Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Implanon NXT, 68 mg implant for subdermal use.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

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

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Implant for subdermal use.

Product imported from the UK:
Radiopaque, non-biodegradable, white to off-white, soft flexible rod with a length of 4 cm and 2 mm in diameter.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Contraception.

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

4.2 Posology and method of administration

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 (Schering-Plough, telephone 00 44 1707 363418).

Prior to inserting the implant, carefully read and follow the instructions for insertion and removal of the implant in section 4.2.3 “How to insert Implanon NXT” and section 4.2.4 “How to remove Implanon NXT”.

4.2.1 How to use Implanon NXT

Implanon NXT is a long-acting hormonal contraceptive. A single implant is inserted subdermally and can be left in place for three years. Remove the implant no later than three years after the date of insertion. The user should be informed that she can request the removal of the implant at any time. HCPs may consider earlier replacement of the implant in heavier women (see section 4.4.1 “Warnings”). After the removal of the implant, immediate insertion of another implant will result in continued contraceptive protection.

If the woman does not wish to continue using Implanon NXT, but wants to continue preventing pregnancy, another contraceptive method should be recommended.

The basis for successful use and subsequent removal of the Implanon NXT implant is a correct and carefully performed subdermal insertion of the implant in accordance with the instructions. If the implant is not inserted in accordance with the instructions, and on the correct day, this may result in an unintended pregnancy.
The Implanon NXT implant should be inserted subdermally just under the skin at the inner side of the upper arm to avoid the large blood vessels and nerves that lie deeper in the connective tissue between the biceps and triceps muscles.

Immediately after insertion, the presence of the implant should be verified by palpation. In case the implant cannot be palpated or when the presence of the implant is doubtful, other methods must be applied to confirm its presence (see section 4.2.3 "How to insert Implanon NXT"). Until the presence of the implant has been verified, the woman should be advised to use a non-hormonal contraceptive method.
The Implanon NXT package contains a User Card intended for the woman which records the batch number of the implant. HCPs 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.

4.2.2 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:
The implant should be inserted between Day 1 (first day of menstrual bleeding) and Day 5 of the menstrual cycle.
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. Not all contraceptive methods (transdermal patch, vaginal ring) may be available in all countries.
Changing from a progestagen-only contraceptive method (e.g. progestagen-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.
- Progestagen-only pill: A woman may switch to Implanon NXT on any day from the progestagen-only pill. The implant should be inserted on the day after stopping the progestagen-only pill.
- Implant/Intrauterine system (IUS): Insert the implant on the day the previous implant or IUS is removed.

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.

Postpartum
- Breast-feeding: The implant should be inserted after the fourth postpartum week (see Section 4.6 "Pregnancy and Lactation").
- Not breast-feeding: The implant should be inserted between 21 to 28 days postpartum.

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.

4.2.3 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.

If the implant is inserted too deep, neural or vascular damage may occur. Too 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. Moreover, when the implant is inserted too deep, it may not be palpable and the localization and/or removal can be difficult.

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 can be clearly seen.

- 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).

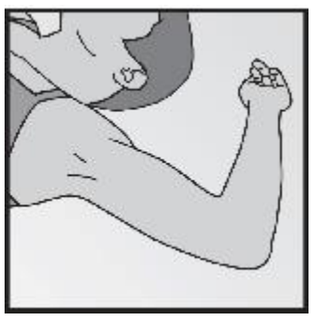

Figure 1

- 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.

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

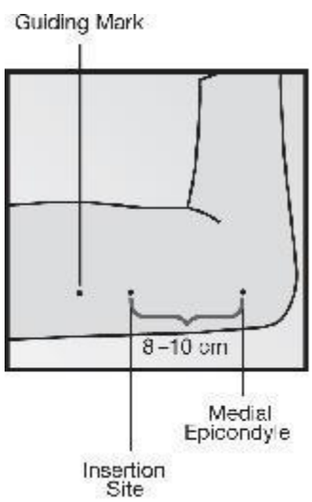

Figure 2

- Clean the insertion site with an antiseptic solution.
- 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).
- Remove the sterile preloaded disposable Implanon NXT applicator carrying the implant from its blister.
- Hold the applicator just above the needle at the textured surface area and remove the transparent protection cap from the needle which contains the implant (Figure 3). If the cap does not come off easily the applicator should not be used. You may 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 it will retract the needle and release the implant from the applicator.**

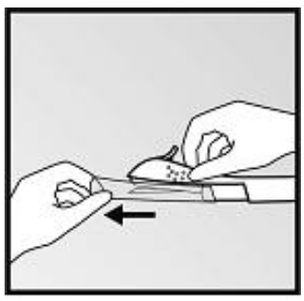

Figure 3

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

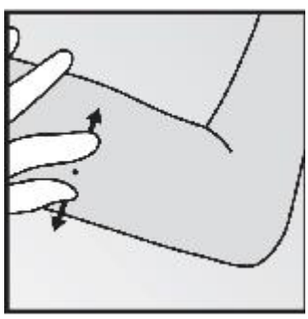

Figure 4

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

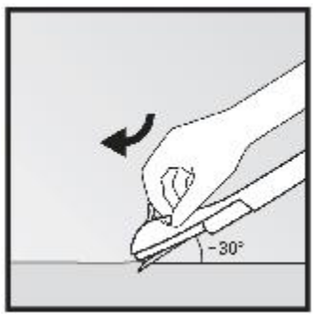

Figure 5

- Lower the applicator to a horizontal position. While lifting the skin with the tip of the needle, 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.**

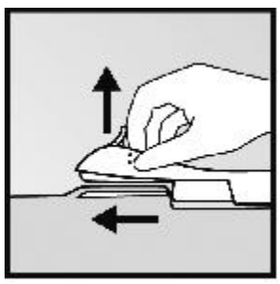

Figure 6

- While keeping the applicator in the same position and the needle inserted to its full length, unlock the purple slider by pushing it slightly down. Move the slider fully back until it stops, leaving the implant now in its final subdermal position and locking the needle inside the body of the applicator (Figure 7). **If the slider is not completely moved to the back, the needle will not be fully retracted and the implant will not be inserted properly.** The applicator can now be removed.

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).

Figure 8

If you cannot feel the implant or in doubt of its presence,

- Check the applicator. The needle should be fully retracted and only the purple tip of the obturator should be visible.
- Use other methods to confirm its presence. Suitable methods 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). Prior to the application of X-ray CT, USS or MRI for the localizatio of the implant, it is recommended to consult the local supplier of Implanon NXT 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 the local supplier will provide the appropriate procedure. **Until you have verified the presence of the implant, a non-hormonal contraceptive method must be used.**
- Apply a small adhesive bandage over the insertion site. Request that the woman palpate the implant.
- Apply sterile gauze with a pressure bandage to minimize 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.

4.2.4 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.

If the implant is not palpable, two-dimensional X-ray can be performed to verify its presence. A non-palpable implant should always be first located prior to removal. Suitable methods for localization include, X-ray computer tomography (CT), ultrasound scanning (USS) with a high-frequency linear array transducer (10 MHZ or greater) or magnetic resonance imaging (MRI). If these imaging methods fail to locate the implant, etonogestrel determination can be used for verification of the presence of the implant. Please contact your local supplier for further guidance.

After localization of a non-palpable implant, consider conducting removal with ultrasound guidance.

There have been occasional reports of migration of the implant; usually this involves minor movement relative to the original position unless inserted too deeply (see also section 4.4.1 “Warnings”). This may complicate localization of the implant by palpation, USS and/or MRI, and removal may require a larger incision and more time.

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

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 damage to deeper neural or vascular structures in the arm and should be performed by HCPs familiar with the anatomy of the arm.

If the implant cannot be removed, please contact your local supplier for further guidance.

- 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).

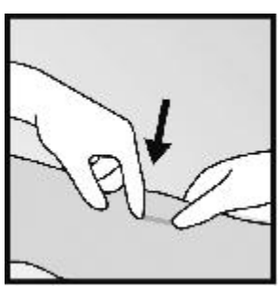

Figure 9

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

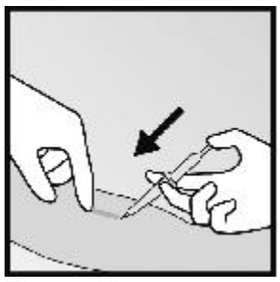

Figure 10

- Push down the proximal end of the implant (Figure 11) to stabilize 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.

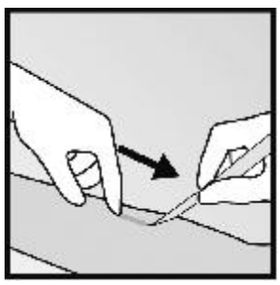

Figure 11

- 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).

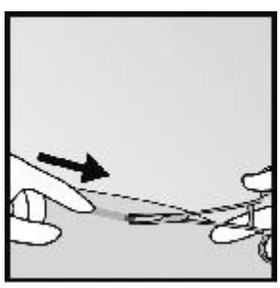

Figure 12

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

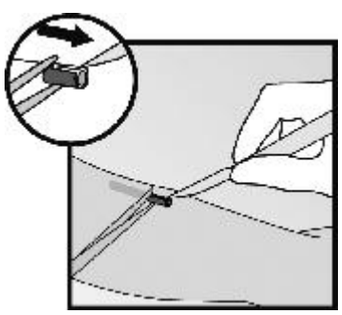

Figure 13

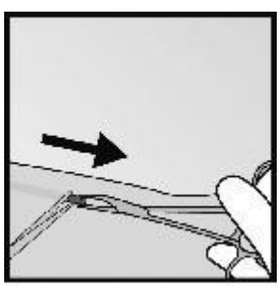

Figure 14

- If the tip of the implant does not become visible in the incision, gently insert a forceps into the incision (Figure 15). Grasp the implant. 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.

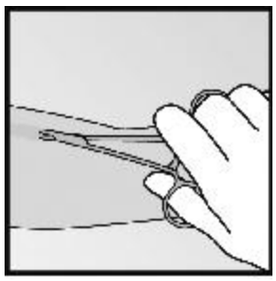

Figure 15

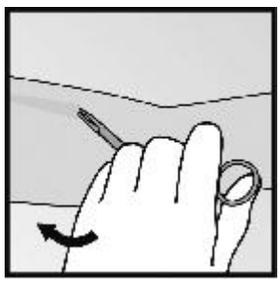

Figure 16

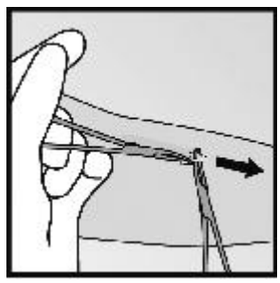

Figure 17

- Confirm that the entire rod, which is 4 cm long, has been removed by measuring its length.
- 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 section 4.2.5 “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 minimize bruising. The woman may remove the pressure bandage after 24 hours and the small bandage after 3-5 days.

4.2.5 How to replace Implanon NXT

Immediate replacement can be done after removal of the previous implant and is similar to the insertion procedure described in section 4.2.3 “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, 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.

4.3 Contraindications

- Active venous thromboembolic disorder.
- Known or suspected sex-steroid sensitive malignances.
- Presence or history of severe hepatic disease as long as liver function values have not returned to normal.
- Undiagnosed vaginal bleeding.
- Hypersensitivity to the active substance or to any of the excipients of Implanon NXT.

4.4 Special warnings and precautions for use

4.4.1 Warnings

If any of the conditions / risk factors mentioned below is present, the benefits of progestagen use should be weighed against the possible risks for each individual woman and discussed with the woman before she decides to start with Implanon NXT. In the event of aggravation, exacerbation or first appearance of any of these conditions, the woman should contact her HCP. The HCP should then decide on whether the use of Implanon NXT should be discontinued.

- The risk for breast cancer increases in general with increasing age. During the use of (combined) oral contraceptives (OCs) the risk of having breast cancer diagnosed is slightly increased. This increased risk disappears gradually within 10 years after discontinuation of OC use and is not related to the duration of use, but to the age of the woman when using the OC. The expected number of cases diagnosed per 10 000 women who use combined OCs (up to 10 years after stopping) relative to never users over the same period have been calculated for the respective age groups to be: 4.5/4 (16-19 years), 17.5/16 (20-24 years), 48.7/44 (25-29 years), 110/100 (30-34 years), 180/160 (35-39 years) and 260/230 (40-44 years). The risk in users of contraceptive methods, which only contain progestagens, is possibly of 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.

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

- Epidemiological investigations have associated the use of combined OCs with an increased incidence of venous thromboembolism (VTE, deep venous thrombosis and pulmonary embolism). Although the clinical relevance of this finding for etonogestrel (the biologically active metabolite of desogestrel) used as a contraceptive in the absence of an estrogenic component is unknown, the implant should be removed in the event of a thrombosis. Removal of the implant should also be considered in case of long-term immobilization due to surgery or illness. Although Implanon NXT is a progestagen-only contraceptive, it is recommended to assess risk factors which are known to increase the risk of venous and arterial thromboembolism. Women with a history of thrombo-embolic disorders should be made aware of the possibility of a recurrence.

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

- The use of progestagen-containing contraceptives may have an effect on peripheral insulin resistance and glucose tolerance. Therefore, diabetic women should be carefully monitored during the first months of Implanon NXT use.

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

- 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 can not be excluded that the contraceptive effect in these women during the third year of use may be lower than for women of normal weight. HCPs may therefore consider earlier replacement of the implant in heavier women.

- Expulsion may occur especially if the implant is inserted not according to the instructions given in section 4.2.2 “How to insert Implanon NXT”, or as a consequence of a local inflammation.

- In rare cases, mostly related to either a too deep initial insertion (see also section 4.2.3 “How to insert Implanon NXT”) and/or to external forces (e.g. manipulation of the implant or contact sports) the implant may migrate from the insertion site. In these cases localisation of the implant may be more difficult and removal may require a larger incision (see also section 4.2.4 “How to remove Implanon NXT”). If the implant is not removed, contraception and the risk of progestagen-related undesirable effects may continue beyond the time desired by the woman.

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

- 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 inhibit ovulation, ectopic pregnancy should be taken into account in the differential diagnosis if the woman gets amenorrhea or abdominal pain.

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

4.4.2 Medical examination/consultation

Prior to the initiation or reinstitution of Implanon NXT a complete medical history (including family medical history) should be taken and pregnancy should be excluded. Blood pressure should be measured and a physical examination should be performed, guided by the contraindications (Section 4.3) and warnings (Section 4.4.1). 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 judgment.

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

4.4.3 Reduced efficacy

The efficacy of Implanon NXT may be reduced when concomitant medication is used (See section 4.5.1 'Interactions').

4.4.4 Changes in the menstrual bleeding pattern

During the use of Implanon NXT, women are likely to have changes in their menstrual bleeding patterns which are unpredictable beforehand. These may include the occurrence of an irregular bleeding pattern (absent, less, more frequent or continuous), and changes in bleeding 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. The bleeding pattern experienced during the first three months is broadly predictive of future bleeding patterns for many women. Information, counselling and the use of a bleeding diary can improve the woman's acceptance of a bleeding pattern. Evaluation of vaginal bleeding should be done on an ad hoc basis and may include an examination to exclude gynaecological pathology or pregnancy.

4.5 Interaction with other medicinal products and other forms of interaction

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

- Influence of other medicinal products on Implanon NXT

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

Hepatic metabolism

Interactions can occur with medicinal products that induce hepatic enzymes, specifically cytochrome P450 enzymes, which can result in increased clearance of sex hormones (e.g., phenytoin, phenobarbital, primidone, carbamazepine, rifampicin and HIV-medication (e.g. ritonavir, nelfinavir, nevirapine) and possibly also oxcarbazepine, topiramate, felbamate, griseofulvin and the herbal remedy St. John's wort).

Management

Women on treatment with any of the above mentioned drugs should use a non-hormonal contraceptive method in addition to Implanon NXT. With hepatic enzyme-inducing drugs, the non-hormonal contraceptive 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 the implant and to prescribe a non-hormonal method.

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

- Influence of Implanon NXT on other medicinal products

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

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

4.6 Fertility, pregnancy and lactation

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

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

Clinical data indicate that Implanon NXT does not influence the production or the quality (protein, lactose or fat concentrations) of breast milk. However, small amounts of etonogestrel are excreted in breast milk. Based on an average daily milk ingestion of 150 ml/kg, the mean daily infant etonogestrel dose calculated after one month of etonogestrel release is approximately 27 ng/kg/day. This corresponds to approximately 2.2% of the weight-adjusted maternal daily dose and to approximately 0.2% of the estimated absolute maternal daily dose. Subsequently the milk etonogestrel concentration decreases with time during the lactation period.
Limited long-term data is available on 38 children, whose mothers had an implant inserted during the 4^{th} to 8^{th} 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 mother used an IUD (n=33). Nevertheless, development and growth of the child should be carefully followed. Based on the data, Implanon NXT may be used during lactation and should be inserted after the 4^{th} post partum week.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

During the use of Implanon NXT, women are likely to have changes in their menstrual bleeding pattern which are predictable beforehand. These may include the occurrence of an irregular bleeding pattern (absent, less, more frequent or continuous), and changes in bleeding intensity (reduced or increased) or duration. Amenorrhoea was reported in about 1 of 5 women while another 1 of 5 women reported frequent and/ or prolonged bleeding. Occasionally, heavy bleeding has been reported. In clinical trials, bleeding changes were the most common reason for stopping treatment (about 11%). The bleeding pattern experienced during the first three months is broadly predictive of future bleeding patterns for many women.

Possibly related undesirable effects reported in the clinical trials have been listed in the Table below.

System Organ Class	**Adverse reaction in MedDRA Term[1]**		
	Very Common > 1/10	**Common < 1/10, ≥ 1/100**	**Uncommon < 1/100, ≥ 1/1000**
Infections and infestations	vaginal infection		pharyngitis, rhinitis, urinary tract infection
Immune system disorders			hypersensitivity
Metabolism and nutrition disorders		increased appetite	
Psychiatric disorders		affect lability, depressed mood, nervousness, libido decreased	anxiety, insomnia
Nervous system disorders	headache	dizziness	migraine, somnolence
Vascular disorders		hot flush	
Gastro-intestinal disorders		abdominal pain, nausea, flatulence	vomiting, constipation, diarrhoea
Skin and subcutaneous tissue disorders	acne	alopecia	hypertrichosis, rash, pruritus
Muculoskeletal and connective tissue disorders			Back pain, arthralgia, myalgia, musculoskeletal pain
Renal and urinary disorders			dysuria
Reproductive system and breast disorders	breast tenderness , breast pain, menstruation irregular	dysmenorrhoea, ovarian cyst	genital discharge, vulvovaginal discomfort, galactorrhoea, breast enlargement, pruritus genital
General disorders and administration site conditions		implant site pain, implant site reaction, fatigue, influenza like illness, pain	pyrexia, oedema
Investigations	weight increased	weight decreased	

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

Durind post marketing surveillance, a clinically relevant rise in blood pressure has been observed in rare cases. Seborrhoea has also been reported. 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 insertion site may occur, a scar may be formed or abscess may develop. Paresthesia or paresthesia-like events may occur. Expulsion or migration of the implant may be possible (see also section 4.4.1 “Warnings”). Surgical intervention might be necessary when removing the implant.

On rare occasions, ectopic pregnancies have been reported (see Section 4.4.1 Warnings)

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

4.9 Overdose

An implant should always be removed before inserting a new one. There is no data available on overdose with etonogestrel. There have been no reports of serious deleterious effects from an overdose of contraceptives in general.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

(PHARMACOTHERAPEUTIC GROUP: PROGESTAGENS, ATC-classification G03ACO8)
The Implanon NXT implant is a non-biodegradable, radiopaque, etonogestrel-containing implant for subdermal use, preloaded in a sterile, disposable applicator. Etonogestrel is the biologically active metabolite of desogestrel, a progestagen widely used in OCs. It is structurally derived from 19-nortestosterone and binds with high affinity to progesterone receptors in the target organs. The contraceptive effect of etonogestrel is primarily achieved by inhibition of ovulation. Ovulations were not observed in the first two years of use of the implant and only rarely in the third year. Besides inhibition of ovulation, etonogestrel also causes changes in the cervical mucus, which hinders the passage of spermatozoa. Clinical trials were conducted in women between 18 and 40 years. Although no direct comparison was made, the contraceptive efficacy appeared to be at least comparable to that known for combined oral contraceptives. . During the clinical studies no pregnancies were observed during 35,057 cycles of exposure; the Pearl Index observed is 0.00 (95% confidence limits: 0.00-0.14). However, it must be realized that in practice no method can be considered 100% effective. The high degree of protection against pregnancy is obtained, amongst other reasons, because the contraceptive action of Implanon NXT is not dependent on adherence to a dosing regimen by the woman herself. The contraceptive action of etonogestrel is reversible, which is apparent from the rapid return of the normal menstrual cycle after removal of the implant. Although etonogestrel inhibits ovulation, ovarian activity is not completely suppressed. Mean estradiol concentrations remain above the level seen in the early-follicular phase. In a two-year study, in which the bone mineral density in 44 users has been compared to that in a control group of 29 IUD-users no adverse effects on bone mass have been observed. No clinically relevant effects on lipid metabolism have been observed. The use of progestagen-containing contraceptives may have an effect on insulin resistance and glucose tolerance. Clinical trials further indicate that users of Implanon NXT often have a less painful menstrual bleeding (dysmenorrhea).

5.2 Pharmacokinetic properties

ABSORPTION
After the insertion of the implant, etonogestrel is rapidly absorbed into the circulation. Ovulation-inhibiting concentrations are reached within 1 day. Maximum serum concentrations (between 472 and 1270 pg/ml) are reached within 1 to 13 days. The release rate of the implant decreases with time. As a result serum concentrations decline rapidly over the first few months. By the end of the first year a mean concentration of approximately 200 pg/ml (range 150-261 pg/ml) is measured, which slowly decreases to 156 pg/ml (range 111-202 pg/ml) by the end of the third year. The variations observed in serum concentrations can be partly attributed to differences in body weight.

DISTRIBUTION
Etonogestrel is for 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 27 l and 220 l, respectively, and hardly change during the use of Implanon NXT.

METABOLISM
Etonogestrel undergoes hydroxylation and reduction. Metabolites are conjugated to sulfates and glucuronides. Animal studies show that enterohepatic circulation probably does not contribute to the progestagenic activity of etonogestrel.

ELIMINATION
After intravenous administration of etonogestrel, the mean elimination half-life is approximately 25 hours and the serum clearance is approximately 7.5 l/hour. Both clearance and elimination-half-life remain constant during the treatment period. The excretion of etonogestrel and its metabolites, either as free steroids or as conjugates, is with urine and feces (ratio 1.5:1). After insertion in lactating women, etonogestrel is excreted in breast milk with a milk/serum ratio of 0.44-0.50 during the first four months. In lactating women, the mean transfer of etonogestrel to the infant is approximately 0.2% of the estimated absolute maternal etonogestrel daily dose (2.2% when values are normalized per kg body weight). Concentrations show a gradual and statistically significant decrease over the time.

5.3 Preclinical safety data

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

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Implant
Core: Ethylene vinylacetate copolymer (28% vinyl acetate, 43 mg) barium sulfate (15 mg).

Skin: Ethylene vinylacetate copolymer (14% vinyl acetate, 15 mg).

6.2 Incompatibilities

Not applicable

6.3 Shelf life

The shelf life expiry date for this product shall be the date shown on the blister pack and outer package of the product on the market in the country of origin. Implanon NXT should not be inserted after the expiry date as indicated on packaging.

6.4 Special precautions for storage

Implanon NXT does not require any special storage conditions.

6.5 Nature and contents of container

The pack contains one implant (4 cm in length and 2 mm in diameter) in an over labelled carton, which is preloaded in the stainless steel needle of a ready-for-use, disposable, sterile applicator. The applicator containing the implant is packed in a blister pack made of transparent polyethyleneterephtalate glycol (PETG) sealed with a lidding made of made of high density poly ethylene (HDPE). The content of the blister pack is sterile unless the package is damaged or opened.

6.6 Special precautions for disposal and other handling

See Section 4.2 (“Posology and Method of Administration”).
The applicator is for single use only.

7 PARALLEL PRODUCT AUTHORISATION HOLDER

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8 PARALLEL PRODUCT AUTHORISATION NUMBER

PPA1659/33/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 23rd June 2011

10 DATE OF REVISION OF THE TEXT