# Summary of risk management plan for etonogestrel (ENG) implant

This is a summary of the risk management plan (RMP) for the ENG implant. The RMP details important risks of the ENG implant, how these risks can be minimised, and how more information will be obtained about the ENG implant 's risks and uncertainties (missing information).

The ENG implant Summary of Product Characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how the ENG implant should be used.

Important new concerns or changes to the current concerns will be included in updates of the ENG implant's RMP.

## I. The Medicine and What it is Used For

The ENG implant is authorised for contraception (see SmPC for the full indication). It contains ENG as the active substance and it is given by subdermal insertion.

## II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of the ENG implant, together with measures to minimise such risks and the proposed studies for learning more about risks, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and prescribing information addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In the case of the ENG implant, these measures are supplemented with *additional risk minimisation measures* mentioned under the relevant important risk, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

## II.A List of Important Risks and Missing Information

Important risks of the ENG implant are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of the ENG implant. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

### Table II.A.1: List of Important Risks and Missing Information

| **List of Important Risks and Missing Information** | |
|---|---|
| Important identified risks | • Insertion and removal related events (IRREs)<br>- Incorrect insertions<br>- Implant migrations (including intravascular migration)<br>- Difficult localizations<br>- Difficult removals |
| Important potential risks | ▪ Venous thrombotic events<br>▪ Cerebral vascular accidents<br>▪ Breast cancer |
| Missing information | None |

## II.B Summary of Important Risks

### Table II.B.1: Important Identified Risk: Insertion and Removal Related Events - Incorrect Insertions, Implant Migrations (Including Intravascular Migration), Difficult Localizations, Difficult Removals

| | |
|---|---|
| Evidence for linking the risk to the medicine | With ENG implant radiopaque, the radiopaque ENG implant is inserted using the NGIA. The NGIA is designed to further facilitate proper insertions. The insertion characteristics of the NGIA are investigated in study P05702 (former Organon trial number 34530). The results are summarized below.<br>- Insertion Characteristics of the NGIA in Study P05702 (Former Organon Trial Number 34530)<br>- In total, 301 insertions were performed with the NGIA. Insertions were performed by both experienced (n=11) and non-experienced (n=12) investigators. "Non-experienced" investigators had performed ≤10 ENG implant insertions within the past year. "Experienced" investigators were those who had performed > 10 insertions within the past year. The insertion procedure was considered easy in 98.0 % of the insertions. Six out of 301 insertion procedures (2.0%) were reported as difficult by 3 investigators, all unexperienced with ENG implant. The reported reasons were difficulty in skin puncturing, and/or sliding the needle subdermally or because it was one of their first insertions.<br>- Difficulties in puncturing the skin or in sliding the needle superficially |

**Table II.B.1: Important Identified Risk: Insertion and Removal Related Events - Incorrect Insertions, Implant Migrations (Including Intravascular Migration), Difficult Localizations, Difficult Removals**

| | |
|---|---|
| | in the subdermal tissue were reported for 14 (4.7%) and 27 (9.0%) insertions, respectively, with no difference between the experienced or non-experienced investigators. The skin was punctured at an angle of ≥45 degrees for 24 (8.0%) insertions at 4 centers (2 non-experienced and 2 experienced investigators). Unlocking the purple slider was difficult in 2 (0.7%) insertions. According to the investigators, 2 implants were not inserted correctly, i.e. too deep, but both implants were still palpable. The implant was inserted over the sulcus bicipitalis medialis in 66.8% of the subjects, over the biceps muscle in 20.6% of the subjects and over the triceps muscle in 12.6% of the subjects.<br>- From the 301 insertions, in 2 cases the implant partially protruded out of the insertion canal immediately after insertion. Technical inspection suggested that the needles were not inserted completely.<br>- One implant expulsion was reported and the implant was removed on Day 15. The investigator reported that the implant was inserted *intra*cutaneously instead of *sub*cutaneously (i.e. too superficial).<br><br>In addition to clinical studies, the safety of the ENG implant (radiopaque) and the NGIA have been studied in the U.S. in Nexplanon[a] Observation Risk Assessment (NORA), a prospective, observational study, as a post-approval regulatory commitment for the Food & Drug Administration (FDA) [Ref. 5.3.6: 04WCMG].<br>The results for Insertion and Removal Related Events are summarized below.<br><br>- Eighty percent of Healthcare Professionals (HCPs) inserted the ENG implant in more than 97% of 7,364 study participants without encountering difficulty or an insertion related event.<br>- The proportion of incorrect insertions (i.e., non-insertion, partial insertion, or deep insertion) was low and involved 1.2% of all insertion procedures or 12.6 per 1,000 insertions. Exclusion of a single outlier (1 clinician reporting 40% of deep insertion events) reduced the proportion of incorrect insertions to 0.9% of all insertion procedures or 9.2 per 1,000 insertions.<br>- Incorrect insertions included:<br>o One (initially) unrecognized non-insertion (which resulted in a pregnancy).<br>o 27 partial insertions (0.4% of all insertion procedures).<br>o 65 deep insertions[b] (0.9% of all insertion procedures; reducing to 0.5% after exclusion of a single outlier who reported 26 deep insertions). The majority of deep insertions were reported in those reported to have a palpable implant at the time of insertion; In 6 of the 65 cases reported to be deep insertions, the implant was reported as non-palpable at the time of insertion.<br>▪ Further assessment of the 26 cases reported by a single provider (post final study report) demonstrated that all implants were described as |

[a] Nexplanon is the tradename for the radiopaque etonogestrel implant within the United States.

[b] Deep insertions were defined as injury to a nerve or blood vessel, the depth of the implant being within the muscle or adjacent to the fascial tissue or non-palpable at insertion.

**Table II.B.1: Important Identified Risk: Insertion and Removal Related Events - Incorrect Insertions, Implant Migrations (Including Intravascular Migration), Difficult Localizations, Difficult Removals**

| | |
|---|---|
| | being located 'adjacent to the fascial tissue' immediately after the insertion procedure (7 insertions) or when the implant was subsequently localized/removed (19 insertions). All 26 of the implants reported to be deeply inserted were palpable immediately following the insertion procedure.<br>▪ Removal data was available for 24 of these 26 cases. All 24 were palpable at the time of localization/removal and all were successfully removed. One other implant was still in the patient's arm at the time of study closure; it is unknown whether the implant was removed. Information on the removal of the final deeply inserted implant was not available.<br>▪ None of the 26 patients reported to have a deeply inserted implant by one provider reported a significant event in the implant arm at baseline (i.e. immediately after insertion), during follow-up, or after removal of the implant (i.e. 6 months after removal).<br>▪ Removal reasons are known for 20 of the 24 patients who had the implant removed. The main reasons for implant removal involved the implant having been in place for at least 3 years or menstrual/bleeding problems.<br><br>- There was one report of an insertion-related injury to a nerve or blood vessel reported by an HCP (i.e. a hematoma). It resolved without sequelae and the patient eventually discontinued Implanon NXT use due to menstrual/bleeding problems and the desire for pregnancy. In addition to incorrect insertions, HCPs reported other challenges during the insertion procedure primarily involving issues handling the applicator.<br>o Difficulty removing the protection cap was the most commonly reported event (reported by 25 HCPs during 93 insertion procedures, incidence of 12.6 per 1,000 insertions).<br>o The second most common insertion-related event (experienced during 30 insertions, incidence of 4.1 per 1,000 insertions) involved difficulty sliding the needle to its full length underneath the skin.<br>o Difficulty moving the purple slider fully to the back was reported during 14 insertions (incidence of1.9 per 1,000 insertions)<br>o Difficulty unlocking the purple slider was reported during 6 insertions (incidence of 0.8 per 1,000 insertions)<br>o Needle visible after insertion (not fully retracted) was reported during 4 insertions (incidence of 0.5 per 1,000 insertions).<br>o Needle inserted too deeply was reported during 2 insertions (incidence of 0.3 per 1,000 insertions).<br>o Needle inserted too superficially and needle stick injury (to the HCP) were each reported during 1 insertion (incidence of 0.1 per 1,000 insertions).<br>o There were other challenges experienced during insertion |

**Table II.B.1: Important Identified Risk: Insertion and Removal Related Events - Incorrect Insertions, Implant Migrations (Including Intravascular Migration), Difficult Localizations, Difficult Removals**

| | |
|---|---|
| | events not falling into the categories specified above reported during 29 insertion events including: difficulty handling the device/ visualization (17 events; incidence of 2.3 per 1,000 insertions), reaction at the insertion site (5 events; incidence of 0.7 per 1,000 insertions), difficulty penetrating the skin with the needle (3 events; incidence of 0.4 per 1,000 insertions), patient reaction to insertion procedure (4 events; incidence of 0.5 per 1,000)<br>- At the time of implant insertion, 49 patients (0.7% of the study population; incidence of 6.7 per 1,000 insertions) reported a cumulative total of 54 events associated with the arm in which the implant was inserted.<br>o Patient-reported pins and needles/numbness in the fingers/hand/arm was the single issue with the highest reported incidence at baseline (2.3 per 1,000 insertions) immediately following insertion and during follow-up (27.7 per 1,000 insertions).<br>- During follow-up, the incidence proportion of any patient-reported event in the implant arm for which a physician was visited was 50.1 per 1,000 insertions.<br>- Most insertion-related events reported by patients were transitory. The clinical consequences of these events were generally not suggestive of serious injury.<br><br>*User Satisfaction with the NGIA in Study P05702 (Former Organon Trial Number 34530)*<br>- Almost all investigators were very satisfied with the applicator from the first insertions onwards. One investigator was dissatisfied after 4 insertions, not satisfied nor dissatisfied after 8 insertions and satisfied after the 12$^{th}$ insertion. She indicated that she adjusted her position after a few insertions, i.e. from performing the insertion standing to sitting down. Another investigator was neither satisfied nor dissatisfied after four insertions, but was very satisfied after 8 and 12 insertions. She indicated that she adjusted her position after a few insertions, i.e. from performing the insertion standing to sitting down. Another investigator was neither satisfied nor dissatisfied after 4 insertions, but was very satisfied after 8 and 12 insertions. All other investigators were very satisfied with the applicator from the first insertion onwards.<br>- The majority of the investigators reported the strengths of NGIA as the ease of use, the one-hand action, and/or the fast insertion time. Several mentioned that it is not possible to perform too deep or wrong insertions, and that the implant cannot fall out of the needle before insertion. Other reported strengths of the applicator were the clear verification of the implant in the needle before insertion and the full retraction of the needle into the applicator after insertion. The most frequently reported points for improvements were a better visualization of the needle during insertion, the sharpness of the needle and easier subdermal sliding.<br><br>*Location of the implant*<br>- In study P05702 (Former Organon trial Number 34530) to investigate whether the NGIA further facilitates subdermal insertion, the location and depth of the implant at removal was assessed. At removal, the |

**Table II.B.1: Important Identified Risk: Insertion and Removal Related Events - Incorrect Insertions, Implant Migrations (Including Intravascular Migration), Difficult Localizations, Difficult Removals**

| | |
|---|---|
| | implant was located in the subdermal tissue in 290 of the 293 subjects (99.0%) with a localization assessment. One implant was located intracutaneously and for 2 implants the location was not determined. No implants were located in the muscle or muscle fascia. The mean (Standard Deviation (SD)) depth of the implant was 1.8 (1.06) mm before removal.<br>- In study P05702 (former Organon trial number 34530), the distance from the closest tip of the implant and the insertion scar was assessed at removal for 273 of the 301 subjects. The mean (SD) distance between the closest tip of the implant and the insertion scar was 3.9 (4.0) mm. The majority of the implants were located proximally from the scar.<br><br>*Implant palpability*<br>- Implant palpability was investigated in study P05702 (former Organon trial number 34530). For 300 of 301 treated subjects the implant was clearly palpable after implant insertion. One implant was not palpable immediately after insertion and up to and including Month 12. However, it was palpable at Month 18, 24, 30, and at the removal assessment. The implant was clearly visible on the two-dimensional X-ray after insertion.<br>- Before removal, the implant was palpable for 293 subjects (100%) with data on palpability. For 4 subjects, palpability was not assessed and another 4 subjects were lost to follow up before removal.<br>- Implant palpability was also studied in the NORA study. For 7,358 of 7,364 participants, the implant was palpable after insertion. For the 6 implants that were not palpable by the HCP immediately following insertion (0.1% of all insertion procedures; 0.8 per 1,000 insertions), 3 were located via x-ray and left *in situ*, 2 were successfully removed 16 months and 3 years later, respectively, and information was not reported concerning attempts to locate these implants. The HCP who inserted the final non-palpable implant reported no further effort to locate the implant and information on removal was not available.<br>- In the NORA study, 18 implants were not palpable at the time of removal (the implants of 0.4% of patients who had a localization attempt). Eleven of these implants were localized (using x-ray (n=2), ultrasound (n=6), MRI (n=1), and unspecified methods (n=2)) and removed, 1 was localized and left *in situ* and 6 implants were neither localized nor removed within the study period.<br>*Implant localization (imaging)*<br>- In study P05702 (former Organon trial number 34530), X-ray imaging was performed for 63 subjects after implant insertion and for 54 subjects before implant removal. All implants were clearly visible.<br>- In study P05720 (former Organon trial number 34528), the radiopaque ENG implant was clearly visible by X-ray imaging in almost all subjects after implant insertion and in all subjects before removal. For 2 subjects, the implant was not clearly visible after insertion, but it was confirmed that these x-rays were technically not performed correctly.<br><br>*Migration of the implant*<br>- Migration of the ENG implant was assessed in a prospective study |

**Table II.B.1: Important Identified Risk: Insertion and Removal Related Events - Incorrect Insertions, Implant Migrations (Including Intravascular Migration), Difficult Localizations, Difficult Removals**

| | |
|---|---|
| | involving 100 women who had ENG implant inserted over the biceps muscle by a trained health care professional [Ref. 5.4: 00VLS0]. Measurements were made from the insertion site to the distal end of the rods at 3 and 12-months post-insertion. The results indicated that significant migration of the ENG implant does not occur if correctly inserted. If migration does occur, in the majority of cases (44 out of 87 patients) this was found to be in a caudal direction. Furthermore, in all but 1 case where migration was noted, this was less than 2 cm.<br>- Migration of the ENG implant was also assessed in the NORA study. There were 48 cases of HCP-reported local migration within the arm (involving 1.1% of all patients who had localization and/or removal procedures). There were no reports of implant migration more than a few cm away from the insertion site when localized and/or removed (e.g. no reports of implants having been localized in a site other than the arm). No implants were localized in an intravascular location within the arm.<br><br>*Removal characteristics*<br><br>- In study P05702 (former Organon trial number 34530), the removal characteristics of ENG implant radiopaque were investigated. The results are summarized below:<br>o No removal complications were reported for 280 of the 296 evaluated subjects (94.6%). The main reported complication was the presence of fibrotic tissue around the implant (4.4% of subjects).<br>o At removal, no abnormalities at the implant site were observed for 289 of the 292 subjects (99.0%) with an implant site assessment. For 3 subjects (1.0%), implant site pain was reported and for 1 subject, in addition to implant site pain, also implant expulsion was reported on Day 15, as a result of incorrect intracutaneous insertion of the implant.<br>o At removal, the implant was located in the subdermal tissue in 290 of the 293 subjects (99.0%) with a localization assessment. One implant was located intracutaneously and for 2 implants the location was not determined. No implants were located in the muscle or muscle fascia. The mean (SD) depth of the implant was 1.8 (1.06) mm before removal. The mean (SD) distance between the closest tip of the implant and the insertion scar was 3.9 (4.0) mm. The majority of the implants were located proximally from the scar. The mean (SD) and median implant removal times were 119.3 (120.2) sec and 77.5 sec, respectively (excluding time for anesthesia). For 4 subjects, the removal time was 10 minutes or longer, but only for 1 of these subjects a removal complication was reported (fibrotic tissue around the implant).<br>- The NORA study also investigated the removal characteristics of ENG implant radiopaque. The results are summarized below:<br>o HCPs reported experiencing 73 complications during 60 removal procedures (13.7 per 1,000 removal procedures). The most commonly reported complication was the encasement of the implant in fibrotic tissue (incidence of 6.6 per 1,000 |

**Table II.B.1: Important Identified Risk: Insertion and Removal Related Events - Incorrect Insertions, Implant Migrations (Including Intravascular Migration), Difficult Localizations, Difficult Removals**

| | |
|---|---|
| | removals). There were no HCP reports of injuries to nerves or blood vessels at localization or removal.<br>o Six implants were not localized and removal procedures were therefore not initiated. In 3 cases, the implants were not localized using ultrasound, no X-rays were taken, and a hormonal assay was not performed. In 2 other cases, the methods used to attempt to localize the implant were not specified by the HCP. In one other case, after the implant was not localized via ultrasound or X-ray, a hormonal assay was performed and the results were negative (i.e. no ENG was detected).<br>o One of the 5,159 removal procedures was unsuccessful due to placement of the implant in deep muscle tissue within the arm and the inability of the HCP to remove the implant under a local anesthetic. The implant was left in situ and the HCP planned to prescribe another form of contraception for the patient. Information on duration of implant use was not available for this patient.<br>o Five patients were hospitalized for the localization/removal procedure and in all 5 cases the implant was successfully removed.<br>o One of the patients hospitalized for the removal procedure experienced moderate post-operative pain in the arm extending along the path of the ulnar nerve. The pain subsequently resolved. There have been no other reports of injury involving the ulnar nerve.<br><br>The MAH contracted with an expert anatomist to perform an independent anatomic assessment to determine a potential area with the least neurovascular structures as a potential site for implant insertion. The anatomic assessment was conducted using 40 cadaveric female arms [Ref. 5.4: 04T24C].<br>The dissections performed in the anatomic assessment confirmed that implant placement overlying the triceps muscle rather than the biceps muscle is preferred due to the more prominent neurovascular anatomy that lies anterior to the sulcus, including the large cephalic vein, radial artery and median nerve. In the region previously recommended in the CCDS for implant placement (i.e., 8-10 cm from the medial epicondyle and away from the sulcus overlying the triceps muscle), dissections demonstrated that the basilic vein, ulnar nerve and other superficial nerves are variably located overlying the surface of the triceps muscle and are not usually confined to the sulcus as depicted in anatomy textbooks. Specifically, the medial brachial cutaneous nerve, ulnar nerve, basilic vein, and medial antebrachial cutaneous nerve were identified in windows 8-10 cm from the medial epicondyle and approximately 2-3 cm posterior to the sulcus in 57.5%, 40.0%, 40.0% and 17.5% of the arms, respectively. Only 25% of windows in this location were free of any major neurovascular structure and 45% had more than one major neurovascular structure present; thus, improper deep implant insertion in this location could potentially lead to neurovascular injury. No major neurovascular structures were identified windows 3-5 cm posterior to the sulcus, thus improper deep insertion in this location has less risk of resulting in neurovascular injury. Flexion at the elbow resulted in the ulnar nerve becoming more taut and deflecting anteriorly (i.e., closer to the sulcus). Neither flexion nor extension at the elbow was found to affect the position of the other identified structures.<br><br>These results from the cadaveric assessment suggest that the implant should be |

## Table II.B.1: Important Identified Risk: Insertion and Removal Related Events - Incorrect Insertions, Implant Migrations (Including Intravascular Migration), Difficult Localizations, Difficult Removals

| | |
|---|---|
| | inserted 8-10 cm from the medial epicondyle and 3-5 cm posterior to the sulcus so that, in the event of an incorrect deep insertion, the risk of neurovascular injury is mitigated. As a result of the cadaveric assessment, the MAH updated the insertion instruction within the CCDS (which previously recommended that the implant be inserted 8-10 cm from the medial epicondyle "avoiding the sulcus") to specify that the implant should be inserted 8-10 cm from the medial epicondyle and 3-5 cm posterior to the sulcus overlying the triceps muscle. Furthermore, to further minimize the risk of ulnar nerve injury (by deflecting the nerve away from the insertion site), implant insertion and removal should be performed with the arm maximally flexed at the elbow and the ipsilateral hand underneath or as close as possible to the head (i.e., the position used for dissection during the anatomic assessment) rather than as previously stated in the CCDS, "wrist is parallel to her ear or her hand is positioned next to her head."<br><br>**Post Marketing Data**<br><br>Events related to implant insertion and removal will continue to be monitored through routine pharmacovigilance activities. |
| Risk factors and risk groups | Unknown |
| Risk minimisation measures | **Routine risk minimisation measures:**<br>Detailed insertion, localization, and removal instructions in the Posology and Method of Administration section and Special Warnings and Precautions for use sections of the prescribing information. Section 4.4 of the SmPC and Section 2 of the PL recommends implant palpation by the HCP during medical check-ups. Additionally, Section 3 of the PL recommends women occasionally gently palpate the implant to be aware of its location and to contact the doctor as soon as possible if the implant is unable to be felt.<br>To minimize the risk of intravascular migration (including to the pulmonary artery and lung), the labelling text recommends the localization and removal of an implant if it is not palpable.<br>Provision of training materials and voluntary sessions on ENG implant insertion, localization and removal to health care providers in all countries where ENG implant is marketed.<br>Package Leaflet For The User - section 2 and section 3<br>**Additional risk minimisation measures:**<br>The updated Patient Alert Card will also inform women of the importance of maintaining awareness of the presence and location of the implant by occasional gentle implant palpation. Additionally, the Patient Alert Card will provide instruction to women to contact their HCP as soon as possible if the implant is non-palpable at any time.<br><br>Videos of the implant insertion and removal procedures described in the SmPC will be available online, for which the weblink will be included in the SmPC where allowed by the individual national competent authority. The weblink to the instructional videos will also be included in the DHPC, as indicated below.<br><br>A DHPC will be disseminated after local approval of the updated Product Information. This DHPC will inform HCPs that the SmPC and PL have been updated to:<br>• Clarify the recommended implant insertion site and implant insertion |

## Table II.B.1: Important Identified Risk: Insertion and Removal Related Events - Incorrect Insertions, Implant Migrations (Including Intravascular Migration), Difficult Localizations, Difficult Removals

| | |
|---|---|
| | and removal procedures<br>• Recommend implant palpation by the HCP and women and provide instructions for the provision of the Patient Alert Card from the HCP to the women<br>• Provide a weblink to the implant insertion and removal procedures videos<br><br>This DHPC is a one-time communication, as the DHPC contains the same updated information regarding the implant insertion site and implant insertion and removal procedures as the updated SmPC, training sessions/materials, and implant insertion and removal procedures videos. |

## Table II.B.2: Important Potential Risk: Venous thrombotic events

| | |
|---|---|
| Evidence for linking the risk to the product | A blood clot in a vein (known as a 'venous thrombosis') can block the vein. This can happen in veins of the leg (deep vein thrombosis, DVT), the lung (pulmonary embolus, PE), or any other organ.<br>Using a combined contraceptive pill increases a woman's risk of developing such clots compared with a woman not taking any combined pill. The risk of developing a blood clot in a vein is highest during the first year a woman uses the pill. The risk is also higher if a woman restarts the use of a combined pill (the same product or a different product) after a break of 4 weeks or more. The risk is not as high as the risk of developing a blood clot during pregnancy.<br>The risk of blood clots in a vein increases further:<br>with increasing age (beyond about 35 years); if one of your close relatives has had a blood clot in the leg, lung or other organ at a young age (less than about 50 years); if you are overweight; if you must have an operation, or if you are off your feet for a long time because of an injury or illness, or you have your leg in a plaster cast; air travel (>4 hours) may temporarily increase your risk of a blood clot particularly if you have some other factors listed; if you have any of the following medical conditions associated with VTE: cancer, systemic lupus erythematosus (SLE-a disease affecting your natural defense system), Crohn's disease or ulcerative colitis (chronic inflammatory bowel disease), haemolytic uraemic syndrome (HUS-a disorder of blood clotting causing failure of the kidneys) or sickle cell anaemia (an inherited disease of the red blood cells).<br>Blood clots in veins have been reported during use of Implanon or Implanon NXT/Nexplanon but it is not known if the implant caused them.<br>Women should not use Implanon or Implanon NXT/Nexplanon if they have a blood clot in a blood vessel (venous thrombosis) of their legs (deep vein thrombosis, DVT), lungs (pulmonary embolus, PE) or other organs. If they have had a blood clot previously, they will be kept under close observation. If they need an operation or if their ability to move around is limited for a long period of time, the doctor may recommend that the implant is removed before surgery or while they are less mobile. If they have several risk factors that may increase the risk of a clot in the vein (venous thromboembolism) they will be kept under close observation.<br>Women who have recently given birth are at an increased risk of blood clots should ask their doctor how soon after delivery they can start using Implanon or Implanon NXT/ Nexplanon. |

## Table II.B.2: Important Potential Risk: Venous thrombotic events

| | |
|---|---|
| Risk factors and risk groups | Risk factors for VTE are:<br>Hereditary risk factors:<br>• Antithrombin III deficiency<br>• Protein C deficiency<br>• Protein S deficiency<br>• Activated protein C resistance (Factor V Leiden gene mutation)<br>• Prothrombin gene mutation (G20210A)<br>• Hyperhomocysteinemia<br><br>Acquired risk factors:<br>• Obesity<br>• Varicose veins<br>• Antiphospholipid antibodies (lupus anticoagulant and anticardiolipin antibodies)<br>• Postpartum period<br>• Pregnancy<br>• Surgery<br>• Trauma<br>• Stasis (eg, due to prolonged immobility)<br>• Increasing age<br>• Positive (family) history<br>• Other diseases (eg, hemolytic uremic syndrome, inflammatory bowel disease, auto-immune states such as systemic lupus erythematosus, HBsAg, hypothyroidism, malignancy, renal disease)<br>• Smoking |
| Risk minimisation measures | Inclusion of a warning in section 4.4 of the EU SmPC. |

## Table II.B.3: Important Potential Risk: Cerebral vascular accidents

| | |
|---|---|
| Evidence for linking the risk to the product | A blood clot in an artery (known as 'arterial thrombosis') can block an artery and cause serious problems. For example, a blood clot in an artery in the in the brain causes a stroke.<br>The risk of a blood clot in an artery increases with increasing age (beyond about 35 years); if you smoke, if you are overweight; if you have high blood pressure; if a close relative has had a heart attack or stroke at a young age (less than about 50 years); if you get migraines; if you or someone in your immediate family have a high level of fat in the blood (cholesterol or triglycerides); if you have other medical conditions associated with adverse vascular events such as systemic lupus erythematosus (SLE-a disease affecting your natural defense system); if you have an abnormally high level of homocysteine in the blood; if you have diabetes, or if you have a problem with your heart (valve disorder, disturbance of the rhythm).<br>Blood clots in arteries and strokes have been reported during use of Implanon or Implanon NXT/Nexplanon but it is not known if the implant caused them.<br>Women should not get Implanon or Implanon NXT/Nexplanon: if they have a blood clot in the artery.<br><br>Women using Implanon or Implanon NXT/Nexplanon who are overweight, have diabetes, cancer or high blood pressure, will be closely monitored while using Implanon or Implanon NXT/Nexplanon. |

## Table II.B.3: Important Potential Risk: Cerebral vascular accidents

| | |
|---|---|
| Risk factors and risk groups | Risk factors for ATE are:<br>• Increasing age, particularly above 35 years.<br>• Smoking.<br>• Hypertension<br>• Obesity (body mass index over 30kg/$m^2$)<br>• Positive family history (arterial thromboembolism ever in a sibling or parent especially at relatively early age, e.g, below 50)<br>• Migraine<br>• Other medical conditions associated with adverse vascular events (e.g, diabetes mellitus, hyperhomocysteinaemia, valvular heart disease and atrial fibrillation, dyslipoproteinemia and systemic lupus erythematosus). |
| Risk minimisation measures | Inclusion of a warning in section 4.4 of the EU SmPC. |

## Table II.B.4: Important Potential Risk: Breast cancer

| | |
|---|---|
| Evidence for linking the risk to the product | Breast cancer has been found slightly more often in women using combined oral contraceptive (COC) pills than in the general population, but it is not known whether this is caused by the treatment. For example, it may be that tumors are found more in women on COC pills because they are examined by the doctor more often. The increased occurrence of breast cancer becomes gradually less after stopping the COC pill. The risk for breast cancer increases in general with increasing age. During the use of COCs the risk of having breast cancer diagnosed is slightly increased. This increased risk disappears gradually within 10 years after discontinuation of COC use and is not related to the duration of use, but to the age of the woman when using the COC. The expected number of cases diagnosed per 10,000 women who use COCs (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 (such as Implanon or Implanon NXT/Nexplanon) is possibly of a similar magnitude to that associated with COCs. 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 COCs is low. The cases of breast cancer diagnosed in COC users tend to be less advanced than in those who have not used COCs. The increased risk observed in COC users may be due to an earlier diagnosis, biological effects of the COC or a combination of both.<br>In clinical trials of the etonogestrel implant, 3 in-treatment cases of breast cancer have been reported. In all 3 cases, the diagnosis of breast cancer was made in a relatively short time after the start of the study and the study investigators considered the cases to be unrelated to the implant.<br>Women should not get Implanon or Implanon NXT/Nexplanon if they have, have had, or may have cancer of the breast or of the genital organs.<br>Women with risk factors for developing breast cancer, such as obesity, family history, and certain breast abnormalities will be closely monitored. |
| Risk factors and risk groups | Risk factors for breast cancer are:<br>• Female gender<br>• Age<br>• Reproductive history (age at menarche, age at first birth, parity, breastfeeding, age at menopause)<br>• Increased hormone levels, (Increased endogenous estrogens, increased exogeneous estrogens, hormonal contraception and hormone replacement therapy)<br>• Personal history of breast cancer<br>• Certain benign proliferative breast lesions |

**Table II.B.4: Important Potential Risk: Breast cancer**

| | |
|---|---|
| | • Family history (especially mother and sister)<br>• Obesity<br>• Certain breast changes: Atypical hyperplasia and lobular carcinoma in situ found in benign breast conditions such as fibrocystic breast changes are correlated with an increased breast cancer risk. |
| Risk minimisation measures | Inclusion of a warning in section 4.4 of the EU SmPC. |

## II.C Post-Authorisation Development Plan

### II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies that are conditions of the marketing authorisation or specific obligation of the etonogestrel implant.

### II.C.2 Other Studies in Post-Authorisation Development Plan

There are no studies that are in a post-authorisation development plan for the etonogestrel implant.