Roche

Pharmaceuticals

November 20, 1998

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products
5600 Fishers Lane, HFD-510
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 18-044 (S/025) -- Rocaltrol® (calcitriol) Capsules
NDA 21-068 -- Rocaltrol® (calcitriol) Oral Solution
Amended Final Draft labeling

Reference is made to a Rocaltrol Final Draft Labeling submission dated Wednesday, November 18, 1998. Reference is also made to a telephone discussion with Ms. Jena Weber, the Division Project Manager, on Thursday, November 19, 1998, during which time she indicated the need for additional labeling changes to our final draft.

In response to the November 19th teleconference, Hoffmann-La Roche Inc. is hereby submitting an amended final draft package insert for Rocaltrol. These revisions include further qualifying the solution dosage form by stating "Oral" Solution. In addition, revisions were made to the **Description** and **Indications and Usage** section of the Package insert. This submission will include both a clean copy of the amended final draft labeling and a highlighted copy indicating the changes made

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE

Anthony J. Corrado
Program Director
Drug Regulatory Affairs

Telephone (973) 562-3698
Facsimile (973) 562-3700/3554

AJC/LK
Attachment
HLR No. 1998-3012

Desk Copy: Desk Copy: Ms. Jena Weber, Metabolic and Endocrine Division, HFD-510

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Roche

Pharmaceuticals

November 20, 1998

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products
5600 Fishers Lane, HFD-510
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 18-044 (S/025) -- Rocaltrol® (calcitriol) Capsules
NDA21-068 -- Rocaltrol® (calcitriol) Oral Solution
Response to FDA Request to Provide Packaging Labels

Reference is made to a teleconference with Ms. Jena Weber, Project Manager, Metabolic and Endocrine Drug Products, on Friday, November 20, 1998. As discussed, Hoffmann-La Roche Inc. has agreed to submit to the FDA revised carton and packaging labels to further qualify the Rocaltrol solution dosage form by stating "Oral" Solution.

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE

Anthony J. Corrado
Program Director
Drug Regulatory Affairs

Telephone (973) 562-3698
Facsimile (973) 562-3700/3554

AJC/LK
Attachment
HLR No. 1998-3013

Desk Copy: Ms. Jena Weber, Metabolic and Endocrine Drug Products, HFD-510

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

November 18, 1998

ORIGINAL BC

Roche

SE1-025
NDA SUPP AMEND

Pharmaceuticals

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products
5600 Fishers Lane, HFD-510
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 18-044 (S/025) -- Rocaltrol® (calcitriol) Capsules
NDA 21--068 -- Rocaltrol® (calcitriol) Solution
Final Draft Labeling

At the request of the Division Project Manager, Ms. Jena Weber, Hoffmann-La Roche Inc. is hereby submitting the Final Draft Labeling for Rocaltrol which incorporates all of the previous labeling revisions discussed an agreed upon with the FDA. This submission will include both a clean copy of the final draft labeling and a highlighted copy indicating the revisions made.

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE

Anthony J. Corrado
Program Director
Drug Regulatory Affairs

Telephone (973) 562-3698
Facsimile (973) 562-3700/3554

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
NOV 19 1998
HFD-510

AJC/LK:mi
Attachment
HLR No. 1998-2979

Desk Copy: Desk Copy: Ms. Jena Weber, Metabolic and Endocrine Division, HFD-510

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

ORIGINAL

BM

SEL-025
NDA SUPP AMEND

Roche

November 18, 1998

)d and Drug Administration
Division of Metabolic and Endocrine Drug Products
5600 Fishers Lane, HFD-510
Rockville, Maryland 20857-1706

Pharmaceuticals

Ladies and Gentlemen:

Re: NDA 18-044 (S/025) Rocaltrol® (calcitriol) Capsules
NDA-21-068 -- Rocaltrol® (calcitriol) Solution
Response to FDA Request to Revise Warnings, Precautions,
Overdosage and Dosage and Administration Sections of Labeling

Reference is made to an FDA fax dated Thursday, November 12, 1998, in which the Metabolic and Endocrine Division Medical Reviewer, Dr. Eric Coleman, had proposed labeling revisions to the Rocaltrol package insert sections indicated above. Reference is also made to a teleconference that was held on Wednesday, November 18, 1998, to discuss the revisions requested by the FDA.

In response to the FDA request to revise the Rocaltrol package insert, Hoffmann-La Roche Inc. is hereby submitting the agreed upon changes to the labeling sections in question, as discussed with Dr. Coleman in our November 18th teleconference.

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely

HOFFMANN-LA ROCHE

Anthony J. Corrado
Program Director
Drug Regulatory Affairs

Telephone (973) 562-3698
Facsimile (973) 562-3700/3554

AJC/LK
Attachment
HLR No. 1998-2975

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

Desk Copy: Desk Copy: Ms. Jena Weber, Metabolic and Endocrine Division, HFD-510

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Roche

Pharmaceuticals

November 13, 1998

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products
5600 Fishers lane, HFD-510
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 18-044 (S/025) -- Rocaltrol® (calcitriol) Capsules
NDA 21-068 -- Rocaltrol® (calcitriol) Solution
Response to FDA Request to Revise Drug Interactions Section of Labeling

Reference is made to an FDA fax dated Friday, October 30, 1998, in which the Biopharmaceutical Reviewer has proposed labeling revisions to the Drug Interactions subsection of the Rocaltrol labeling. Hoffmann-La Roche Inc. agrees with and accepts the proposed revisions made by the Division Reviewer. A copy of the FDA fax is also attached.

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE, INC

Anthony J. Corrado
Program Director
Drug Regulatory Affairs

Telephone (973) 562-3698
Facsimile (973) 562-3700/3554

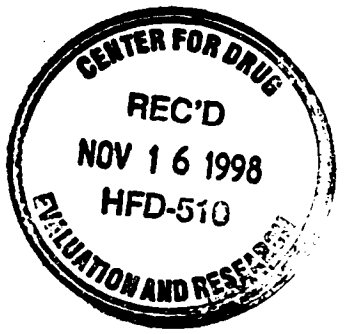
Attachment
HLR No. 1998-2938

Desk Copy: Ms. Jena Weber, Project manager, Division of Metabolic and Endocrine Drug Products, HFD-510

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Roche

Pharmaceuticals



November 13, 1998

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products
5600 Fishers Lane, HFD-510
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 21-068 - Rocaltrol® (calcitriol) Solution
NDA Number Assigned to Solution Dosage Form

As requested by the Division, all submissions that will be sent to the FDA regarding Rocaltrol Solution will now be submitted to NDA 21-068. Please refer to NDA 18-044 (S/025) for proposed revised labeling for a solution dosage form.

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE

Anthony J. Corrado
Program Director
Drug Regulatory Affairs

Telephone (973) 562-3698
Facsimile (973) 562-3700/3554

Attachment
HLR No. 1998-2931

DESK COPY: Ms. Jena Weber, Project Manager, Division of Metabolic and Endocrine Drug Products, HFD-510

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

DUPLICATE

Roche

November 12, 1998

NDA SUPP AMEND
SE1-025 BC

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 18-044 / S-025
Rocaltrol® (calcitriol) Capsules/Solution
Response to FDA CMC Questions

Reference is made to telephone discussions between Dr. David Lewis, Chemistry Reviewer, and the undersigned on October 26 and 28, 1998 regarding questions raised during the review of the CMC section. Reference is also made to information provided to Dr. Lewis by facsimile on October 30, 1998, in response to his questions and the amendment dated November 2, 1998 that provided updated stability data in addition to a hard copy of the October 30, 1998 facsimile.

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Please do not hesitate to contact me if you have any questions regarding the information provided herein.

Sincerely,

HOFFMANN-LA ROCHE INC.

Betty C. Holland
Program Director
Drug Regulatory Affairs
Phone: (973) 562-5549
Fax: (973) 562-3554/3700

BCH/LK
Attachment
HLR No. 1998-2910

Desk copies: **Ms. Jena Weber, DMEDP, HFD-510**
Dr. David Lewis, DMEDP, HFD-510
Field Copy: **Ms. Regina Brown**

DUPLICATE

Roche

Pharmaceuticals

November 2, 1998

NDA SUPP AMEND

SE1-625 BC

Food and Drug Administration
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 18-044 / S-025
Rocaltrol® (calcitriol) Capsules/Solution
Response to FDA CMC Questions and Provision of Updated Stability Data

Reference is made to telephone discussions between Dr. David Lewis, Chemistry Reviewer, and the undersigned on October 26 and 28, 1998 regarding questions raised during the review of the CMC section. Reference is also made to information provided to Dr. Lewis by facsimile on October 30, 1998, in response to his questions.

As discussed on October 28, 1998, enclosed herein is the following information:

- Hard copy of the facsimile message sent to Dr. Lewis on October 30, 1998 (Attachment 1). The facsimile message included information available at that time. Supporting data were appended; data that will follow are so indicated in the responses (submission targeted for on or before November 13, 1998).
- Updated stability report for Rocaltrol Solution, including data from the 24-month time point for the registration lots. (Attachment 2).

At this time we would also propose the following two amendments to the subject SNDA.

1. Based on the 24-month stability data and the supporting documentation provided in Attachment 2, we propose extension of expiration dating from the proposed 30 months to 36 months.

2. The proposed extension is based on a recommended storage at 15° to 30° C. However, in accordance with with several other recent Roche NDA/SNDA approvals and the draft "Guidance for Industry on Stability Testing of Drug Substances and Drug Products," we hereby recommend revision of the proposed storage statement to the following:

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Roche

Pharmaceuticals

Please do not hesitate to contact me if you have any questions regarding the information provided herein.

Sincerely,

HOFFMANN-LA ROCHE INC.

Deana d. Kimball for

Betty C. Holland
Program Director
Drug Regulatory Affairs
Phone: (973) 562-5549
Fax: (973) 562-3554/3700

BCH/LK
Attachments
HLR No. 1998-2809

Desk copies: **Ms. Jena Weber, DMEDP, HFD-510**
Dr. David Lewis, DMEDP, HFD-510

Field Copy: **Ms. Regina Brown**

X Conrad 3696

Roche

Pharmaceuticals

October 27, 1998

Food and Drug Administration
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: NDA 18-044 / S-025
Rocaltrol® (calcitriol) Capsules/Solution
Labeling Revisions Requested by the FDA

Reference is made to an FDA fax dated October 20, 1998, in which the Division had requested labeling revisions to the clinical portion of the Rocaltrol application referenced above. In response to this request, Hoffmann-La Roche Inc. is hereby submitting a revised package insert highlighting the revisions. These revisions include:

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Pharmaceuticals

Lastly, in order to comply with a revised guidance, "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements", the following statement has been deleted from the Rocaltrol package insert: "CAUTION: Federal law prohibits dispensing without prescription".

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE INC.

Anthony J. Corrado
Program Director
Drug Regulatory Affairs

Phone (973) 562-3698
Fax (973) 562-3700

HLR No.: 1998-2752
Attachments
Desk Copy: Ms. Jena Weber, Project Manager, HFD-510

Roche

September 1, 1998

Food and Drug Administration
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 18-044 / S-025
Rocaltrol® (calcitriol) Capsules/Solution
Response to FDA Pharmacology and Toxicology Proposed Labeling Revisions

Reference is made to an FDA facsimile dated July 24, 1998, in which the FDA had proposed text revisions to the pre-clinical portion of the Rocaltrol draft labeling submitted within supplement 025. In response to this FDA proposed labeling, a teleconference was held with Dr. Ronald Steigerwalt, the Division Pharmacology Reviewer, to discuss these labeling revisions.

The revised labeling that had been agreed upon both by Hoffmann-La Roche Inc. and the FDA is being provided within this submission. For you reviewing convenience, this submission includes a copy of the original July 24, 1998 FDA facsimile (Attachment 1) and an annotated copy highlighting (in bold) the changes discussed at our teleconference (Attachment 2).

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE INC.

Anthony J. Corrado
Program Director
Drug Regulatory Affairs
Phone: (973) 562-3698
Fax: (973) 562-3554/3700

AJC/DBD:js
Attachment
HLR No. 1998-2230

Desk copies: Ms. Jena Weber, DMEDP, HFD-510
Dr. Ronald Steigerwalt, DMEDP, HFD-510

BC

Roche

ORIGINAL

ORIG AMENDMENT

Pharmaceuticals

July 21, 1998

Ronald Steigerwalt, Ph.D.
Food and Drug Administration
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857-1706

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 22 1998
HFD-510

Re: NDA 18-044 / S-025
Rocaltrol® (calcitriol) Capsules/Solution
Revision to July 15, 1998 Submission

Dear Dr. Steigerwalt:

Reference is made to our submission dated July 15, 1998, which provided preclinical information that you have requested to update the Rocaltrol labeling.

After reviewing this submission further, an error was noticed within the cover letter that we would like to bring to your attention.

Should you require any additional information, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE INC.

Anthony J. Corrado
Program Director
Drug Regulatory Affairs
Phone: (973) 562-3698
Fax: (973) 562-3554/3700

AJC/DBD:js
HLR No. 1998-1843

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

Desk Copies: Document Control Room (No. 14B19), HFD-510 (2 copies)

Roche

Pharmaceuticals

July 15, 1998

Ronald Steigerwalt, Ph.D.
Food and Drug Administration
Division of Metabolic and Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: NDA 18-044 / S-025
Rocaltrol® (Calcitriol) Capsules/Solution
FDA Request for Information to Update Product Labeling

Dear Dr. Steigerwalt:

The preclinical information that you have requested to update the Rocaltrol® labeling and have discussed with our pharmacologist in a June 1998 teleconference is being provided within.

Preclinical studies of calcitriol conducted by Roche, *McClain RM, Langhoff L and Hoar RM; Reproduction Studies with 1-α,25-dihydroxyvitamin D3 (calcitriol) in Rats and Rabbits.* Toxicol Appl Pharmacol, 52:89-98, 1980 **(See Attachment 1),** suggested that calcitriol of dosages of up to 0.3μg/kg/day in the rats did not adversely affect reproduction or pup development, except for changes in serum chemistry values. Calcitriol in rabbits produced material and some feto-toxic effects at 0.3μg/kg/day, but not at 0.02or 0.08μg/kg/day.

However, based on the above data, the FDA concluded that calcitriol was teratogenic in rabbits at **0.08 and 0.03μg/kg/day**, i.e.,_____ the dose recommended for human use **(See Attachment 2,** page 7 of the Roche Research Report N-12797.1, May 28, 1992; *Agnish ND, A Survey of Published Literature on the Teratogenicity of Vitamin D).* Presumably, the human dosage of calcitriol used in the above calculation is 0.02μg/kg/day.

Details of the preclinical safety studies of calcitriol in rabbits and rats are reported in *McClain RM, Langhoff L and Rudiger H; Reproduction Study of RO 21-5535 in Rabbits Phase II Teratological Study,* Roche Research Report N-29559, August 30, 1976 **(See Attachment 3),** *McClain RM, Rusin G and Di Nardo B; Reproduction Study of RO 21-5535 in Rats Phase II Teratological Study.* Roche Research Report N-31482, September 10, 1976 **(See Attachment 4)** and *Hoar RM, Di Nardo B and Rusin G; Reproduction Studies of RO 21-5535 in Rats Phase III Perinatal and Postnatal Study.* Roche Research Report N-31491, September 10, 1976 **(See Attachment 5).**

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Roche

Pharmaceuticals

In the Rocaltrol package insert, it is stated that _____

_____ The reference for this section is *Marx et al., Normal Interuterine Development of the Fetus of a Woman Receiving Extraordinarily High Doses of 1,25-Dihydroxyvitamin D3.* J Clin Endocrinol Metab 51: 1138-1142, 1980 **(See Attachment 6).** These authors suggested that an extraordinarily high concentration of calcitriol in maternal serum throughout gestation was not apparently toxic to the feto-placental unit, though the maternal metabolite entered the fetal circulation.

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE INC.

Anthony J. Corrado
Program Director
Drug Regulatory Affairs
Phone: (973) 562-3698
Fax: (973) 562-3554/3700

Attachments
HLR No. 1998-1787

Desk Copies: Ms. Jena M. Weber, Project Manager, HFD-510 (1 copy)
Document Control Room (No. 14B19), HFD-510 (2 copies)

Roche

Pharmaceuticals

April 30, 1998

Food and Drug Administration
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: NDA 18-044 / S-025
Rocaltrol® (calcitriol) Capsules/Solution
FDA Request for Information Regarding
Exposure to Rocaltrol During Pregnancy

Ladies and Gentlemen:

As requested by your Division Medical Reviewer, Eric Colman, M.D., in an e-mail message dated Wednesday, April 8, 1998, Hoffmann-La Roche Inc. is hereby submitting post-marketing data on exposure to Rocaltrol during pregnancy.

In response to this request, the Hoffmann-La Roche Inc. safety data base was searched for post-marketing reports of all of the following terms through December 31, 1997:

1. All cases of pregnancy.
2. Fetal disorders with a temporal association with Rocaltrol treatment in the mother.
3. Number of cases of teratogenicity temporally associated with Rocaltrol therapy in the mother.

The results of this search are given in detail in the attached document (Tables 1-3). Nineteen pregnancies were identified. Ten pregnancies are known to have resulted in the birth of normal babies. In one case, the patient was lost to follow-up. In six instances the pregnancies were ongoing at the time they were reported. Two pregnancies resulted in infants with birth defects.

Of the two pregnancies in which infants were born with birth defects (Table 3), the mother in the first case took Rocaltrol before and throughout her pregnancy at variable dosages, up to 1 mcg/day (Table 1). The baby's birth weight was normal, as was the Apgar score. At 6 weeks of age, the baby was noted to have premature closure of the anterior fontanel. The attending physician felt that Rocaltrol was not in any way responsible for the event. The second infant was born with a cleft palate and absence of the left kidney (Table 3). Neither the time, nor the duration of intrauterine exposure of this baby is known nor is the relationship of Rocaltrol to the event. Nothing is known

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

concerning the serum calcium values during their pregnancies of the mothers of these 2 infants.

A review of the literature from 1988 to present yielded no references to any association of birth defects with the use of calcitriol during pregnancy.

Should you require any additional information or clarification, please direct all requests to my attention.

Sincerely,
HOFFMANN-LA ROCHE INC.

Anthony J. Corrado
Program Director
Drug Regulatory Affairs

Telephone (973) 562-3698
Facsimile (973) 562-3700/3554

Attachment
HLR No. 1998-1099

DESK COPIES: Ms. Jena M. Weber, Project Manager HFD-510 (Cover Letter Only)
Eric Colman, M.D., Medical Reviewer HFD-510 (Full Copy)

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Roche

Pharmaceuticals

March 6, 1998

Food and Drug Administration
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: NDA 18-044 / S-025
Rocaltrol® (calcitriol) Capsules/Solution
FDA Request for Data on Vital signs and Blood Chemistries for Protocol N2086

Ladies and Gentlemen:

Hoffmann-La Roche Inc. is hereby submitting the Rocaltrol® information that was requested by your Division Medical Reviewer, Eric Colman, M.D. in a faxed memo dated February 18, 1998. This submission contains summary statistics and analysis by repeated measures for vital signs and blood chemistries for Protocol N2086. The information that is being provided is divided into the following sections:

Tab 1 FDA Request
Tab 2 Statistical Methods
Tab 3 Results (Including Tables and Listings)
Tab 4 Discussion
Tab 5 Statistical Output

Please note that SAS data sets are available upon request.

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE INC.

Anthony J. Corrado
Program Director
Drug Regulatory Affairs
Phone: (973) 562-3698
Fax: (973) 562-3554/3700

Attachments
HLR No. 1998-643

Desk Copies: Ms. Jena M. Weber, Project Manager HFD-510 (Cover Letter Only)
Dr. Eric Colman, Medical Reviewer, HFD-510 (Full Copy)

NDA SUPPLEMENT
SEI-025 #3

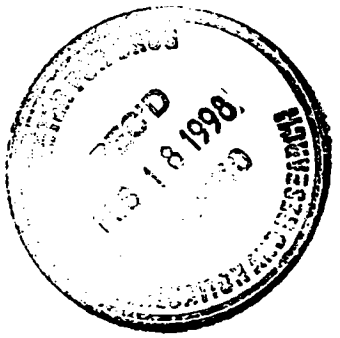
ORIGINAL

Roche

Pharmaceuticals

February 17, 1998

Food and Drug Administration
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857-1706



Re: NDA 18-044 / S-025
Rocaltrol® (calcitriol) Capsules/Solution
FDA Request for Pharmacokinetic Information

Ladies and Gentlemen:

As requested by Dr. Carolyn Jones, the Pharmacokinetics Reviewer for NDA 18-044 / S-025, Hoffmann-La Roche Inc. is hereby submitting an electronic copy of Section 6 - Pharmacokinetics Summary from the November 18, 1997 supplemental NDA referenced above and the SAS data sets for Rocaltrol PK/PD Protocol NR15059 also from the November 18th submission.

Recently, in a request for Rocaltrol® supplemental NDA information, Dr. Eric Colman, Medical Reviewer, suggested that an electronic copy be provided to him in WP 6.1. Although Hoffmann-La Roche Inc. was able to provide Dr. Colman his requested information in WP6.1, numerous unsuccessful attempts have been made to convert Section 6-Pharmacokinetics Summary to WP 6.1 version. Therefore, Section 6 is being provided on diskette in Word 7.0.

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE INC.

REVIEWS COMPLETED
CSO
☐ LETTER ☐ MEMO
CSO INITIALS DATE

Anthony J. Corrado
Program Director
Drug Regulatory Affairs
Phone: (973) 562-3698
Fax: (973) 562-3554/3700

Attachments
HLR No. 1998-419

Desk Copies: Ms. Jena M. Weber, Project Manager HFD-510 (Cover Letter Only)
Dr. Carolyn Jones, Pharmacokinetics Reviewer, HFD-510 (Full Copy)

Roche

Pharmaceuticals

February 13, 1998

Food and Drug Administration
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: NDA 18-044 / S-025
Rocaltrol® (calcitriol) Capsules/Solution
FDA Request for Information Regarding Protocol N2086

Ladies and Gentlemen:

Hoffmann-La Roche Inc. is hereby submitting the Rocaltrol® information that was requested by your Division Medical Reviewer, Eric Colman, M.D., in a faxed memo dated January 27, 1998. Please refer to the "Note to Reviewer" provided within regarding the information requested.

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE INC.

Anthony J. Corrado
Program Director
Drug Regulatory Affairs
Phone: (973) 562-3698
Fax: (973) 562-3554/3700

Attachments
HLR No. 1998-418

DESK COPIES: **Ms. Jena M. Weber, Project Manager HFD-510 (Cover Letter Only)**
Dr. Eric Colman, M.D. Medical Reviewer HFD 510 (Full Copy)

Roche

Pharmaceuticals

February 13, 1998

Food and Drug Administration
Division of Metabolism and Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
5600 Fishers Lane
Rockville, Maryland 20857-1706

Re: NDA 18-044 / S-025
Rocaltrol® (calcitriol) Capsules/Solution
FDA Request for Statistical Information

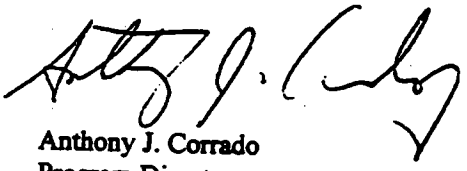
Ladies and Gentlemen:

As requested by your Statistical Reviewer, Dr. Lee Ping Pian, Hoffmann-La Roche Inc. is hereby submitting SAS datasets for the efficacy portion of Protocol N2086 for the supplemental NDA referenced above. Also included is a description (PROC CONTENTS) of the variable names in each of the five datasets: coreset, bone, bone 2, vital and chem.

Should you require any additional information or clarification, please do not hesitate to contact me.

Sincerely,

HOFFMANN-LA ROCHE INC.



Anthony J. Corrado
Program Director
Drug Regulatory Affairs
Phone: (973) 562-3698
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Attachments
HLR No. 1998-428

Desk Copies: Ms. Jena M. Weber, Project Manager HFD-510 (Cover Letter Only)
Dr. Lee Ping Pian, Pharmacokinetics Reviewer, HFD-510 (Full Copy)

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

NDA SUPPLEMENT ORIGINAL

NDA NO. 18044 REF. NO. 065

NDA SUPPL FOR SE1

Roche

Pharmaceuticals

November 18, 1997

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Attn.: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 18-044 -- Rocaltrol® (Calcitriol)
Supplemental New Drug Application
Request for Priority Review

In accordance with 21CFR314.54(a)(1)(ii), we are herewith submitting a Supplemental New Drug Application documenting the safety and efficacy of Rocaltrol in the treatment of secondary hyperparathyroidism in patients with moderate to severe chronic renal failure (creatine clearance of 15 to 55 mL/min) who are not yet undergoing dialysis (predialysis patients) and we wish to request priority review for this application.

This application was prepared in response to the April 27, 1993 letter from Stuart Nightingale, M.D., Associate Commissioner of Health Affairs, requesting assistance in the identification of approved drugs currently being used off-label and for which unpublished data and/or data derived from the literature are available to support the established off-label use.

The use of Rocaltrol for the treatment of secondary hyperparathyroidism in patients with moderate to severe chronic renal failure (creatine clearance of 15 to 55 mL/min) is such an established off-label use. Because of the early onset and severity of the clinical manifestations of secondary hyperparathyroidism, especially in children, and an absence of effective alternative treatments, it has become common medical practice to use vitamin D derivatives, and specifically Rocaltrol, for the management of this condition, despite the lack of FDA approval. In fact, discussions of this off-label use of calcitriol in predialysis patients are to be found in the American Hospital Formulary Services (AHFS) Drug Information, 1997, pages 2826-2830, American Medical Association (AMA) Drug Evaluations, 1997, pages 2412-2413 and USP DI (Drug Information for the Health Care Professional) 1997, pages 2986-2992, copies of which follow this letter.

We are requesting priority review for the subject submission based on the following:

- The lack of any currently approved therapy for treatment of secondary hyperparathyroidism in patients with moderate to severe chronic renal failure.

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- The use of calcitriol for the treatment of these patients represents common off-label use of the drug.

- The substantial body of information reviewed in this submission supports the safety and effectiveness of Rocaltrol in the management of secondary hyperparathyroidism in patients with moderate to severe chronic renal failure.

- Current labeling for vitamin D derivatives does not provide any information concerning the proper and safe use of these drugs in the management of predialysis patients. This lack of proper safety and dosage information is particularly problematic given that a significant portion of the patient population are children who are more susceptible to complications due to overdosage and in which proper dosage adjustments are required.

- Approval of this indication will allow the dissemination of important information to health care providers on the proper and safe use of Rocaltrol in this patient population.

Rocaltrol has been marketed since 1978 and is currently approved for the management of hypocalcemia in patients undergoing chronic renal dialysis, management of hypocalcemia and its clinical manifestations in patients with postsurgical hypoparathyroidism, idiopathic hypoparathyroidism and pseudohypoparathyroidism and the treatment of osteitis fibrosa cystica and defective mineralization in dialysis patients. Calcitriol promotes intestinal absorption of calcium and reduces PTH levels in patients with end-stage renal disease. Experience with populations of moderate to severely ill patients (e.g. renal osteodystrophy, hypoparathyroidism) treated for prolonged periods with Rocaltrol has shown Rocaltrol to be safe in clinical practice.

This Supplemental New Drug Application supporting the safety and efficacy of Rocaltrol in the treatment of predialysis patients is derived from one Hoffmann-La Roche-sponsored, double-blind, placebo-controlled trial and five controlled clinical trials from the literature (four of which were double-blind, placebo-controlled), which used calcitriol or alfacalcidol at the proposed recommended dosage of 0.25μg to 0.5μg daily, as well as a literature-based review of 28 additional clinical studies in adults and 16 clinical studies in pediatric patients.

Rocaltrol is currently supplied as a soft gelatin capsule in two dosage strengths, 0.25 mcg and 0.5 mcg. Additionally, the subject supplement provides for a new Rocaltrol dosage form, an oral solution containing 1 mcg/mL of calcitriol, to be supplied in bottles containing 15 mL of solution, with single-use, 1 mL, graduated, oral dispensers.

Roche

Pharmaceuticals

This submission consists of an archival (42 volumes) and a review copy and is organized as follows:

An identical field copy containing a complete Form 356h, Section 2 (Application Summary) and Section 3 (CMC) of this supplement is being submitted simultaneously to the Newark District Office of the FDA. The undersigned hereby certifies that the copy submitted to the District Office is a true copy if that submitted to the Division of Metabolism and Endocrine Drug Products

Please contact the undersigned if you have any questions regarding this submission.

Sincerely,

HOFFMANN-LA ROCHE INC.

Rud. Jh W Lucek

Rudolph W. Lucek
Group Director
Drug Regulatory Affairs
Phone: (973) 562 3688
Fax: (973) 562 3700

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

RWL/LK:js
Attachment
HLR No. 1997-2577

SECTION 1 SECTION 2 SECTION 3 SECTION 4 SECTION 5

J Weber
HFD-510

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 17 1998

Elisa Scordato Mandra
Associate, Labeling
Drug Regulatory Affairs
Hoffmann-La Roche, Inc.
340 Kingsland Street, Building 719/4
Nutley, New Jersey 07110-1199

**RE: Invoice for Application Fees for NDA 21-068,
Rocaltrol (calcitriol) Oral Solution 1 mcg/mL**

Dear Ms. Mandra:

This communication contains an invoice (Attachment A) for application fees for Fiscal Year (FY) 1998 for NDA 21-068, Rocaltrol (calcitriol) Oral Solution 1 mcg/mL, under the Prescription Drug User Fee Act of 1992 as amended by the Food and Drug Administration Modernization Act of 1997.

On November 20, 1997, the Division of Metabolic and Endocrine Drug Products (DMEDP) received a supplement (S-025) to NDA 18-044, Rocaltrol (calcitriol) oral capsules, for the treatment of secondary hyperparathyroidism in patients with moderate to severe chronic renal failure. In addition to this new indication for use, the supplement also included a new Rocaltrol dosage form, an oral solution containing 1 mcg/mL of calcitriol to be supplied in bottles containing 15 mL of solution with single-use, 1 mL, graduated, oral dispensers. Hoffmann-La Roche submitted the supplement with the payment for a supplement that requires clinical data for approval. During the course of the review, the DMEDP determined that the new dosage form should have been submitted as a new drug application (NDA) in accordance with agency policy as expressed in the "Interim Guidance: Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees Under the Prescription Drug User Fee Act of 1992" (copy enclosed). The supplemental application was divided and the new application for Rocaltrol (calcitriol) Oral Solution 1 mcg/mL was assigned a new number, NDA 21-068.

The enclosed invoice is for the entire FY 1998 application fee) for NDA 21-068 Rocaltrol oral solution, for which clinical data are not required for approval. In this case, Roche is relying on the clinical data submitted under NDA 18-044, S-025. The fee previously paid covered the previously submitted supplement with clinical data required for approval, NDA 18-044, S-025. **Payment is due within 30 days of the date of the invoice.**

Instructions for payment are included in Attachment B.

If you have any questions concerning the invoice, please contact:

Ms. Beverly Friedman
Consumer Safety Officer
Center for Drug Evaluation and Research
Food and Drug Administration, HFD-5
5600 Fishers Lane
Rockville, MD 20857
(301) 594-2041
Internet address: FRIEDMANB@CDER.FDA.GOV

We appreciate your continued cooperation and thank you in advance for your prompt payment.

Sincerely yours,

/S/

Jim Donahue, Director
Office of Financial Management

Enclosures:

Attachment A - Action Invoice
Attachment B - Payment Instructions
Interim Guidance