

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-840

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

NDA 21-840
SEASONIQUE
(levonorgestrel/ethinyl estradiol tablets 0.15 mg/0.03 mg
and ethinyl estradiol tablets 0.01 mg)

Duramed Pharmaceuticals, Inc.
Original New Drug Application

CONFIDENTIAL

Item 14 Patent Certification

As stated in item 13 of this NDA 21-840, In accordance with Section 505 (b) of the Federal Food, Drug and Cosmetic Act and as specified by 21 CFR 314.50 9h) and 21 CFR 314.53 (c) (3), Duramed Pharmaceuticals, Inc., hereby declares that there are no patents which claim an extended cycle (91-day regimen) oral contraceptive product containing levonorgestrel/ethinyl estradiol tablets 0.15mg/0.03mg and ethinyl estradiol tablets 0.01mg or which claim a method of using an extended cycle (91-day regimen) oral contraceptive product containing levonorgestrel/ethinyl estradiol tablets 0.15mg/0.03mg and ethinyl estradiol tablets 0.01mg and with respect to which a claim of patent infringement could reasonable be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of an extended cycle (91-day regimen) oral contraceptive product containing levonorgestrel/ethinyl estradiol tablets 0.15mg/0.03mg and ethinyl estradiol tablets 0.01mg.

Therefore, a patent certification is not applicable.

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PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT
For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
NO21840
NAME OF APPLICANT / NDA HOLDER
Duramed Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
Seasonique™

ACTIVE INGREDIENT(S)
(levonorgestrel / ethinyl estradiol tablets) 0.15 mg / 0.03 mg and
(ethinyl estradiol tablets) 0.01 mg

STRENGTH(S)

DOSAGE FORM
tablet

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the only information relied upon by FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
d. Name of Patent Owner	Address (of Patent Owner)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address (of agent or representative named in 1.e.)	
	City/State	
	ZIP Code	FAX Number (if available)
	Telephone Number	E-Mail Address (if available)
f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	<input type="checkbox"/> Yes	<input type="checkbox"/> No
If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	<input type="checkbox"/> Yes	<input type="checkbox"/> No

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

Drug Substance (Active Ingredient)

Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.

2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

3. Drug Product (Composition/Formulation)

Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? Yes No

4.2 Patent Claim Number (as listed in the patent)	Does the patent claim referenced in 4.2 claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? <input type="checkbox"/> Yes <input type="checkbox"/> No
---	---

4.2a If the answer to 4.2 is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.	Use: (Submit indication or method of use information as identified specifically in the approved labeling.)
---	--

5. No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)

Date Signed



10/18/04

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

NDA Applicant/Holder

NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official

Patent Owner

Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name

Duramed Research, Inc.

Address

One Belmont Ave
11th Floor

City/State

Bala Cynwyd, PA

ZIP Code

19004

Telephone Number

610-747-2600

FAX Number (if available)

E-Mail Address (if available)

The public reporting burden for this collection of information has been estimated to average 9 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CDER (HFD-007)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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INFORMATION AND INSTRUCTIONS FOR FORM 3542a
PATENT INFORMATION SUBMITTED WITH THE FILING
OF AN NDA, AMENDMENT OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplemental approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use.
- Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book Publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. An additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of July 2003) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: <http://forms.psc.gov/forms/fdahtm/fdahtm.html>.

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

- 1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.
- 1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

- 1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the pending NDA, amendment, or supplement.

- 2.4) Name the polymorphic form of the drug identified by the patent.
- 2.5) A patent for a metabolite of the approved active ingredient may not be submitted. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be submitted as a method of use patent depending on the responses to section 4 of this form.
- 2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the pending NDA, amendment, or supplement.

- 3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims a method of use of the drug product that is the subject of the pending NDA, amendment, or supplement.

- 4.2) Identify by number each claim in the patent that claims the use(s) of the drug for which approval is being sought. Indicate whether or not each individual claim is a claim for a method(s) of use of the drug for which approval is being sought.
- 4.2a) Specify the part of the proposed drug labeling that is claimed by the patent.

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

- 6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

EXCLUSIVITY SUMMARY

NDA # 21-840

SUPPL #

HFD # 580

Trade Name Seasonique

Generic Name levonorgestrel/ethinyl estradiol & ethinyl estradiol

Applicant Name Duramed Pharmaceuticals

Approval Date, If Known May 25, 2006

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

3 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 21-544

Seasonale (levonorgestrel/ethinyl estradiol) Tablets

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

PSE-301, PSE-302

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

PSE-301, PSE-302

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1
IND # 62,735 YES ! NO
! Explain:

Investigation #2
IND # 62,735 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES

Explain:

!

!

! NO

! Explain:

Investigation #2

YES

Explain:

!

!

! NO

! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES

NO

If yes, explain:

=====

Name of person completing form: Jennifer Mercier
Title: Chief, Project Management Staff
Date: 4-24-06

Name of Office/Division Director signing form: Daniel Shames, M.D.
Title: Director, Division of Reproductive and Urologic Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**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 03:05:37 PM

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA #: 21-840 Supplement Type (e.g. SE5): _____ Supplement Number: _____

Stamp Date: October 21, 2004: Original submission

Action Date: August 17, 2005

March 24, 2006: Resubmission for 2nd cycle

Action Date: May 25, 2006

HFD 580 Trade and generic names/dosage form: Seasonique™ (levonorgestrel/ethinyl estradiol/ethinyl estradiol) tablets

Applicant: Duramed Pharmaceuticals, Inc.

Therapeutic Class: 3S

Indication(s) previously approved: None

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: For the prevention of pregnancy in women who elect to use an oral contraceptive for contraception

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

Too few children with disease to study

There are safety concerns

Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

Products in this class for this indication have been studied/labeled for pediatric population

Disease/condition does not exist in children

- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed

Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

 Jennifer Mercier
Chief, Project Management Staff

cc: NDA 21-860
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG

NDA 21-860

Page 3

DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

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Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	kg _____	mo. _____	yr. _____	Tanner Stage _____
Max _____	kg _____	mo. _____	yr. _____	Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

cc: NDA21-860
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 10-14-03)

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

/s/

Jennifer L. Mercier
5/25/2006 03:04:10 PM

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NDA 21-840
SEASONIQUE

(levonorgestrel/ethinyl estradiol tablets 0.15 mg/0.03 mg
and ethinyl estradiol tablets 0.01 mg)

Duramed Pharmaceuticals, Inc.
Original New Drug Application

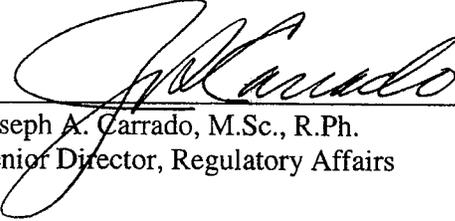
CONFIDENTIAL

Item 16 Debarment Certification

Duramed Research, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this application

This includes any person employed or contracted by Duramed Research, Inc., or any of its outside contractors and clinical investigators.

10/4/2004
Date



Joseph A. Carrado, M.Sc., R.Ph.
Senior Director, Regulatory Affairs

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-840

Duramed Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Vice President, Clinical Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

We acknowledge receipt of your June 28, 2006, submission containing final printed labeling in response to our May 25, 2006, letter approving your new drug application (NDA) for Seasonique™ (levonorgestrel / ethinyl estradiol tablets 0.15 mg. / 0.03 mg) and (ethinyl estradiol 0.01 mg) Tablets.

We have reviewed the labeling that you submitted in accordance with our May 25, 2006, letter, and we find it acceptable.

If you have any questions, call Nenita Crisostomo, Regulatory Health Project Manager, at 301-796-0875.

Sincerely,

{See appended electronic signature page}

Jennifer L. Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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Jennifer L. Mercier
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Division of Reproductive and Urologic Products
REGULATORY PROJECT MANAGER REVIEW

Applications: NDA 21-840

Drug Name: Seasonique™ (levonorgestrel / ethinyl estradiol tablets 0.15 mg. / 0.03 mg) and (ethinyl estradiol 0.01 mg)

Applicant: Duramed Pharmaceuticals, Inc.

Submission Date: June 28, 2006

Receipt Dates: June 29, 2006

Materials Reviewed: Final Printed Labeling

Background and Summary: The sponsor was sent a May 25, 2006 approval letter requesting final printed labeling.

Review: The labeling is identical to that in the approval letter; the sponsor should be sent an acknowledge and retain letter.

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/s/

Jennifer L. Mercier
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Clinical Pharmacology Memo

Date: 5-22-06

NDA #: 21-840 (Complete Response, Date March 27, 2006)

Drug Product: Seasonique (levonorgestrel/ethinyl estradiol)

Indication: Contraception

Subject: Concurrence of Clinical Pharmacology Review and Label

NDA 21840 was originally reviewed by Dr. Julie Bullock. This memo documents my concurrence of the label submitted in the complete response.

Ameeta Parekh, Ph.D.
Team Leader, Clinical Pharmacology (DCP3)

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/s/

Ameeta Parekh
5/22/2006 04:40:04 PM
BIOPHARMACEUTICS

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Office of Drug Safety

MEMO

To: Daniel Shames, MD
Director, Division of Reproductive and Urology Products, HFD-580

From: Felicia Duffy, RN, BSN, MSED
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420; WO 22, Mail Stop 4447

Through: Alina Mahmud, RPh, MS, Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420; WO 22, Mail Stop 4447

Date: April 14, 2006

Re: ODS Consult 04-0267-2
Seasonique (Levonorgestrel/Ethinyl Estradiol and Ethinyl Estradiol Tablets)
0.15 mg/0.03 mg and 0.01 mg
NDA#: 21-840

This memorandum is in response to an April 7, 2006 request from your Division for a re-review of the proprietary name, Seasonique. The proposed proprietary name, Seasonique, was previously found unacceptable by the Division of Medication Errors and Technical Support (DMETS) in ODS Consult # 04-0267, dated December 6, 2004, based on the potential for confusion with the currently marketed oral contraceptive product, Seasonale. The product characteristics of these two products are listed below.

Proprietary Name	Seasonique <i>Seasonique</i>	Seasonale <i>Seasonale</i>
Established name	Levonorgestrel/Ethinyl Estradiol and Ethinyl Estradiol	Levonorgestrel/Ethinyl Estradiol
Sponsor	Duramed	Duramed
Indication	Oral contraceptive	Oral contraceptive
Strength	0.15 mg/0.03mg and 0.01 mg	0.15 mg/0.03 mg
How Supplied	Extended cycle tablet dispenser	Extended cycle tablet dispenser
Usual Dose	One tablet	One tablet
Frequency	Once daily	Once daily
Route	Oral	Oral
Dosage formulation	Tablets	Tablets
Cycle regimen	91 days = 84 days (levo/EE) 7 days (EE)	91 days = 84 days (levo/EE) 7 days (inert pills)

DMETS maintains concern with potential confusion between Seasonique and Seasonale based on the aforementioned similarities in addition to orthographic and phonetic similarities.

Revised labels and labeling were not submitted for review and comment. The labels and labeling were reviewed in DMETS' initial review. Therefore, we have repeated those comments for your convenience.

A. GENERAL COMMENT

1. The sponsor currently markets Seasonale, another extended-cycle oral contraceptive. We note that the sponsor has elected to use the same logo in the labeling of Seasonale on the labeling of Seasonique. The four pink dots in a square formation appear above the middle of each name. Although Seasonique is slightly italicized, the names appear almost identical (see example below). We recommend removing the four dot logo and differentiating the names more prominently to ensure that the potential for confusion is minimized. In addition, both product labeling contains a raspberry, blue, green and white colored panel on the carton and pouch. Although the design layout of the primary display panel of Seasonique and Seasonale appears to be different, the colors apparent on the Seasonique panel may be a cognitive reminder to the health care provider that the product is Seasonale. Therefore, we recommend using an entirely different color scheme to differentiate these products.



2. DMETS does not have a sample of the proposed blister pack container for Seasonique. Therefore, we recommend significantly differentiating the color of the blister pack container in order to alert the user that the product is different from Seasonale.
3. The term "extended-cycle" is used on the blister label and carton labeling. DMETS is concerned the terminology "extended-cycle" implies these oral contraceptive tablets or dosing schedule provides an additional benefit over other oral contraceptive tablets or dosing schedules. DMETS recommends the removal of the terminology "extended-cycle".

B. BLISTER LABEL (Physician sample and Commercial product)

Please ensure the lot number and expiration date are located on the blister label.

C. CARTON LABELING (Physician sample and Commercial product)

See General Comment A1.

D. INSERT LABELING

See General Comment A3.

E. PATIENT PACKAGE INSERT

No comment.

In summary, DMETS does not recommend the use of the proprietary name, Seasonique as noted in ODS consult 04-0267 section III. Additionally, DDMAC has no objections to the name from a promotional perspective. DMETS recommends implementation of the label and labeling revisions outlined above. If you have any questions or need clarification, please contact Diane Smith, Project Manager, at 301-796-0538.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Director, Division of Medication Errors and Technical Support (DMETS), HFD-420 WO22, RM 4447		FROM: Jennifer Mercier Chief, Project Management Staff Division of Reproductive and Urologic Products		
DATE April 7, 2006	IND NO.	NDA NO. 21-840	TYPE OF DOCUMENT Resubmission	DATE OF DOCUMENT March 27, 2006
NAME OF DRUG Seasonique (levonorgestrel/ethinyl estradiol) Tablets		PRIORITY CONSIDERATION Rush	CLASSIFICATION OF DRUG	DESIRED COMPLETION DATE April 21, 2006
NAME OF FIRM: Duramed				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> MEETING PLANNED BY <input type="checkbox"/> PRE--NDA MEETING <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> PAPER NDA <input type="checkbox"/> CONTROL SUPPLEMENT <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW): Trade name review				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Please re-review the label, tradename, and container labels for the above application. This is a complete response and is a class 1 resubmission (2-month clock). PDUFA goal date: May 27, 2006. Please contact Jennifer Mercier if you have any questions 301-796-0957. All documents are located on the EDR.				
PDUFA DATE: 5-27-06 ATTACHMENTS: Draft Package Insert, Container and Carton Labels CC: Archival IND/NDA 21-840 HFD-580/Division File HFD-580/RPM HFD-580/Reviewers and Team Leaders				
NAME AND PHONE NUMBER OF REQUESTER Jennifer Mercier 301-796-0957		METHOD OF DELIVERY (Check one) <input checked="" type="checkbox"/> DFS ONLY <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER				

	SIGNATURE OF DELIVERER
--	------------------------

5/28/05

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/s/

Jennifer L. Mercier
4/7/2006 11:17:41 AM

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Mercier, Jennifer L

From: Best, Jeanine A
Sent: Thursday, April 06, 2006 2:28 PM
To: Mercier, Jennifer L
Subject: RE: NDA 21-840 Seasonique

Jen,
No, I do not need to see this one again. My original comments will suffice.

Jeanine

*Jeanine Best, MSN, RN, PNP
Patient Product Information Specialist
FDA/CDER/ODS/DSRCS
White Oak/Bldg. 22/Room 4472
Mail Stop 4447
phone 301-796-0086
fax 301-796-9836
jeanine.best@fda.hhs.gov*

From: Mercier, Jennifer L
Sent: Thursday, April 06, 2006 1:32 PM
To: Kulick, Corrinne; Best, Jeanine A
Subject: NDA 21-840 Seasonique

Corrine and Jeanine,

The sponsor has resubmitted to the approvable letter sent to them. The label they have submitted appears to be the same as what was submitted previously and reviewed by you. Do you want to do another review? Please let me know if I need to put in another consult.

Thanks,

Jen

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Memo to the file

Date: 4-5-06

NDA #: 21-840 Resubmission

Date of submission: 3-24-06

Sponsor: Duramed Research Inc.

Drug Product: Seasonique (levonogestrel/ethinyl estradiol and ethinyl estradiol)

Indication: oral contraceptive

Subject: Labeling review

Reviewer: Krishan L. Raheja, D.V.M., Ph.D.

Through P/T Supervisor: Lynnda Reid, Ph.D.

Regulatory action: The label for Seasonique is similar to Seasonale which was approved under NDA 21-544. Both Seasonale and Seasonique have same active ingredients i.e. 84 tablets containing 0.15 mg LNG and 0.03 mg of EE. The only difference is that whereas Seasonale has 7 inert tablets, Seasonique has 7 tablets containing 0.01 mg EE. No new P/T studies have been submitted. From the Pharmacology prospective labeling is adequate.

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/s/

Krishan L. Raheja
4/5/2006 12:04:56 PM
PHARMACOLOGIST

Yangmee Shin
4/5/2006 03:45:32 PM
PHARMACOLOGIST
Signed off for Lynnda Reid

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-840

Duramed Research, Inc.
Attention: Joseph Carrado, M.Sc., R.Ph.
Vice President, Clinical Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

We acknowledge receipt on March 27, 2006 of your March 24, 2006 resubmission to your new drug application for Seasonique™ (levonorgestrel/ethinyl estadiol) Tablets.

We consider this a complete, class 1 response to our August 17, 2005 action letter. Therefore, the user fee goal date is May 27, 2006.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

If you have any question, me at (301) 796-0957.

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-840

Duramed Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, MSc., RPh
Sr. Director, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SeasoniqueTM (levonorgestrel/ethinyl estradiol tablets and ethinyl estradiol tablets).

Your January 6, 2006, request for formal dispute resolution was received on January 6, 2006. The appeal concerned 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 per day of ethinyl estradiol to the previously hormone free period (HFP). You also requested a meeting with the Director, Office of New Drugs, to discuss this appeal.

In your appeal, you contend 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 meet or exceed the Agency's established standards for approval of a new hormonal contraceptive product, including a new molecular entity. You also contend that the requirement that an additional clinical study be completed to demonstrate a meaningful clinical benefit from the addition of estrogen during the hormone free period of your product, Seasonale, is unreasonable and unnecessary. In support of this conclusion you note the small absolute increase in the total exposure to estrogen, the favorable safety profile observed in your clinical trials completed to date using Seasonique¹, and the fact that in cross study comparisons it appears that Seasonique provides clinical benefit related to relief of symptoms during the previously HFP in comparison to Seasonale. You ask that the Agency withdraw its requirement for a new clinical study and immediately approve Seasonique for the proposed indication of prevention of pregnancy.

I have reviewed the information contained in your appeal and the information discussed at the February 16, 2006, meeting.² 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

¹ In your appeal you make reference to new safety data from a long-term extension of Study 304 that was submitted as an interim safety report to IND 63-735 on 1/12/06. Those new safety data have not been reviewed by the Agency and were not considered at the time of the original action on NDA 21-840. Accordingly, these new safety data were not considered in reviewing your appeal of the original action on NDA 21-840.

² Official minutes of that meeting are attached to this letter.

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.

Prior to approval it will be necessary for you to resubmit the application to the Division of Reproductive and Urology Products for further review. Your resubmission should provide an update of any new data related to the safety and effectiveness of Seasonique that were not a part of your original NDA. Your resubmission should also include a draft package insert and draft carton and container labeling for review. I recommend that you consult with the Division regarding the content and format of your resubmission in order to facilitate the Division's review of your application.

I note that in your appeal and in your presentations at the February 16, 2006, meeting you made reference to cross-study comparisons of Seasonique and Seasonale. While these comparisons are of interest for hypothesis generation, I concur with the Division's advice from the pre-NDA meeting that these data are not adequate to support labeling or advertising claims regarding the clinical significance of the 7 days of additional ethinyl estradiol during the previously HFP.

If you have any questions regarding this decision, please call Nenita Crisostomo, Regulatory Project Manager, Division of Reproductive and Urologic Products at (301) 796-2130.

Sincerely,

{See appended electronic signature page}

John K. Jenkins, M.D., F.C.C.P.
Director
Office of New Drugs
Center for Drug Evaluation and Research

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Meeting Minutes

Meeting Date: February 16, 2006

Type of Meeting: Formal Dispute Resolution

NDA Application: 21-840

Product: Seasonique™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol tablets)

Sponsor: Duramed Research, Inc.

Formal Dispute Resolution Request Date/Received: January 6, 2006

Meeting Chair: John Jenkins, M.D.

Meeting Recorder: Kim Colangelo

Attendees:

Office of New Drugs

John Jenkins, M.D.	Director, Office of New Drugs (OND)
Kim Colangelo	Associate Director for Regulatory Affairs, OND
Robert Temple, M.D.	Associate Director, Office of Medical Policy
Julie Beitz, M.D.	Acting Director, Office of Drug Evaluation III
Daniel Shames, M.D.	Director, Division of Reproductive and Urologic Products (DRUP)
Scott Monroe, M.D.	Deputy Director, DRUP
Shelley Slaughter, M.D.	Clinical Team Leader, DRUP
Lisa Soule, M.D.	Clinical Team Leader, DRUP
Ronald Orleans, M.D.	Medical Officer, DRUP
Phill Price, M.D.	Medical Officer, DRUP
Jennifer Mercier	Chief, Project Management Staff, DRUP
Edward Nevius, Ph.D.	Director, Division of Biometrics II (DBII)
Sonia Castillo, Ph.D.	Statistician, DBII

Duramed Research, Inc.

Carole Ben-Maimon, M.D.	President/COO
Joseph Carrado, M.Sc., R.Ph.	Vice President, Regulatory Affairs
Howard Hait	Vice President, Data Management and Biostatistics
Wayne Mulcahy, Ph.D.	Vice President, Clinical Operations
Kathleen Reape, M.D.	Senior Director, Clinical Operations
Michele Walsh	Manager, Regulatory Affairs

BACKGROUND

On October 21, 2004, Duramed Research, Inc. ("Duramed"), submitted the above referenced New Drug Application (NDA) requesting marketing approval for Seasonique for the prevention of pregnancy. Seasonique is an extended-regimen oral contraceptive that includes 10 micrograms of ethinyl estradiol (EE) during the previously hormone free (7-day) interval. An Approvable letter was issued on August 17, 2005, by the Division of Reproductive and Urologic Drug Products (DRUP). The letter requested an additional randomized controlled clinical trial comparing Seasonique to Seasonale® to demonstrate a clinically meaningful benefit of the addition of the EE to the previously hormone free period.

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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 cycle control, 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 agreeing with the 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. This appeal is the subject of this meeting.

DISCUSSION

Duramed provided a presentation (attached). The presentation summarized the data submitted 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 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 the data did in fact demonstrate a benefit of the addition of the EE to the hormone free interval.

In addition, Duramed shared data from a long-term extension study (Study 304) providing additional data on 317 patients. An interim safety report was 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 will not be considered as part of this appeal.]

Rationale for the addition of ethinyl estradiol

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Safety of added ethinyl estradiol

Approved oral contraceptives on the market deliver incremental doses of EE: Seasonale delivers 10.08 mg EE per year, while Nordette (comparator studied in PSE-302, a safety study submitted in the Seasonique NDA), delivers approximately 8 mg EE per year. The Seasonique regimen delivers 10.36 mg EE per year.

There was a 50% drop-out rate of women taking Seasonique during the clinical trials. Duramed stated that according to literature and publicly available information, a drop-out rate of 40-60% is standard for pregnancy prevention trials. DRUP requested further documentation of these figures. In addition, Duramed reported that most women dropped out of the trials for "other reasons", while ~7% dropped out due to bleeding.

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Duramed indicated their understanding that there could be no claims for added benefit of EE to the previously hormone free interval based on the trials conducted, and that the labeling claims would be similar to Seasonale at this time. They did acknowledge that they do plan

Cross-study comparisons of efficacy as measured by the Pearl Index

Cross-study comparisons of the Pearl Index were provided. All studies were conducted in the United States in women ages 18-35, for a period of one year. The same inclusion and exclusion criteria were utilized in each. In addition, the same clinical study sites were used for Seasonale and Seasonique, and the same Duramed statistician analyzed the data. Differences between the trials include the type of electronic diaries used, and the use of alternative forms of birth control.

SUMMARY

The decision regarding this appeal will 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.

A decision on this appeal will issue from Dr. Jenkins by March 17, 2006.

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 Deliberative Process

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John Jenkins

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-840

Duramed Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, MSc., RPh
Sr. Director, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SeasoniqueTM (levonorgestrel/ethinyl estradiol tablets and ethinyl estradiol tablets).

We refer also to your January 6, 2006, request for formal dispute resolution received on January 6, 2006. The appeal concerned 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 ethinyl estradiol to the previously hormone free period. You also requested a meeting with the Director, Office of New Drugs to discuss this appeal.

As per our discussion on January 27, 2006, we have granted this meeting to be held on February 16, 2006. The meeting will be held from 2:30 p.m. – 4:00 p.m., at 10903 New Hampshire Avenue, Silver Spring, MD, White Oak Conference Room 1419, Building 22. Attendees at this meeting will include representatives from the Office of New Drugs, Office of Drug Evaluation III, and the Division of Reproductive and Urologic Products.

Pursuant to the CDER/CBER Guidance for Industry "Formal Dispute Resolution: Appeals Above the Division Level" we will have thirty calendar days from the date of the meeting to respond to your appeal, so long as we do not find it necessary to request additional information from you. If no additional information is requested, our response to you will be sent on or before March 17, 2006. If additional information is requested, our response will issue within 30 calendar days of the receipt of the requested information.

If you have any questions, please call me at (301) 796-0140.

Sincerely,

{See appended electronic signature page}

Kim Colangelo
Associate Director for Regulatory Affairs
Office of New Drugs
Center for Drug Evaluation and Research

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Kim Colangelo
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-840

Duramed Research, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Vice President, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Seasonique™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets.

We also refer to your December 14, 2005, correspondence containing your proposed revision to the November 9, 2005, teleconference minutes (second to the last paragraph) as follows:

From:

“Duramed does not wish to dispute the issue further and believes that it has the data to demonstrate improved cycle control.”

To:

“It is Duramed’s preference not to further pursue Dispute Resolution at this time, as they believe they have the data to demonstrate a meaningful clinical benefit.”

We have completed our review of your submission and we agree with your revision. Our records will be revised accordingly.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Health Project Manager at 301-796-2130.

Sincerely,

{See appended electronic signature page}

Julie Beitz, M.D.
Acting Director,
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Julie Beitz

1/17/2006 03:13:52 PM

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-840

Duramed Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Senior Director, Regulatory Affairs
One Belmont Ave., 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SeasoniqueTM (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets.

We also refer to the guidance meeting between representatives of your firm and the FDA on December 6, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Nenita Crisostomo, R.N., Regulatory Project Manager, at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: December 6, 2005
TIME: 1:15 – 2:10 PM
LOCATION: Teleconference
SPONSOR: Duramed Pharmaceuticals, Inc.
APPLICATION: NDA 21-840
DRUG NAME: Seasonique™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets
TYPE OF MEETING: Type A - Guidance for resubmission
MEETING CHAIR: Daniel Shames, M.D. - Director, Division of Reproductive and Urologic Products (DRUP)
MEETING RECORDER: Karen Kirchberg, N.P. - Regulatory Project Manager, DRUP

FDA ATTENDEES:

Daniel Shames, M.D. - Director, DRUP
Scott Monroe, M.D. - Acting Deputy Director, DRUP
Shelley R. Slaughter, M.D., Ph.D. - Medical Team Leader, DRUP
Phill Price, M.D. - Medical Officer, DRUP
Jennifer Mercier - Chief, Project Management Staff, DRUP
Karen Kirchberg, N.P. - Project Manager, DRUP
Nenita Crisostomo, R.N. - Project Manager, DRUP

BARR/DURAMED ATTENDEES:

Carole Ben-Maimon, M.D. - President and COO
Joseph Carrado, M.Sc., R.Ph. - Senior Director, Regulatory Affairs
Howard Hait, M.S. - Vice President, Biostatistics and Data Management
Kathleen Reape, M.D. - Director, Clinical Operations
Wayne Mulcahy, Ph.D. - Vice President, Clinical Operations

BACKGROUND:

NDA 21-840 for Seasonique was submitted October 21, 2004. Seasonique is an extended oral contraceptive dosing regimen consisting of 150 micrograms levonorgestrel and 30 micrograms ethinyl estradiol tablets administered for 84 days and 10 micrograms ethinyl estradiol tablets administered for 7 days (days 85-91). The application received an approvable action; letter dated August 17, 2005. The sponsor requested an end-of-review meeting with the Division and that was held September 29, 2005. Following the meeting, Duramed filed a dispute resolution request with the Agency. A letter, dated November 9, 2005, sent to Duramed from Dr. Florence Houn, Director, Office of Drug Evaluation III, upheld the Division's Approvable action. Duramed has requested a guidance meeting to discuss the approvable action and their proposal for a path forward.

MEETING OBJECTIVES:

To discuss a path forward. The following proposal was submitted to the Division for consideration:

1. Comparative analysis of the Clinical Data from Seasonique Studies PSE-301 and PSE-302 and the Clinical Trial data from Seasonale Study 301.
2. Results from Clinical Study PSE-312.
3. Additional Safety Data from the Ongoing Seasonique PSE-304 Clinical Study.

DISCUSSION SUMMARY:

FDA/DRUP: The proposal as submitted would not constitute a complete response to the Approvable (AE) action. The Division would agree to one of the following options:

1. A Seasonique/Seasonale cross comparison, randomized, controlled study to demonstrate _____ for Seasonique.
2. A Seasonique /Seasonale cross comparison, randomized, controlled efficacy study to demonstrate a decreased pregnancy rate in Seasonique users.
3. _____

It was also noted that the Sponsor has the option of continuing with their dispute resolution.

Duramed proposed the option of a _____
 _____ The Division responded that the surrogate endpoints of _____
 _____ are not acceptable to justify the increase in exposure to ethinyl estradiol associated with the use of Seasonique. The Division will only accept a decrease in pregnancy rates as the endpoint.

ACTION ITEMS:

- Sponsor to send in study synopsis for two additional studies in support of a complete response.
- Sponsor will send in references mentioned in the meeting package.
- Division to discuss the theoretical questions posed in the meeting.
- Meeting Minutes to the Sponsor by January 6, 2006.

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Concurrence by:

{see appended electronic signature}

Daniel Shames, M.D.
Director

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/s/

Jennifer L. Mercier
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MEMORANDUM

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

DATE: January 5, 2006

TO: NDA 21-840

FROM: Maria R. Walsh, RN, MS
Project Management Officer
Office of Drug Evaluation III

SUBJECT: **Revision to November 9, 2005 Teleconference Minutes**
NDA 21-840, Seasonique (levonorgestrel/ethinyl estradiol and
ethinyl estradiol) Tablets

Duramed Pharmaceuticals, Inc. submitted a formal dispute resolution request (FDR) on October 11, 2005 regarding the approvable action for NDA 21-840 taken on August 17, 2005. A teleconference between representatives of Duramed and the Office of Drug Evaluation III (ODE III) was held on November 9, 2005 to discuss the issues presented in the FDR. The minutes of the teleconference were finalized on November 14, 2005 and sent to the sponsor on November 17, 2005 (see minutes below).

The sponsor proposed the following revision to the minutes (second to the last paragraph) in a submission dated December 14, 2005:

From:

“Duramed does not wish to dispute the issue further and believes that it has the data to demonstrate improved cycle control.”

To:

“It is Duramed’s preference not to further pursue Dispute Resolution at this time, as they believe they have the data to demonstrate a meaningful clinical benefit.”

This proposed revision was reviewed by Dr. Florence Houn, Director, ODE III, and is acceptable.

MEMORANDUM OF TELECON

DATE: November 9, 2005

APPLICATION NUMBER: NDA 21-480

DRUG NAME: Seasonique (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets

BETWEEN:

Duramed Pharmaceuticals, Inc.

Carol Ben-Manion, President

Joseph A. Carrado, MSc, RPh, Senior Director, Regulatory Affairs

AND:

FDA:

Office of Drug Evaluation III

Florence Houn, MD, Director

Maria R. Walsh, RN, MS, Project Management Officer

SUBJECT: Response to the Formal Dispute Resolution Request

BACKGROUND: NDA 21-480, Seasonique (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets, was submitted on October 21, 2004 for prevention of pregnancy. The sponsor proposed an extended cycle contraceptive regimen (91 days) consisting of 150 mcgs levonorgestrel and 30 mcgs ethinyl estradiol administered for 84 days and 10 mcgs ethinyl estradiol administered on days 85-91. An approvable letter was issued on August 17, 2005 recommending that a randomized controlled clinical trial be conducted to demonstrate that the addition of 10 mcgs of ethinyl estradiol on days 85-91 compared to the exact same regimen that has placebo during days 85-91 (approved in the sponsor's NDA for Seasonale) provides a meaningful clinical benefit, such as _____

Duramed Pharmaceuticals, Inc. submitted a formal dispute resolution request on October 11, 2005 which states the following:

1. Approval standards for efficacy of an oral contraceptive to show adequate pregnancy prevention have been met.
2. The safety database of 1,100 women treated for four 91-day cycles (one year), did not raise any increased risk of endometrial hyperplasia or increased risk of venous thromboembolism.
3. Previously approved Mircette has 5 days of 10 mcg of unopposed estrogen and 2 days of hormone free interval.
4. FDA has never required a sponsor of contraceptives to demonstrate a meaningful clinical benefit beyond contraception, that this is a novel approval standard that exceeds the Agency's statutory authority and is arbitrary and capricious. In fact, Duramed stated on

September 29, 2005 that a clinically meaningful benefit of Seasonique over Seasonale was demonstrated relative to bleeding and/or spotting.

The response to the formal dispute resolution request was issued to the sponsor today. A copy of the letter was sent to the sponsor via facsimile before this teleconference.

TODAY'S CALL:

Ms. Ben-Manion made the following points:

- During the pre-IND meeting in September 2001, the Division of Neuropharmacological Drug Products advised Duramed that ~~the Division was unable to provide a definition of "meaningful clinical benefit."~~
~~the Division did not provide any clear direction.~~
- During the pre-NDA meeting on August 30, 2004, the Division of Reproductive and Urologic Drug Products did not raise any objections to Duramed's proposal to submit an NDA for Seasonique for the prevention of pregnancy nor to the addition of 7 days of ethinyl estradiol.
- It wasn't until the issuance of the 74-day filing communication letter that Duramed was informed that the Division would be looking at whether the addition of 7 days of ethinyl estradiol provides sufficient clinical benefit to justify risk.
- After the issuance of the 74-day letter, Duramed contacted the Division several times with questions but was unable to obtain a substantive response about how to address the concern regarding clinical benefit of the additional ethinyl estradiol. It wasn't until June 2005, two months before the due date, that Duramed spoke to the Division Director on the phone and received a short facsimile on June 20, 2005 requesting clinical trial data comparing Seasonique to Seasonale. If Duramed was aware of the Division's information request early in the review cycle, it may have been able to address the concern before the action letter was issued.
- Pharmacokinetic data provided in the NDA for Seasonique demonstrated that low dose unopposed ethinyl estradiol monotherapy following active combination therapy suppresses hormone levels.
- The clinical trials demonstrated a lower overall Pearl Index for Seasonique as compared to Seasonale with less occurrences of pregnancy in the first four weeks (one for Seasonique versus six for Seasonale, three of which were due to non-compliance).
- During the End-of Review meeting on September 29, 2005, the Division was unable to provide a definition of "meaningful clinical benefit." Although Duramed proposed ~~the Division did not provide any clear direction.~~

Dr. Houn said Duramed has three options: 1) dispute further; 2) discuss at an Advisory Committee (AC) meeting; 3) provide information to support a clinically meaningful benefit. Ms. Ben-Manion said Duramed wishes to obtain approval in a timely fashion. Since Duramed was told by the Division that an AC meeting could not be scheduled for 6-12 months, this option is not acceptable. Duramed does not wish to dispute the issue further and believes that it has the

Dr. Houn recommended that the easiest path forward is for Duramed to request a telecon with the Division Director and Acting Deputy Division Director to discuss ideas on demonstrating a clinically meaningful benefit and then make a proposal in writing and request a meeting with the Division and the Office Director. Duramed agreed with this plan.

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/s/

Maria Walsh
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: 11.23.05

To: Joe Carrado

From: Karen Kirchberg, NP

Duramed Pharmaceuticals, Inc.

Division of Reproductive and Urologic
Drug Products

Fax number: (610) 747-6607

Fax number: (301) 796-9897

Phone number: (610) 747-2910

Phone number: (301) 796-0933

Subject: Seasonique MM 11.09.05

Total no. of pages including cover: 3

Document to be mailed: YES

Comments:

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**Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III**

FACSIMILE TRANSMITTAL SHEET

DATE: 11.23.05

To: Joe Carrado	From: Karen Kirchberg, NP
Duramed Pharmaceuticals, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: (610) 747-6607	Fax number: (301) 796-9897
Phone number: (610) 747-2910	Phone number: (301) 796-0933
Subject: Seasonique MM 11.09.05	

Total no. of pages including cover: 3

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-840

Duramed Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Senior Director, Regulatory Affairs
One Belmont Ave., 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your Investigational New Drug Application (IND submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seasonique™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets.

We also refer to your November 10, 2005, correspondence, received November 11, 2005, requesting a guidance meeting.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type C meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: Tuesday, December 6, 2005
Time: 1:15 – 2:15 PM
Location: Telephone conference (please provide a conference call in number)

CDER, Division of Reproductive and Urologic Products (DRUP) invited participants:
Florence Houn, M.D. – Director, Office of Drug Evaluation III
Daniel Shames, M.D. – Director
Scott Monroe, M.D. – Acting Deputy Director
Shelley Slaughter, M.D., Ph.D. - Medical Team Leader
Jennifer Mercier - Chief, Project Management Staff
Karen Kirchberg, N.P. - Project Manager

Any background information for this meeting should be sent at least 2 weeks prior to the meeting. If possible, we would like to receive the package by November 30, 2005. The Division move is scheduled for September 15 and 16.

NDA 21-840
Page 2

The mailing address for your meeting package is:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me at (301) 796-0933.

Sincerely,

(See appended electronic signature page)

Karen Kirchberg, N.P.
Project Manager
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Karen Kirchberg
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-840

Duramed Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, MSc, RPh
Senior Director, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SeasoniqueTM (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets.

We also refer to the teleconference between representatives of your firm and the FDA on November 9, 2005. The purpose of the teleconference was to discuss your October 11, 2005 formal dispute resolution request.

The official minutes of that teleconference are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the teleconference outcomes.

If you have any questions, call Karen Kirchberg, Regulatory Project Manager, at (301) 796-0933.

Sincerely,

{See appended electronic signature page}

Maria R. Walsh, RN, MS
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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MEMORANDUM OF TELECON

DATE: November 9, 2005

APPLICATION NUMBER: NDA 21-840

DRUG NAME: Seasonique (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets

BETWEEN:

Duramed Pharmaceuticals, Inc.

Carol Ben-Manion, President

Joseph A. Carrado, MSc, RPh, Senior Director, Regulatory Affairs

AND:

FDA:

Office of Drug Evaluation III

Florence Houn, MD, Director

Maria R. Walsh, RN, MS, Project Management Officer

SUBJECT: Response to the Formal Dispute Resolution Request

BACKGROUND: NDA 21-840, Seasonique (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets, was submitted on October 21, 2004 for prevention of pregnancy. The sponsor proposed an extended cycle contraceptive regimen (91 days) consisting of 150 mcgs levonorgestrel and 30 mcgs ethinyl estradiol administered for 84 days and 10 mcgs ethinyl estradiol administered on days 85-91. An approvable letter was issued on August 17, 2005 recommending that a randomized controlled clinical trial be conducted to demonstrate that the addition of 10 mcgs of ethinyl estradiol on days 85-91 compared to the exact same regimen that has placebo during days 85-91 (approved in the sponsor's NDA for Seasonale) provides a meaningful clinical benefit, such as _____

Duramed Pharmaceuticals, Inc. submitted a formal dispute resolution request on October 11, 2005 which states the following:

1. Approval standards for efficacy of an oral contraceptive to show adequate pregnancy prevention have been met.
2. The safety database of 1,100 women treated for four 91-day cycles (one year), did not raise any increased risk of endometrial hyperplasia or increased risk of venous thromboembolism.
3. Previously approved Mircette has 5 days of 10 mcg of unopposed estrogen and 2 days of hormone free interval.
4. FDA has never required a sponsor of contraceptives to demonstrate a meaningful clinical benefit beyond contraception, that this is a novel approval standard that exceeds the Agency's statutory authority and is arbitrary and capricious. In fact, Duramed stated on September 29, 2005 that a clinically meaningful benefit of Seasonique over Seasonale was demonstrated relative to bleeding and/or spotting.

The response to the formal dispute resolution request was issued to the sponsor today. A copy of the letter was sent to the sponsor via facsimile before this teleconference.

TODAY'S CALL:

Ms. Ben-Manion made the following points:

- During the pre-IND meeting in September 2001, the Division of Neuropharmacological Drug Products advised Duramed that _____
- During the pre-NDA meeting on August 30, 2004, the Division of Reproductive and Urologic Drug Products did not raise any objections to Duramed's proposal to submit an NDA for Seasonique for the prevention of pregnancy nor to the addition of 7 days of ethinyl estradiol.
- It wasn't until the issuance of the 74-day filing communication letter that Duramed was informed that the Division would be looking at whether the addition of 7 days of ethinyl estradiol provides sufficient clinical benefit to justify risk.
- After the issuance of the 74-day letter, Duramed contacted the Division several times with questions but was unable to obtain a substantive response about how to address the concern regarding clinical benefit of the additional ethinyl estradiol. It wasn't until June 2005, two months before the due date, that Duramed spoke to the Division Director on the phone and received a short facsimile on June 20, 2005 requesting clinical trial data comparing Seasonique to Seasonale. If Duramed was aware of the Division's information request early in the review cycle, it may have been able to address the concern before the action letter was issued.
- Pharmacokinetic data provided in the NDA for Seasonique demonstrated that low dose unopposed ethinyl estradiol monotherapy following active combination therapy suppresses hormone levels.
- The clinical trials demonstrated a lower overall Pearl Index for Seasonique as compared to Seasonale with less occurrences of pregnancy in the first four weeks (one for Seasonique versus six for Seasonale, three of which were due to non-compliance).
- During the End-of Review meeting on September 29, 2005, the Division was unable to provide a definition of "meaningful clinical benefit." Although Duramed proposed _____
the Division did not provide any clear direction.

Dr. Houn said Duramed has three options: 1) dispute further; 2) discuss at an Advisory Committee (AC) meeting; 3) provide information to support a clinically meaningful benefit. Ms. Ben-Manion said Duramed wishes to obtain approval in a timely fashion. Since Duramed was told by the Division that an AC meeting could not be scheduled for 6-12 months, this option is not acceptable. Duramed does not wish to dispute the issue further and believes that it has the _____

Dr. Houn recommended that the easiest path forward is for Duramed to request a telecon with the Division Director and Acting Deputy Division Director to discuss ideas on demonstrating a clinically meaningful benefit and then make a proposal in writing and request a meeting with the Division and the Office Director. Duramed agreed with this plan.

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/s/

Maria Walsh
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MEMORANDUM OF TELECON

DATE: November 9, 2005

APPLICATION NUMBER: NDA 21-480

DRUG NAME: Seasonique (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets

BETWEEN:

Duramed Pharmaceuticals, Inc.

Carol Ben-Manion, President

Joseph A. Carrado, MSc, RPh, Senior Director, Regulatory Affairs

AND:

FDA:

Office of Drug Evaluation III

Florence Houn, MD, Director

Maria R. Walsh, RN, MS, Project Management Officer

SUBJECT: Response to the Formal Dispute Resolution Request

BACKGROUND: NDA 21-480, Seasonique (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets, was submitted on October 21, 2004 for prevention of pregnancy. The sponsor proposed an extended cycle contraceptive regimen (91 days) consisting of 150 mcgs levonorgestrel and 30 mcgs ethinyl estradiol administered for 84 days and 10 mcgs ethinyl estradiol administered on days 85-91. An approvable letter was issued on August 17, 2005 recommending that a randomized controlled clinical trial be conducted to demonstrate that the addition of 10 mcgs of ethinyl estradiol on days 85-91 compared to the exact same regimen that has placebo during days 85-91 (approved in the sponsor's NDA for Seasonale) provides a meaningful clinical benefit, such as improved cycle control or clinically significant ovulation suppression.

Duramed Pharmaceuticals, Inc. submitted a formal dispute resolution request on October 11, 2005 which states the following:

1. Approval standards for efficacy of an oral contraceptive to show adequate pregnancy prevention have been met.
2. The safety database of 1,100 women treated for four 91-day cycles (one year), did not raise any increased risk of endometrial hyperplasia or increased risk of venous thromboembolism.
3. Previously approved Mircette has 5 days of 10 mcg of unopposed estrogen and 2 days of hormone free interval.
4. FDA has never required a sponsor of contraceptives to demonstrate a meaningful clinical benefit beyond contraception, that this is a novel approval standard that exceeds the Agency's statutory authority and is arbitrary and capricious. In fact, Duramed stated on

the Division did not provide any clear direction.

Dr. Houn said Duramed has three options: 1) dispute further; 2) discuss at an Advisory Committee (AC) meeting; 3) provide information to support a clinically meaningful benefit. Ms. Ben-Manion said Duramed wishes to obtain approval in a timely fashion. Since Duramed was told by the Division that an AC meeting could not be scheduled for 6-12 months, this option is not acceptable. Duramed does not wish to dispute the issue further and believes that it has the

Dr. Houn recommended that the easiest path forward is for Duramed to request a telecon with the Division Director and Acting Deputy Division Director to discuss ideas on demonstrating a clinically meaningful benefit and then make a proposal in writing and request a meeting with the Division and the Office Director. Duramed agreed with this plan.

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/s/

Florence Houn
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-480

Duramed Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, MSc, RPh
Senior Director, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

We refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SeasoniqueTM (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets.

Your October 11, 2005 request for formal dispute resolution, received on October 11, 2005, concerned the decision by the Division of Reproductive and Urologic Products to not approve your NDA for marketing.

I have reviewed your arguments against the approvable letter issued on August 17, 2005 by the Division of Reproductive and Urologic Products for NDA 21-840 Seasonique (levonorgestrel/ethinyl estradiol and ethinyl estradiol tablets).

In the Division's approvable letter, the deficiency is stated as:

The application for the Seasonique extended cycle contraceptive regimen (consisting of 150 mcg of levonorgestrel and 30 mcg of ethinyl estradiol [EE] administered for 84 days and 10 mcg of EE administered for days 85-91) did not provide clinical trial data that demonstrated benefit of the addition of 10 mcg EE 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 [approved as Seasonale, Duramed Research, Inc.]. 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.

You dispute this finding and state that:

1. Approval standards for efficacy of an oral contraceptive to show adequate pregnancy prevention have been met.
2. The safety database of 1,100 women treated for four 91-day cycles (one year), did not raise any increased risk of endometrial hyperplasia or increased risk of venous thromboembolism.
3. Previously approved Mircette has 5 days of 10 mcg of unopposed estrogen and 2 days of hormone free interval.
4. FDA has never required a sponsor of contraceptives to demonstrate a meaningful clinical benefit beyond contraception, that this is a novel approval standard that exceeds the Agency's

statutory authority and is arbitrary and capricious. In fact, Duramed stated on September 29, 2005 that a clinically meaningful benefit of Seasonique over Seasonale was demonstrated relative to bleeding and/or spotting.

Issue 1: Efficacy has been met for pregnancy prevention

Pregnancy prevention efficacy was found acceptable for Seasonale (150 mcg levonorgesterol/30 mcg EE for 84 days followed by 7 days of inactive on days 85-91). Seasonique is identical to Seasonale, except Seasonique has 7 days of 10 mcg of EE, an active prescription drug, replacing the 7 days of inactive on days 85-91. It is unclear what purpose the EE tablets on days 85 to 91 serves as these active tablets are NOT needed for pregnancy prevention. The efficacy evidence in the Seasonale NDA demonstrates this. Your claim that the Seasonique regimen has 7 days of active EE for pregnancy prevention appears to be inconsistent. Given the known risks of estrogens, you have been asked to demonstrate what contribution the active tablets of EE are providing women in terms of increased pregnancy prevention or other clinically meaningful benefit.

Issue 2: Safety database is acceptable showing the extra EE is safe

Estrogens increase risk of venous thromboembolic events and they are also tumor promoters. There are other adverse events associated with exogenous estrogens. We do not know a "threshold" no effect dose of EE. All drugs have their safety profile balanced against their benefits. You have not established the benefit of the increased EE in Seasonique. It may be argued that the safety database was not large enough to detect changes in risk from the increased EE.

Issue 3: Mircette has 5 days of unopposed estrogen and 2 days of hormone-free interval

The sponsor misinterprets the Division's concern to be primarily about unopposed estrogen with Seasonique. The major concern is that you are proposing increased EE exposure in women compared to Seasonale, not that EE is unopposed. The Division and manufacturers, along with global public health agencies, for over 30 years, have been trying to lower the exposure to hormones in contraceptives for young, reproductive women.

Mircette was approved with a progestin that was also a new molecular entity (NME). As with all NMEs, after limited Phase 2 dose-ranging studies, a dose (or doses) that is most likely to demonstrate efficacy is selected to advance in Phase 3. Such doses are oftentimes at exposure levels ensuring efficacy, not minimization of drug effects. For Mircette, no higher exposure for the desogesterol/EE has been approved after the initial approval.

Seasonale is the first and only approved extended cycle 91 day oral contraceptive regimen. Although there is higher exposure compared to many 21 day regimens due to absent hormone-free days for 3 months, once dropouts occur due to undesirable break-through bleeding from this regimen, the subset of patients remaining has a benefit of absent menstrual bleeding for 3 months. It is this convenience that FDA accepts in exchange for the higher cumulative hormone exposure for the approval of Seasonale. Seasonique offers more exposure to EE than Seasonale for the same 91 day regimen without evidence of a benefit for this increased exposure.

NMEs and new methods of hormonal delivery as well as new regimens are approved with careful consideration of the risks and benefits these new agents pose. Seasonique does not provide a novel molecular entity, novel delivery, or novel regimen, but a variant of Seasonale, with added EE exposure instead of 7 days of placebo. The present Division members could not identify a sponsor of a modern,

approved contraceptive that has subsequently sought higher EE exposure once their product has been approved. The sole exception is Duramed, after approval of your Seasonale, seeking to increase EE exposure with Seasonique.

Issue 4: FDA has never required a sponsor of contraceptives to demonstrate a meaningful clinical benefit beyond contraception. This is a novel standard that exceeds the Agency's statutory authority and is arbitrary and capricious. Nevertheless, Duramed stated on September 29, 2005 that a clinically meaningful benefit of Seasonique over Seasonale was demonstrated relative to bleeding and/or spotting.

This is untrue. Because the information is non-public, I cannot disclose many details other than to say that the Division's action on your NDA with its proposed increase in hormone exposure over an approved regimen, without data-demonstrated benefit to justify the addition, is justified and consistent with prior actions. The action is also consistent with FDA simultaneously having data for an approved contraceptive regimen for pregnancy prevention at a dose lower than an alternative regimen with higher exposure that is being considered for approval.

I disagree with your statements that FDA cannot require demonstration of a clinically meaningful benefit beyond contraception for the added EE. If sponsors of daily oral contraceptives were to insert during the "off week" one half to one-third the approved dose of an active prescription drug, say an SSRI, on the belief that these quantities are safe and the sponsors claim such a regimen is for pregnancy prevention, FDA can require demonstration of an additional benefit or purpose for such insertions of an active new drug. In your case, you claim you've added EE for 7 days for pregnancy prevention when data from you're your own Seasonale application shows contraception is acceptable without the added 7 days of EE exposure.

Unfortunately, while science has advanced in many respects, it seems our knowledge of sex hormones and their health effects are still actively evolving. For the same indication of pregnancy prevention, you are proposing addition of active prescription drug for 7 days each 91-day cycle, when a safe and effective approved regimen of the exact same drug products now has placebo for those 7 days. It is logical to ask what health or convenience benefit the extra active drug contributes and that this benefit is evidenced in the data. In fact, Duramed stated on September 29, 2005 that

Your cross trial data comparisons between Seasonale and Seasonique may be suggestive, but this claim needs validation in a head-to-head comparative trial.

You have been offered an Advisory Committee discussion to review your extended-cycle regimens and whether existing data already demonstrate the benefit of the added EE. I find that our guidance materials you've cited are outdated and this extremely important area of contraceptive drug development should be publicly aired regarding efficacy and safety standards. I have asked the Division of Reproductive and Urologic Products to work on updating Agency guidance on contraceptive clinical trials for future public discussion and I thank you for bringing this to my attention.

NDA 21-840

Page 4

In summary, I agree with the Division's decision that Seasonique's 7 extra days of 10 mcg of EE needs clinical justification, when there is a lower dose regimen approved that is safe and effective. Dose-dependent side effects are known with estrogens. Given my review of the record, I deny your appeal.

If you have any questions, call Kim Colangelo, Formal Dispute Resolution Project Manager, at (301) 796-0140.

Sincerely,

{See appended electronic signature page}

Florence Houn, MD, MPH
Director
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Florence Houn
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-840

Duramed Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Senior Director, Regulatory Affairs
One Belmont Ave., 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seasonique™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets.

We also refer to the end-of-review meeting between representatives of your firm and the FDA on September 29, 2005.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Karen Kirchberg, N.P., Regulatory Project Manager, at (301) 796-0933.

Sincerely,

{See appended electronic signature page}

Daniel Shames, M.D.
Director
Division of Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure

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MEMORANDUM OF MEETING MINUTES

MEETING DATE: September 29, 2005
TIME: 1:00 – 2:30 PM
LOCATION: FDA White Oak Campus, Building 22, Conference Room 1309
SPONSOR: Duramed Pharmaceuticals, Inc.
APPLICATION: NDA 21-840
DRUG NAME: Seasonique™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets
TYPE OF MEETING: Type A, End-of-Review
MEETING CHAIR: Daniel Shames, M.D. - Director, Division of Reproductive and Urologic Products (DRUP)
MEETING RECORDER: Karen Kirchberg, N.P. - Regulatory Project Manager, DRUP

FDA ATTENDEES:

Daniel Shames, M.D. - Director, DRUP
Shelley R. Slaughter, M.D., Ph.D. - Medical Team Leader, DRUP
Lisa Soule, M.D. - Acting Medical Team Leader, DRUP
Jennifer Mercier - Chief, Project Management Staff, DRUP
Ronald Orleans, M.D. - Medical Officer, DRUP
Phill Price, M.D. - Medical Officer, DRUP
Audrey Gassman, M.D. - Medical Officer, DRUP
Karen Kirchberg, N.P. - Project Manager, DRUP

BARR/DURAMED ATTENDEES:

Carole Ben-Maimon, M.D. - President and COO
Joseph Carrado, M.Sc., R.Ph. - Senior Director, Regulatory Affairs
Howard Hait, M.S. - Vice President, Biostatistics and Data Management
Wayne Mulcahy, Ph.D. - Vice President, Clinical Operations
Kathleen Reape, M.D. - Director, Clinical Operations
Michele Walsh, B.S. - Manager, Regulatory Affairs

BACKGROUND: NDA 21-840 for Seasonique™ was submitted October 21, 2004. Seasonique™ is an extended oral contraceptive regimen consisting of 150 micrograms levonorgestrel and 30 micrograms ethinyl estradiol administered for 84 days and 10 micrograms ethinyl estradiol administered for days 85-91. The application received an approvable letter dated August 17, 2005. The sponsor requested an End-of-Review meeting to discuss the approvable action.

MEETING OBJECTIVES: To discuss the scientific and regulatory issues surrounding this application and the approvable action.

DISCUSSION SUMMARY:

The sponsor gave a presentation covering the precedence for continuous use oral contraceptive products in support of an approval action for the Seasonique™ product. The Sponsor requested approval of the application based on the following points:

- Clinical data meeting the longstanding approval standard for safe and effective oral contraceptives.
- Clinical data in the application is consistent with clinical data submission accepted by FDA for all other recently approved oral contraceptives
- Not to approve the application would be inconsistent with FDA's legal and regulatory requirements.
- The Sponsor has demonstrated adequately that the product provides sufficient meaningful clinical benefit to prevent pregnancy and improve cycle control with no evidence of an increase safety risk.

The Division reiterated its opinion that this application did not sufficiently address the added ethinyl estradiol to days 85-91 in the submission.

The Division also stated that it has never approved an application with an increased dose of an already approved drug product without showing additional benefit for that increase.

The Division acknowledged the Sponsor's position and offered the following options:

- Hold an Advisory Committee meeting either on the application or the concept topic of continuous use oral contraceptives.
- Conduct a randomized controlled clinical trial demonstrating the clinically meaningful benefit of adding 10 micrograms of ethinyl estradiol to the previously hormone-free week of placebo pills.
- Follow one of the options under 21 CFR 314.110.

ACTION ITEMS:

- The sponsor will follow-up with one of the options listed above.
- Meeting Minutes to the Sponsor by October 28, 2005.

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/s/

Daniel A. Shames
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-840

Duramed Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Senior Director, Regulatory Affairs
One Belmont Ave., 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your Investigational New Drug Application (IND submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for SeasoniqueTM (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets.

We also refer to your August 18, 2005, correspondence, received August 19, 2005, requesting an End-of-Review meeting.

Based on the statement of purpose, objectives, and proposed agenda, we consider the meeting a type A meeting as described in our guidance for industry titled *Formal Meetings with Sponsors and Applicants for PDUFA Products* (February 2000). The meeting is scheduled for:

Date: September 29, 2005
Time: 1:00 – 2:30 PM
Location: CDER Building, FDA White Oak Campus
10903 New Hampshire Avenue
Silver Spring, MD 20993

CDER, Division of Reproductive and Urologic Drug Products (DRUDP) invited participants:

Daniel Shames, M.D. - Director
Shelley Slaughter, M.D., Ph.D. - Medical Team Leader
Ronald Orleans, M.D. - Medical Officer
Jennifer Mercier - Chief, Project Management Staff
Karen Kirchberg, N.P. - Project Manager

Please have all attendees bring photo identification and allow 15-30 minutes to complete security clearance. The security staff will prepare temporary badges in advance for your participants. If there are additional attendees, email that information to me at <kirchbergk@cder.fda.gov>.

NDA 21-840

Page 2

Provide the background information for this meeting (three copies to the IND and 6 desk copies to me) at least 2 weeks prior to the meeting. If possible, we would like to receive the package by September 12, 2005. The Division move is scheduled for September 15 and 16.

The mailing address for your meeting package is:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please call me at (301) 827-4254.

Sincerely,

{See appended electronic signature page}

Karen Kirchberg, N.P.
Project Manager
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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Karen Kirchberg
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Food and Drug Administration
Center for Drug Evaluation and
Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: June 20, 2005

To: Joe Carrado Michele Walsh Regulatory Affairs	From: Karen Kirchberg, N.P. Project Manager
Company: Duramed	Division of Reproductive and Urologic Drug Products
Fax number: (610) 747-2979	Fax number: (301) 827-4267
Phone number: (610) 747-2644	Phone number: (301) 827-4254

Subject: NDA 21-840 Information Request - Clinical

Total no. of pages including cover: 3

Document to be mailed: No

**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS
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NDA 21-840

SEASONIQUE™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets

Clinical Information Request:

Please provide any clinical trial data from a randomized and controlled trial(s) directly comparing Seasonique™ to Seasonale® that would support benefit to the patient of the additional 10 micrograms of ethinyl estradiol for day 85 -91 of the Seasonique™ regimen compared to the Seasonale® regimen with placebo pills for days 85-91.

Please send your response to the NDA by June 28, 2005. Thank you.

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/s/

Karen Kirchberg
6/20/05 01:09:53 PM
CSO

Shelley Slaughter
6/20/05 01:20:38 PM
MEDICAL OFFICER
I concur.

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MEMORANDUM

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

DATE: June 14, 2005

FROM: Antoine El-Hage, Ph.D.
Good clinical Practice Branch I
Division of Scientific Investigations, HFD-46

THROUGH: Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations, HFD-46

TO: Karen Kirchberg, Regulatory Project Manager
Ronald Orleans, M.D., Medical Officer
Division of Reproductive and Urologic Drug Products, HFD-580

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-840

APPLICANT: Duramed

DRUG: Seasonique (levonorgestrel/ethinyl esradiol and ethinyl estradiol)

CHEMICAL CLASSIFICATION: 3

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATION: Prevention of pregnancy in women _____ who desire to use oral contraceptives.

CONSULTATION REQUEST DATE: February 7, 2005

ACTION GOAL DATE: August 19, 2005

BACKGROUND:

In this application, the sponsor has included the results of protocol PSE- 301 entitled: “ A phase III, randomized, multicenter, clinical trial to evaluate the efficacy for the prevention of pregnancy in women and safety by obtaining endometrial biopsies of combination oral contraceptive regimens utilizing ethinyl estradiol during the pill-free interval”; and protocol PSE-302 entitled: “ A phase III, randomized, multicenter, clinical trial to evaluate the efficacy and safety of combination contraceptive regimens utilizing ethinyl estradiol during the pill-free interval for the prevention of pregnancy in women”.

These studies were designed to evaluate three different oral contraceptive (OC) regimens containing 150 ug of levonorgesterol/30ug ethinyl estradiol as combination tablets administered for 25 days (DP3-25/30) or 84 days (DP3-84/30 and DP3-84/10) followed by a single ethinyl estradiol agent. The studies would also collect information on the incidence and severity of hormonally related symptoms during treatment regimens.

Site inspections were requested by the review division in a memo dated February 7, 2005, for two sites: Drs Lackey and Feldman, for protocols PSE-301 and PSE-302 respectively. These sites have been selected for data audit due to high enrollment and a large number of discontinuation. The goals of the inspection included validation of the submitted data and compliance of study activities with applicable statutes and FDA regulations. Among the study records reviewed included informed consent procedures, appropriate selection of subjects based on inclusion/exclusion criteria, adherence to the protocol, randomization procedures, documentation of adverse events and drug accountability records.

II. RESULTS

NAME	CITY	STATE	ASSIGNED DATE	RECEIVED DATE	CLASSIFICATION
Lackey	Oklahoma city	OK	3/16/05	6/3/05	VAI/AEH
Feldman	Miami	FL	3/16/05	5/13/05	VAI/AEH

Protocol PSE-301

1. Dr. James Lackey

At this site, 230 subjects were screened for study PSE-301. 147 subjects were randomized for the study and 83 subjects were reported as screen failures. The reason(s) for discontinuations were accurately documented (e.g. non-compliance, mood swings adverse events /bleeding, withdrew consent, and lost to follow-up etc.). 74 subjects were randomized and completed the study. 55

subjects withdrew from the study; for adverse events (21 subjects), lost to follow-up (34 subjects). Study records, including informed consents, medical histories, protocol-required tests and assessments, drug accountability records, medical records and correspondence with the sponsor and IRB, and data listing for 22 subjects were reviewed during the inspection.

The deviations from FDA regulations were discussed with Dr. Lackey and presented to him on the Form FDA 483 at the conclusion of the inspection. The inspectional observations included:

1. Protocol deviations
 - a. The protocol allows a maximum of 28 days post screening for randomization; however, subject 2685 was randomized 46 days post screening.
 - b. The protocol specified that the clinical site contact the subject after visit 1 by phone to confirm the beginning of the subject's menstrual period and the initiation of study treatment. Subsequently, at approximate monthly intervals prior to each visit, the site was to contact the subject by phone to continue assessments of adverse events, smoking history, concomitant medications, and compliance. There was no documentation of phone calls to the following subjects at the specified time points:
 - i.) Phone calls to subjects 2637, 2640, 2644, 2653, 2655, 2659, 2672, 2675, and 2682 after visit 1 to confirm the onset of the subjects' menstrual periods and initiation of study treatment.
 - ii.) Phone calls to subjects 2655 and 2659 at one and two months after visit 1 for continued assessments.
 - iii.) Phone call to subject 2666 one month after visit 1 for continued assessments.
 - iv.) Phone call to subject 2640 two months after visit 1 for continued assessments.
2. Failure to reconsent subjects 2653, 2666, 2720, and 2748 with a revised version which changes in protocol procedures and risks.

Adverse events were documented and reported to the sponsor and IRB. The investigator responded to the Form FDA 483 in writing, acknowledged the inspectional observations and promised to exercise more care in the future. Data from this site appear acceptable in support of the pending application.

Protocol PSE -302

2. Dr. Robert Feldman

At this site, 69 subjects were screened for study PSE-302. There were 43 subjects discontinued the study and their reason(s) of discontinuation were accurately documented (e.g. non-compliance, adverse events /bleeding, withdrew consent, and lost to follow-up etc.). 26 subjects

were randomized and completed the study. Study records, including informed consents, medical histories, protocol-required tests and assessments, drug accountability records, medical records and correspondence with the sponsor and IRB, and data listing were reviewed for 16 subjects during the inspection.

Two deviations from FDA regulations were discussed with Dr. Feldman and presented to him on the Form FDA 483 at the conclusion of the inspection. The inspectional observations included:

1. Protocol Deviation
 - a. For subject 642, end of study endometrial biopsy sample was not sufficient for evaluation.
 - b. The protocol required post-study 3 months follow up via a monthly call to subjects in order to obtain update information on the occurrence of pregnancy and until the menstrual cycle return to normal were not performed for five subjects: subject 642 and 643 at post visit 4, calls 1 and 2; subject 673 at post study call 2 and 3; subject 680 post study calls 1, 2, and 3; and subject 655 post visit 3, call 2.

2. AE reporting

Subject 655 had experienced headaches 3 months prior to the study, and while on the study drug, the subject reported that the headaches are occurring with greater severity and frequency. This was not recorded in the adverse events section of the case report form.

The investigator responded to the Form FDA 483 verbally, acknowledged the inspectional observations and promised to exercise more care in the future. Data from this site appear acceptable in support of the pending application.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

As stated above, there were instances of protocol deviations at the study sites inspected. These deviations did not seem to have any significant impact on the study data. No follow is necessary at this time. The data generated from these sites appear acceptable in support of the relevant submission.

Antoine El-Hage, Ph.D
Regulatory Pharmacologist
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

Ni A. Khin, M.D.
Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

Key to Classification:

NAI = No deviation from regulations. Data acceptable

VAI = Minor deviation(s) from regulations. Data acceptable

cc:

HFD-530 Doc.Room NDA 21-840

HFD-45 Division File/Reading File

HFD-46/AEH/6/7/05

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/s/

Antoine El-Hage
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CSO

Ni Aye Khin
6/24/05 01:32:37 PM
MEDICAL OFFICER

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Karen Kirchberg
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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-840

Duramed Research, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph
Senior Director, Regulatory Affairs
One Belmont Avenue, 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your New Drug Application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for levonorgestrel/ethinyl estradiol and ethinyl estradiol Tablets.

Your NDA application was submitted under section 505(b)(2). After reviewing the criteria for a 505(b)(2) submission, we have concluded that the application qualifies under section 505(b)(1). This correspondence is for your information only and no further action is necessary.

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

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
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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: March 1, 2005
From: Corrinne Kulick, DDMAC
To: Karen Anderson, DRUDP
Re: Seasonique (levonorgestrel/ethinyl estradiol tablets) 0.15 mg/0.03 mg and (ethinyl estradiol tablets) 0.01 mg NDA 21-840

Comments are provided on the draft labeling for Seasonique (levonorgestrel/ethinyl estradiol tablets) 0.15 mg/0.03 mg and (ethinyl estradiol tablets) 0.01 mg submitted by Duramed Pharmaceuticals Inc. October 21, 2004.

General

Although the content of this label and specifically the Risk information, follows the Draft Guidance for Industry: Labeling for Combined Oral Contraceptives dated March 2, 2004 verbatim, the Warnings, Precautions, and Adverse events sections differ greatly in content and detail from the alternative 84-day option,, i.e., Seasonale whose label was approved on September 5, 2003. Is the review division concerned that the revised abbreviated version of the risk information as it appears in this label may potentially provide Seasonique a better risk profile and therefore marketing advantage over Seasonale? Of greatest concern is the fact that the new labeling guidance and the Seasonique label do not classify use in pregnancy as Category X.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption:

- The Seasonale label states 43% in a similar sentence. Please clarify.
- The daily exposure to levonorgestrel and ethinyl estradiol on Day 21, corresponding to the end of a typical 3-week contraceptive regimen, and on Day 84, at the end of an extended cycle regimen, were similar.

Is there adequate evidence to support that daily exposure to Seasonique is similar to traditional 28-day cycle contraceptives? If not, DDMAC recommends deletion of the

underlined text to avoid implied comparative claims.

Excretion:

- The terminal elimination half-life for levonorgestrel after a single dose of Seasonique™ was about 34 hours. The terminal elimination half-life of ethinyl estradiol after a single dose of Seasonique™ was found to be about 18 hours.

The Seasonale label states 30 and 15 hours, respectively, in similar sentences. Please clarify.

INDICATIONS AND USAGE

- Although the Table in this section was taken from the Draft Guidance for Industry: Labeling for Combined Oral Contraceptives, the Seasonale label and labels from other drugs in the category contain a more complete Table. Please consider including a similar table here for completeness and consistency. Also consider providing the table with a number designation, e.g. Table 1.

DDMAC recommends deleting internal company study titles, e.g., "_____". These are generally meaningless to the reader. Studies should simply be titled "Studies A and B" or "Studies 1 and 2."

- The Pearl Index was ~~_____~~ based on 1577 completed 91-day cycles.

WARNINGS

ADVERSE _____

- Should this header be revised to "ADVERSE REACTIONS" for consistency?

- _____

- _____
- Are there additional details beyond the class labeling information provided regarding adverse experiences and cycle control unique to Seasonique that should be included here?

DOSAGE AND ADMINISTRATION

- _____

REFERENCES

Supplied upon request.

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

Guide for Using Seasonique™

HOW DO I TAKE SEASONIQUE™?

- 4. ... If the bleeding lasts for more than a _____, talk to your healthcare provider.

The Seasonale label qualifies _____ with "> 7 days." Should this information be provided here as well for context and consistency? This information would be useful to the reader.

Carton and Container Labels

The carton and container labels include the claim "_____"
_____ that makes representations about the use of the drug. Promotional labeling is misleading if it fails to reveal facts that are material in light of other representations or suggestions made regarding the drug or with respect to consequences which may result from the use of the drug. This claim makes representations or suggestions relating to Seasonique and therefore requires inclusion of other facts that are material regarding the drug, including risk information. Therefore, DDMAC recommends deletion of this claim from the proposed carton and container labeling as the simplest resolution.

Thank you for including DDMAC in this review.

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/s/

Corrinne Kulick
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DDMAC REVIEWER

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MEMORANDUM

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

DATE: January 5, 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 of Patient Labeling for Seasonique
(levonorgestrel/ethinyl estradiol tablets) 0.15 mg / 0.03 mg and
(ethinyl estradiol tablets) 0.01 mg), NDA 21-840

Background and Summary

The sponsor submitted patient labeling dated October 21, 2004, as required for oral contraceptives (21 CFR § 310.501). The patient labeling for Seasonique follows the March 2004, Draft Guidance; *Guidance for Industry: Labeling for Combined Oral Contraceptives*. The labeling has a Flesch-Kincaid Grade Level of 7.3 and a Flesch Reading Ease Score of 68%; both acceptable scores for patient materials.

Comments and Recommendations

We have the following comment:

Avoid the use of UPPER CASE lettering to emphasize important information. Upper case lettering is difficult to read. Bold or underline for word or statement emphasis. The tradename is the exception to this recommendation and may be in upper case letters.

Please call us if you have any questions.

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/s/

Jeanine Best
1/5/05 01:14:01 PM
DRUG SAFETY OFFICE REVIEWER

Toni Piazza Hepp
1/5/05 01:50:49 PM
DRUG SAFETY OFFICE REVIEWER
for Gerald Dal Pan

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NDA: 21-840 Seasonique™ by Duramed Pharmaceuticals, Inc.**45 Day Filing Meeting Checklist
CLINICAL**

ITEM	YES	NO	COMMENT
1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	X		
2) Is the clinical section of the NDA indexed and paginated in a manner to allow substantive review to begin?	X		
3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	X		
4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)?	X		
5) On its face, do there appear to be the requisite number of adequate and well controlled studies in the application?	Two		
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X		
7) Are all data sets for pivotal efficacy studies complete for all indications requested?	X		
8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X		

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ITEM	YES	NO	COMMENT
9) Has the applicant submitted line listings in a format to allow reasonable review of the patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?	X		
10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			N/A
11) Has the applicant submitted all additional required case record forms (beyond deaths and drop-puts) previously requested by the Division	X		Case Report Forms were submitted electronically. It was not verified if each required case report form was submitted.
12) Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously agreed to by the Division?	X		
13) Has the applicant presented safety assessment based on <u>all</u> current world-wide knowledge regarding this product?	X		
14) Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional policies, and the design of the development package?	X		
15) Has the applicant submitted <u>all</u> special studies/data requested by the Division during pre-submission discussions with the sponsor?	X		
16) From a clinical perspective, is this NDA fileable? If "no", please state in item #17 below why it is not.	Yes		
17) Reasons for refusal to file:			

Ronald J. Orleans, M.D. / January 01, 2005
 Reviewing Medical Officer
 Division of Reproductive and Urologic Drug Products

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NDA 21-840: Filing Meeting Clinical Comments

Filing Meeting Date: December 1, 2004

Drug: Seasonique™ Tablets (91-day extended oral contraceptive regimen)

Sponsor: Duramed Pharmaceuticals, Inc.

Dose: 84 levonorgestrel and ethinyl estradiol tablets (0.15 mg/0.03 mg) followed by 7 ethinyl estradiol tablets (0.01 mg)

Indication: Prevention of pregnancy

Sponsor: Duramed Research Inc., Bala Cynwyd, PA. 19004

Submission Date: October 21, 2004

Goal Date: July 21, 2005

Related Submission: IND 63,735

Medical Reviewer: Ronald J. Orleans, M.D.

Submission Resume

Background: In September 2003, Seasonale®, the first extended cycle oral contraceptive, was approved. The approved Seasonale® 91-day extended cycle includes 84 days of active combination tablets of levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg followed by 7-days of placebo pills. With this regimen, the frequency of withdrawal bleeding is reduced to 4 times a year.

Seasonique™ is also an extended cycle oral contraceptive. It differs from Seasonale® in that it is a 91-day extended cycle oral contraceptive containing levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg followed by 7 tablets of ethinyl estradiol 0.01 mg monotherapy instead of placebo. It is this formulation (DP3-84/10) for which the Sponsor is seeking approval for prevention of pregnancy.

Efficacy and Safety studies: Duramed submitted the results of 2 clinical trials: Study PSE-301 and Study PSE-302 to support efficacy and safety. PSE-302 was conducted as a supportive study to PSE-301.

Study PSE-301 is titled “A Phase III, Randomized, Multicenter, Clinical Trial to Evaluate the Efficacy and Safety of Combination Oral Contraceptive Regimens Utilizing Ethinyl Estradiol During the Pill-Free Interval for Prevention of Pregnancy in Women”. This study was a two-arm, randomized, open-label study which lasted for one year in 36 U.S. centers. For the DP3-84/30 arm, 1025 subjects were randomized and 1013 were treated. For the DP3-84/10 arm, 1024 subjects were randomized and 1006 were treated.

The primary objective of this study was to demonstrate the efficacy and safety of the 91-day extended regimen oral contraceptives, DP3-84/10 and DP3-84/30, which include 84 days of combination therapy followed by 7 days of ethinyl estradiol monotherapy, taken for one year (four 91-day cycles) in women desiring pregnancy prevention. Secondary objectives included 1) observation of the incidence and severity of hormonal-related symptoms during the treatment period and 2) observation of the number of reported days of scheduled (withdrawal) and unscheduled (breakthrough) bleeding and/or spotting.

Per the submission, the efficacy of DP3-84/10 and DP3-84/30 91-day extended therapy are comparable to that reported for conventional 28-day oral contraceptive therapy and also comparable to Seasonale®. The Pearl Index in the Intent to Treat population was 1.27 for DP3-84/10 and 2.74 for DP3-84/30.

The median number of total observed bleeding and/or spotting days normalized to a 28-day cycle, for the last 91-day extended regimen (cycle 4) was lower for DP3-84/10 (2.0 days) than for DP3-84/30 (2.2 days).

Study PSE-302 is titled “A Phase III Randomized, Multicenter, Clinical Trial to Evaluate the Efficacy For Prevention of Pregnancy in Women and Safety by Obtaining Endometrial Biopsies of Combination Oral Contraceptive Regimens Utilizing Ethinyl Estradiol During the Pill-Free Interval”. This study was a four-arm, randomized, open-label study which lasted for one year in 7 U.S. centers. A total of 380 subjects were randomized and 372 treated. For the DP3-84/30 arm, 96 subjects were randomized and 95 treated. For the DP3-84/10 arm, 95 subjects were randomized and 95 treated. For the DP3-25/30 (includes 3 days of ethinyl

estradiol monotherapy following 25 days of active combination treatment) arm, 94 subjects were randomized and 89 treated and for the Nordette®-28 arm, 94 subjects were randomized and 93 treated.

The study had two primary objectives: 1) to demonstrate the efficacy and safety of the 91-day extended combination oral contraceptive regimens, DP3-84/10 and DP3-84/30 (both of which include 84 days of combination therapy followed by 7 days of ethinyl estradiol monotherapy), taken for one year in women desiring pregnancy prevention, and 2) evaluation of endometrial biopsies done before and at the end of the study. Secondary objectives included 1) observation of the incidence and severity of hormonal-related symptoms during the treatment period and 2) observation of the number of reported days of scheduled (withdrawal) and unscheduled (breakthrough) bleeding and/or spotting.

Per the submission, the Pearl Index for DP3-84/10 and DP3-84/30 was 2.41 and 2.61, respectively. Endometrial biopsy results showed no evidence of any pathologic changes; hyperplasia was not observed in any of the end of treatment biopsy samples. Other safety results for all DP3 doses were comparable to those for Nordette®.

Fileability of NDA 21-840/S-000

NDA 21-840/S-000 is fileable.

Review Issues

Given the known risks associated with exogenous estrogen use in combined oral contraceptives for women of reproductive age, the Division will be looking very carefully to evaluate whether the addition of 10 micrograms of ethinyl estradiol in this new 91-day regimen provides sufficient clinical benefit to justify potential risk.

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/s/

Ronald Orleans
1/5/05 10:55:53 AM
MEDICAL OFFICER

Shelley Slaughter
1/5/05 11:31:00 AM
MEDICAL OFFICER

Per the MO no deficiencies that would necessitate a
refuse to file action.

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REQUEST FOR CONSULTATION

TO (Division/Office):
Division of Drug Marketing, Advertising and Communications (DDMAC)
HFD-42; Parklawn Bldg. Room 17B-17
Attention: Barbara Chang and Corrine Kulick

FROM:
Karen Anderson, Regulatory Health Project Manager
Division of Reproductive and Urologic Drug Products, HFD-580
301-827-4259

DATE
Dec. 22, 2004

IND NO.

NDA NO.
21-480

TYPE OF DOCUMENT
NDA

DATE OF DOCUMENT
October 21, 2004

NAME OF DRUG
Seasonique™
(levonorgestrel/ethinyl estradiol plus ethinyl estradiol) tablets

PRIORITY CONSIDERATION
Standard

CLASSIFICATION OF DRUG
Oral Contraceptive

DESIRED COMPLETION DATE
February 25, 2005

NAME OF FIRM: **Duramed Pharmaceuticals, Inc.**

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> SAFETY/EFFICACY | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION | <input type="checkbox"/> CONTROL SUPPLEMENT | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | | |

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH

STATISTICAL APPLICATION BRANCH

- | | |
|--|---|
| <input type="checkbox"/> TYPE A OR B NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END OF PHASE II MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|---|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE IV STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG EXPERIENCE

- | | |
|--|--|
| <input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

CLINICAL

PRECLINICAL

This NDA has a goal date of August 189, 2005. This is an extended use oral contraceptive. It is a 84 / 7 regimen meaning the active ingredient tablets are taken daily for 84 days (levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg) followed by 7 days of a lower dose estrogen alone (ethinyl estradiol 0.01 mg). The NDA is electronic and the folder is marked "labeling."

SIGNATURE OF REQUESTER

METHOD OF DELIVERY (Check one)

MAIL

HAND

SIGNATURE OF RECEIVER

SIGNATURE OF DELIVERER

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Karen Kirchberg
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DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION		REQUEST FOR CONSULTATION		
TO (Division/Office): Mail: ODS (Room 15B-08, PKLN Bldg.) Attn: Jeanine Best, N.P.		FROM: Daniel Shames, M.D. Director, Division of Reproductive and Urologic Drug Products (DRUDP: HFD-580)		
DATE Dec. 22, 2004	IND NO.	NDA NO. 21-840	TYPE OF DOCUMENT NDA	DATE OF DOCUMENT October 21, 2004
NAME OF DRUG Seasonique™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol)		PRIORITY CONSIDERATION Standard	CLASSIFICATION OF DRUG Oral Contraceptive (3S)	DESIRED COMPLETION DATE February 14, 2005
NAME OF FIRM: Duramed Pharmaceuticals, Inc.				
REASON FOR REQUEST				
I. GENERAL				
<input type="checkbox"/> NEW PROTOCOL <input type="checkbox"/> PRE-NDA MEETING <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER <input type="checkbox"/> PROGRESS REPORT <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> FINAL PRINTED LABELING <input type="checkbox"/> NEW CORRESPONDENCE <input type="checkbox"/> RESUBMISSION <input type="checkbox"/> LABELING REVISION <input type="checkbox"/> DRUG ADVERTISING <input type="checkbox"/> SAFETY/EFFICACY <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE <input type="checkbox"/> ADVERSE REACTION REPORT <input type="checkbox"/> PAPER NDA <input type="checkbox"/> FORMULATIVE REVIEW <input type="checkbox"/> MANUFACTURING CHANGE/ADDITION <input type="checkbox"/> CONTROL SUPPLEMENT <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW):				
II. BIOMETRICS				
STATISTICAL EVALUATION BRANCH		STATISTICAL APPLICATION BRANCH		
<input type="checkbox"/> TYPE A OR B NDA REVIEW <input type="checkbox"/> END OF PHASE II MEETING <input type="checkbox"/> CONTROLLED STUDIES <input type="checkbox"/> PROTOCOL REVIEW <input type="checkbox"/> OTHER (SPECIFY BELOW):		<input type="checkbox"/> CHEMISTRY REVIEW <input type="checkbox"/> PHARMACOLOGY <input type="checkbox"/> BIOPHARMACEUTICS <input type="checkbox"/> OTHER (SPECIFY BELOW):		
III. BIOPHARMACEUTICS				
<input type="checkbox"/> DISSOLUTION <input type="checkbox"/> BIOAVAILABILITY STUDIES <input type="checkbox"/> PHASE IV STUDIES		<input type="checkbox"/> DEFICIENCY LETTER RESPONSE <input type="checkbox"/> PROTOCOL-BIOPHARMACEUTICS <input type="checkbox"/> IN-VIVO WAIVER REQUEST		
IV. DRUG EXPERIENCE				
<input type="checkbox"/> PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL <input type="checkbox"/> DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP		<input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE <input type="checkbox"/> POISON RISK ANALYSIS		
V. SCIENTIFIC INVESTIGATIONS				
<input type="checkbox"/> CLINICAL		<input type="checkbox"/> PRECLINICAL		
COMMENTS/SPECIAL INSTRUCTIONS: Goal Date August 19, 2005. Please review this label for consumer comprehension. FYI - The active pills in this OC are taken for 84 days (levonorgestrel 0.15 mg and ethinyl estradiol 0.03 mg) followed by 7 days of a lower dose estrogen tablets in place of placebo (ethinyl estradiol 0.01 mg). The label is in the EDR under the NDA number in a folder entitled "labeling." Patient labeling begins on page 15.				
SIGNATURE OF REQUESTER Karen Kirchberg, N.P. – PM		METHOD OF DELIVERY (Check one) <input type="checkbox"/> MAIL <input type="checkbox"/> HAND		
SIGNATURE OF RECEIVER		SIGNATURE OF DELIVERER		

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Karen Kirchberg
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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: 12.22.2004

To: Michelle Walsh, Regulatory Affairs	From: Karen Kirchberg, NP
Duramed Pharmaceuticals, Inc.	Division of Reproductive and Urologic Drug Products
Fax number: (610) 747-2979	Fax number: (301) 827-4267
Phone number: (610) 747-2644	Phone number: (301) 827-4254

Subject: NDA 21-840

Total no. of pages including cover: 4

Document to be mailed: YES

Comments:

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-840

Duramed Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Senior Director, Regulatory Affairs
One Belmont Ave., 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

Please refer to your October 21, 2004 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Seasonique™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets.

We also refer to your submission dated December 1, 2004.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on December 20, 2004 in accordance with 21 CFR 314.101(a).

In our filing review, we have identified the following potential review issues or requests for information.

Clinical:

Given the known risks associated with exogenous estrogen use in combined oral contraceptives for women of reproductive age, the Division will be looking very carefully to evaluate whether the addition of 10 micrograms per day of ethinyl estradiol for the seven days of the previous hormone free period of a 91-day regimen (Seasonale®) provides sufficient clinical benefit to the patient using Seasonique™ to justify risk.

Chemistry, Manufacturing and Controls:

1. Provide additional stability data when it is available.
2. Confirm the Master Batch Formula for the manufacture of each type of tablet used in clinical and/or stability studies. Indicate the presence or absence of an overage for either of the active pharmaceutical ingredients (levonorgestrel, ethinyl estradiol).

3. Submit a Letter of Authorization for DMF _____.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If you have any questions, call 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
12/22/04 11:36:08 AM

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NDA FILEABILITY CHECKLIST

NDA Number: 21-840

Applicant: Duramed Research, Inc.

Stamp Date: 21-OCT-2004

Drug Name: Seasonique™ (levonorgestrel/ethinyl estradiol tablets) 0.15 mg/0.03 mg
(ethinyl estradiol tablets) 0.01 mg

IS THE CMC SECTION OF THE APPLICATION FILEABLE? (Yes or No) Yes

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies.

	<i>Parameter</i>	<i>Yes</i>	<i>No</i>	<i>Comment</i>
1	On its face, is the section organized adequately?	√		
2	Is the section indexed and paginated adequately?	√		
3	On its face, is the section legible?	√		
4	Are ALL of the facilities (including contract facilities and test laboratories) identified with full <u>street</u> addresses and CFNs?	√		Drug substance manufacture is referenced to DMF _____, DMF _____ and DMF _____
5	Is a statement provided that all facilities are ready for GMP inspection?	√		
6	Has an environmental assessment report or categorical exclusion been provided?	√		Reference to CFR 25.31(b) – the Sponsor has filed a claim for categorical exclusion.
7	Does the section contain controls for the drug substance?	√		See DMF _____, DMF _____, and DMF _____
8	Does the section contain controls for the drug product?	√		
9	Has stability data and analysis been provided to support the requested expiration date?	√		Additional data requested during review clock.
10	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	√		
11	Have draft container labels been provided?	√		
12	Has the draft package insert been provided?	√		
13	Has an investigational formulations section been provided?	√		
14	Is there a Methods Validation package?	√		
15	Is a separate microbiological section included?		√	Not necessary, since this is a solid oral dosage form (tablet).

Review Chemist: Sarah C. Pope, Ph.D.

Date: 02-DEC-2004

Team Leader: Moo-Jhong Rhee, Ph.D.

Date: 06-DEC-2004

Original NDA 21-840
HFD-580/Division File
HFD-580/M. Rhee/S. Pope
HFD-580/K. Kirchberg

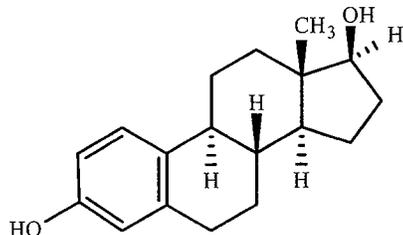
Inclusive DMF References

<i>DMF Number</i>	<i>DMF Holder</i>	<i>Description</i>	<i>LOA Included</i>	<i>Status</i>
			No	See non-filing review comments.
			Yes	Under Review
			Yes	Under Review.
			Yes	Under Review.
			Yes	Under review.
			Yes	Under review.

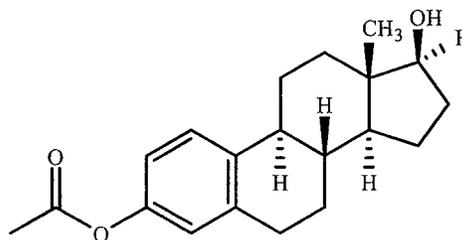
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Drug Substances

Levonorgestrel is a compendial compound. It is present as a white powder at room temperature, and its observed melting range is 232-239°C. All Chemistry, Manufacturing, and Controls information for levonorgestrel, USP has been cross-referenced to DMF [redacted] and DMF [redacted]. Letters of Authorization have been provided for these references, and the cross-referenced information will be reviewed under separate cover.



Levonorgestrel
(-)-13-Ethyl-17-hydroxy-18,19-dinor-17 α
pregn-4-en-20-yn-3-one
MW = 312.45 g/mole
C₂₁H₂₈O₂



Ethinyl estradiol
19-Nor-17 α -pregn-1,3,5(10)-trien-
20-yne-3,17-diol
MW = 296.41 g/mole
C₂₀H₂₄O₂

Ethinyl estradiol is also a compendial compound, and all related Chemistry, Manufacturing, and Controls information has been cross-referenced to DMF [redacted]. A Letter of Authorization has been provided, and the reference is acceptable. The cross-referenced information will be reviewed under separate cover.

The Sponsor has listed the following sites for drug substance manufacturing:

[redacted]

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CFN# _____

Levonorgestrel for commercial production of the drug product will be manufactured by _____ while some clinical and stability supplies were manufactured using levonorgestrel from the _____ site. The Sponsor has presented a discussion of the equivalency of the drug substance, as produced by the _____ sites. Additionally, comparative stability data are presented for drug product manufactured using levonorgestrel from both sites (see the following Drug Product – Stability section).

All sites have been entered into EES.

Drug Product

Seasonique tablets are manufactured in two strengths: 0.15/0.03 levonorgestrel/ethinyl estradiol, and 0.01 mg ethinyl estradiol. The two tablet formulations are listed in the tables below. Clinical trials included the administration of white combination and single entity tablets, and the final formulations and color coatings were adjusted for the desired colors (blue-green for the combination; yellow for the ethinyl estradiol).

All tablet components are controlled under Drug Master Files, or are compendial (USP or NF).

<i>Combination Tablets (Levonorgestrel/Ethinyl estradiol)</i>			Amount per Tablet (mg)	
Component	Compendial Status	Function	White tablets	Blue/green tablets
Levonorgestrel	USP DMF DMF		0.1500	0.1500
Ethinyl estradiol	DMF		0.03000	0.03000
Anhydrous lactose				
Magnesium stearate				
Hypromellose 2208				
Microcrystalline cellulose				
Opadry II White	DMF			
Opadry II Blue	DMF			
Total				

<i>Single Entity Tablets (Ethinyl estradiol)</i>			Amount per Tablet (mg)	
Component	Compendial Status	Function	White tablets	Yellow tablets
Ethinyl estradiol	USP/DMF		0.01000	0.01000
Anhydrous lactose				
Polacrillin potassium				
Magnesium stearate				
Microcrystalline cellulose				
Opadry II White	DMF			
Opadry II Yellow	DMF			
Total				

Both types of tablets are manufactured using _____ Master batch formulae have been provided for each of the dosage strengths. The proposed commercial scale of manufacture is _____ tablets/batch, for both tablet types.

The manufacturing sites are listed below, with the specific functions outlined:

Manufacturing
Barr Laboratories, Inc.
2 Quaker Road
Pomona, NY 10970-0519

Packaging and Labeling

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, OH 45213

Analytical and Testing
Barr Laboratories, Inc.
2 Quaker Road
Pomona, NY 10970-0519

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, OH 45213

Barr Laboratories, Inc.
2150 Perrowville Road
Forest, VA 24551

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All sites have been entered into EES.

Release specifications for both tablet types include methods and criteria for description, identification, loss on content uniformity (levonorgestrel and ethinyl estradiol), assay (levonorgestrel and ethinyl estradiol), related substances, and dissolution.

Once manufactured, Seasonique will be packaged for commerce in blister packages (3 blister cards/compact). Each compact will contain two blister cards of 28 tablets each, and a third blister card will contain 28 combination tablets and 7 ethinyl estradiol tablets.

The Sponsor has provided six (6) months of accelerated stability data, twelve (12) months of intermediate stability data, and eighteen (18) months of realtime stability data for scale tablets/batch) batches for the clinical (white) combination tablet. Two (2) months of accelerated and intermediate data have also been provided for scale batch of the proposed commercial product (blue-green) tablet. Additional stability data (covering six months of accelerated, intermediate, and real time conditions) will be available during the review cycle.

The Sponsor has provided six (6) months of accelerated data, nine (9) months of intermediate data, and eighteen (18) months of real time data for scale batches of ethinyl estradiol diol (white)

tablets. Three months of accelerated, intermediate, and real time data for the proposed commercial formulation (yellow tablets) will be available during the review cycle.

Packaging components for the clinical, primary stability, and proposed commercial batches were confirmed in an amendment dated 01-DEC-2004, and are listed in the following table. The Sponsor has submitted a justification for equivalency of the initial clinical packaging configuration with that used for primary stability and intended for commercial production

Component	Clinical/Primary Stability	Proposed Commercial
Base	+	+
Lidding	+	+

The Sponsor has proposed an _____ expiry (controlled room temperature) for the drug product.

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Comments (non-filing review issues, for 74-day letter)

1. Provide additional stability data when available.
2. Confirm the Master Batch Formula for manufacture of each type of tablet used in clinical and/or stability studies. Indicate the presence or absence of an overage for either of the active pharmaceutical ingredients (levonorgestrel, ethinyl estradiol).
3. Submit a Letter of Authorization for DMF —

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/s/

Sarah Pope
12/2/04 11:21:52 AM
CHEMIST

Moo-Jhong Rhee
12/6/04 05:15:37 PM
CHEMIST
I concur

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Food and Drug Administration
Center for Drug Evaluation and Research
Office of Drug Evaluation ODE III

FACSIMILE TRANSMITTAL SHEET

DATE: November 29, 2004

To: Michelle Walsh Regulatory Affairs	From: Karen Kirchberg, N.P. Regulatory Project Manager
Company: Duramed	Division of Reproductive and Urologic Drug Products
Fax number: (610) 747-2979	Fax number: (301) 827-4267
Phone number: (610) 747-2644	Phone number: (301) 827-4254
Subject: NDA 21-840 - Information Request from the Chemistry Reviewer	

Total no. of pages including cover: 3

Comments:

Document to be mailed: YES NO

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NDA 21-840

Levonorgestrel/ Ethinyl Estradiol 0.15mg/0.03mg and Ethinyl Estradiol 0.01mg Tablets

Chemistry Request:

1. Confirm the proposed commercial scale for drug product manufacture.
2. Provide a comparison of the packaging configurations for the primary stability, clinical batches, and proposed commercial batches for both types of tablets (combination levonorgestrel/ ethinyl estradiol tablets as well as the ethinyl estradiol tablets).

Please submit your responses to the NDA by Thursday, December 2, 2004. A fax copy is also requested. Thank you.

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/s/

Karen Kirchberg
11/29/04 10:47:16 AM
CSO

Suong Tran
11/29/04 10:53:34 AM
CHEMIST
Acting for Moo-Jhong Rhee

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-840

Duramed Pharmaceuticals, Inc.
Attention: Joseph A. Carrado, M.Sc., R.Ph.
Senior Director, Regulatory Affairs
One Belmont Ave., 11th Floor
Bala Cynwyd, PA 19004

Dear Mr. Carrado:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Seasonique™ (levonorgestrel/ethinyl estradiol and ethinyl estradiol)
Tablets

Review Priority Classification: Standard (S)

Date of Application: October 21, 2004

Date of Receipt: October 21, 2004

Our Reference Number: NDA 21-840

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on December 20, 2004 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be August 19, 2005.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We are waiving the requirement for pediatric studies for this application.

NDA 21-840

Page 2

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. Address all communications concerning this NDA as follows:

U.S. Postal Service/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products, HFD-580
Attention: Document Room 8B45
5600 Fishers Lane
Rockville, Maryland 20857

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

Sincerely,

{See appended electronic signature page}

Jennifer Mercier
Chief, Project Management Staff
Division of Reproductive and Urologic Drug
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

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/s/

Jennifer L. Mercier
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5 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

NDA 21-840	Efficacy Supplement Type SE-	Supplement Number
Drug: Seasonique (levonorgestrel/ethinyl estradiol and ethinyl estradiol) Tablets		Applicant: Duramed Pharmaceuticals, Inc.
RPM: J. Mercier		HFD-580 Phone # 301-796-0957
<p>Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p> <p>If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.</p> <p><input type="checkbox"/> Confirmed and/or corrected</p>		Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):
❖ Application Classifications:		
• Review priority		<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
• Chem class (NDAs only)		3
• Other (e.g., orphan, OTC)		
❖ User Fee Goal Dates		
		May 27, 2006
❖ Special programs (indicate all that apply)		
		<input checked="" type="checkbox"/> None Subpart H <input type="checkbox"/> 21 CFR 314.510 (accelerated approval) <input type="checkbox"/> 21 CFR 314.520 (restricted distribution) <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input type="checkbox"/> CMA Pilot 1 <input type="checkbox"/> CMA Pilot 2
❖ User Fee Information		
• User Fee		<input checked="" type="checkbox"/> Paid UF ID number 4839
• User Fee waiver		<input type="checkbox"/> Small business <input type="checkbox"/> Public health <input type="checkbox"/> Barrier-to-Innovation <input type="checkbox"/> Other (specify)
• User Fee exception		<input type="checkbox"/> Orphan designation <input type="checkbox"/> No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) <input type="checkbox"/> Other (specify)
Application Integrity Policy (AIP)		
• Applicant is on the AIP		<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

() Yes () No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "No," continue with question (5).

- (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?

() Yes () No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).

If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).

If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.

❖ Exclusivity (approvals only)	
<ul style="list-style-type: none"> • Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.) 	X
<ul style="list-style-type: none"> • Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification. 	() Yes, Application # _____ (X) No
❖ Administrative Reviews (Project Manager, ADRA) (indicate date of each review)	N/A

Actions	
• Proposed action	(X) AP () TA () AE () NA
• Previous actions (specify type and date for each action taken)	AE 8-17-05
• Status of advertising (approvals only)	(X) Materials requested in AP letter () Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	() Yes (X) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	(X) None () Press Release () Talk Paper () Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	X
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	10-21-04
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings (indicate dates of reviews and meetings)	DMETS 1-3-05/4-20-06 DSRCS 2-14-05 DDMAC 2-25-05
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	X
• Applicant proposed	10-21-04
• Reviews	X
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
• Outgoing correspondence (i.e., letters, E-mails, faxes)	X
• Memoranda and Telecons	X
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other	
❖ Advisory Committee Meeting	
• Date of Meeting	N/A
• 48-hour alert	N/A
• Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A

❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) (indicate date for each review)	X
❖ Clinical review(s) (indicate date for each review)	X
❖ Microbiology (efficacy) review(s) (indicate date for each review)	N/A
❖ Safety Update review(s) (indicate date or location if incorporated in another review)	See MO review
❖ Risk Management Plan review(s) (indicate date/location if incorporated in another rev)	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Demographic Worksheet (NME approvals only)	N/A
❖ Statistical review(s) (indicate date for each review)	X
❖ Biopharmaceutical review(s) (indicate date for each review)	X
❖ Controlled Substance Staff review(s) and recommendation for scheduling (indicate date for each review)	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	X
• Bioequivalence studies	N/A
❖ CMC review(s) (indicate date for each review)	X
❖ Environmental Assessment	
• Categorical Exclusion (indicate review date)	See review
• Review & FONSI (indicate date of review)	See review
• Review & Environmental Impact Statement (indicate date of each review)	See review
❖ Microbiology (validation of sterilization & product sterility) review(s) (indicate date for each review)	N/A
❖ Facilities inspection (provide EER report)	Date completed: (X) Acceptable () Withhold recommendation
❖ Methods validation	() Completed () Requested (X) Not yet requested
❖ Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	X
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies (indicate date for each review)	N/A
❖ CAC/ECAC report	N/A

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