# CENTER FOR DRUG EVALUATION AND RESEARCH

## APPLICATION NUMBER: NDA 20-756

## CORRESPONDENCE

NDA 20-756

MAR 25 1997

Columbia Research Laboratories, Inc.
Attention: Howard Levine, Pharm. D.
Vice President
100 North Village Avenue - Suite 32
Rockville Centre, NY 11570

Dear Dr. Levine:

Please refer to your pending November 13, 1996, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crinone® (progesterone gel).

We have completed our review of the Chemistry, Manufacturing and Controls section of your submission and have the following comments and requests for information:

Drug Substance

1. The acceptance specification and the certificate of analysis for progesterone from (bulk drug product manufacturer) should be provided. The acceptance specification should include at least an identification test, preferably by Infrared analysis.

2. The source of the reference standard for progesterone and the related substances of progesterone should be provided. A certificate of analysis should be provided for non-compendial reference standards. If non-compendial reference standards other than are used, the methods of manufacture and characterization including the proof of structure should be provided.

General Tests and Specifications:

1. The certificate of analysis containing acceptance specifications of all excipients should be provided.

2. The source of reference standard for sorbic acid should also be provided.

3. Purified water and Sodium hydroxide used in the formulation should comply with USP or NF specifications.

4. Since Crinone is a low dose %) emulsion with progesterone particles suspended in the product, the content uniformity of progesterone should be a part of the quality control test. A method for content uniformity determination (uniformity differences from applicator to applicator) should be provided. The content uniformity should be

included in the release specification for the product. The Methods Validation for the content uniformity test should be provided.

5. The assay method for progesterone and total progesterone related substances in the finished product do not provide the method for preparation of a composite sample. The composite sample preparation method should be provided and adopted.

6. The limits of detection for each of the related substances in the finished product should be provided in the method of determination of total progesterone related substances in Crinone®.

7. The release rate should be part of quality control and its specification should be included in the Regulatory Specifications. Since the release rate test is a three-day test, the number of batches to be tested for release rate could be reduced by using a statistical scheme in case a large number of batches are to be produced in a year. The Methods Validation for the release rate test should be included in the Methods Validation package. Further comments, if any, on the release rate will be provided in the Clinical Pharmacology and Biopharmaceutics reviews.

8. The Microbial Limit Test on the finished product should be conducted according to the method described in the USP 23.

Stability

1. The storage conditions should be provided for test intervals in the proposed protocol for the first three commercial lots to be placed on stability. The stability data may be generated according to the ICH guidelines, although an alternate protocol with scientific rationale is acceptable.

2. The stability specification for sorbic acid contains only an upper limit. Since the preservative effectiveness is directly related to the sorbic acid concentration, a lower limit for sorbic acid should be provided.

Labeling

1. The established name "progesterone vaginal gel" and storage conditions should be included on the overwrap. Please submit the actual draft labeling for carton, overwrap and packaging insert.

2. The first sentence of Labeling Text in the **DESCRIPTION** Section of the Package Insert reads

The established name "Progesterone vaginal gel" should follow the TRADENAME "Crinone". In the same sentence the word should be clarified; otherwise, it should be deleted.

DMF

1. The DMF is being reviewed separately. The DMF holder will be notified of any deficiencies.

We would appreciate your prompt written response so we can continue our evaluation of your NDA.

If you have any questions, please contact Diane Moore, Consumer Safety Officer, at (301) 827-4260.

Sincerely,

Lisa D. Rarick, M.D.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-756
HFD-580/Div. Files
HFD-580/CSO/D.Moore
HFD-580/LRarick/HJolson/AMitra/MRhee
HFD-820/ONDC Division Director

Drafted by: dm/March 7, 1997/n20756cm.dl

Concurrences:
LPauls 03.07.97/AMitra, MRhee 03.07.97/HJolson 03.19.97

INFORMATION REQUEST (IR)

Diane Moore 3/20/97

NDA 20-756

FEB - 4 1997

Columbia Research Laboratories, Inc.
Attention: Howard Levine, Pharm.D.
100 N. Village Avenue
Rockville Centre, NY 11570

Dear Dr. Levine:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crinone® (progesterone gel), NDA 20-756.

In accordance with 21 CFR 314.101, your submission was accepted for filing on January 12, 1997.

Should you have any questions concerning this NDA, please contact Diane Moore, Consumer Safety Officer, at (301) 827-4260.

Sincerely,

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

cc:
Original NDA 20-756
HFD-580/Div. Files
HFD-580/CSO/D.Moore
HFD-580/LRarick/HJolson/RBennett/MRhee/AMitra/AJordan/KRaheja/LPauls
DISTRICT OFFICE

Drafted by: dm/January 17, 1997/n20756.fl

Concurrence:
LPauls 01.22.97/RBennett, AMitra, MRhee, KRaheja, AJordan 01.29.97/HJolson01.30.97
LRarick 01.31.97
LRarick 01.31.97

ACKNOWLEDGEMENT (AC)

Dm 1/31/97

NDA 20-756

JAN 29 1997

Columbia Research Laboratories, Inc.
Attention: Howard Levine, Pharm.D.
100 N. Village Avenue
Rockville Centre, NY 11570

Dear Dr. Levine:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Crinone® (progesterone gel), NDA 20-756.

In accordance with 21 CFR 314.101, your submission was accepted for filing on January 12, 1997.

Should you have any questions concerning this NDA, please contact Diane Moore, Consumer Safety Officer, at (301) 827-4260.

Sincerely,

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

cc:
Original NDA 20-756
HFD-580/Div. Files
HFD-580/CSO/D.Moore
HFD-580/LRarick/HJolson/PPrice/MRhee/AMitra/AJordan/KRaheja/LPauls
DISTRICT OFFICE

Drafted by: dm/January 17, 1997/n20756.fl

Concurrence:
LPauls 01.22.97

ACKNOWLEDGEMENT (AC)

NDA 20-756

NOV 19 1996

Columbia Research Laboratories, Inc.
Attention: Howard Levine, Pharm.D.
100 N. Village Avenue
Rockville Centre, NY 11570

Dear Dr. Levine:

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: | Crinone® (progesterone gel) |
| Therapeutic Classification: | Priority |
| Date of Application: | November 13, 1996 |
| Date of Receipt: | November 13, 1996 |
| Our Reference Number: | 20-756 |

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 12, 1997, in accordance with 21 CFR 314.101(a).

Under 21 CFR 314.102(c) of the new drug regulations, you may request an informal conference with this Division (to be held approximately 90 days from the above receipt date) for a brief report on the status of the review but not on the application's ultimate approvability. Alternatively, you may choose to receive such a report by telephone. Should you wish a conference, a telephone report, or if you have any questions concerning this NDA, please contact Diane Moore, Consumer Safety Officer, at (301) 827-4260.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application.

Sincerely,

11/18/96

Lana L. Pauls, M.P.H.
Chief, Project Management Staff
Division of Reproductive and Urologic Drug Products (HFD-580)
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Original NDA 20-756
HFD-580/Div. Files
HFD-580/CSO/D.Moore
HFD-580/LRarick/HJolson/PPrice/MRhee/AMitra/AJordan/KRaheja/LPauls
DISTRICT OFFICE

Drafted by: dm/November 18, 1996/n20756ac.118

ACKNOWLEDGEMENT (AC)

COLUMBIA
RESEARCH
LABORATORIES INC

May 13, 1997

Food & Drug Administration
Center for Drug Evaluation and Research
Documents and Records Section
12420 Parklawn Drive
Rockville, MD 20852

**Attention:** Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

**RE:** Amendment to NDA 20-756
CRINONE® (progesterone gel)

Dear Dr. Rarick:

We reference our NDA 20-756 for CRINONE® (progesterone gel) submitted on November 13, 1996 to support the use of CRINONE® for progesterone supplementation or replacement as part of an ART treatment for infertile women with progesterone deficiency.

This letter serves to document a commitment that the final study report for the Treatment Protocol being conducted under IND entitled "Use of Crinone (COL-1620) in Women Undergoing ART Procedures", protocol number COL1620-120US, will be submitted to the Division.

If there are any questions concerning this submission, please contact the undersigned at (516) 766-2660.

Yours truly,

Howard Levine, Pharm.D
Vice President
Columbia Research Laboratories, Inc.

100 No. Village Avenue
Rockville Centre, NY 11570

TEL: (516) 766-2847
FAX: (516) 766-2873

COLUMBIA
RESEARCH
LABORATORIES, INC

ORIGINAL

May 6, 1997

ORIG AMENDMENT

REVIEWS COMPLETED

CSO ACTION
☐ LETTER ☐ N.A.I ☐ MEMO

CSO INITIALS DATE

Food & Drug Administration
Center for Drug Evaluation and Research
Documents and Records Section
12420 Parklawn Drive
Rockville, MD 20852

**Attention:** Diane Moore, Consumer Safety Officer
Division of Reproductive and Urologic Drug Products

**RE:** Amendment to NDA 20-756
CRINONE® (progesterone gel)
Response to FDA Request

Dear Ms. Moore:

We reference our NDA 20-756 for CRINONE® (progesterone gel) submitted on November 13, 1996 to support the use of CRINONE® for progesterone supplementation or replacement as part of an ART tretament for infertile women with documented or suspected progesterone deficiency. In response to your request, we are amending the application with the enclosed information:

- Draft labeling , consisting of 4 boxes each of the eighteen applicator package and six applicator package (Note: the packaging will include three boxes of the six applicator package within a box of the eighteen applicator package)
- Draft labeling, consisting of the 4 copies of the printing on the flow wrapper for the applicators

If there are any questions concerning this submission, please contact the undersigned at (516) 766-2660.

Yours truly,

Howard Levine, Pharm.D.
Vice President
Columbia Research Laboratories, Inc.

Attachments

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
MAY 08 1997
HFD-580

100 No Village Avenue
Rockville Centre, NY 11570

TEL. (516) 766-2847
FAX (516) 766-2873

ORIGINAL

COLUMBIA
RESEARCH
LABORATORIES, INC

April 19, 1997

**ORIG AMENDMENT**

| REVIEWS COMPLETED |
|---|
| CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ ME |
| CSO INITIALS |

Food & Drug Administration
Center for Drug Evaluation and Research
Documents and Records Section
12420 Parklawn Drive
Rockville, MD 20852

**Attention:** Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

**RE:** Amendment to NDA 20-756
CRINONE® (progesterone gel)
Response to FDA Requests

Dear Dr. Rarick:

We reference our NDA 20-756 for CRINONE® (progesterone gel) submitted on November 13, 1996 to support the use of CRINONE® for progesterone supplementation or replacement as part of an ART treatment for infertile women with documented or suspected progesterone deficiency. In response to the request of Dr. Mitra for an MSDS for progesterone, and concerning the Environmental Assessment section of the submission, we are amending the application with the following information and enclosures:

1. MSDS sheet for progesterone as provided by the suppler

2. Concerning Disposal of Returned/Damaged Goods - As stated in the Environmental Assessment, all Crinone® manufacturing occurs outside the United States. Section 3.12.4E (Disposal Sites) and referenced appendices describe the disposal method during manufacture, as well as that associated with patient use. Drug product returned to Columbia Laboratories after entry into the United States will be disposed of in a solid waste management system. Columbia Laboratories is in the process of identifying a site for return in the United States.

3. In lieu of cross-referencing Section 3.12 (Environmental Assessment) of NDA 20-701, enclosed is Section 3.12 (Environmental Assessment) prepared for NDA 20-756.

If there are any questions concerning this submission, please contact the undersigned at (516) 766-2660.


Yours truly,

Howard Levine, Pharm.D.
Vice President
Columbia Research Laboratories, Inc.

100 No. Village Avenue
Rockville Centre, NY 11570

TEL: (516) 766-2847
FAX: (516) 766-2873

ORIGINAL

COLUMBIA
RESEARCH
LABORATORIES INC

April 19, 1997

ORIG AMENDMENT

Food & Drug Administration
Center for Drug Evaluation and Research
Documents and Records Section
12420 Parklawn Drive
Rockville, MD 20852

| REVIEWS COMPLETED | |
|---|---|
| CSO ACTION: ☐ LETTER ☐ N.A.I. ☐ MEMO | |
| CSO INITIALS | DATE |

**Attention:** Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

**RE:** Amendment to NDA 20-701
CRINONE® (progesterone gel)
Response to FDA Request

Dear Dr. Rarick:

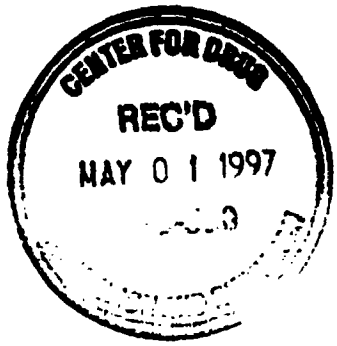
We reference our NDA 20-701 for CRINONE® (progesterone gel) submitted on July 31, 1996 to support the use of CRINONE® in the treatment of secondary amenorrhea and abnormal uterine bleeding due to hormonal imbalance in the absence of organic pathology, such as fibroids or uterine cancer. In response to the request of Dr. Mitra for a MSDS for progesterone and concerning the Environmental Assessment section of the submission, we are amending the application with the following information and enclosures:

1. MSDS sheet for progesterone as provided by the suppler.

2. Concerning Disposal of Returned/Damaged Goods - As stated in the Environmental Assessment, all Crinone® manufacturing occurs outside the United States. Section 3.12.4E (Disposal Sites) and referenced appendices describe the disposal method during manufacture, as well as that associated with patient use. Drug product returned to Columbia Laboratories after entry into the United States will be disposed of in a solid waste management system. Columbia Laboratories is in the process of identifying a site for return in the United States.

3. Page 229 of Section 3.12, with the appropriate signature.

If there are any questions concerning this submission, please contact the undersigned at (516) 766-2660.




Yours truly,

Howard Levine, Pharm.D.
Vice President
Columbia Research Laboratories, Inc.

Attachments

100 No. Village Avenue
Rockville Centre, NY 11570

TEL: (516) 766-2847
FAX: (516) 766-2873

COLUMBIA
RESEARCH
LABORATORIES, INC.

April 14, 1997

Food & Drug Administration
Center for Drug Evaluation and Research
Documents and Records Section
12420 Parklawn Drive
Rockville, MD 20852

ORIG AMENDMENT

**Attention:** Lisa Rarick, M.D., Director
Division of Reproductive and Urologic Drug Products

**RE:** Amendment to NDA 20-756
CRINONE® (progesterone gel)
Response to FDA Comments and Requests

Dear Dr. Rarick:

We reference our NDA 20-756 for CRINONE® (progesterone gel) submitted on November 13, 1996 to support the use of CRINONE® for progesterone supplementation or replacement as part of an ART treatment for infertile women with documented or suspected progesterone deficiency. In response to your comment and requests in your letter of March 25, 1997 concerning the Chemistry, Manufacturing and Controls section of the submission, we are amending the application with the information and enclosures:

Drug Substance

1. The Certificate of Analysis, containing the acceptance specification for progesterone from along with the Certificate of Analysis from is provided in Appendix 1.

2. The reference standard for progesterone used by is the U.S.P. reference standard. reference standard for progesterone. itself uses the U.S.P. reference standard for progesterone. There are no reference standards for the progesterone related substance, Δ14-progesterone. The method for the determination of this substance does not require the preparation of a standard, as the content is calculated against the main progesterone peak. Standards of 6α-hydroxyprogesterone, 6 keto-progesterone, and 6β-hydroxyprogesterone (provided by , were used to determine relative response factors used in the development and validation of this method. Representative reference IR spectra for the standard and the standard can be found in Appendix 2.



100 No. Village Avenue
Rockville Centre, NY 11570

TEL: (516) 766-2847

Lisa Rarick, M.D.
April 14, 1997

General Tests and Specifications

1. The Certificates of Analysis containing the acceptance specifications of all excipients are provided in Appendix 3. The sample Certificates of Analysis (included) for Purified Water U.S.P. and Sodium Hydroxide N.F. will be used for these raw materials for all production batches.

2. The source of the sorbic acid reference standard Representative IR spectra for the reference standard and the can be found in Appendix 4.

3. The purified water and sodium hydroxide used in the formulation will comply with U.S.P. and N.F. specifications, respectively.

4. The method for determination of Uniformity of Content in Crinone® applicators can be found in Appendix 5. The test for Content Uniformity is included in the revised release specifications for the product (Appendix 6). As the Method Validation for progesterone content determination has already been provided (NDA 20-701, Volume 1.04, page 305), no additional method validation is included in this submission.

5. The method for preparation of a Composite Sample is provided in Appendix 7. This method is used in preparing the sample for assay of progesterone and related substances.

6. The limit of detection and quantification of Δ14-progesterone, the only identified related substance, is shown in Appendix 8. The other substances listed (6α-hydroxyprogesterone, 6-ketoprogesterone and 6β-hydroxyprogesterone) are degradants, not related substances.

7. The release rate testing is included in the revised specifications (Appendix 6). Release rate testing will be performed on the first three production batches, and on one of each five batches produced. The forecast is to produce batches per year, therefore this testing will be performed approximately monthly on a randomly selected batch. The Method Validation for this testing has previously been submitted (NDA 20-701, Volume 1.04, page 238), therefore it is not included in this submission.

8. The Microbial Limit test will be conducted according to the method described in U.S.P. 23.

Stability

1. In accordance with the ICH Guidelines, the storage conditions and test intervals to be used for the first three production batches is shown in Appendix 9.

2. The sorbic acid is used in this product as an "in-process" preservative, protecting the product from microbes which may be introduced from the raw materials during the manufacturing process. Once the product is formulated, the gel's intrinsic low pH (2.5-3.5) makes it self-preserving. Therefore, it is only of concern to document that there is sufficient sorbic acid present during production and at release of the product to assure that any potential microbial contamination is removed. Due to the rapid degradation of sorbic acid, its concentration declines to below "effective" levels, however preservative efficacy testing shows the product to pass. Thus, the specifications have included limits for sorbic acid upon release %), but do not maintain a lower limit during the stability testing period.

Labeling

1. As per Diane Moore, the Nomenclature Committee has accepted the established name "progesterone gel". On February 28, 1997, in response to a request by Ms. Moore, an Amendment to NDA 20-701 was submitted which included Draft Labeling for the carton and overwrap. Although not present on the overwrap submitted on February 28, 1997, the storage conditions will be included on the overwrap used for production as requested. The initial production will have the storage conditions printed by ink-jet on the overwrap. Subsequent production will have it pre-printed in a currently blank area. The draft Labeling Text was submitted as part of the initial NDA filing. A draft Patient Package Information is included in Appendix 10.

2. As requested, the established name "progesterone gel" will be inserted following the tradename "Crinone" in the Description section of the Labeling Text. The word "diluted" will be deleted as requested.

If there are any questions concerning this submission, please contact the undersigned at (516) 766-2660.

Yours truly,

Howard Levine, Pharm.D.
Vice President
Columbia Research Laboratories, Inc.

ORIGINAL

COLUMBIA
RESEARCH
LABORATORIES INC.

February 28, 1997

ORIG AMENDMENT

**NDA 20-756 SECTION 9 - SAFETY UPDATE**

Lisa Rarick, M.D., Director
Division of Reproductive & Urologic Drug Products (HFD-580)
Food & Drug Administration
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, MD 20857

**RE:** NDA 20-756 Section 9 - Safety Update
CRINONE® (progesterone gel)

Dear Dr. Rarick:

Pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act and in reference to 21 CFR 314.50(d)(5)(vi)(b), we submit in duplicate, this Safety Update (Section 9) to New Drug Application #20-756 for CRINONE® (progesterone gel), that was originally submitted on November 13, 1996. Because there are two active NDAs for the same product, this document also contains the safety update for NDA #20-701 (CRINONE®) that was originally submitted on July 23, 1996. Please note that this document is also being submitted to NDA 20-701.

Attachment 1 to this letter is a disk containing WordPerfect® files for the text of the Safety Update and the accompanying documentation.

Attachment 2 to this letter is a disk containing the original and SAS® analysis data sets for the database and the accompanying documentation. Only those subjects from COL1620-007US who were enrolled in the study and completed or withdrew from the study after 15 June 1996 are included in the database.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(J).

If there are any overall questions concerning this application, please contact the undersigned at (516) 766-2660.

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Yours truly,

Howard Levine, Pharm.D.
Vice President
Columbia Research Laboratories, Inc.

Attachments

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 28 1997
HFD-580

3. Village Avenue
Rockville Centre, NY 11570

TEL: (516) 766-2847
FAX: (516) 766-2873

ORIGINAL

COLUMBIA
RESEARCH
LABORATORIES, INC.

February 17, 1997 ORIG AMENDMENT

**AMENDMENT TO A PENDING NDA - RESPONSE TO FDA REQUEST**

Food & Drug Administration
Center for Drug Evaluation and Research
Division of Reproductive and Urologic Drug Products (HFD-580)
5600 Fisher Lane
Rockville, MD 20857

**Attention:** Diane Moore, Consumer Safety Officer
Division of Reproductive and Urologic Drug Products

**RE:** Amendment to NDA #20-756
CRINONE® (progesterone gel)
Response to FDA Request

Dear Ms. Moore:

We reference our NDA 20-756 for CRINONE® (progesterone gel) submitted on November 13, 1996 to support the use of CRINONE® in women undergoing advanced reproductive technology (ART) procedures. In response to your request, we are amending the application with the enclosed information:

- Diskette containing SAS files of the efficacy and demographic data from Study COL1620-F01 and data documentation consisting of the contents and printout of these files

If there are any questions concerning this submission, please contact the undersigned at (516) 766-2660.

Yours truly,

Howard Levine, Pharm.D.
Vice President
Columbia Research Laboratories, Inc.

Enc.

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
FEB 16 1997
HFD-580

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Village Avenue
Rockville Centre, NY 11570

TEL: (516) 766-2847
FAX: (516) 766-2873

COLUMBIA
RESEARCH
LABORATORIES INC

November 13, 1996


**ORIGINAL NDA SUBMISSION**

Food & Drug Administration
Center for Drug Evaluation and Research
Documents and Records Section
12420 Parklawn Drive
Rockville, MD 20852

**Attention:** Lisa Rarick, M.D.
Director, Division of Reproductive and Endocrine Drug Products

**RE:** Original NDA Submission #20-756
CRINONE® (progesterone gel)

Dear Dr. Rarick:

Pursuant to Section 505 of the Federal Food, Drug and Cosmetic Act and in reference to 21 CFR 314, we submit in duplicate, this original New Drug Application #20-756 for CRINONE® (progesterone gel). We submitted an original New Drug Application #20-701 for CRINONE® on July 23, 1996, to support the use of this product in the treatment of secondary amenorrhea and abnormal bleeding due to hormonal imbalance. Because that application is currently under review, we are submitting NDA #20-756 to support an additional indication for CRINONE® as a source of natural progesterone for women undergoing Assisted Reproductive Technology (ART) procedures when complete, partial and/or relative progesterone insufficiency is documented or suspected. It should be noted that a treatment protocol for the use of CRINONE® in women undergoing ART procedures was recently approved pending approval of manufacturing facilities. In keeping with the intent of a treatment protocol, which is to provide potentially beneficial therapies where none exist to patients with significant medical conditions, we are requesting that the review of this application be given a priority status.

This application was the topic for discussion at several meetings held between Columbia Research Laboratories and the Division of Metabolism and Endocrine Drug Products (now, Reproductive and Endocrine Drug Products), the most important of these on December 17, 1992, and December 20, 1993, with a follow-up teleconference on April 19, 1994. The agreements reached at these meetings are delineated in Attachment 1, entitled "Summary of Prior Agreements with the Division of Metabolism and Endocrine Drug Products."


100 No. Village Avenue
Rockville Centre, NY 11570

TEL: (516) 766-2847
FAX: (516) 766-2873

COLUMBIA
RESEARCH
LABORATORIES, INC.

Attachment 2 to the Clinical and Archive copy of this letter are disks containing WordPerfect® files for the NDA Summary, the Clinical Data Section Summary, and the text portion for the primary study in support of this indication, Study COL1620-007US. A copy of the accompanying documentation is provided in all copies of this letter.

Attachment 3 to the Statistical and Archive copy of this letter is a disk containing the SAS® data sets for Study COL1620-007US. A copy of the accompanying documentation is provided in all copies of this letter.

Please be advised that material and data contained in this submission are confidential. The legal protection of such confidential material is hereby claimed under applicable provisions of 18 U.S.C., Section 1905 or 21 U.S.C., Section 331(J).

If there are any overall questions concerning this application, please contact the undersigned at (516) 766-2660.

Yours truly,

Howard Levine, Pharm.D.
Vice President
Columbia Research Laboratories, Inc.

Attachments

100 No. Village Avenue
Rockville Centre, NY 11570

TEL: (516) 766-2847
FAX: (516) 766-2873

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

# APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

*(Title 21, Code of Federal Regulations, 314)*

*Form Approved: OMB No. 0910-0001*
*Expiration Date: March 31, 1990.*
*See OMB Statement on Page 3.*

| FOR FDA USE ONLY | |
|---|---|
| DATE RECEIVED | DATE FILED |
| DIVISION ASSIGNED | NDA/ANDA NO ASS |

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

| NAME OF APPLICANT | DATE OF SUBMISSION |
|---|---|
| Columbia Research Laboratories, Inc. | January 10, 1997 |
| ADDRESS (Number, Street, City, State and Zip Code) | TELEPHONE NO (Include Area Code) |
| 100 North Village Avenue, Suite 32<br>Rockville Centre, NY 11570 | (516) 766-2660 |
| | NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued)<br>20-756 |

## DRUG PRODUCT

| ESTABLISHED NAME (e.g., USP/USAN) | PROPRIETARY NAME (If any) |
|---|---|
| | CRINONE® |

| CODE NAME (If any) | CHEMICAL NAME |
|---|---|
| COL-1620 | |

| DOSAGE FORM | ROUTE OF ADMINISTRATION | STRENGTH(S) |
|---|---|---|
| gel | vaginal | 8% |

PROPOSED INDICATIONS FOR USE

progesterone supplementation or replacement as part of an ART treatment for infertile women with documented or suspected progesterone deficiency.

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21CFR 314.420) REFERRED TO IN THIS APPLICATION:

IND

DMF

NDA 20-701 (CRINONE®)

## INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

☐ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

| NAME OF DRUG | HOLDER OF APPROVED APPLICATION |
|---|---|
| | |

STATUS OF APPLICATION (Check one)

☐ PRESUBMISSION ☐ ORIGINAL APPLICATION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION ☐ SUPPLEMENTAL APPLICATION

PROPOSED MARKETING STATUS (Check one)

☐ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

## CONTENTS OF APPLICATION

This application contains the following items: *(Check all that apply)*

| | |
|---|---|
| | 1. Index |
| | 2. Summary (21 CFR 314.50 (c)) |
| | 3. Chemistry, manufacturing, and control section (21 CFR 314.50 (d) (1)) |
| | 4. a. Samples (21 CFR 314.50 (e) (1)) (Submit only upon FDA's request) |
| | b. Methods Validation Package (21 CFR 314.50 (e) (2) (i)) |
| | c. Labeling (21 CFR 314.50 (e) (2) (ii)) |
| | i. draft labeling *(4 copies)* |
| | ii. final printed labeling (12 copies) |
| | 5. Nonclinical pharmacology and toxicology section (21 CFR 314.50 (d) (2)) |
| | 6. Human pharmacokinetics and bioavailability section (21 CFR 314.50 (d) (3)) |
| | 7. Microbiology section (21 CFR 314.50 (d) (4)) |
| XX | 8. Clinical data section (21 CFR 314.50 (d) (5)) |
| | 9. Safety update report (21 CFR 314.50 (d) (5) (vi) (b)) |
| | 10. Statistical section (21 CFR 314.50 (d) (6)) |
| | 11. Case report tabulations (21 CFR 314.50 (f) (1)) |
| | 12. Case reports forms (21 CFR 314.50 (f) (1)) |
| | 13. Patent information on any patent which claims the drug (21 U.S.C. 355 (b) or (c)) |
| | 14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b) (2) or (j) (2) (A)) |
| | 15. OTHER *(Specify)* |

I agree to update this application with new safety information about the drug that may reasonably affect the statement of contraindications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit these safety update reports as follows: (1) 4 months after the initial submission, (2) following receipt of an approvable letter and (3) at other times as requested by FDA. If this application is approved, I agree to comply with all laws and regulations that apply to approved applications, including the following:

1. Good manufacturing practice regulations in 21 CFR 210 and 211.
2. Labeling regulations in 21 CFR 201.
3. In the case of a prescription drug product, prescription drug advertising regulations in 21 CFR 202.
4. Regulations on making changes in application in 21 CFR 314.70, 314.71, and 314.72.
5. Regulations on reports in 21 CFR 314.80 and 314.81.
6. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the controlled substances Act I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

| NAME OF RESPONSIBLE OFFICIAL OR AGENT | SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT | DATE |
|---|---|---|
| Howard Levine, Pharm. D. | | January 10, 19 |

| ADDRESS *(Street, City, State, Zip Code)* | TELEPHONE NO. *(Include Area Code)* |
|---|---|
| 100 North Village Avenue, Suite 32<br>Rockville Centre, NY 11570 | (516) 766-2660 |

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)