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RESEARCH**

APPLICATION NUMBER:

21-529

APPROVABLE LETTER



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-529

Organon USA Inc.
Attention: Albert P. Mayo
Vice President, Regulatory Affairs
375 Mount Pleasant Avenue
West Orange, New Jersey 07052

Dear Mr. Mayo:

We received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act on September 30, 2003 for Implanon™ (etonogestrel implant) 68 mg For Subdermal Use Only.

We acknowledge receipt of your submissions dated December 18, 2003, January 19 (2) and 20, February 10, March 5, 10, 18, 23 (2), and 30 (2), April 7, 15, 21, and 27, May 4, 11 (2), 20, 26, 27 (2), and 28 (2), June 1 and 30 (2), July 14 (2), 20 (2), and 29, August 4 (2), September 9 (4), 13 (3), 17, and 24 (2), October 5, 6 (3), 11 (4), 12, 14, 15 (2), 20 (2), 21 (2), 22 (2), and 27, November 1, December 13, 2004, February 17, May 11, 13 (3), 17 (2), 18 (2), 20 (2), 25, June 1, 3, and 7 (3), 2005.

Your submission of December 13, 2004 constituted a complete response submission to the October 29, 2004 Approvable letter.

We completed our review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following issues and requests.

In our approvable letter dated October 29, 2004, we stated that irregularities in study conduct identified by European regulatory authorities' inspections of the clinical trial sites for Study 34507 (including its Canadian component) have raised concerns about the quality of the data from this study. These concerns are outlined in the October 11, 2004 letter from the Dutch Medicines Evaluation Board to European Union countries and the summary comments of the September 23, 2004 Report of the Inspectorate of Health Care in the Netherlands (Integrated Inspection Report IGZ 2004-015), which were included in your October 15, 2004 submission to FDA. You were given two options to address this issue. The first was to provide a detailed justification of why Study 34507 and Study 34507 Canada are in fact adequate and well-controlled trials that provide data sufficient to support a conclusion that Implanon™ is safe and effective for prevention of pregnancy and can support accurate product labeling. The alternative was that you could conduct another clinical trial to provide safety and efficacy data to support product labeling.

In your complete response, submitted on December 13, 2004, you provided information you believe establishes that Study 34507 and Study 34507 Canada provide data sufficient to support approval of

Implanon™. However, the materials that you submitted, including an “independent audit” of the German study sites conducted at your request by a contract research organization, do not establish that event reporting was complete and accurate at those sites. In addition, your submission of the post marketing spontaneous adverse event report summaries and the summary of Periodic Safety Update Reports of pregnancies for calculation of an approximate Pearl Index based on market use and estimates of under-reporting, cannot substitute for clinical trial data to establish the safety and efficacy of Implanon™ and is not sufficient to support product labeling in this regard.

Because you have not established that the data from Studies 34507 are complete and accurate, we remain concerned that there is insufficient information about Implanon™ to determine whether the product is safe for use under the conditions prescribed in its proposed labeling and to precisely define its effectiveness in its labeling. We have found that the data submitted are insufficient for the following reasons:

- 1) Two of the six studies (Indonesia) submitted in the original NDA submission had to be withdrawn from the NDA because of significant Good Clinical Practice (GCP) violations that rose to the level of fraud.
- 2) Inspections by representatives of the Dutch Medicines Evaluation Board (DMEB) and regional inspectors, representing the European Regulatory Authorities, of clinical trial sites for two additional studies in the NDA submission, Study 34507 and Study 34507 Canada, resulted in revisions of the approved Implanon™ labeling in Europe, including removal of the specific number of treatment cycles, removal of the Pearl Index value, and modification of the safety data to suggest an increase in frequency of several adverse event categories. The DMEB concluded that the conduct of the inspected sites had not been consistent with GCP and that the reliability of the data from those sites could not be assured.
- 3) There are inconsistencies across studies in adverse event reporting, which contributes to a concern that collection and reporting of adverse events in the trials could be incomplete or inaccurate. For example, the proportion of patients that discontinued prematurely is different between the US Study 69001 (49%) compared to Study 34507 (33%) and Thailand Study 34505 (32%). The proportion of discontinuations for adverse events that included “bleeding complaints” also was higher in the US study (36%) compared to Study 34507 (28%) and the Thai study (12%).
- 4) With elimination of the Indonesian studies and the data from all sites in Study 34507 that have not been inspected by the FDA, the remaining dataset (consisting of data from the US Study 69001, the centers of Drs. Urbancsek and Croxatto in Study 34507, and Thai Study 34505 – a study that has not been inspected by the FDA) consists of 648 women treated for the equivalent of 7,520 28-day cycles in the first year. This total exposure is substantially less than the 10,000 28-day cycles equivalents in the first year of use that we customarily review in hormonal contraceptive applications for a new molecular entity or a new delivery system. Although there are 5,931 additional 28-day cycle equivalents available from the second year (505 women) and 2,737 28-day cycle equivalents from the third year (369 women), the minimum dataset considered adequate to establish safety and efficacy is 10,000 cycles in the first year. Ten thousand (10,000) 28-day cycles in the first year of treatment assures a minimum number of new exposures to the drug. Incorporating cycles beyond one year enriches the dataset with subjects who have demonstrated tolerance to therapy and diminishes the potential to identify

the important adverse events of interest associated with hormonal contraceptive products, thrombotic and thromboembolic events. It has been our experience that these events are more likely to manifest in the earlier months of exposure to hormonal contraceptive products, and that women who tolerate the product in the first year are less likely to have thromboembolic events in cycles of exposure that occur in the years that follow. In addition, the available post-marketing data on pregnancies from Implanon™ product failures suggest that these also tend to occur in the first year of use.

To address the issue of the adequacy of the data to support approval of Implanon™, you will need to submit new clinical trial data from a clinical trial(s) that has been conducted in accordance with Good Clinical Practices. The new clinical trial data should include a sufficient number of subjects so that the assessment of the safety and efficacy of Implanon™ can be derived from a clinical trial database containing the equivalent of at least 10,000 28-day cycles obtained during the first year of treatment.

You will also need to submit an acceptable plan for a post-marketing monitoring program for Implanon™-related insertion and removal adverse events in U.S patients.

Labeling remains unresolved. Further discussions regarding this topic will occur in the next review cycle.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

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If you have any questions, contact Karen Kirchberg, N.P., Regulatory Project Manager, at (301) 827-4254.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Donna Griebel

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We also acknowledge receipt of your submission dated October 15, 2004. This submission was not reviewed in the current review cycle for this action. You may incorporate this submission by specific reference as part of your response to this letter.

We completed our review of this application, as amended, and it is approvable. Before this application may be approved, however, it will be necessary for you to address the following issues and requests.

1. Irregularities in study conduct identified by European regulatory authorities' inspections of the clinical trial sites for Study 34507 (including its Canadian component) have raised concerns about the quality of the data from this study. These concerns are outlined in the October 11, 2004 letter from the Dutch Medicines Evaluation Board to Concerned Member States and the summary comments of the September 23, 2004 Report of the Inspectorate of Health Care in the Netherlands (Integrated Inspection Report IGZ 2004-015), which were included in your October 15, 2004 submission to FDA. To address this issue, you will need to submit the Integrated Inspection Report IGZ 2004-015 entitled "Evaluation of Implanon Non-compliance Issues," the independent audit report, and Organon's response to the Dutch Medicines Evaluation Board to the NDA. You will also need to submit a detailed justification of why Study 34507 (including its Canadian component) are adequate and well-controlled trials that provide data sufficient to support (1) a conclusion that Implanon is safe and effective for prevention of pregnancy and (2) accurate product labeling. Alternatively, you can conduct another clinical trial to provide safety and efficacy data to support product labeling.

2. Because findings from the review of the materials described above in #1 may impact the labeling of the product, labeling can not be finalized at this time. To address this issue, appropriate product labeling should be submitted to the FDA with the information requested in #1 above.
3. The inspection of the sterilization facility
has not been completed because the facility was not ready for inspection.
A satisfactory inspection report is required before this application may be approved.

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all non-clinical and clinical studies of the drug under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.
2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies for the proposed indication using the same format as the original NDA submission.
 - Present tabulations of the new safety data combined with the original NDA data.
 - Include tables that compare frequencies of adverse events in the original NDA with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature study discontinuation by incorporating the drop-outs from the newly completed studies. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each patient who died during a clinical study or who did not complete a study because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original NDA data.
6. Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
7. Provide English translations of current approved foreign labeling not previously submitted.

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. If you do not follow one of these options, we will consider your lack of response a request to withdraw the application under 21 CFR 314.65. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all deficiencies have been addressed.

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Under 21 CFR 314.102(d), you may request an informal meeting or telephone conference with the Division to discuss what steps need to be taken before the application may be approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Karen Kirchberg, N.P., Regulatory Project Manager, at (301) 827-4254.

Sincerely,

{See appended electronic signature page}

Donna Griebel, M.D.
Deputy Director
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/s/

Donna Griebel
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