

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-870

CORRESPONDENCE

ORIG AMENDMENT

RHÔNE-FOULENC RORER PHARMACEUTICALS INC.

500 ARCOLA ROAD
P O BOX 1200
COLLEGEVILLE PA 19426-0107

MARSA D HATFIELD Ph.D
ASSOCIATE DIRECTOR
REGULATORY AFFAIRS
TEL 610-454-5305
FAX 610-454-5299
VM# 610-454-8666. BOX 5305

August 07, 1997

BM
*noted
Aug 8/15/97*

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

*Noted
8/21/97*

REVIEWS COMPLETED
CSO ACTION:
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CSO INITIALS <i>LR</i> DATE <i>8/15/97</i>

NDA # 20,870
ALIATIS™
(estradiol/norethindrone acetate
transdermal system)

*noted
14/15/97
8/21/97*

NEW DRUG APPLICATION
AMENDMENT

Dear Dr. Rarick:

Reference is made to our New Drug Application #20-870, Aliatis™ (estradiol/norethindrone acetate transdermal system) and to the telephone conversation between Mr. John Markow and Dr. Marsa Hatfield on August 13, 1997. This submission provides the appropriate certification statement as required by Section 335A(k)(1) of the Federal Food, Drug and Cosmetic Act.

If you have any questions regarding this submission please contact me at (610) 454-5305.

Sincerely yours,

Marsa Hatfield

Marsa Hatfield, Ph.D.
Associate Director
Regulatory Affairs



Attachment
Desk Copy: John Markow

RHÔNE-POULENC RORER PHARMACEUTICALS INC.

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

ORIGINAL

*Notes
will be reviewed
- Review
- [Signature]
9/23/97*

ORIG AMENDMENT

32

September 23, 1997

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



**NDA #20-870
ALIATIS
(estradiol/norethindrone acetate
transdermal system)**

Dear Dr. Rarick:

Reference is made to our New Drug Application #20-870, Aliatis™ (estradiol/norethindrone acetate transdermal system) on August 7, 1997. This submission provides the unannotated WordPerfect version of the annotated US PI included in the original filing for Aliatis™. Please note, there were some graphs provided in the original proposed PI which could not be duplicated in WordPerfect (estradiol and NET Serum Concentrations at Steady State). In those instances, the reader was referred to the original annotated PI for visualization of the graphs.

REVIEWS COMPLETED	
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CSO INITIALS	DATE

Dr. Lisa Rarick, Director
Page Two
September 23, 1997
NDA #20-870



If you have any questions regarding this submission please contact me at (610) 454-5305.

Sincerely yours,

A handwritten signature in cursive script that reads 'Marsa Hatfield'.

Marsa Hatfield, Ph.D.
Associate Director
Regulatory Affairs

MDH/tc
Desk Copy: John Markow
Enclosures: Diskette

RHÔNE-POULENC RORER PHARMACEUTICALS INC.

500 ARCOLA ROAD
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COLLEGEVILLE, PA 19426-0107
TEL 610-454-8000

ORIGINAL

John J. Savarese
October 8, 1997
10/20/97

NEW CORRESP

Mr. John Markow, CSO
Division of Reproductive and Urologic
Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REVIEWS COMPLETED	
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John J. Savarese
10-20-97

NDA #20-870
ALIATIS
(estradiol/norethindrone acetate
transdermal system)

John J. Savarese
12/21/95

Dear Mr. Markow:

During a telephone discussion on October 7, 1997 your division requested that Rhône-Poulenc Rorer supply a number of items regarding the Biometrics, CMC, and Biopharmaceutics submitted in NDA #20-870. The division also requested that RPR respond to the requests within the next three weeks. It is RPR's intention to comply with the divisions requests. These items were reiterated in a fax from you on the same day. If necessary RPR will be in contact with your division if further clarification is required. It is our understanding that receipt of this letter of commitment is sufficient for the division to accept the filing of NDA #20-870.

You may contact me (610-454-5471) or Mark Learn (610-454-3053) as necessary.

Sincerely yours,

John J. Savarese
John J. Savarese, M.D., Ph.D.
Director, Regulatory Affairs



JJS/tc

RHÔNE-POULENC RORER PHARMACEUTICALS INC.

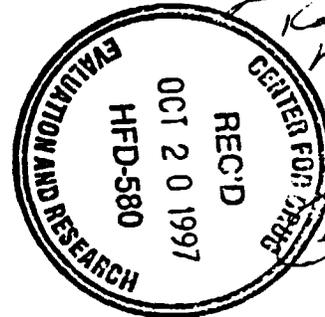
500 ARCOLA ROAD
 P.O. BOX 1200
 COLLEGEVILLE, PA 19426-0107
 TEL 610-454-8000

ORIG AMENDMENT

October 17, 1997

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Diskette
to
for Kammerman
Weed
copy
for
for
for
10/27/97

M. J. Savarese
K. DeLoja
10/28/97



John Markow, CSO
 Division of Reproductive and Urologic
 Drug Products (HFD-580)
 Office of Drug Evaluation II
 Center for Drug Evaluation and Research
 Document Control Room #17B-45
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, MD 20857

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CSO INITIALS	DATE

NDA #20-870
ALIATIS
 (estradiol/norethindrone acetate
 transdermal system)

M. J. Savarese
10/27/97

Dear Mr. Markow:

Regarding NDA# 20-870, enclosed are two copies and a diskette of the expanded index you and Dr. Kammerman requested. Note, sections 8.6 Controlled Clinical Studies, 8.7 ISE and 8.8 ISS have been expanded.

If you have any questions regarding this submission please contact me at (610) 454-5471.

Sincerely yours,

John J. Savarese
 John J. Savarese, M.D., Ph.D
 Director, Regulatory Affairs

JJS/tc

RHÔNE-POULENC RORER PHARMACEUTICALS INC.

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL 610-454-8000

October 28, 1997

ORIG AMENDMENT
BS

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



REVIEWS COMPLETED	
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NDA #20-870
ALIATIS
(estradiol/norethindrone acetate
transdermal system)
RESPONSE TO FDA REQUEST
FOR INFORMATION

Dear Dr. Rarick:

During a telephone conversation on October 7, 1997, your division made several Biometrics, CMC, and Biopharmaceutics requests. This letter and appended materials address those requests. Because this submission contains no data from previously unreported studies nor any significant new analyses of previously submitted data, RPR does not consider this to be a major amendment as described in 21CFR 314.60(a).

Biometrics

Dr. Lisa Kammerman made four biometrics requests. The first request was that RPR provide descriptive results of each of the three placebo groups along with justification for combining the three groups as the comparator arm for Studies 303 and 304. Patients randomized into the placebo groups for these studies received patches matched in size to one active arm. Since there is no reason to believe that there would be a placebo effect based on size difference and since the placebo patches were all manufactured using the same formulation

RPR believes it is methodologically acceptable to group the placebo patients into one comparator arm for the analysis. We included tables of the descriptive results in the Biometrics attachment (Tables E1.1 - E1.3). The tables demonstrate no clinically significant difference in change from baseline in the number of hot flushes between the different size patches in the placebo group.

The second request stated that RPR adjusts the statistical models for imbalances at baseline. Dr. Kammerman requested that RPR identify the variables that the models are adjusting for and asked RPR to report the unadjusted analyses. In fact, all of RPR's statistical models adjust only for treatment and center effects. RPR made no other adjustments.

Dr. Kammerman's third request was that RPR provide two copies of the SAS datasets. RPR has included with this submission the datasets contained in self-extracting zip files for all six studies. We included paper printouts of the contents of each of these datasets, along with the first 10 observations, in the Biometrics attachment. We also included documentation of the data sets and a format program.

Dr. Kammerman also requested that RPR provide a detailed index indicating the contents of each volume. We sent this information to John Markow on October 17.

CMC

Dr. Rhee made three CMC requests. RPR addressed two of the requests, regarding shelf-life calculations and characterization of impurity RRT 0.43, in a fax sent to Mr. Markow on October 14 (see CMC attachment). The third FDA request was that RPR request a categorical exclusion from the Environmental Assessment. We have included a copy of this request in the CMC attachment. Because the request for a categorical Environmental Assessment exclusion amends the materials submitted pursuant to 21CFR 314.50(d)(1), RPR certifies that a field copy of this amendment will be sent to our home FDA district office in accordance with 21CFR 314.60(c).

Biopharmaceutics

Dr. Hardan asked whether the drug products used in clinical trials were the same as the ones planned for marketing. The clinical supplies used in the following studies was the same formulation that RPR intends to market as our commercial product: studies 103, 104, 122, 125, 126, 201, 202, 303, and 304. Dr. Hardan also asked that RPR submit electronic copies of the raw PK data from the 201, 202, 303, and 304 studies. We enclosed four diskettes, one for each study, containing Excel files of the raw PK data.

If you have any questions regarding this submission please contact me at (610) 454-5471.

Sincerely yours,



John J. Savarese, M.D., Ph.D.
Director, Regulatory Affairs

RPR RHÔNE-POULENC RORER HUMAN LIFE

ORIGINAL

RHÔNE-POULENC RORER PHARMACEUTICALS INC.

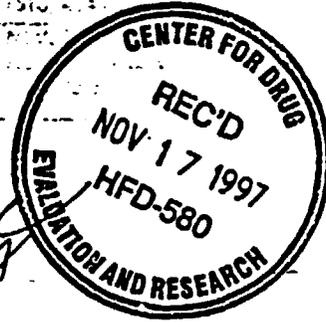
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

November 6, 1997

NEW CORRESP

*Noted
for follow up
12/12/97*

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



*Noted
for follow up
11/20/97*

REVIEWS COMPLETED
CSO ACTION:
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<i>JJS</i> CSO INITIALS <i>11/20/97</i> DATE

NDA #20-870
ALIATIS
(estradiol/norethindrone acetate
transdermal system)

Dear Dr. Rarick:

As stated in our New Drug Application, submitted on August 7, 1997, RPR chose 'ALIATIS' as the trade name for our estradiol/norethindrone acetate transdermal system. After further consideration and research, RPR has decided to market the product under the trade name 'COMBI-PATCH'. RPR will reflect this name change the next time we submit copies of our labeling to you.

If you have any questions regarding this submission please contact me at (610) 454-5471.

REGISTRATION ON APPLICATION

TYPE OF APPLICATION: **Sincerely yours,**

Carol Sabrosky for

HOLDER OF APPROVED APPLICATION
John J. Savarese, M.D., Ph.D
Director, Regulatory Affairs

JJS/ML/tc

TYPE OF SUBMISSION: A PENDING APPLICATION

REGISTRATION (e.g. Part 314 Form 200)

MARKETING STATUS

APPLICANT'S STATUS

PREVIOUS EDITIONS CANCELLED



ORIGINAL

RHÔNE-POULENC RORER RESEARCH AND DEVELOPMENT
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

December 4, 1997

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



ORIG AMENDMENT
34

[Handwritten signature]
12/9/97

REVIEWS COMPLETED
CSD ACTION:
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CSD INITIALS <i>[initials]</i> DATE <i>4/2/98</i>

NDA #20-870
ALIATIS
(estradiol/norethindrone acetate
transdermal system)
SAFETY UPDATE REPORT

Dear Dr. Rarick:

This letter serves as the Safety Update Report [21 CFR § 314.50(d)(5)(vi)(b)] for our New Drug Application, NDA # 20-870, submitted on August 7, 1997. RPR has treated no patients with the drug since the data cut-off for the NDA, thus there is no human exposure data to report nor any changes needed to the labeling.

If you have any questions regarding this submission please contact me at (610) 454-5471.

*(Noted
KE
4/27/98)*

Sincerely yours,

[Handwritten signature: John J. Savarese]

John J. Savarese, M.D., Ph.D
Director, Regulatory Affairs

JJS/ML/tc

RHÔNE-POULENC RORER RESEARCH AND DEVELOPMENT

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P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

*Noted
B. Page
12/7/97*

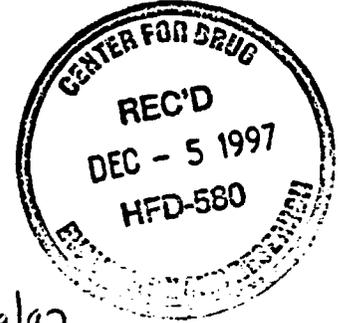
December 4, 1997

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

ORIG AMENDMENT

EC

12/4/97



REVIEWS COMPLETED	
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**NDA #20-870
ALIATIS (estradiol/norethindrone
acetate transdermal system)
RESPONSE TO FDA REQUEST
FOR INFORMATION**

Dear Dr. Rarick:

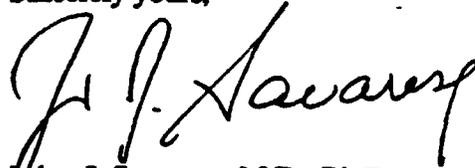
During a telephone conversation on October 7, 1997, Dr. Mitra asked RPR to submit shelf-life calculations with individual slopes and intercepts for individual lots. In an October 14 fax and follow-up October 28 submission, RPR indicated we would provide this information by December 5. This submission provides the requested information.

Appended to this letter are shelf-life calculations for individual lots of the Aliatis estradiol/NETA combination transdermal delivery system. RPR calculated these data using the 18 month NDA stability data, see report ARR 97-021. Also enclosed is the updated stability data for the NDA stability batches.

Eighteen months data are provided in report SEC 97-022. The data in this report support a shelf-life of 24 months at refrigeration (5°C) plus an additional 9 months at room temperature (25°C/60% RH). This represents a 3 month extension of the room temperature shelf-life from the 6 months contained in the original application. Because the updated shelf-life amends the materials submitted pursuant to 21 CFR § 314.50(d)(1), RPR certifies that a field copy of this amendment will be sent to our home FDA district office in accordance with 21 CFR § 314.60(c).

If you have any questions regarding this submission please contact me at (610) 454-5471.

Sincerely yours,

A handwritten signature in black ink, appearing to read "John J. Savarese". The signature is fluid and cursive, with the first name "John" and last name "Savarese" clearly distinguishable.

John J. Savarese, M.D., Ph.D
Director, Regulatory Affairs

JJS/ML/tc
Attachments

cc: Debra L. Pagano, Philadelphia District Office

RHÔNE-POULENC RORER RESEARCH AND DEVELOPMENT

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

SUPL NEW CORRESP

12 June, 1998

Dr. Samuel Haidar
Food and Drug Administration
HFD-870 Room 17B45
5600 Fishers Lane
Rockville, MD 20857



**NDA #20-870
COMBIPATCH
(estradiol/norethindrone acetate
transdermal system)**

GENERAL CORRESPONDENCE

Dear Dr. Haidar:

Per your request during our telephone conversation on 27 May, 1998, enclosed please find study reports for studies 101, 102, 103 and 105. Revisions include: inclusion of analytical method summaries, inclusion of pharmacokinetic tables and reformatting of summary text into WORD 7.0.

All other requests were provided in the package sent to you on 11 June, 1998.

If you have any additional questions regarding these submissions, please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

Sincerely yours,

John J. Savarese, M.D., Ph.D.
Director, Regulatory Affairs

JJS/MEE
haidar2.doc
Attachments

REVIEWS COMPLETED	
CSO ACTION:	
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CSO INITIALS	DATE

RHÔNE-POULENC RORER

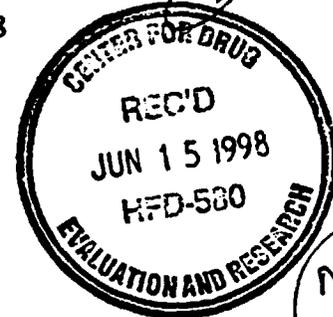
RHÔNE-POULENC RORER RESEARCH AND DEVELOPMENT

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COLLEGEVILLE, PA 19426-0107
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ORIG AMENDMENT

June 12, 1998

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



Handwritten notes:
2/2 6/30/98
HFD-580

NDA #20-870

Combipatch (estradiol/norethindrone acetate transdermal system)

**REVISED CARTON LABELS,
POUCH ARTWORK and PATIENT
INFORMATION LEAFLET**

Dear Dr. Rarick:

Based upon a discussion with J. Markow, attached are the revised carton labels, pouch artwork and patient information leaflet for your review. RPR has made minor modifications to these based upon our development of the market image.

We also intend to deliver an updated package insert (prior to the FDA Label review meeting on 16 June) which will reflect similar changes.

If you have any questions regarding this submission or if RPR can provide additional information please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

Sincerely yours,

John J. Savarese
John J. Savarese, M.D., Ph.D
Director, Regulatory Affairs

REVIEWS COMPLETED	
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Attachments

ORIGINAL

RHÔNE-POULENC RORER RESEARCH AND DEVELOPMENT

500 ARCOLA ROAD
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COLLEGEVILLE, PA 19426-0107
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ORIG AMENDMENT

BL

June 13, 1998



Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA #20-870
Combipatch (estradiol/norethindrone acetate transdermal system)
REVISED PACKAGE INSERT and ARTICLES

Dear Dr. Rarick:

Based upon a discussion with J. Markow and as mentioned in our correspondence of 12 June, 1998 attached is the revised package insert for review at the FDA Label review meeting on 16 June. Also attached are reference articles for your information.

If you have any questions regarding this submission or if RPR can provide additional information please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

Sincerely yours,

John J. Savarese

John J. Savarese, M.D., Ph.D
Director, Regulatory Affairs

REVIEWS COMPLETED	
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CSO INITIALS	DATE

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sub0613a.doc
Attachments

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

ORIG AMENDMENT

B2



June 17, 1998

Mr. John Markow
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NDA #20-870
Combipatch (estradiol/norethindrone acetate transdermal system)
REVISED PACKAGE INSERT AND PATIENT INFORMATION LEAFLET ON DISK

Dear Mr. Markow:

As requested on 16 June, enclosed is a copy of the revised package insert and patient information leaflet (WORD 7.0) on disk for your review.

If RPR can provide additional information please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

Sincerely yours,

John J. Savarese
John J. Savarese, M.D., Ph.D
Director, Regulatory Affairs

JJS/ME/mec
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RHÔNE-POULENC RORER PHARMACEUTICALS INC.

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

ORIG AMENDMENT

June 23, 1998

*Noted
7/1/98
I see the change
7/1/98*



John Markow, Esq.
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA #20-870
**CombiPatch (estradiol/norethindrone
acetate transdermal system)**

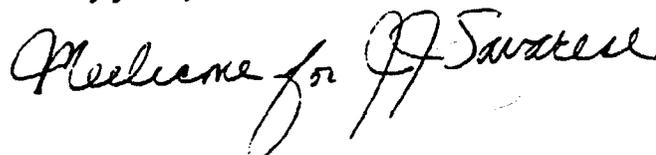
Dear Mr. Markow,

Per your request, I have enclosed an electronic copy of the revised package insert in WORD 7.0 format. The change in this version (from that sent on 13 June) is a modification of the dosage and administration section. Based on our discussion of 19 June, we understand that this minor change will not affect the Division's review clock.

If you have any questions regarding this submission please contact me at (610) 454-5471 or Ms. Mary Elicone at (610)-454-5859.

REVIEWS COMPLETED	
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CSO INITIALS	DATE

Sincerely yours,



John J. Savarese, M.D., Ph.D
Director, Regulatory Affairs

RHÔNE-POULENC RORER PHARMACEUTICALS INC.
 500 ARCOLA ROAD
 P.O. BOX 1200
 COLLEGEVILLE, PA 19426-0107
 TEL. 610-454-8000

SUPPL NEW CORRESP

*Noted
 case reviewed
 case reviewed
 June 24, 1998*

Dr. Lisa Rarick
 Division of Reproductive and Urologic Drug Products (HFD-580)
 Center for Drug Evaluation and Research
 Document Control Room #17B-45
 Food and Drug Administration
 5600 Fishers Lane
 Rockville, MD 20857



*81-5-98
 KR*

*Noted
 KR 7/1/98*

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NDA #20-870
 CombiPatch (estradiol/norethindrone acetate transdermal system)

CRFs for Dr. P. Price (Desk copy already sent to J. Markow for Dr. Price)

Dear Dr. Rarick,

Per the request of Dr. P. Price (via J. Markow), I have enclosed Case Report Forms for selected patients in the #201 and #202 studies who had endometrial hyperplasia and who we believe "fit" the description J. Markow provided to RPR on 22 June, 1998. We have also provided a summary of the hyperplasia follow-up.

The patients can be summarized as follows:

a) Patients treated with CombiPatch who had endometrial hyperplasia confirmed by two out of three pathologists and were included in the ITT at one year population analysis.

Study 201(Pt.	50/140 grp. and	50/400 grp.)*
Study 202 (pt.	50/140 grp. and	- 50/400 grp).*

b) Patients treated with CombiPatch who had hyperplasia confirmed by two out of three pathologists in tissue other than the endometrium (endometrial polyp).

Study 201(pt. #1721- 50/250 grp.)
 Study 202- N/A.

c) Patients who were enrolled in the study with hyperplasia present at screening (confirmed by two out of three pathologists).

Study 201 (Pt. 50/140 grp.) Also included in item 1.

Study 202 (pt. 50/250 grp) Note: First pathologist diagnosed atrophic endometrium, second pathologist diagnosed hyperplasia in tissue other than the endometrium and the third pathologist diagnosed endometrial hyperplasia.

d) Patients for whom hyperplasia resolution information was not available at the time of the Final Study Report.

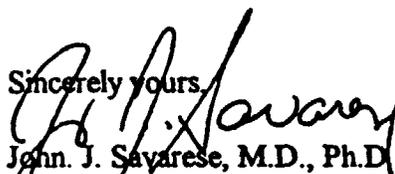
Study 201 - N/A

Study 202 - (Pt. 50/250 grp. also included in item 3 and E2 50 grp.)

*NOTE: Patients for whom CRFs were not previously submitted to FDA

If you have any questions regarding this submission please contact me at (610) 454-5471 or Ms. Mary Elicone at (610)-454-5859.

Sincerely yours,



John J. Savarese, M.D., Ph.D.
Director, Regulatory Affairs

Attachments
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RHÔNE-POULENC RORER PHARMACEUTICALS INC.

500 ARCOLA ROAD
P.O. BOX 1200
COLLEGEVILLE, PA 19426-0107
TEL. 610-454-8000

ORIG AMENDMENT

33

July 06, 1998

Dr. Lisa Rarick.
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857



NDA #20-870
CombiPatch (estradiol/norethindrone acetate transdermal system)

Dear Dr. Rarick,

Per the 30 June request of Mr. Markow/Dr. S. Haidar, I have enclosed a bioequivalence analysis for Study #122 illustrating application of CombiPatch on the abdomen versus buttocks. This analysis is similar to that done for study #104.

If you have any questions regarding this submission please contact me at (610) 454-5471 or Ms. Mary Elicone at (610)-454-5859.

Sincerely yours,

John J. Savarese, M.D., Ph.D
Director, Regulatory Affairs

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I. <input type="checkbox"/> MEMO
CSO INITIALS	DATE

RPR RHÔNE-POULENC RORER

RHÔNE-POULENC RORER PHARMACEUTICALS INC.

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BL

July 15, 1998

Dr. Lisa Rarick,
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

REVIEW	
CSO APPROVED	
<input type="checkbox"/> LETTER	<input type="checkbox"/> MEMO
CSO INITIALS	DATE

**NDA #20-870
CombiPatch (estradiol/norethindrone
acetate transdermal system)**

Dear Dr. Rarick,

RPR has reviewed FDA's comments on the labeling for CombiPatch. Attached are the updated versions of the package insert (PI) and patient information leaflet (PIL) reflecting FDA's requested edits.

RPR would like to respectfully request further agency consideration of the two specific issues mentioned below.

1) Quality of Life

RPR requests that the FDA reconsider the deletion of the Quality of Life statement originally included in the CLINICAL PHARMACOLOGY section of the labeling (cited below).

To the best of RPR's knowledge, the CombiPatch dossier was the first in which the clinical program included the collection of Quality of Life data for all Phase II and III trials using validated Quality of Life instruments. These data were measured prospectively and compared to both placebo and active controls. The results noted in the statement below were consistently increased in 3, 6, and 12 month studies. These were seen as significant by our experts from Bowman Gray School of Medicine.

The Quality of Life data provide the physician with information that can help respond to questions menopausal women frequently ask regarding hormone replacement therapy and its effect on sexuality. Additionally, this data has the potential to reinforce patient compliance with



therapy by improving sleep disturbance, another presenting symptom typical of menopausal women.

Drs. Sally Shumaker and Michelle Naughton of the Bowman Gray School of Medicine, were the experts who designed these instruments and conducted the analyses on these Quality of Life data. Both women would be willing to discuss the data and conclusions with the Agency, if helpful.

Below is the reference in the package insert

In two *Continuous Combined* regimen and two *Continuous Sequential* regimen studies with CombiPatch™ (two studies versus active controls [VIVELLE®] and two studies versus placebo) the patients who received estradiol therapy experienced an improvement in sexual arousal and satisfaction, as well as sleep disturbance as assessed in Quality of Life surveys.

2) Black Box

In the 22 June 1998 Pink Sheet, Dr. Rarick was quoted at a recent DIA conference in Boston as indicating that the guidelines for Osteoporosis claims and the estrogen guidance issued in 1992 were under revision. RPR would like to respectfully inquire as to the status of revisions related to this article as it pertains to proposed RPR labeling statements.

a. Osteoporosis Bone Marker Data:

RPR would like to know the status of the FDA revisions regarding osteoporosis claims and whether the language below is perhaps appropriate in the context of revised guidances and therefore not so premature to consider in the labeling for CombiPatch™?

The language proposed by RPR in the June 1998 labeling was:

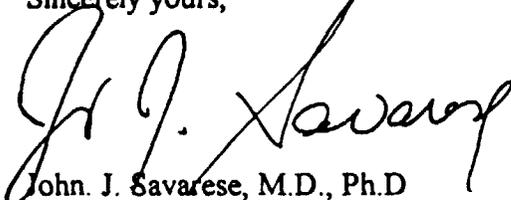
A long-term consequence of estrogen deprivation in women is development of osteoporosis. Several studies have shown that estrogens alone, as well as estrogens in combination with progestins, prevent loss of bone mass and bone fractures. At the conclusion of two one year studies in 955 postmenopausal women, CombiPatch™, in *Continuous Combined* or *Continuous Sequential* regimens, demonstrated marked mean percent decreases from baseline of C-telopeptide/ and N-telopeptide/Creatinine ratios (biochemical markers of bone resorption), as well as, osteocalcin and alkaline phosphatase levels (biochemical markers of bone formation). These decreases were generally noted by the first assessment (week 24 of therapy). All markers at week 52 of therapy were at published pre-menopausal levels.

b. Boxed warning regarding endometrial carcinoma with estrogen/progestin combinations and use during pregnancy

Are there any intentions to modify the boxed warning regarding these topics?

Thank you in advance for your consideration of these two issues. If you have any questions regarding this submission please contact me at (610) 454-5471 or Ms. Mary Elicone at (610)-454-5859.

Sincerely yours,

A handwritten signature in black ink, appearing to read "John J. Savarese". The signature is fluid and cursive, with the first letters of the first and last names being capitalized and prominent.

John J. Savarese, M.D., Ph.D
Director, Regulatory Affairs

Attachments

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ORIG AMENDMENT

3U

July 16, 1998

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

**NDA #20-870
CombiPatch
(estradiol/norethindrone acetate
transdermal system)
SAFETY UPDATE REPORT**

Dear Dr. Rarick:

In accordance with your request and 21 CFR § 314.50(d)(5)(vi)(b), attached is an updated Safety Update Report for our New Drug Application, NDA # 20-870, submitted on August 7, 1997.

If you have any questions regarding this submission please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

Sincerely yours,

John J. Savarese, M.D., Ph.D
Director, Regulatory Affairs

JJS/MEE/mee
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RHÔNE-POULENC RORER PHARMACEUTICALS INC.

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ORIG AMENDMENT

BB

Dr. Lisa Rarick
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

June 22, 1998

*Noted
Review
By Haidar*



*note
KR
7/2/98*

**NDA #20-870
CombiPatch (estradiol/norethindrone
acetate transdermal system)
OFFICIAL SUBMISSION TO FILE**

*Reviewed desk copy
7-01-98*

Dear Dr. Rarick:

As requested on 19 June by J. Markow, enclosed is a copy of our 11 June submission to Dr. S. Haidar. We are resubmitting this officially to ensure it reaches our NDA file.

If RPR can provide additional information please contact me at (610) 454-5471 or Ms. Mary Elicone at (610) 454-5859.

Sincerely yours,

[Signature]
John J. Savarese, M.D., Ph.D.
Director, Regulatory Affairs

JJS/ME/mec
subm0622.doc

REVIEWS COMPLETED	
CSO ACTION:	
<input type="checkbox"/> LETTER	<input checked="" type="checkbox"/> N.A.I.
<input type="checkbox"/> MEMO	
CSO INITIALS <i>[Signature]</i>	DATE <i>7/2/98</i>

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ORIG AMENDMENT

3L



August 4, 1998

Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products (HFD-580)
Center for Drug Evaluation and Research
Document Control Room #17B-45
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NDA 20-870
CombiPatch™ (estradiol/norethindrone acetate)
transdermal system
Response to Request for Information

Dear Dr. Rarick:

Reference is made to our NDA 20-870 for CombiPatch™ (estradiol/norethindrone acetate) transdermal system and to the phone contacts, teleconferences and RPR's written responses of July 15, 1998, July 29, 1998 and August 3, 1998 concerning your letters dated July 7, 1998 and July 31, 1998.

The purpose of this letter is to respond to all issues in your July 31, 1998 letter. Per your request, response to the Labeling Comment number 2 of your July 7, 1998 letter is also included.

The enclosed submission has been formatted as follows: each comment or request for information has been reiterated in bold lettering and the RPR response follows immediately in normal text.

Lisa Rarick, M.D., Director
CombiPatch™
NDA 20-870
August 4, 1998
Page 2



It is the intention of RPR to assist the Division in any way to expedite the review process of this pending application. If you require any additional information, please contact me at (610) 454-5471.

Sincerely yours,

John J. Savarese, M.D., Ph.D.
Director, Regulatory Affairs

JJS/SC
Attachments