CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-103

Correspondence

General Correspondence

Novo Nordisk

Novo Nordisk Pharmaceuticals, Inc.
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810
Tel. 609-987-5800
Fax 609-921-8082

April 10, 2000

John K. Jenkins, M.D., F.C.C.P.
Acting Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: General Correspondence
Activella, NDA 21-103

Dear Dr. Jenkins:

Reference is made to Activella™ (1 mg estradiol/ 0.5 mg norethindrone acetate tablets), NDA 21-103.

At the request of Randy Hedin Novo Nordisk Pharmaceuticals Inc. is submitting the final draft labeling of the physician insert (version 4/10/2000) incorporating all the negotiated changes for Activella for the indication of prevention of osteoporosis. The patient insert remains the same as the submitted label (version 6/3/99) of June 10, 1999.

Enclosed is a copy of the revised physician insert, version 4/10/2000. The HFD-510 additions to the label are located on page 12 to page 15 and page 25 and page 28.

If you have any questions concerning this submission, please contact Lieselotte Bloss, DVM, Assistant Director, Regulatory Affairs at 609-987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cc: Randy Hedin

Request for Information

Novo Nordisk

Novo Nordisk Pharmaceuticals, Inc.
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Tel. 609-987-5800
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April 5. 2000

John K. Jenkins. M.D., F.C.C.P.
Acting Director
Division of Metabolic and
Endocrine Drug Products. HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Request for Information; Study KLIM/PD/11/USA
Activella, NDA 21-103

Dear Dr. Jenkins:

Reference is made to NDA 21-103 for Activella™ (estradiol, norethindrone acetate tablets) 1mg/0.5 mg and to the request of March 23/24, 2000 by Dr. Japo Choudhury, statistical reviewer, concerning study KLIM/PD/11/USA. The questions and responses to Dr. Choudhury are presented in the attached pages.

At this time, we understand that these answers are considered to be satisfactory by Dr. Choudhury.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Asst. Dir. Regulatory Affairs at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cc: Dr. Japo Choudhury
Randy Hedin

Dear Dr. Choudhury:

Per our conversation March 23/24, we prepared the following information to address your questions.

Question 1: For Study PD/11, when were the treatment codes unblinded? Three different dates were mentioned in the NDA, 7/19/1998, 5/20/1998 and 5/20/1999.

Answer: The correct date should be 5/20/1998. This date was documented in the study report as well as supplemental analyses (page 4) for this study. The 7/19/1998 date is the date last subject came for last visit. The 5/20/1999 date is a typographical error.

Question 2: In Study PD/11, 11 placebo and 10 Activella treated subjects were excluded from the modified ITT analysis. These subjects dropped out and did not have post baseline BMD data. You requested a sensitivity analysis to be done to evaluate the impact of excluding these 21 subjects on the efficacy.

The reasons for these 21 subjects withdrawing from the study include: adverse event (menopausal symptom and other), non-compliance, lost to follow-up, and withdrew consent. None of these reasons were associated with the centrally evaluated efficacy response, i.e. BMD. Table 1 summarizes the baseline characteristics of all randomized subjects as well as those dropped out and did not have post baseline data.

Table 1. Demographic and Baseline Characteristics

	Activella		Placebo	
	All Randomized Subjects (n=47)	Dropouts (n=10)	All Randomized Subjects (n=48)	Dropouts (n=11)
Age (yr)	53 (46-61)	52 (49-61)	54 (47-62)	53 (47-61)
Height (cm)	163 (155-175)	165 (155-175)	164 (150-175)	160 (150-171)
Weight (kg)	67 (47-100)	73 (53-100)	66 (48-91)	67 (55-91)
Years since last menses	3 (1-5)	3 (1-5)	3 (1-5)	4 (1-5)
BMD of Lumbar Spine	1.07 (0.88-1.54)	1.06 (0.94-1.54)	1.07 (0.83-1.48)	1.03 (0.87-1.44)
Oophorectomized	12 (26%)	2 (20%)	7 (15%)	1 (10%)

Median (Range) for age, height, weight, BMD, and years since last menses.

As indicated in Table 1, in general, within each treatment group, the characteristics of dropouts are similar to those of all randomized subjects. The median weight is slightly higher in Activella dropouts. However, as demonstrated in the "supplemental analysis", there is no association between weight and the % change in BMD. We also examined other information such as medical and gynecological history; the profiles for these dropouts are similar to all randomized subjects. Therefore, one would argue that the drop out pattern was "missing completely at random", and not response dependent. Based on Little and Rubin (1987), when data are missing completely at random, the subjects can be removed from the analysis without introducing potential bias. In other words, one can assume that the unobserved data from these dropouts were random samples from the complete data, and analysis of the completers is therefore unbiased.

Nevertheless, per your request, we carried out the following sensitivity analyses to demonstrate that excluding of those dropouts who did not have post baseline data should not be of concern in the general interpretation of results. In these analyses, all randomized subjects are included and LOCF was applied to dropouts with at least one post-baseline BMD data.

1. ITT Analysis I – Worst Response Analysis: We replaced missing values with 0%. The value 0% is regarded as the least favorite outcome for Activella treated subjects, i.e., assuming Activella is not effective; and is the most favorite outcome for the placebo treated subjects, i.e., assuming the BMD did not deteriorate over 2 years in these subjects. The variability might increase or decrease depending on the distribution of the observed data.
2. ITT analysis II – Worst response as defined in ITT analysis I and worst variability (sample standard deviation from the modified ITT analysis).
3. ITT Analysis III – "Worst" Worst Response Analysis: As requested by your medical reviewer, we replaced the missing values in one group by the population mean estimated from the other treatment group. That is, in the Activella group, a value of –2.61% is used to replace the missing value, and in the placebo group, a value of 4.45% is used.

Results from these analyses are summarized in the following table.

Table 2: Percent Change in Lumbar Spine BMD from Baseline

	Activella			Placebo				
Analysis	N	Mean	SD	N	Mean	SD	d.f.	p-value
Completers	28	4.45	2.844	29	-2.61	2.823	55	<0.001
Modified ITT	37	3.80	3.304	37	-2.12	2.860	72	<0.001
ITT – I	47	2.99	3.111	48	-1.63	2.660	93	<0.001
ITT – II	47	2.99	3.304	48	-1.63	2.860	93	<0.001
ITT - III	47	2.44	3.774	48	-0.61	3.747	93	<0.001

As shown in Table 2, there is a broad comparability of results. Even in the "worst" worst case scenario, the effect of Activella is still highly significantly superior to that of placebo. Therefore, these dropouts do not affect the original conclusion of the effect of Activella in preventing bone loss in postmenopausal women. Should all subjects complete the study, we would have expected the mean difference between two treatment groups would be approximately 7%.

You also suggested that we look into the propensity-based multiple imputation approach, a new methodology developed by Lavori et al. (1995), to generate "reasonable hypothetical" responses to replace the missing data. Lavori et al. pointed out that, by conditioning on a "good" estimate of the "propensity score", one could use the multiple imputation approach to produce ignorable imputations from the estimated posterior predictive distribution of the missing data. The "propensity score $e(X)$" is the conditional probability of observing the outcome in patient with certain baseline characteristics or other historical information (X), which means one needs to have prior knowledge about potential prognostic variables and/or large sample sizes to characterize the propensity function. With small size study, we are likely to characterize the dropouts wrongly by an unreliable propensity score and generate unreasonable hypothetical responses. As a result, the risk of making incorrect inferences is high. We sincerely hope that you would reconsider the use of this method in this study.

We appreciate your valuable input during your review of this NDA. We sincerely hope that the information provided in this document would satisfy the basis for approval of Activella. We can, in the future, perform analyses based on "multiple imputation for missing data" using SOLAS, but we do not have this software available at the present time.

Request for Information

April 5, 2000

John K. Jenkins, M.D., F.C.C.P.
Acting Director
Division of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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Re: Request for Information
Activella, NDA 21-103

Dear Dr. Jenkins:

Reference is made to NDA 21-103 for Activella™ (estradiol, norethindrone acetate tablets) 1mg/0.5 mg and to the request made on April 5, 2000 for paper copies of the Activella dispenser, carton and shipper labels. At this time, these copies represent the final proofs for these labels since the final printed labels are not yet available.

Enclosed please find the following:

Activella dispenser
Activella dispenser-free sample
Activella carton
Activella carton-free sample
Activella 5 pack
Activella 5 pack—free sample
Activella Shipper
Activella Shipper—free sample

If you have any questions, please contact Lieselotte Bloss, D.V.M., Asst. Dir. Regulatory Affairs at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cc: Randy Hedin

SAFETY UPDATE

March 24, 2000

ORIG AMENDMENT
N-SE

Novo Nordisk

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John K. Jenkins, M.D., F.C.C.P.
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5600 Fishers Lane
Rockville, MD 20857

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
MAR 27 2000
HFD-510

Re: Safety Update
Activella, NDA 21-103

Dear Dr. Jenkins:

Reference is made to NDA 21-103 for Activella™ (estradiol, norethindrone acetate tablets) 1mg/0.5 mg and to 21CFR 314.50 (d)(5) (vi)(b) submitted on June 10, 1999. During the time period from June 1, 1999 to March 20, 2000, there have been no serious adverse events reported.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Asst. Dir. Regulatory Affairs at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

Dan Cupi for B. Reit

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE

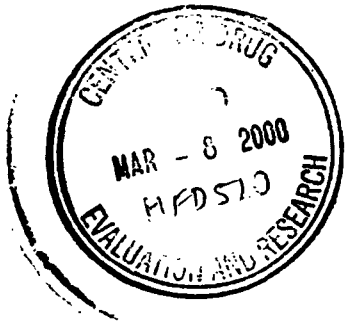
cc: Randy Hedin

General Correspondence

DUPLICATE

NEW CORRESP

March 7, 2000



John K. Jenkins, M.D., F.C.C.P.
Acting Director
Division of Metabolic and
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Novo Nordisk

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Re: Changes Being Effected Supplement for Activelle™ Name Change to Activella™
Activelle, NDA 20-907
Activelle, NDA 21-103

Dear Dr. Jenkins:

Reference is made to NDA 20-907, Activelle™ (estradiol, norethindrone acetate tablets) 1mg/0.5 mg and to the Changes Being Effected supplement of November 16, 1999 requesting the name change from Activelle to Activella in the FDA approved label of November 18, 1998.

This correspondence is to notify NDA 21-103, Activelle (osteoporosis indication), of this name change. On February 10, 2000, the name change in the approved label for NDA 20-907 from Activelle to Activella was granted by the FDA. Attached is a copy of the approval letter.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Asst. Dir. Regulatory Affairs at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cc: Randy Hedin

General Correspondence

December 22, 1999

BS

Solomon Sobel, M.D.
Director, Division of Metabolism & Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
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Re: Activelle™ NDA 21-103
Response to Statistical Reviewer

Dear Dr. Sobel:

Reference is made to Activelle (1 mg estradiol/0.5 mg norethindrone acetate tablets), NDA 21-103.

At the request of Japo Choudhury (Statistician, Division of Metabolism and Endocrine Drugs Products). Won-Chin Huang, Director, Biostatistics and Lieselotte Bloss, Asst. Director, Regulatory Affairs Novo Nordisk and Japo Choudhury conducted a teleconference on Monday October 4, 1999 at 2 pm to discuss statistical issues regarding NDA 21-103.

Please find attached the supplemental analyses of KLIM/PD/11/USA in response to Japo Choudhury's questions and comments. An electronic file of the document on CD-ROM, pdf format, is also provided; this is labeled NDA 21-103, Activelle, Dec. 21, 1999; Contents PD11SUPP.PDF, PD11SUPP.DOC.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Asst. Dir. Regulatory Affairs at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

General Correspondence

November 23, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism & Endocrine
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Office of Drug Evaluation II
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5600 Fishers Lane
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Novo Nordisk

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Re: Activelle™ NDA 21-103
SAS Data Sets for KLIM/PD/11/USA and KLIM/PD/4/F

Dear Dr. Sobel:

Reference is made to Activelle (1 mg estradiol/0.5 mg morethindrone acetate tablets), NDA 21-103.

At the request of Japo Choudhury (Statistician, Division of Metabolism and Endocrine Drugs Products), we are submitting SAS data sets for the following clinical studies: KLIM/PD/11/USA and KLIM/PD/4/F.

Enclosed please find two copies on diskette and one paper copy.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Asst. Dir. Regulatory Affairs at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

SUPPLEMENT - CBE

Novo Nordisk

Novo Nordisk Pharmaceuticals, Inc.
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August 17, 1999

Solomon Sobel, M.D.
Director, Division of Metabolism & Endocrine
Drug Products (HFD-510)
Office of Drug Evaluation II
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Changes Being Effected Supplement for CMC QC Testing Site Change
Bundling of: Activelle™, NDA 20-907
Activelle™, NDA 21-103

Dear Dr. Sobel:

We are submitting this CBE Supplement to NDA 21-103 at the request of Dr. Markofsky. Previously this document was sent to the Division of Reproductive and Urologic Drug Products, HFD 580 for Activelle (NDA 20-907) and subsequent to conversations with the Division of New Drug Chemistry.

In March Dr. Susan Lange spoke with Lieselotte L. Bloss, DVM, Asst. Dir. Regulatory Affairs regarding the Site Change in reference to NDA 20-907 for Activelle™ approved on November 18, 1998. At that time she suggested that we present to Nancy Sager information relevant to the Guidance for Industry PAC-ATLS: Postapproval Changes, April 1998 and request agreement from FDA to submit information as a changes being effected supplement. This request was made and granted by Nancy Sager on May 21, 1998. A copy has been provided in Attachment 1. Since the CBE supplement affects both Activelle and we are submitting the pertinent information to the Division of Reproductive and Urologic Drug Products, HFD 580 to be bundled. Copies for both NDA 20-907 are being provided for archival purposes.

In an effort to consolidate production and testing to product specific locations Novo Nordisk expects to move from the current facilities in sites Soeborg and Bagsvaerd to a new facility located under Site Maaloev

For Activelle has performed will continue this testing in the new facility under identical conditions as done previously.

Please note that:

- The same analytical equipment as previously will be used. It will be requalified after transfer.
- The same technicians and chemists as previously will perform the analysis.
- The same analytical methods and SOP's will be used as previously.
- The only difference is the building, which has been constructed specifically for that purpose.

A table identifying the names and addresses of the current and new testing site as well as a description of the testing to be performed is shown below. For location in relevant NDAs please refer to Attachment 2.

Activelle and Vagifem Quality Control Facilities

Department	Current facility Name/Address	New facility Name/Address	Activity
	Novo Nordisk A/S Novo Allé. DK-2880 Bagsvaerd	Novo Nordisk A/S Novo Nordisk Park. DK-2760 Maaloev	
	Novo Nordisk A/S Sydmarken 5, DK-2860 Soeborg	Novo Nordisk A/S Novo Nordisk Park. DK-2760 Maaloev	

The Guidance for Industry PAC-ATLS allows sponsors to make postapproval changes as Changes Being Effected providing the new testing site meets four criteria discussed below:

(1) "The test methods approved in the application or methods that have been implemented under 21CFR 314.70 are used."

The testing ; performed at the current testing facilities in Soeborg and Bagsvaerd respectively will be transferred to Maaloev and the analytical methods will remain unchanged by the transfer. Please refer to Attachment 3.

(2) "All post approval commitments made by the applicant relating to the test method(s) have been fulfilled."

APPEARS THIS WAY
ON ORIGINAL

(3) *"The new testing facility has the capability to perform the intended testing."*

The same analytical equipment as previously will be used. It will be requalified after transfer. The same technicians and chemists as previously will perform the analysis. The same analytical methods and SOP's will be used as previously. The only difference is the building, which has been constructed specifically for that purpose. Please see Attachment 4.

(4) *"The new testing facility has had a satisfactory current good manufacturing (cGMP) inspection within the past 2 years."*

The new testing facility will be a new building on site Maaloev that has had a satisfactory cGMP inspection within the past two years. An establishment inspection for Activelle was conducted at Novo Nordisk's testing sites in Soeborg, Maaloev and Gentofte, Denmark from February 18 to March 5,1998 by FDA with an acceptable rating. During this inspection the testing facility in Soeborg was inspected.

Consequently, the testing laboratory in terms of analytical equipment, instructions, SOP's and personnel has received and passed a GMP inspection by FDA. The physical lay-out of the new testing facility has not been inspected, because it has recently been built for this purpose. However, it belongs under Site Maaloev which has already been FDA inspected as mentioned above.

Supporting Documentation

The guideline asks for a full description of the testing to be performed by the new facility. We consider that reference to the NDA methods for testing, that remain unchanged, to be adequate.

Please let us know if any additional information is needed to be submitted to the review division. We look forward to hearing from you.

If you have any questions, please contact Lieselotte Bloss, D.V.M., Asst. Dir. Regulatory Affairs at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

GENERAL CORRESPONDENCE

August 17. 1999

Dr. Lisa Rarick
Director. Division of Reproductive and
Urologic Drug Products, HFD 580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food & Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk
Novo Nordisk Pharmaceuticals, Inc.
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Re: S-001
Changes Being Effected Supplement for CMC QC Testing Site Change
Bundling of: Activelle™, NDA 20-907

Dear Dr. Rarick:

This correspondence is a note to the file for S-001 to NDA 20-907 (Activelle)
Please note that this supplement has also been submitted to NDA 21-103 currently under review in HFD-580 for the indication of Osteoporosis.

Please find attached a copy of the cover letter sent to Dr. Sobel regarding the submission of the above CBE to the NDA 21-103

If you have any questions, please contact Lieselotte Bloss. D.V.M., Asst. Dir. Regulatory Affairs at (609) 987-5852.

Sincerely,

NOVO NORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

NEW DRUG APPLICATION

Novo Nordisk Pharmaceuticals, Inc.
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June 10, 1999

Solomon Sobel, M.D.
Division of Metabolic & Endocrine Drug Products, HFD 510
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: NDA 21-103, Activelle® (estradiol/norethindrone acetate tablets) 1mg/0.5 mg
Efficacy Supplement to NDA 20-907

Dear Dr. Sobel:

Pursuant to 21 CFR 314.54, Novo Nordisk Pharmaceuticals, Inc. (NNPI) is herewith submitting a type 6 NDA for Activelle®, for use in the prevention of osteoporosis. This is an efficacy supplement to Activelle NDA 20-907 application, approved November 18, 1998 by the Division of Reproductive and Urologic Drug Products (HFD 580) for the treatment of moderate to severe vasomotor symptoms associated with the menopause, and vulvar and vaginal atrophy, in women with an intact uterus.

This application consists of 73 volumes and is being submitted in duplicate (FDA archive copy and technical review copies). For each technical review section, a copy of volumes 1 and 2 of the NDA is provided. These volumes contain various administrative documents, the NDA index and the Application Summary.

This submission contains information pertaining to the indication for osteoporosis. Reference is made to NDA 20-907, particularly for the Non-Clinical Pharmacology and Toxicology, Human Pharmacokinetics and Bioavailability Data, and Chemistry, Manufacturing and Controls sections. Please note that the technical review sections for Item 3, Chemistry Manufacturing Controls, Item 5 Non-Clinical Pharmacology and Toxicology and Item 6 Human Pharmacokinetics and Bioavailability Data consist only of the sections' summaries and the corresponding item table of contents from NDA 20-907. There are no ongoing clinical studies for the osteoporosis indication.

Two primary or pivotal studies for efficacy and safety are being presented, one domestic study (KLIM/PD/11/USA) and one European study (KLIM/PD/4/F). For ease review, the French study report (KLIM/PD/4/F) and appendices were separated into two sections: the English translation of the report and appendices; and the corresponding French sections. A third study (KLIM/PD/18/J) is being presented as a supportive efficacy and safety study. Only the main report of this study has been included. Two additional study reports are included one domestic (KLIM/PD/19/USA) and one foreign (KLIM/PD/15/IRL). These studies investigated the metabolic impact of Activelle. Only preliminary metabolic impact results from the studies were available for the 120-day safety update for the original NDA 20,907. Therefore these results are included in this application.

The approved Activelle package insert and patient information has been modified to incorporate information regarding the osteoporosis indication. Annotation appears only where new information was inserted. For ease of review, the approved (November 18, 1998) label and the originally submitted annotated label (November 1997) have also been provided.

The proposed indication) draft label contains the following wording for pediatric use: "Safety and effectiveness in pediatric patients have not been established" as studies have not been conducted in this population subgroup. Novo Nordisk requests a waiver from conducting pediatric studies for the following reasons: 1) The approved Activelle label indication is for relief of symptoms of the menopause, which is an indicated disease on the list published in FR63, vol. 231, p 66648 (12/2/98). The label is only being modified to include the osteoporosis indication. 2) Although the above Federal Register notice states that osteoporosis is not included on this list since it may occur in children, it is unlikely that a hormone replacement therapy product would be suitable in treating the pediatric population for osteoporosis. Use of this class of drug would not represent a meaningful benefit over existing pediatric therapies and would not be used in a substantial number of pediatric patients, if any. Novo Nordisk certifies that there is adequate justification for a waiver request.

Following this letter is FDA Form 356h and the User Fee Cover Sheet. The User Fee was wired to the Mellon Bank in Pittsburgh, PA on April 14, 1999. Confirmation of receipt was made via telephone to Michael Jones, 301-594-2041 on April 20, 1999.

Questions or comments regarding this application should be directed to Lieselotte Bloss, D.V.M., Assistant Director, Regulatory Affairs, at 609-987-5852.

Sincerely,
NOVO NORDISK PHARMACEUTICALS INC.

Barry Reit, Ph.D.
Vice President, Regulatory Affairs

/LbLo

Hedin

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 Overlook Center
Suite 200
Princeton, NJ 08540

Dear Dr. Reit:

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:	Activelle® (estradiol/norethindrone acetate tablets) 1mg/0.5mg
Therapeutic Classification:	Standard (S)
Date of Application:	June 10, 1999
Date of Receipt:	June 11, 1999
Our Reference Number:	21-103

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 August 10, 1999 in accordance with 21 CFR 314.101(a). If the application is filed, the primary user fee goal date will be April 11, 2000, and the secondary user fee goal date will be June 11, 2000.

Be advised that, as of April 1, 1999, all applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred (63 *FR* 66632). If you have not already fulfilled the requirements of 21 CFR 314.55 (or 601.27), please submit your plans for pediatric drug development within 120 days from the date of this letter unless you believe a waiver is appropriate. Within 120 days of receipt of your pediatric drug development plan, we will notify you of the pediatric studies that are required under section 21 CFR 314.55.

If you believe that this drug qualifies for a waiver of the study of the pediatric study requirement, you should submit a request for a waiver with supporting information and documentation in accordance with the provisions of 21 CFR 314.55 within 60 days from the date of this letter. We will notify you within 120 days of receipt of your response whether a waiver is granted. If a waiver is not granted, we will ask you to submit your pediatric drug development plans within 120 days from the date of denial of the waiver.

Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products (pediatric exclusivity). You should refer to the *Guidance for Industry on Qualifying for Pediatric Exclusivity* (available on our web site at www.fda.gov.cder/pediatric) for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request" in addition to your plans for pediatric drug development described above. If you do not submit a Proposed Pediatric Study Request within 120 days from the date of this letter, we will presume that you are not interested in obtaining pediatric exclusivity and will notify you of the pediatric studies that are required under section 21 CFR 314.55. Please note that satisfaction of the requirements in 21 CFR 314.55 alone may not qualify you for pediatric exclusivity.

Please cite the NDA number listed above at the top of the first page of any communications concerning this application. All communications concerning this NDA should be addressed as follows:

U.S. Postal/Courier/Overnight Mail:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Metabolic and Endocrine Drug Products, HFD-510
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

If you have any questions, contact Randy Hedin, R.Ph., Senior Regulatory Management Officer, at (301)827-6392.

Sincerely,

/S/

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 21-103
HFD-510/Div. Files
HFD-510/R.Hedin
HFD-510/Reviewers and Team Leaders
DISTRICT OFFICE

Drafted by: dk/June 15, 1999
Initialed by: MAO 6/15/99
final:
filename: 21103.WPD

ACKNOWLEDGEMENT (AC)