CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

75-796

CORRESPONDENCE

DURAmed

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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

ORIG AMENDMENT

N-FA

April 11, 2001

Gary Buehler, Acting Director
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-796: Levonorgestrel and Ethinyl Estradiol 0.1 mg / 0.02 mg Tablets, USP

Subject: Telephone Amendment

Dear Mr. Buehler:

Reference is made to a telephone conversation on 4/11/01 between Ms. Angie Stewart of Duramed and Ms. Ruby Yu of the Office concerning our abbreviated new drug application (ANDA) #75-796 for Levonorgestrel and Ethinyl Estradiol 0.1 mg / 0.02 mg Tablets, USP. We now amend the application by providing a revised specification sheet for Ethinyl Estradiol, USP to meet current USP requirements.

This amendment is submitted in one (1) volume. Duramed is filing an archival copy (blue folder) and a technical review copy (red folder). In addition, a copy of this amendment was faxed to the document control room. We certify that a true copy of this amendment as described in 21 CFR 314.50 (d)(5) has been provided to the Food and Drug Administration, Cincinnati, District Office in Cincinnati, Ohio.

Please direct any written communications regarding this amendment to me at the above address. If you have any questions or require any additional information, please contact Ms. Angie Stewart at (513) 731-9900, by fax at (513) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

Astewart /for

John R. Rapoza, M.S., R.Ph.
Sr. Vice President, Regulatory Affairs

DURAmed

The Art of Leadership...
The Science of Change

Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

April 3, 2001

Gary Buehler, Acting Director
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

RE: ANDA 75-796: Levonorgestrel and Ethinyl Estradiol 0.1 mg / 0.02 mg Tablets, USP

Subject: Telephone Amendment

Dear Mr. Buehler:

Reference is made to an amendment faxed today to Ms. Ruby Yu and the Document Control Room concerning our abbreviated new drug application (ANDA) #75-796 for Levonorgestrel and Ethinyl Estradiol 0.1 mg / 0.02 mg Tablets, USP. Reference is also made to a phone conversation between Ms. Ruby Yu of the Office and Ms. Angie Stewart of Duramed concerning the fax. In this conversation, Ms. Yu informed us that our statement contained in the Overview regarding the type of supplement required for expiration date extension was incorrect. We now administratively withdraw the amendment that was faxed to the Document Control Room (hard copy not submitted) and replace it with the attached corrected amendment.

Reference is made to a telephone conversation on 4/2/01 between Mr. John Rapoza of Duramed and Ms. Ruby Yu and Dr. Upinder Atwal of the Office concerning our abbreviated new drug application (ANDA) #75-796 for Levonorgestrel and Ethinyl Estradiol 0.1 mg / 0.02 mg Tablets, USP. We now amend the application by withdrawing the proposed six (6) month expiration dating for the bulk powder preparations and revising the specification for residual for the in-process Prep.

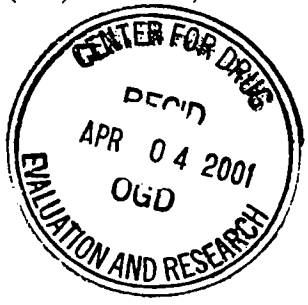
This amendment is submitted in one (1) volume. Duramed is filing an archival copy (blue folder) and a technical review copy (red folder). We certify that a true copy of this amendment as described in 21 CFR 314.50 (d)(5) has been provided to the Food and Drug Administration, Cincinnati, District Office in Cincinnati, Ohio.

Please direct any written communications regarding this amendment to me at the above address. If you have any questions or require any additional information, please contact Ms. Angie Stewart at (513) 731-9900, by fax at (513) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

A Stewart /for

John R. Rapoza, M.S., R.Ph.
Sr. Vice President, Regulatory Affairs



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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

March 1, 2001

Gary Buehler, Acting Director
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/FA

RE: ANDA 75-796: Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg / 0.02 mg

Subject: Amendment to February 26, 2001 Facsimile Amendment

Dear Mr. Buehler:

Reference is made to a letter dated February 13, 2001 concerning minor deficiencies in our abbreviated new drug application (ANDA) #75-796 for Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg / 0.02 mg and to our response dated February 26, 2001. Reference is also made to a telephone conversation between Ms. Ruby Yu, project manager and Ms. Annette Arlinghaus of Duramed in which Ms. Yu was informed that the facsimile response is being amended. Specifically, this submission is to provide two (2) corrected drug substance COAs.

This amendment is submitted in one (1) volume. Duramed is filing an archival copy (blue folder) and a technical review copy (red folder).

We certify that a true copy of this amendment as described in 21 CFR 314.50 (d)(5) has been provided to the Food and Drug Administration, Cincinnati, District Office in Cincinnati, Ohio.

Please direct any written communications regarding this amendment to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus /for

John R. Rapoza, M.S., R.Ph.
Sr. Vice President, Regulatory Affairs

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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

February 26, 2001

Gary Buehler, Acting Director
Office of Generic Drugs, CDER
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/FA

RE: ANDA 75-796: Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg / 0.02 mg

Subject: FACSIMILE Amendment

Dear Mr. Buehler:

Reference is made to a letter dated February 13, 2001 concerning minor deficiencies in our abbreviated new drug application (ANDA) #75-796 for Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg / 0.02 mg. We have noted the deficiencies and are amending the application, having responded to all of the deficiencies. For each item we first restate the deficiency then present our response or explanation.

This amendment is submitted in one (1) volume. Duramed is filing an archival copy (blue folder) and a technical review copy (red folder).

We certify that a true copy of this amendment as described in 21 CFR 314.50 (d)(5) has been provided to the Food and Drug Administration, Cincinnati, District Office in Cincinnati, Ohio.

Please direct any written communications regarding this amendment to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus /for

John R. Rapoza, M.S., R.Ph.
Sr. Vice President, Regulatory Affairs

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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

November 30, 2000

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

AF
FDA ORIG AMENDMENT

RE: ANDA 75-796: Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg / 0.02 mg
Subject: Labeling Amendment

Dear Mr. Buehler:

Reference is made to a letter dated September 7, 2000 concerning labeling deficiencies in our abbreviated new drug application (ANDA) #75-796 for Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg / 0.02 mg. We have noted the deficiencies and are amending the application, having responded to all of the deficiencies. For each item we first restate the deficiency then present our response or explanation:

This amendment is submitted in one (1) volume. Duramed is filing an archival copy (blue folder) and a technical review copy (red folder).

We certify that a true copy of this amendment as described in 21 CFR 314.50 (d)(5) has been provided to the Food and Drug Administration, Cincinnati, District Office in Cincinnati, Ohio.

Please direct any written communications regarding this amendment to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

A Stewart for

John R. Rapoza, M.S., R.Ph.
Sr. Vice President, Regulatory Affairs

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

(513) 731-9900
(800) 543-8338

September 15, 2000

ORIG AMENDMENT
N/AC

Mr. Gary Buehler
Acting Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-796: Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg / 0.02 mg
Subject: MAJOR Amendment

Dear Mr. Buehler:

Reference is made to a letter dated August 2, 2000 concerning major deficiencies in our abbreviated new drug application (ANDA) #75-796 for Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg / 0.02 mg. We have noted the deficiencies and are amending the application, having responded to all of the deficiencies. For each item we first restate the deficiency then present our response or explanation.

This amendment is submitted in one (1) volume. Duramed is filing an archival copy (blue folder) and a technical review copy (red folder).

We certify that a true copy of this amendment as described in 21 CFR 314.50 (d)(5) has been provided to the Food and Drug Administration, Cincinnati, District Office in Cincinnati, Ohio.

Please direct any written communications regarding this amendment to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

A Stewart for

John R. Rapoza, M.S., R.Ph.
Sr. Vice President, Regulatory Affairs

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BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 75-796 APPLICANT: Duramed Pharmaceuticals, Inc.

DRUG PRODUCT: Ethinyl Estradiol and Levonorgestrel Tablets, USP 0.02 mg/0.1 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

We acknowledge that the dissolution testing will be incorporated into your stability and quality control programs as specified in USP 24.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

for

Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Mean Plasma PK Parameters for Ethinyl Estradiol

Parameter	Test Mean (A)	Test %CV (A)	Ref Mean (B)	Ref %CV (B)	T/R Ratio (A)/(B)
AUCT	877.202	32.173	814.885	30.84	1.076
AUCI	1009.609	30.49	953.201	27.76	1.059
CMAX	110.065	29.409	102.422	26.976	1.075
TMAX	1.559	30.313	1.829	31.139	0.853
KEL	0.055	26.914	0.059	27.9	0.939
THALF	13.71	32.774	12.88	32.707	1.064

Mean Plasma PK Parameters for Levonorgestrel

Parameter	Test Mean (A)	Test %CV (A)	Ref Mean (B)	Ref %CV (B)	T/R Ratio (A)/(B)
AUCT	36.066	42.354	36.383	46.373	0.991
AUCI	38.937	39.265	39.352	42.483	0.989
CMAX	3.348	33.856	3.416	35.205	0.98
TMAX	1.548	54.686	1.72	42.829	0.9
KEL	0.028	26.452	0.028	26.604	0.999

Figure 1

Mean Plasma Ethinyl Estradiol Concentrations

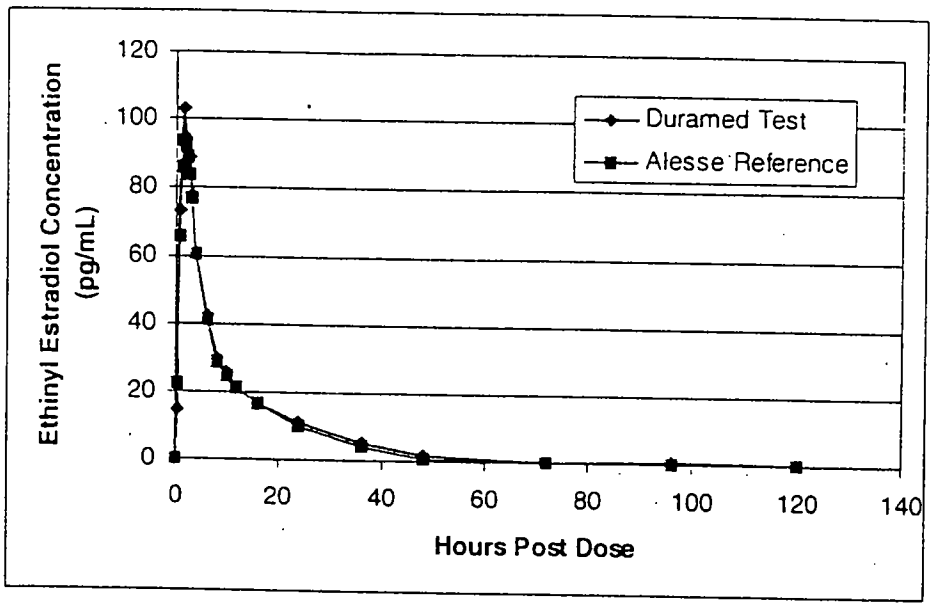

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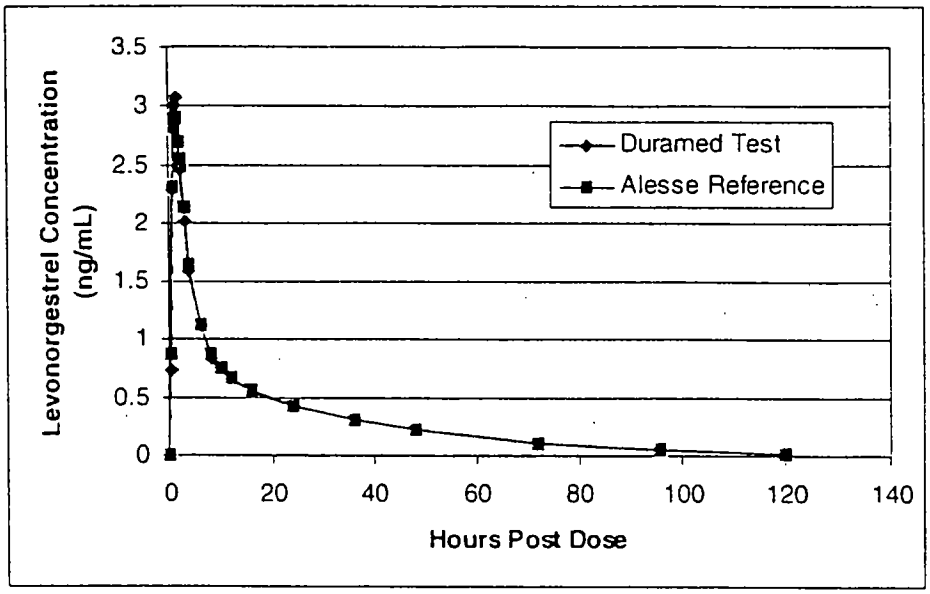
Figure 2

Mean Plasma Levonorgestrel Concentrations



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

(513) 731-9900
(800) 543-8338

March 16, 2000

NDA ORIG AMENDMENT

AB

NAI
PMP
3/27/00

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-796: Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg / 0.02 mg
Subject: Amendment

Dear Mr. Sporn:

Reference is made to correspondence dated March 7, 2000 filed to ANDA 75-796 for Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg. In that letter, Duramed committed to providing patient case report forms (CRF) and a new blank placebo tablets commercial batch record as requested. In this amendment, we provide a copy of a new blank placebo tablets batch record and the CRFs.

This ANDA is submitted in three (3) volumes. Duramed is filing an archival copy (blue folders) of the application that contains all the information, a technical review copy (red folders) containing the commercial placebo BMR and a bioequivalence review copy (orange folders) containing the CRFs for the bioequivalence study.

We certify that a true copy of the technical section as described in 21 CFR 314.50 (d)(5) has been provided to the Food and Drug Administration, Cincinnati, District Office in Cincinnati, Ohio.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

Angie Stewart
for

John R. Rapoza, M.S., R.Ph.
Sr. Vice President, Regulatory Affairs

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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

March 10, 2000

BA/BE & CMC EVA Amendment

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

NC

RE: **ANDA 75-796: Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg / 0.02 mg**
Subject: **BA/BE & CMC EVA Amendment**

Dear Mr. Sporn:

Reference is made to the original ANDA submission dated January 31, 2000.

We now amend this application to provide for an Entry and Validation Application (EVA) diskettes containing the EVA BA/BE and CMC information.

We declare that the electronic data contained on the enclosed diskettes is the same as that data submitted in the hardcopy that was filed in the original submission of January 31, 2000. Please note that subsequent to the original ANDA filing, Duramed made a commitment to the FDA to reduce the size of the blank commercial placebo batch record from [redacted] ablets to [redacted] ablets.

This **Amendment** is enclosed in one (1) volume and includes three (3) copies, an archival (blue) copy, and two review copies. The red copy is provided for the CMC reviewer with a CD-ROM containing the CMC ESD, the log file and the Companion Document. The orange copy is provided for the bioequivalence reviewer with a diskette containing the BA/BE ESD, the log file and the Companion Document.

If you have any questions, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax (513) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus /for

John R. Rapoza, M.S., R.Ph.
Sr. Vice President, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH
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MAR 13 2000
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Duramed Pharmaceuticals, Inc.
5040 Duramed Drive
Cincinnati, Ohio 45213
(513) 731-9900

March 7, 2000

NEW CORRESP
NC

Mr. Paras Patel, Regulatory Support
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: ANDA 75-796: Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg / 0.02 mg
Subject: Correspondence

Dear Mr. Patel:

Reference is made to a telephone conference call of today between Mr. Paras Patel, Regulatory Support, Patrick Nwakama and Vijay Kharidia, bio-reviewers, and Ken Phelps, John Rapoza and Annette Arlinghaus from Duramed regarding clarifications to ANDA 75-796 for Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg.

In this teleconference, the following items were discussed:

Bio Reviewers:

- Request for analytical SOPs. Clarifications were provided to the reviewers in the form of referenced ANDA page numbers containing assay methodology, reanalysis and calculations (pages 02-280 through 02-283). The reviewer indicated that the information was sufficient.
- Request for the manufacture date of the bio-batch. The page number containing this information was provided (page 02-039a).
- Request for medical records. **Duramed hereby commits to submit the case report forms (CRFs) generated during the bioequivalence study.**

Chemistry Reviewer:

- Request for the ANDA references to the executed packaging records for the placebo batch. Pages 04-362, 04-318 and 04-391 were provided.

- Request for new blank commercial placebo batch record for not more than (NMT) a 10-fold scale-up from the executed batch. **Duramed hereby commits to submit a blank commercial placebo batch record for tablets.**

This correspondence is submitted in one (1) volume and three (3) copies: an archival copy (blue folder) and two (2) technical review copies (red and orange folders) containing all of the information in the archival copy. In addition, a copy was faxed to you at 301-594-1174.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

Annette Arlinghaus /for

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs

DURAmed

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The Science of Change

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

(513) 731-9900
(800) 543-8338

January 31, 2000

Mr. Douglas L. Sporn
Director, Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

RE: New ANDA Submission for Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg / 0.02 mg

Dear Mr. Sporn:

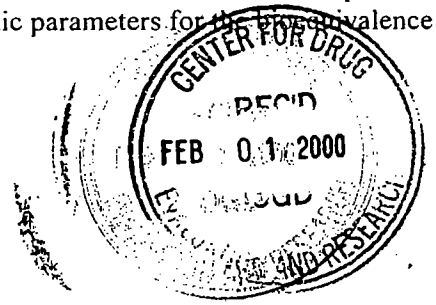
Duramed Pharmaceuticals, Inc. (Duramed) submits today, in accordance with 21CFR 314.94, an original abbreviated new drug application (ANDA) seeking approval to market Levonorgestrel and Ethinyl Estradiol Tablets, USP 0.1 mg/0.02 mg that are bioequivalent to the reference drug, Alesse™ Tablets, manufactured by Wyeth-Ayerst pursuant to NDA # 20-683.

Aviane™ is the proposed trade name for Duramed's brand of Levonorgestrel and Ethinyl Estradiol Tablets. If this trade name is unacceptable, we propose the trade name [redacted].

In accordance with the study protocol, Duramed conducted one (1) definitive *in vivo* bioequivalence study for which we include the protocol and final report.

Levonorgestrel and Ethinyl Estradiol Tablets, USP are stable and a two-year expiration dating is requested. Three months accelerated stability testing supports the proposed two-year expiration dating.

This ANDA is submitted in five (5) volumes. Duramed is filing an archival copy (blue folders) of the application that contains all the information required in the ANDA and a technical review copy (red folders) containing all the information in the archival copy with the exception of the Bioequivalence section. The Bioequivalence section (orange folders) contains the bioequivalence data as well as a computer disk containing ASCII files of the measured plasma concentrations of the drug analytes and the pharmacokinetic parameters for the bioequivalence study.



For detailed information on the organization of this application, please refer to the following "EXECUTIVE SUMMARY - Organization of the ANDA".

We certify that a true copy of the technical section described in 21 CFR 314.50 (d)(1), the chemistry, manufacturing, and controls section of this submission, has been provided to the Food and Drug Administration, Cincinnati, District Office in Cincinnati, Ohio.

We will also prepare for submission an electronic validation application (EVA) of this ANDA. This EVA and its certification will be filed as an amendment within 30 days.

Please direct any written communications regarding this ANDA to me at the above address. If you have any questions or require any additional information, please contact Ms. Annette Arlinghaus at (513) 731-9900, by fax at (513) 458-6007, or the undersigned at (513) 458-7274.

Sincerely,

A. Stewart for

John R. Rapoza, M.S., R.Ph.
Vice President, Regulatory Affairs