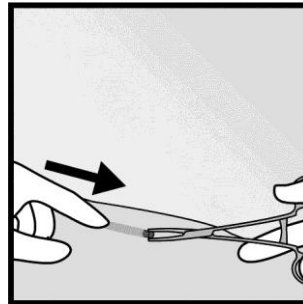


Figure 12

- If the implant is encapsulated, make an incision into the tissue sheath and then remove the implant with the forceps (Figures 13 and 14).

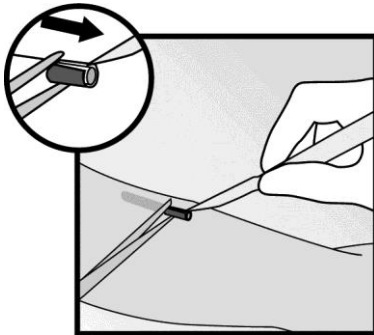


Figure 13

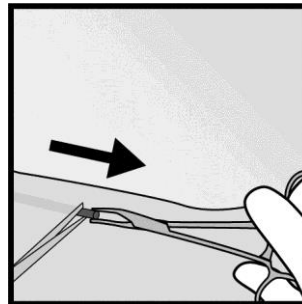


Figure 14

- If the tip of the implant does not become visible in the incision, gently insert a forceps into the incision (Figure 15). Flip the forceps over into your other hand (Figure 16). With a second pair of forceps carefully dissect the tissue around the implant and grasp the implant (Figure 17). The implant can then be removed.

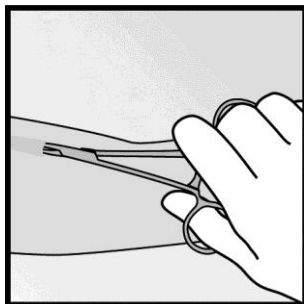


Figure 15

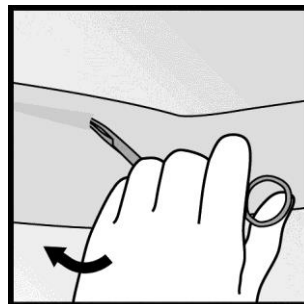


Figure 16

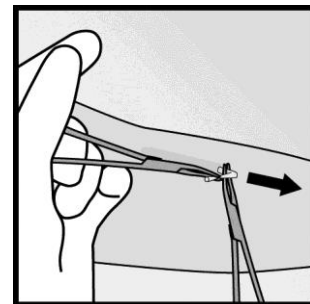


Figure 17

- Confirm that the entire implant, which is 4 cm long, has been removed by measuring its length. There have been reports of broken implants while in the patient's arm. In some

cases, difficult removal of the broken implant has been reported. If a partial implant (less than 4 cm) is removed, the remaining piece should be removed.

- If the woman would like to continue using Implanon NXT, a new implant may be inserted immediately after the old implant is removed using the same incision (see **How to replace Implanon NXT**).
- After removing the implant, close the incision with a steri-strip and apply an adhesive bandage.
- Apply sterile gauze with a pressure bandage to minimise bruising. The woman may remove the pressure bandage after 24 hours and the small bandage 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 (see **PRECAUTIONS**), but may lead to the implant not being palpable at the location in which it was placed. An implant that has been deeply inserted or has migrated may not be palpable and therefore imaging procedures, as described below, may be required for 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 computer tomography (CT). Ultrasound scanning (USS) with a high-frequency linear array transducer (10 MHz or greater) or magnetic resonance imaging (MRI) may be used. Once the implant has been localized in the arm, the implant should be removed according to the instructions in "Procedure for removal of an implant that is palpable", and 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; HCPs familiar with the anatomy of the chest should be consulted.

If at any time these imaging methods fail to locate the implant, etonogestrel blood level determination can be used for verification of the presence of the implant. Please contact MSD for further guidance.

Removal of the implant should only be performed under aseptic conditions by an HCP who is familiar with the removal technique. 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 prevent damage to deeper neural or vascular structures in the arm and should be performed by HCPs familiar with the anatomy of the arm.

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

If the implant cannot be removed, please contact MSD for further guidance.

How to replace Implanon NXT

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

The new implant may be inserted in the same arm, and through the same incision from which the previous implant was removed. If the same incision is being used to insert a new implant, anaesthetise the insertion site (e.g. 2 mL lignocaine (1%)) applied just under the skin commencing at the removal incision along the 'insertion canal' and follow the subsequent steps in the insertion instructions.

OVERDOSAGE

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.

PRESENTATION AND STORAGE CONDITIONS

Nature and contents of containers

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

Each implant contains 68 mg of etonogestrel.

Shelf-life and Storage

The shelf-life of Implanon NXT is 5 years when stored below 30°C.

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

NAME AND ADDRESS OF THE SPONSOR

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POISON SCHEDULE OF THE MEDICINE / CLASSIFICATION

Prescription Only Medicine (S4)

Date of most recent amendment (AU) / Date of Preparation (NZ)

22 September 2015