

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

***APPLICATION NUMBER:***

**21-529**

**OTHER REVIEW(S)**

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

**Predecisional Agency Information**

---

Date: June 22, 2006  
From: Corrinne Kulick, DDMAC  
To: Charlene Williamson, DRUD  
Re: Implanon (etonogestrel subdermal implant)  
NDA 21-529

I have reviewed the Implanon working label provided 6/15/06 and offer the following 10 comments:

1. Throughout the label the sponsor uses the terms studies. Are these qualifiers necessary? If not, DDMAC recommends deletion. Implanon has yet to be approved in the U.S. and thus, does not have any information associated with it.

b(4)

**2. Special Populations/Hepatic Insufficiency:**

Here and in the contraindications section the term is used to categorize liver disease. Is this term an appropriate descriptor; is the extent of disease limited to disease? Other labels use "significant" liver disease (depo-subQ provera 104) or "markedly impaired liver function or liver disease" (Norplant).

**3. Indications and Usage:**

"Unlike some other methods of birth control, the efficacy of Implanon™ does not depend on patient self-administration."

DDMAC recommends deletion of this sentence. It is promotional in tone and seems intuitive.

**4. Contraindications:**

This contraindication differs from that in the depo-subQ provera 104 label, which also says that the drug should not be used with "current or past history of thromboembolic disorders, or cerebral vascular disease." Should this label be worded similarly?

b(4)

**5. Warnings:**

The depo-subQ provera-104 label includes a discussion on the effects of the drug on bone mineral density. Should a general discussion regarding this risk also be included here? I agree that the information from the small exploratory study involving Implanon should not be included in the label as it makes a claim, however, a general discussion on the effect of unopposed progestin use on bone mineral density may be useful to the reader.

**6. Warnings/Bleeding Irregularities:**

“These may include changes in bleeding frequency or duration, or amenorrhea.”

Other labels also include “heavy bleeding” in a similar sentence. Should this information be included here as well?

**7. Warnings/ Interaction with Anti-Epileptic and Other Drugs**

The information in this section is also reiterated in the Precautions section verbatim. In addition this section differs from that in the Norplant label, which includes a discussion on the use of the drug in Epilepsy and which epileptic drugs should be cautioned. Should this label be worded similarly?

**8. Warnings/WARNINGS BASED ON EXPERIENCE WITH COMBINATION (PROGESTIN PLUS ESTROGEN) ORAL CONTRACEPTIVES/Thromboembolic Disorders and Other Vascular Problems**

This section specifically, differs markedly from that in the Depo Provera and Norplant label, as well as the Guidance for Combined oral contraceptives, which in addition to a more substantive discussion also include a discussion regarding the risk of MI/ CVD/Vascular Disease. Should this label be worded similarly? In addition, this section in its entirety omits several topics included in the Guidance, e.g., carbohydrate and lipid metabolism, headache, vaginal bleeding problems, ocular lesions. Should these topics be included here as well?

**9. Adverse Reactions**

Is the first sentence necessary? If not please delete. Also, please include the number (n) of patients in addition to the percentage of patients in Tables 3 and 4 for completeness. As written (just percentages), there is a possibility that these could be misread as the n's.

**10. Patient Labeling/ What if I change my mind about birth control?**

“If you want to become pregnant after Implanon™ removal, your ability to get pregnant returns quickly.”

The term “quickly” is vague and can be used promotionally. Please provide an appropriate time frame.

Thank you for including DDMAC in this review.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Corrinne Kulick  
6/27/2006 04:58:06 PM  
DDMAC REVIEWER

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** May 25, 2006

**TO:** Daniel Shames, M.D., Director  
Division of Reproductive and Urologic Products

**VIA:** Charlene Williamson, Regulatory Health Project Manager  
Division of Reproductive and Urologic Products

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support

**THROUGH:** Toni Piazza-Hepp, Pharm.D., Deputy Director  
Division of Surveillance, Research, and Communication Support

**SUBJECT:** DSRCS Review #3 of Patient Labeling for Implanon (etonogestrel subdermal implant), NDA 21-529

**Background and Summary**

The sponsor resubmitted Patient Labeling for Implanon (etonogestrel subdermal implant), NDA 21-529, in their 3rd cycle submission, dated January 16, 2006.

Please refer to our previous reviews of the Patient Labeling dated January 5, 2005 and May 12, 2005.

See the attached for our suggested revisions of the proposed Patient Labeling. We have simplified the wording and removed unnecessary information. Even though Implanon is a progestin-only contraceptive, we have revised the PPI using the template in the March 2, 2004, Draft Guidance, *Guidance for Industry: Labeling for Combined Oral Contraceptives*, in order to achieve consistency among hormonal contraceptive products.

**Comments and Recommendations:**

We also have the following comment:

The submitted Patient Labeling has a Flesch-Kincaid Grade Level of 10.4 and a Flesch Reading Ease of 49.4%. Our suggested revisions have lowered the Flesch-Kincaid Grade Level to 8.2 and Flesch Reading Ease to 60.6% (60% corresponds to an 8<sup>th</sup> grade reading level) to increase

comprehension among a broader range of patients, especially those with lower literacy levels. Approximately 50% of the U.S. population comprehends written information at or less than an 8<sup>th</sup> grade reading level.

Comments to the review division are bolded, underlined and italicized. We can provide revised documents (marked and clean) in Word if requested by the review division. Please call us if you have any questions.

**Appears This Way  
On Original**

9 Page(s) Withheld

           Trade Secret / Confidential

8 Draft Labeling

           Deliberative Process

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Jeanine Best  
5/25/2006 03:32:15 PM  
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
5/26/2006 12:13:39 PM  
DRUG SAFETY OFFICE REVIEWER

5/13/05

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** May 12, 2005

**TO:** Daniel Shames, M.D., Director  
Division of Reproductive and Urologic Drug Products  
HFD-580

**VIA:** Karen Kirchberg, N.P., Regulatory Health Project Manager  
Division of Reproductive and Urologic Drug Products  
HFD-580

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Gerald Dal Pan, M.D., M.H.S., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

**SUBJECT:** DSRCs Review #2 of Patient Labeling for Implanon (etonogestrel subdermal implant), NDA 21-529

**Background and Summary**

The sponsor submitted a Patient Information (PPI) and a Patient Information and Consent form for Implanon (etonogestrel subdermal implant), NDA 21-529, in their 2<sup>nd</sup> cycle submission, December 13, 2004. The submitted PPI has a Flesch-Kincaid Grade Level of 10.2 and a Flesch Reading Ease of 47.6%. The Patient Information and Consent form has a Flesch-Kincaid Grade Level of 12.0 and a Flesch Reading Ease of 38.4%.

**Comments and Recommendations:**

We have the following comments and recommendations:

1. The sponsor should revise and simplify the PPI and the Patient Information and Consent form to a 6<sup>th</sup> to 8<sup>th</sup> grade reading level with a reading ease of at least 60% ( 60% corresponds to an 8<sup>th</sup> grade reading level) to ensure comprehension among a broader range of patients, especially those with low literacy levels. Approximately 50% of adults in the U.S. comprehend written materials at less than an 8<sup>th</sup> grade reading level.

2. Avoid presenting data in tables unless careful explanations are presented at a low reading comprehension level. Many readers have trouble comprehending this type of information.
3. Avoid providing rates or percentages in patient information unless an explanation of rates and percentages are carefully explained in patient-friendly language. For example 57% (57 out of 100 women who take this medicine...).
4. There is no regulatory requirement for the sponsor to provide patient information with this product. This product will be distributed to medical clinics and not directly to the patient. There are no regulatory requirements for non-pharmacists to distribute voluntary or required patient information. The sponsor should state their planned method of distribution of these materials to patients.

We will be glad to review a simplified PPI and Patient Information and Consent form. Please call us if you have any questions.

Appears This Way  
On Original

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Jeanine Best  
5/12/05 03:57:21 PM  
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
5/13/05 07:54:59 AM  
DRUG SAFETY OFFICE REVIEWER  
for Gerald Dal Pan

**FOOD AND DRUG ADMINISTRATION  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications**

**Memorandum**

**Date:** May 11, 2005  
**To:** Karen Kirzburg, NP, Regulatory Health Project Manager  
Division of Reproductive and Urologic Drug Products  
HFD-580  
**From:** Michelle Safarik, PA-C  
Iris Masucci, PharmD, BCPS  
Division of Drug Marketing, Advertising, and Communications  
HFD-042  
**Subject:** NDA 21-529  
DDMAC labeling comments for Implanon

---

DDMAC has reviewed the proposed product labeling (PI) dated December 13, 2004, for Implanon and offer the following comments:

**PI**

**DESCRIPTION**

1. "The release rate is 60-70 µg/day in week 5-6 and decreases 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 then to approximately 25-30 µg/day at the end of the third year."

Is it appropriate to include this information here, as in the Norplant PI, or is it more appropriately placed in the **CLINICAL PHARMACOLOGY** section?

**CLINICAL PHARMACOLOGY**

**Pharmacodynamics**

b(4)

These statements sound promotional - are they accurate and supported by substantial evidence? If not, please consider deleting.

## Pharmacokinetics

### *Absorption*

1. Please consider deleting \_\_\_\_\_ from the first sentence. It is unnecessary because the time to peak serum concentration is given below and it is promotional in tone. **b( b(4)**
2. Would it be possible to provide context for “were reached within the first few weeks,” “serum ENG concentrations,” and “decreases gradually over time”?
3. “The mean peak serum ENG concentrations in 3 pharmacokinetic studies ranged between 781 and 894 pg/mL...”

How do these numbers reconcile with the data points in Figure 2 that follows? The figure seems to show mean peaks for the three studies ranging from just over 300 to around 650 pg/mL. Can this be clarified?

4. Is any explanation needed for the wide range of  $C_{max}$ 's that appear in Figure 2? Do we know enough to say there are differences among races? If so, should this information appear under **Pharmacokinetics – Special Populations**?

### *Excretion*

1. Would it be possible to provide context for “mainly in urine and to a lesser extent in feces”?

## Special Populations

### *Overweight Women*

1. Is it appropriate to include this section under **CLINICAL PHARMACOLOGY**, or should it be moved to **PRECAUTIONS – Special Populations**?

2. \_\_\_\_\_ **b(4)**

Upon what data is this statement based? The concentration vs. time data in Figure 2 seems to show no real decline in serum concentration between

years 2 and 3 in the pharmacokinetic studies. What do we really know here?

### **Drug Interactions**

1. If there is no information presented in this section, please consider deleting this subheading. In general, results from drug interaction studies should be presented in the **CLINICAL PHARMACOLOGY** section and the clinical management of those interactions (e.g., dosage adjustments, increased dosing intervals, etc.) should be described under **PRECAUTIONS – Drug Interactions**.

b(4)

### **INDICATIONS AND USAGE**

1. ...

b(4)

- 2

- 3.

b(4)

4.

5.

## CONTRAINDICATIONS

b(4)

## WARNINGS

### A. *Warnings Based on Experience with Implanon and Other Progestin-Only Contraceptives*

1. This section is very poorly written and is difficult to follow. Much of the information is repeated unnecessarily and is very choppy. Can this information be re-written? Perhaps the general information that appears at the end of the section

b(4)

should appear first. In its current position, this information could be easily overlooked when presented after the exhaustive list of adverse events. Then, individual paragraphs could follow that describe complications first from insertion and then those from removal.



4. The Norplant PI includes a discussion on foreign body carcinogenesis, use before or during early pregnancy, and idiopathic intracranial hypertension in its **WARNINGS** section. For consistency, please consider including similar discussions here in the proposed Implanon PI if clinically relevant.

*B. Warnings Based on Experience with Combination (Progestin Plus Estrogen) Oral Contraceptives*

1. The Norplant PI includes a discussion on ocular lesions in its **WARNINGS** section. For consistency, please consider including a similar discussion here in the proposed Implanon PI if clinically relevant.

## **PRECAUTIONS**

### **General**

1. The Norplant PI includes an "Insertion and Removal" discussion in its **PRECAUTIONS** section. For consistency, please consider including a similar discussion here in the proposed Implanon PI if clinically relevant.

b(4)

### **Carbohydrate and Lipid Metabolic Effects**

1. "-----"

b(4)

### **Liver Function**

1. We recommend adding a cross-reference to the **CONTRAINDICATIONS** section at the end of this section.

## Drug Interactions

1. We recommend mentioning cytochrome P450 3A4 in this section describing interactions with enzyme-inducing drugs for clarity. It is mentioned in the following section for inhibitors.

## Interactions with Laboratory Tests

1. "Sex hormone-binding globulins concentrations may be decreased for the first six months after Implanon insertion followed by a gradual recovery. Thyroxine concentrations may initially be slightly decreased followed by gradual recovery to baseline."

Are these statements accurate? If not, please consider deleting. If so, would it be possible to provide context for "may be decreased/may initially be slightly decreased" and "gradual recovery/gradual recovery to baseline"?

## Carcinogenesis, Mutagenesis, Impairment of Fertility

1. "Fertility returned after withdrawal from treatment."

Would it be possible to provide context for how long after treatment withdrawal did fertility return?

## Nursing Mothers

1. "The health of breast-fed infants whose mothers began using Implanon during the 4<sup>th</sup> to 8<sup>th</sup> week postpartum (n=38) was evaluated in a comparative study with mothers using a non-hormonal IUD (n=33). They were breast-fed for a mean duration of 14 months and followed up to 36 months of age. No significant effects and no differences between the groups were observed on the physical and psychomotor development of these infants." (Please also see *Can I use Implanon when I am breast feeding?* in the proposed PPI)

Was this study specifically designed to evaluate the physical and psychomotor development of breast-fed infants? If not, please consider deleting. This information may be used in promotion to imply that Implanon has no effect on the physical or psychomotor development of breast-fed children whose mothers used Implanon, and that the findings are no different from those in women using non-hormonal contraception.

## Return to Ovulation

1.

b(4)

## ADVERSE REACTIONS

1. To improve ease of readability and to be consistent with competitor PI's, please consider revising this section into tabular format, including adverse events related to Implanon therapy with incidence rates in descending order. In addition, please consider bullet formatting with percentage incidence for other adverse events. Furthermore, please consider incorporating the discussion on discontinuation rates, bleeding patterns, and Table 3 from p. 12 into this section. Moreover, please consider consolidating the detailed information on bleeding irregularities in one place in the label, with cross-references to other sections as needed.

2.

b(4)

If factually correct, please reword this sentence to say, "...is the most frequently reported side effect with Implanon." The current wording is somewhat dismissive of the risks of bleeding with Implanon.

3. The final paragraph of this section discusses implant site complications. As with the information on bleeding irregularities, this detailed information (including incidence rates) should appear in the **WARNINGS** section, rather than buried in the **ADVERSE REACTIONS** section.

## DOSAGE AND ADMINISTRATION

b(4)

2. "Anytime during the seven-day ring free period of NuvaRing (etonogestrel/ethinyl estradiol vaginal ring)."

Mentioning "NuvaRing" (a tradename) sounds promotional, especially since NuvaRing and Implanon are from the same sponsor. Please consider deleting the brand name for consistency with competitor PI's.

## **INSTRUCTIONS FOR INSERTION AND REMOVAL**

1. [REDACTED]

b(4)

## **INSERTION PROCEDURE**

1. Should a statement regarding obtaining informed consent also be included in this section?
2. Under Instruction #3, should a picture of the patient's arm placement be included as in the Norplant PI for clarification?
3. [REDACTED]

b(4)

## **REMOVAL PROCEDURE**

1. [REDACTED]
2. In Instruction #6, it is possible to revise the statement, "Gently push Implanon toward the incision until the tip is visible" to "With your hand, gently push Implanon toward the incision until the tip is visible" for clarification?

b(4)

## **PPI**

### *General*

1. Is it appropriate to include a more thorough explanation of the risks and benefits of hormonal contraception and Implanon at beginning of this PPI as in the Lunelle PPI?

*What is Implanon?*

1.

(b)(4)

2.

*How well does Implanon work?*

1. Should the "Who should not use Implanon?" section be moved to precede this section? This would be consistent with competitor PPI's.
2. Is it appropriate to include more detail about timing of Implanon insertion in this section as in the Lunelle PPI?

*What are the most common side effects I can expect while using Implanon?*

1. Please consider formatting with numbers and bullets to increase ease of readability.
- 2.

(b)(4)

Please consider revising these statements to be consistent with the adverse events listed on p. 24 of the proposed Implanon PI.

*What are the possible risks of using Implanon?*

1. Please consider formatting with numbers and bullets to increase ease of readability.

2. Is it appropriate to include the statement, "The possibility of ovulation and conception should be considered and pregnancy must be excluded before inserting Implanon" for consistency with the risk information in competitor PPI's?
3. Would it be possible to provide context for the incidences of swelling, redness, and bruising?
4. Would it be possible to include the incidence of expulsions, as well as the complications of insertion (implant stayed at needle, slight bleeding/compression, hematoma, difficult insertion) to be consistent with the proposed Implanon PI?
5. Is it appropriate to move the "Interaction with other Medications" section into a new Precautions section of the PPI, which would also discuss the following for consistency with the Precautions section of the proposed Implanon PI:

b(4)

6. Is it appropriate to move the "Breast Cancer" section to "Other Risks" to be consistent with the proposed Implanon PI?

*What if I become pregnant while using Implanon?*

1. "Based on experience with birth control pills, Implanon is not likely to cause birth defects."

This statement sounds promotional and is speculative. Please consider deleting.

*Additional Information*

1. Would it be possible to include an active and inactive ingredient list in this section for consistency with competitor PPI's?

**Appears This Way  
On Original**

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Michelle Safarik  
5/11/05 09:50:52 AM  
DDMAC REVIEWER

## MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Division of Drug Marketing, Advertising, and Communications

### Predecisional Agency Information

---

Date: September 15, 2004  
From: Corrinne Kulick, DDMAC  
To: Karen Anderson, DRUDP  
Re: Implanon (etonogestrel subdermal implant)  
NDA 21-529

Comments are provided on the draft labeling for Implanon (etonogestrel subdermal implant) dated August 2003.

#### DESCRIPTION

- Each Implanon rod consists of an ethylene vinylacetate (EVA) copolymer core, containing 68 mg of the synthetic progestin etonogestrel (ENG), surrounded by an EVA copolymer skin.

Is it appropriate to refer to the active ingredient by an acronym? If not, DDMAC recommends deletion of the acronym here and replacing the acronym throughout the label with the name of the active ingredient.

b(4)

DDMAC recommends deletion of the first sentence as it is promotional in tone and does not belong here. In addition, the second sentence in [] does not belong in this section. DDMAC recommends deleting this text from this section.

- ENG [(17 $\square$ )13-ethyl-17-hydroxy-11-methylene-18,19-dinorpregn-4-en-20-yn-3-one], structurally derived from 19-nortestosterone, is the biologically active metabolite of desogestrel.

Is this drug synthetic? If so, can this information be added here for consistency.

#### CLINICAL PHARMACOLOGY Pharmacodynamics

b(4)

This sentence also appears in the Indications and Usage section and should be deleted here.

b(4)

Is the underlined text adequately supported? If not, DDMAC recommends deletion to avoid an implied benefit that is not adequately supported. In addition, it may provide a marketing advantage over Jadelle, whose label reads "At least two mechanisms are active in preventing pregnancy: ovulation inhibition and thickening of the cervical mucus. Other mechanisms may add to these contraceptive effects."

b(4)

DDMAC recommends deletion of the information which discusses animal studies and speculative human data unless this information is adequately supported or relevant to the human response and necessary for the prescriber.

#### **Pharmacokinetics**

##### Absorption

b(4)

DDMAC recommends deletion of the first sentence as it is unnecessary given the information that follows and is promotional in tone. In regard to the second sentence, what does this data mean clinically? Are patients protected from unwanted pregnancies within 24 hours?

b(4)

DDMAC recommends deletion of this summary sentence as the data is clearly and concisely presented in Table 1 and is thus repetitive.

- Can the concentration/time data that is provided in Figure 2 and the introductory paragraph be instead presented in table format? The Jadelle label is done this way.

b(4)

In general, details of the major clinical efficacy trials should be provided in the Clinical Studies section (Indications and Usage, in this case). Therefore, DDMAC recommends deletion of this information here and inclusion in the Indications and Usage section. Further, DDMAC recommends deletion of the underlined text because it suggests a guarantee of efficacy in the highest weight categories.

Excretion

- The data provided in the text as well as in Table 2 describes excretion of  
Are there no data with the subdermal product?

b(4)

**Special Populations**

Hepatic Insufficiency

b(4)

DDMAC recommends deletion of the underlined text here and under Renal Insufficiency. In general, safety and efficacy information should be presented in the Clinical Studies and Adverse Events section of the label. In regard to the second sentence, can it be revised to read "However, etonogestrel is metabolized by the liver, therefore ..." to accurately communicate that Implanon is metabolized by the liver. In addition, the Jadelle label includes additional context regarding use in patients with impaired liver function, i.e., "use in patients with markedly impaired liver function or liver disease is not recommended." Should similar text be included here as well?

**INDICATIONS AND USAGE**

b(4)

DDMAC recommends deletion of this sentence because it is promotional in tone and unnecessary given the provided Pearl Index.

- b(4)

Are these statements supported by substantial evidence? Were there any ectopic pregnancies? If so, this information should be included here. Zero pregnancies and no ectopic pregnancies will give Implanon a marketing advantage over Jadelle whose label reads "Eight (8) pregnancies occurred within 5 years of Jadelle® placement in multicenter clinical trials involving 1393 women. One of the eight pregnancies was ectopic." Also, DDMAC recommends revising \_\_\_\_\_ to reflect the number of patients in the clinical trials and the number of years these patients were followed for consistency with the Jadelle label. Expressing this data as number of cycles of Implanon suggests a more extensive experience with Implanon than was actually evaluated.

b(4)

b(4)

Should post-marketing experience be included in the label? Implanon has yet to be approved in the U.S. and thus, does not have any "post-marketing" information associated with it. DDMAC recommends deletion here and lines 519-525 in the Adverse Reactions section.

- TABLE 3: Although a similar table appears in the Jadelle label, DDMAC recommends deletion of this table as well as all statements about other methods of contraception discussed in the label. This table and similar statements about other methods of contraception can be used promotionally in comparative claims as well as in superiority claims of Implanon against other methods of contraception. If the table is to remain in the

label, can the column for “% of women continuing use at one year” be deleted? Although it appears in other prescription contraceptive labels, it does not appear in the Jadelle label, and these data could be seen as an implied preference claim that is not adequately supported. In addition, are all the footnotes following the table necessary? They do not appear in the Jadelle or Depo-Provera label. Why are the columns numbered? Also, Norplant and Jadelle are not included in the table.

## CONTRAINDICATIONS

- The Jadelle label includes “History of idiopathic intracranial hypertension” in the list of patient populations for which Jadelle use is contraindicated. Should this be included here as well? Please consider its inclusion if applicable.

## WARNINGS

The Warnings section of the Jadelle label also includes a discussion on weight gain, foreign body carcinogenesis, thrombosis, use before and during early pregnancy (in precautions section), and idiopathic intracranial hypertension with levonorgestrel containing implants; cigarette smoking, use before and during early pregnancy (in precautions section), ocular lesions, and gallbladder disease with combination (progestin plus estrogen) oral contraceptives. Please consider including similar discussions here in the Implanon label if clinically relevant.

### 1. INSERTION AND REMOVAL

- Can the header “Insertion and Removal” be revised to accurately communicate that the information that follows is pertinent to adverse events that stem from the insertion and removal process, e.g. Insertion and Removal Complications as in the Jadelle label. In addition, DDMAC recommends restricting the discussion in this section to complications that arise from the insertion and removal procedure. The warnings/precautions section should include adverse reactions observed in association with the use of a drug for which there is reasonable evidence of a casual association between the drug and the adverse reaction. Therefore, DDMAC recommends deletion of “How-to” text in lines 175-201 here and lines 331-335 and 337-344 in the Precautions section.

### 2. BLEEDING IRREGULARITIES

DDMAC recommends deletion of this sentence as it is promotional in tone and minimizes the risk of this adverse event with Implanon therapy.

b(4)

b(4)

This sentence differs from that in the Jadelle label which reads “Altered bleeding patterns associated with Jadelle® implants could mask symptoms of cervical or endometrial cancer. See also ADVERSE REACTIONS, Menstrual Complaints.” Should the Implanon label be worded similarly strongly? This risk is further minimized by inclusion of the recommendation in the Implanon label “Counseling and the use of a bleeding diary may improve acceptability of bleeding pattern changes.”

3.

b(4)

- Does this heading accurately communicate the adverse event, i.e., the formation of an ovarian cyst?

#### 4. ECTOPIC PREGNANCY

b(4)

DDMAC recommends deletion of this sentence as it is promotional in tone and minimizes the potential of this serious risk with Implanon therapy.

b(4)

DDMAC recommends deletion of the descriptive \_\_\_\_\_ and quantify the incidence of ectopic pregnancy. Use of the term \_\_\_\_\_ minimizes the incidence and seriousness of this adverse event when it does occur. Also, are spotting, cramping, **and** pain necessary before ectopic pregnancy is suspected? The Jadelle label only includes pain. In addition, the Jadelle label includes "However, any pregnancy that does occur with Jadelle® use is more likely to be ectopic than a pregnancy occurring in a woman using no contraception." Should this information be included here as well? This risk is further minimized by inclusion of the third sentence "\_\_\_\_\_".

b(4)

#### 5. CARCINOMA OF THE BREAST AND REPRODUCTIVE ORGANS

b(4)

Do the \_\_\_\_\_ provide substantial evidence to support the claim \_\_\_\_\_ with Implanon therapy? In addition, does \_\_\_\_\_ provide substantial evidence to support \_\_\_\_\_ with Implanon therapy? If not, DDMAC recommends deletion of this discussion because it minimizes the risks of these serious adverse events that may occur with Implanon therapy.

b(4)

- Lines 239-258 discuss the correlation of oral contraceptive use to breast cancer development. This discussion differs markedly from that in the Jadelle label and appears to minimize the potential risk of breast cancer with contraceptive use. Are all statements regarding the relationship between breast cancer risk and contraceptive use discussed in this section adequately supported and accurately communicated? Of particular concern is the \_\_\_\_\_

b(4)

DDMAC recommends deletion of this sentence and a similar sentence (lines 270-270, 283-284) in the following sections because it minimizes the risks of these serious adverse events that may occur with Implanon therapy.

## 6. THROMBOEMBOLIC DISORDERS AND OTHER VASCULAR PROBLEMS

- This section differs from that in the Depo-Provera label, which also says that the drug should not be readministered if thrombosis occurs. Should the Implanon label also include this information?
- There is insufficient information regarding Implanon use in women who have had previous thromboembolic disease... Women with a history of thromboembolic disorders should be made aware of the possibility of a recurrence.

DDMAC recommends deletion of these sentences because they suggest that Implanon can be used in patients with a history of thromboembolic disorder, when Implanon is contraindicated in this patient population.

•

b(4)

Are the underlined diseases attributable to vascular problems? If not, DDMAC recommends deletion of their mention in this discussion. Can you please quantify *very small* with the relative risk of morbidity and mortality? The phrase *very small* is vague and meaningless without quantification. Also, the Jadelle label includes a more lengthy discussion on the risk of myocardial infarction including the statement "Studies indicate a significant trend toward higher rates of myocardial infarctions and strokes with increasing doses of progestin in combination oral contraceptives." Should this information be included here as well?

## 7. ELEVATED BLOOD PRESSURE

•

b(4)

DDMAC recommends deletion of this sentence. In general, statistics are not presented for adverse events unless they were the primary endpoints of a specific safety study.

- The Jadelle label includes the recommendation "Physicians should be aware of the possibility of elevated blood pressure in individual patients using Jadelle® implants." Should this information be included here as well?
- For most women, elevated blood pressure will return to normal after stopping hormonal contraceptives, and there is no difference in the occurrence of hypertension between ever- and never-users.

Is this statement adequately supported? If not, DDMAC recommends deletion because it minimizes the risk of hypertension that may occur with Implanon therapy.

## 8. HEPATIC NEOPLASIA

- The Jadelle label includes a discussion on the relationship between hepatic neoplasia and contraceptive use? Should this information be included here as well?

•

b(4)

DDMAC recommends deletion of this sentence because it minimizes the risk of hepatic neoplasia that may occur with Implanon therapy.

## 9. INTERACTION WITH ANTI-EPILEPTIC AND OTHER DRUGS

b(4)

Are serum levels of etonogestrel lowered when coadministered with these anti-epileptic drugs? If so, can that information be added here for completeness? Can the second sentence be revised

\_\_\_\_\_ to adequately communicate the real concern with the co-administration with ritampin.

b(4)

## PRECAUTIONS

The Precautions section of the Jadelle label also includes a discussion on infections, expulsions and displacement, and autoimmune disease. Please consider including similar discussions in the Implanon label if clinically relevant.

## 2. PHYSICAL EXAMINATION AND FOLLOW-UP

b(4)

Please include reference to implant site in this list for completeness.

b(4)

DDMAC recommends deletion of this sentence here and the underlined text in the Precautions-Information for the Patient section. Inclusion of this sentence may allow the sponsor to selectively present this adverse event as the most significant adverse event with Implanon therapy.

## 3. INSERTION AND REMOVAL

- This section differs markedly from that in the Jadelle label which also includes a discussion on timing of insertion relative to the women's' cycle and necessary precautions to take relative to timing of insertion. Please consider including a similar discussion here if clinically relevant.

4.

•

b(4)

b(4)

## 5. CARBOHYDRATE AND LIPID METABOLIC EFFECTS

b(4)

Can you please quantify and meaningless without quantification.

These terms are vague

•

b(4)

DDMAC recommends deletion of this information, because it can be used promotionally to

•

b(4)

Can you please quantify meaningless without context. In addition, DDMAC recommend deletion of the third sentence because it can be used promotionally

These terms are vague and

b(4)

## 6. DRUG INTERACTIONS

- Contraceptive effectiveness may be reduced when hormonal contraceptives are co-administered with some antibiotics, antifungals, anticonvulsants, and other drugs that increase metabolism of contraceptive steroids.

Can this sentence be revised to accurately communicate that this concern applies to Implanon therapy and include the mechanism of the drug interaction. This information may be useful to the reader. For example, "Contraceptive effectiveness may be reduced when Implanon is co-administered with drugs that may increase metabolism of etonogestrel through induction of microsomal liver enzymes CYP 3A4."

•

In addition, please replace \_\_\_\_\_ with *Implanon* to clearly communicate that this concern applies to Implanon therapy.

b(4)

## 7. INTERACTIONS WITH LABORATORY TESTS

- a. Sex hormone-binding globulins concentrations may be decreased for the first six months after Implanon™ insertion followed by a gradual recovery.

Is the underlined text adequately supported? If so, shouldn't a more definitive term, e.g., *are* be used in place of *may be*?

- Thyroxine concentrations may initially be slightly decreased followed by gradual recovery to baseline.

Is this statement adequately supported? Do thyroxine concentrations return to baseline?

## 8. CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY

- ... no drug-related carcinogenic potential was observed.

We recommend revising this sentence. This wording suggests that there was a carcinogenic potential, but it was not drug related.

- Fertility returned after withdrawal from treatment.

This topic is discussed under item 11. Therefore, DDMAC recommends its deletion here to avoid repetition.

b(4)

## 9. PREGNANCY

- 

Teratology studies have been performed in rats and rabbits, respectively using oral administration up to 390 and 790 times the human Implanon™ dose (based upon body surface) and revealed no evidence of fetal harm due to ENG exposure.

Does this section meet the regulations on wording of information on use in pregnancy for a Category X product? Please consider deletion unless clinically relevant to human therapeutics. In addition, this section includes a cross-reference to the Warnings section; however, no relevant pregnancy information appears there.

## 10. NURSING MOTHERS

b(4)

Can this sentence be revised to more strongly articulate the purpose of the precaution? For example, "Caution should be exercised when Implanon is administered to nursing women because etonogestrel is excreted in breast milk."

- 

DDMAC recommends deletion of this sentence because it is speculative

b(4)

- The health of breast-fed infants whose mothers began using Implanon during the 4th to 8th week postpartum (n=38) was evaluated in a comparative study with mothers using a non-hormonal IUD (n=33). They were breast-fed for a mean duration of 14 months and followed-up to 36 months of age. No significant effects and no differences between the groups were observed on the physical and psychomotor development of these infants.

b(4)

b(4)

11.

•

This paragraph summarizes the data in very broad and ambiguous terms (e.g., within one week, soon, rapid). We recommend including the actual data (e.g., Life-Table Analysis as in the Depo-Provera label) for completeness.

**12. LIVER FUNCTION**

•

b(4)

Does this product actually cause changes in liver function parameters, or is this merely a precaution for use in patients with liver impairment from other causes? Can this be clarified?

**14. FLUID RETENTION**

b(4)

Can this discussion be reworded to more clearly articulate that there is a potential for fluid retention with Implanon. For example, the Depo-Provera label states "Because progestational drugs may cause some degree of fluid retention, conditions that might be influenced by this condition, such as epilepsy, migraine, asthma, and cardiac or renal dysfunction, require careful observation." As written the discussion minimizes the severity and seriousness of this adverse event when it does occur.

15.

•

b(4)

17

**18. PEDIATRIC USE**

**b(4)**

Can this statement be deleted? It is unnecessary and encourages the use of Implanon in patient populations not evaluated.

**ADVERSE REACTIONS**

- Lines 495-509- This summary of adverse events should be revised to a table format, listing events with their incidence rates in descending order, for those events relating to Implanon therapy only.

- 

**b(4)**

DDMAC recommends deletion of this sentence. It is obvious given the rates that follow. In addition, DDMAC recommends deleting from line 513; it is promotional in tone and unnecessary given the information that follows.

**OVERDOSAGE**

- 

**b(4)**

This section differs from the Jadelle label, which says uterine bleeding patterns may be altered.

**DOSAGE AND ADMINISTRATION**

**b(4)**

- 

DDMAC recommends deletion of this sentence as it is promotional in tone and appears in the Indications and Usage section.

**b(4)**

- Is this header necessary? All applicable information should be appropriately covered in the label.

DDMAC has no comments on the Insertion/Removal Procedure (pages 28-43). DDMAC will be happy to opine on the Patient Labeling (pages 44-60) following review and comment by Jeanine Best, Office of Drug Safety.

Thank you for including DDMAC in this review.

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Corrinne Kulick  
9/15/04 11:15:47 PM  
DDMAC REVIEWER

**August 31, 2004**

**Consult Addendum to the file for NDA 21-529**

**This addendum is provided to address only the issue of function of the device.**

I have reviewed the information sent to me via FAX on August 20, 2004. The DMF only addresses the materials used for the device. As I have stated before, CDRH review for 510(k) device types only looks at the finished product and not the manufacturing process for this type of device. As the DMF states, these materials are ones commonly used for this device type.

I believe it is safe to say that this implant device does not need the same scrutiny in my consult review that I would do for a standard piston syringe. This is especially true since the information on sterility, biocompatibility and labeling for the device will be reviewed as Dr. Mitra stated by CDER reviewers.

The only other outstanding question I had from my consult dated March 23, 2004 is the functional testing. Generally the sponsor provides some data that they have collected using the device in either bench testing and/or clinical testing. Primarily this relates to such issues as ease of use by the clinician, any problems with actual delivery of the drug product to the implant site using the device and any other device use problems and how they were resolved. The basic description of the device as I have put in my consult review leads me to think that the device would function as intended.

In the information provided on August 30, 2004, I find that the sponsor has provided a very brief description of a test for ejectability of the implant. In this test the sponsor determines that the implant will not stick to the needle. The information is limited to Page 7 that describes a plan to check for manual ejection of the implant. I find this a basically acceptable method of testing function provided the outcome of each test can be deemed as "passed". The results they will record are "complies" when appropriate. I believe that some clinical observations (data) should have been made using this device. This is assuming that the device has been used with the implant in humans as a premarket study.

 8/31/04

Viola Hibbard, RN., BSN  
Reviewer-CDRH/ODE/DAGID/GHDB  
[VSH@CDRH.fda.gov](mailto:VSH@CDRH.fda.gov)  
301-594-1287 X173

**Appears This Way  
On Original**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

MEMORANDUM

Food and Drug Administration  
Office of Device Evaluation  
9200 Corporate Avenue  
Rockville, MD 20850

**Date:** March 23, 2004

**From:** Viola Hibbard, Nurse Consultant  
DAGID/GHDB, HFZ-480

**Through:** Anthony Watson, Branch Chief, CDRH/ODE/DAGID/GHDB, (HFZ-480)

**Subject:** Consult Review for NDA 21-529

**To:** Amit Mitra, Ph.D.

I. Introduction

This consult is for CDER to provide a review of a device used for implantation of Implanon (containing 68 mg of etonogestrel) whose therapeutic indication is for contraception. The drug component is injected using the device in the subdermal connective tissue

II. Device Description

While this device is referred to as a syringe and needle, the design of the device does not resemble a classical syringe. The device would be more aptly described as an applicator. The components of this device are a cannula, obturator and needle with double-angled bevel. Provided are three samples of the Implanon device. It is described on the package label as a sterile, single use product containing the Etonogestrel for subcutaneous use.

The needle is made of stainless steel which is attached to the acrylonitrile-butadiene-styrene applicator body. The needle is protected by a polypropylene needle shield. The applicator is packed in a blister pack

b(4)

b(4)

Packaging materials are described in MAF . . . Based on a letter of authorization dated July 30, 2002 from . . . I have reviewed that file. The MAF indicates that the packaging material is appropriate for this device. The materials in the packaging have been tested with USP Biological Tests for Class VI plastics. The packaging will maintain the sterility of the device unless the integrity of the package is compromised.

b(4)

### III. Consult Review Issues

I find that additional information . . . are provided in DMF . . . I have tried but I have found that I have no access to this information through the CDRH Image system. I do have access to the MAF for the packaging as noted above.

b(4)

Much of the information provided for the consultative review is the manufacturing process. While the importance of this process is important, in a premarket review, CDRH generally considers only the finished product.

### IV. Conclusion and Recommendations

In order to make this consult review complete, the following information will be needed. This information is most likely in the DMF.

- A. Bench testing to determine if the device will function as intended.
- B. Sterility information to include sterilization method and validation, ETO residuals or Gamma dose, Sterility Assurance Level (SAL) and Pyrogen test method.
- C. Biocompatibility Testing according to ISO 10993.
- D. The prescription statement should appear somewhere on the labeling . I do not find this on the package insert or on the device label.

Please advise or assist me on how I may have access to the Master Files, I will review the information as soon as possible to meet whatever your deadline may be. Unless you have more information that has not been included in the packet set to CDRH, this consult review is incomplete.

Thank you.



Viola Hibbard, RN., BSN  
Reviewer-CDRH/ODE/DAGID/GHDB  
[VSH@CDRH.fda.gov](mailto:VSH@CDRH.fda.gov)  
301-594-1287 X173

**MEMORANDUM**

DEPARTMENT OF HEALTH AND HUMAN SERVICES  
PUBLIC HEALTH SERVICE  
FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**DATE:** January 5, 2004

**TO:** Daniel Shames, M.D., Director  
Division of Reproductive and Urologic Drug Products  
HFD-580

**VIA:** Karen Anderson, N.P., Regulatory Health Project Manager  
Division of Reproductive and Urologic Drug Products  
HFD-580

**FROM:** Jeanine Best, M.S.N., R.N., P.N.P.  
Patient Product Information Specialist  
Division of Surveillance, Research, and Communication Support  
HFD-410

**THROUGH:** Gerald Dal Pan, M.D., M.H.S., Director  
Division of Surveillance, Research, and Communication Support  
HFD-410

**SUBJECT:** ODS/DSRCS Review of Patient Labeling for Implanon  
(etonogestrel subdermal implant), NDA 21-529

**Background**

The sponsor submitted Patient Information for Implanon (etonogestrel subdermal implant), NDA 21-529, in the form of a Patient Package Insert (PPI) on September 30, 2003. The submitted PPI has a Flesch-Kincaid Grade Level of 11.5; a Flesch Reading Ease of 45%; and average words per sentence of 18.5.

**Comments and Recommendations:**

We have the following comments and recommendations:

1. The PPI should be written in a Medication Guide question and answer type format as described in 21 CFR § 208. Research and experience is available to support the communication effectiveness of the Medication Guide format. Alternate formats should have data (i.e., label comprehension studies) to support their communication effectiveness to a broad range of patients, including those with low literacy. Keep the insertion and removal information at the end of the leaflet.

2. Approximately 50% of the U.S. population functions at a low literacy level. Simplify the vocabulary and sentence structure for low literacy readers. A 6-8<sup>th</sup> grade reading comprehension level is optimal for all patient information. The reading ease score should be 60% (which correlates with an 8<sup>th</sup> grade reading level) or greater.
3. We suggest using the January 3, 2003, suggested class labeling for estrogen- and progestin - containing products for postmenopausal women as a template for revising patient information for contraceptive products.
4. Avoid presenting data in tables unless careful explanations are presented at a low reading comprehension level. Many readers have trouble comprehending this type of information.
5. Avoid providing rates or percentages in patient information unless an explanation of rates and percentages are carefully explained in patient-friendly language. For example 57% (57 out of 100 women who take this medicine...).

Please call us if you have any questions.

**Appears This Way  
On Original**

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Jeanine Best  
1/5/04 09:43:11 AM  
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp  
1/5/04 01:31:54 PM  
DRUG SAFETY OFFICE REVIEWER  
for Gerald Dal Pan