CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-840

SUMMARY REVIEW

4.0 Regulatory Action of the Original October 21st, 2006 submission

I agreed with the secondary reviewer (the primary reviewer believed the application should be approved) that NDA 21-840 was Approvable because of the following deficiency which was conveyed to the sponsor in a letter dated August 17, 2005.

"The application for the Seasonique™ extended cycle contraceptive regimen (consisting of 150 micrograms levonorgestrel and 30 micrograms ethinyl estradiol administered for 84 days and 10 micrograms ethinyl estradiol administered days for days 85-91) did not provide clinical trial data that demonstrated benefit of the addition of 10 micrograms of ethinyl estradiol per day on days 85-91 to this extended cycle contraceptive regimen compared to the exact same regimen that has placebo during days 85 to 91. Because of the known risks of exogenous estrogen, replacement of placebo by ethinyl estradiol to this regimen cannot be supported without demonstration of a clinically meaningful benefit to the patient.

To address this deficiency, a randomized controlled clinical trial that demonstrates that the addition of 10 micrograms of ethinyl estradiol to the previous hormone free period provides a meaningful clinical benefit to the patient, such as [redacted] should be conducted. The full details of such a trial and what clinically meaningful benefit is to be demonstrated should be discussed with the Division prior to initiation."

5.0 Regulatory Activity after Approvable Action of August 17, 2005:

Following receipt of the letter, Duramed met with DRUP on September 29, 2005, to discuss their options to address the above deficiency. Duramed was advised that they could conduct a comparative trial of Seasonique and Seasonale looking at ——— request an Advisory Committee meeting, or pursue formal dispute resolution. Duramed submitted a request for formal dispute resolution challenging the scientific, regulatory and legal issues raised by the Approvable action. This appeal was directed to Dr. Florence Houn, Director, Office of Drug Evaluation III.

On November 9, 2005, Dr. Houn issued a letter concurring with DRUP's action and denying Duramed's appeal. Another teleconference was held with DRUP on December 6, 2005, but the matter remained unresolved to Duramed's satisfaction. Therefore, this matter was appealed to Dr. John Jenkins, Director, Office of New Drugs, on January 6, 2006. On February 16th, 2006 a meeting was held between Duramed and Dr. John Jenkins, the Director of the Office of New Drugs/CDER/FDA (OND). Representatives from DRUP and ODE III were present.

5.1 The February 16, 2006 Meeting between Duramed and Dr. John Jenkins

On February 16th, 2006 Duramed provided a presentation which summarized the data submitted in the NDA to support the use of Seasonique for the prevention of pregnancy. They further summarized their justification that the data submitted demonstrated that the addition of Ethinyl Estradiol (EE) to the previously hormone-free period did not change the risk assessment of Seasonique relative to other oral contraceptives. Finally, Duramed presented their position that

(see section 1.0).

In addition, Duramed shared data from a long-term extension study (Study 304) providing additional data on 317 patients. An interim safety report had been submitted to DRUP in IND 63,735 on January 12, 2006. [Note: As discussed prior to and at the beginning of the meeting, new data cannot be submitted for consideration of the original appeal as outlined in the Guidance for Industry "Formal Dispute Resolution: Appeals Above the Division Level." Therefore, this data was not considered as part of this appeal.]

At the conclusion of the meeting, Duramed was informed that the decision regarding their appeal would be limited to the deficiency identified in the August 17, 2005, approvable letter; the request for an additional randomized controlled clinical trial comparing Seasonique to Seasonale to demonstrate a clinically meaningful benefit of the addition of 10 micrograms of EE to the previously hormone-free period. The response to this appeal will either uphold the decision made by DRUP, or will agree with Duramed that an additional clinical trial is not needed. Even if the appeal is granted, the response will not result in immediate approval of Seasonique. Duramed would need to submit a complete response to the Approvable letter, and negotiate labeling, postmarketing study commitments, etc., with DRUP. Duramed was further told that a decision on this appeal will issue from Dr. Jenkins by March 17, 2006.

5.2 Dr. Jenkins's Decision

On March 15th, 2006 Dr. Jenkins sent a Formal Dispute Appeal Letter to Duramed. In the letter, Dr. Jenkins noted Duramed's assertions that the data contained in the Seasonique NDA are

sufficient to demonstrate that the product is safe and effective for its intended use for prevention of pregnancy and that the data met or exceeded the Agency's established standards for approval of a new hormonal contraceptive product, including a new molecular entity. Duramed further asserted that the requirement for an additional clinical study, to demonstrate a meaningful clinical benefit from the addition of estrogen during the hormone free period, is unreasonable and unnecessary.

Dr. Jenkins noted Duramed's statements that the small absolute increase in the total exposure to estrogen, the favorable safety profile observed in the clinical trials, and cross-study comparisons suggesting that Seasonique provides [redacted] previously hormone free period, in comparison to Seasonale, further supported their conclusions.

Dr. Jenkins then acknowledged that Duramed has requested that the Agency withdraw its requirement for a new clinical study and immediately approve Seasonique for the proposed indication of prevention of pregnancy.

Dr. Jenkins concluded that "I have reviewed the information contained in your appeal and the information discussed at the February 16, 2006, meeting. I have also met with staff from the Division of Reproductive and Urology Products and the Office of Drug Evaluation III to discuss the issues in question related to this application.

After carefully considering the available data, the statutory and regulatory standards for approval, the Agency precedents relating to approval of hormonal contraceptives, and the interactions between you and the Division during the development phase, I have concluded that the additional clinical trial requested in the August 17, 2005, approvable (AE) letter is not required prior to approval of Seasonique for the prevention of pregnancy. Your appeal is therefore granted in part. You also requested immediate approval of Seasonique, which is denied. ....While I have determined that the additional clinical trial requested in the AE letter is not required prior to approval, other regulatory business, such as agreement on labeling and any postmarketing commitments, remains to be completed. The remaining regulatory business must be handled through the usual interactions with the Division."

6.0 Resubmission of NDA 21-840

On March 27th, 2006 DRUP acknowledged the resubmission of NDA 21-840 which was dated March 24th, 2006. The user fee goal date was established as May 27th, 2006.
DRUP considered this a complete class 1 response to the August 17th, 2005 action letter.

7.0 Regulatory Action

After agreement on labeling, Duramed was sent an Approval letter for NDA 21-840 on May 25th, 2006.

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

/s/

Daniel A. Shames
5/25/2006 02:47:57 PM
MEDICAL OFFICER

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