CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-103

Administrative Documents

Patent Certification

In the opinion and to the best knowledge of Novo Nordisk, there are no patents that claim the drug or drugs on which investigations that are relied upon in this application were conducted or that claim a use of such drug or drugs.

Barry Rent, Ph. D.
Vice President
Regulatory Affairs

6/10/99
Date

Exclusivity Checklist

NDA: 21-103				
Trade Name: Activella				
Generic Name: Estradiol hemihydrate + Norethindrone Acetate 0.5mg				
Applicant Name: Nova Nordisk				
Division: Metabolism & Endocrine				
Project Manager: Randy Hedin				
Approval Date:				
PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?				
1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.				
a. Is it an original NDA?	Yes	✓	No	
b. Is it an effectiveness supplement?	Yes		No	✓
c. If yes, what type? (SE1, SE2, etc.)				
Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")	Yes	✓	No	
If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.				
Explanation:				
If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:				
Explanation:				
d. Did the applicant request exclusivity?	Yes		No	✓
If the answer to (d) is "yes," how many years of exclusivity did the applicant request?				
IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS.				
2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use?	Yes		No	✓
If yes, NDA #				
Drug Name:				

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS.				
3. Is this drug product or indication a DESI upgrade?	Yes		No	✓
IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS (even if a study was required for the upgrade).				

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.	Yes		No	
Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.	Yes		No	

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product	
NDA #	
Drug Product	
NDA #	
Drug Product	
NDA #	

2. Combination product.	Yes		No	
If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing <u>any one</u> of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)	Yes	✓	No	

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

Drug Product	Estradiol
NDA #	20-538
Drug Product	—
NDA #	—
Drug Product	Norethindrone
NDA	20-654

NDA #	

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS. IF "YES," GO TO PART III.

PART III: THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.	Yes	✓	No	

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application. For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?	Yes	✓	No	

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCKS.**

Basis for conclusion:

b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?	Yes		No	✓
1) If the answer to 2 b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.	Yes		No	

If yes, explain:				
2) If the answer to 2 b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?	Yes		No	✓
If yes, explain:				
c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:				
Investigation #1, Study #:	KLIM/PO/11/USA			
Investigation #2, Study #:	KLIM/PO/4/E			
Investigation #3, Study #:				
3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.				
a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	✓
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?				
Investigation #1	Yes		No	✓
Investigation #2	Yes		No	✓
Investigation #3	Yes		No	
If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:				
Investigation #1 -- NDA Number				
Investigation #2 -- NDA Number				
Investigation #3 -- NDA Number				
If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the				

application or supplement that is essential to the approval (i.e., the investigations listed in #2 (c), less any that are not "new"):

Investigation #1	ICLIM/PD/11/4
Investigation #2	ICLIM/PD/4/F
Investigation #3	

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a. For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1	Yes	✓	No	
IND#: [redacted]				
Explain:				
Investigation #2	Yes	✓	No	
IND#: [redacted]				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

b. For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1	Yes		No	
IND#:				
Explain:				
Investigation #2	Yes		No	
IND#:				
Explain:				
Investigation #3	Yes		No	
IND#:				
Explain:				

c. Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)	Yes		No	✓
If yes, explain:				

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Signature of PM/CSO /S/
Date: 4/3/00

Signature of Division Director /S/
Date: 4/11/00

cc:
Original NDA
Division File
HFD-93 Mary Ann Holovac

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PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21103	**Trade Name:**	ACTIVELLE(ESTRADIOL/NORETHINDRONE ACETAT
Supplement Number:		**Generic Name:**	ESTRADIOL/NORETHINDRONE ACETATE
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:	PN	**Proposed Indication:**	Activella thereapy is indicated in women with an intact uterus for the prevention [redacted] of postmenopausal osteoporosis. 4/3/00

ARE THERE PEDIATRIC STUDIES IN THIS SUBMISSION?

NO, Pediatric content not necessary because of pediatric waiver

What are the INTENDED Pediatric Age Groups for this submission?

____NeoNates (0-30 Days) ____Children (25 Months-12 years)
____Infants (1-24 Months) ____Adolescents (13-16 Years)

Label Adequacy	Adequate for ALL pediatric age groups
Formulation Status	-
Studies Needed	-
Study Status	-

Are there any Pediatric Phase 4 Commitments in the Action Letter for the Original Submission? NO

COMMENTS:
The firm requested a pediatric waiver in their June 10, 1999 cover letter. It would be inappropriate to give hormone replacement therapy to pediatric patients to treat osteoporosis. 4/3/00

See above comment.

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, RANDY HEDIN

/S/

Signature

4/3/00

Date

Debarment Statement

Novo Nordisk Pharmaceuticals Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food, Drug and Cosmetic Act in connection with this submission.

Barry Reit, PhD
Vice President
Regulatory Affairs

TEAM LEADER MEMO
for
NDA 21-103

ACTIVELLA™

NDA#: 21-103

DRUG: Activella™ (1.0 mg estradiol/0.5 mg norethindrone acetate)

SPONSOR: Novo Nordisk Pharmaceuticals

INDICATION: Prevention [redacted] of Postmenopausal Osteoporosis

DATE OF SUBMISSION: 6/10/1999

PRIMARY MEDICAL REVIEWER: Joanna Zawadski, MD

DATE OF MEMO: 04/06/2000

Background

Activella [1.0 mg Estradiol (E2)/0.5 mg norethindrone acetate (NETA)] was originally approved in this country for the treatment of vasomotor symptoms associated with menopause and for vulvar and vaginal atrophy on 11/18/1998. Although currently not marketed in the US, Activella is approved and marketed for menopausal symptoms and/or prevention of postmenopausal osteoporosis (PMO) in ten European countries.

On June 10, 1999 the Sponsor submitted an application seeking approval of Activella for the prevention [redacted] of PMO. Data from two randomized, controlled trials – one in the US and one in France - constitute the primary basis upon which a decision to approve the application will be made. Three additional smaller and shorter studies were also included in the submission. This memo focuses on the results from the two primary clinical studies.

Primary Clinical Studies

The US protocol was a multicenter, randomized, double-blind study of 26 lunar months in which a total of 327 subjects were randomized (in equal fashion) to one of seven groups: placebo, E2 0.25mg, E2 0.5mg, E2 1.0mg, E2 1mg + NETA 0.25mg, E2 1.0mg + NETA 0.5mg, and E2 2.0mg + NETA 1.0mg. Relevant inclusion criteria included age $\geq$ 45 years, LS BMD T-score > -2.0, and 1 to 5 years postmenopausal. There was an extensive list of exclusion criteria, some of which included: MI with the past 6 months, history of CVA, diabetes, > 30% above IBW, hypertension, and cigarette smoking (> 20 cig/day).

The primary efficacy variable for this study was the comparison between active-drug treatment with placebo for the change from baseline to Endpoint in LS BMD. Comparisons were made using ANOVA or ANCOVA analyses. A secondary endpoint included change from baseline to Endpoint in BMD of the hip.

Special safety assessments included mammography, endometrial biopsies, pap smears, and vaginal ultrasound.

There were no significant differences among the groups for baseline demographic variables. Women were primarily Caucasian, on average 53 years of age, with baseline lumbar spine (LS) BMD values of 1.09 g/cm^2. A total of 60% of placebo and Activella subjects completed the 2-year study, with a lower percentage of Activella-treated subjects discontinuing due to adverse events (17% vs. 23%).

For the primary efficacy endpoint – percent change in LS BMD – all active-treatment groups had increases, whereas the placebo group had a reduction in LS BMD. The difference between placebo and Activella was approximately 6% ($p<0.001$) for the LOCF analysis. As expected, a larger difference was seen in the analysis of Completers. Although the study was not designed to evaluate the differences between active-treatment groups, there did appear to be dose-related increases in LS BMD among the groups. Compared with placebo, statistically significant increases in BMD at the hip were also seen for the active-treatment groups. Compared with LS BMD however, a dose-response effect was not as evident for the changes in BMD at the hip.

Two patients died in this study: one in the Activella group from cancer of unknown primary origin and the other, also in the Activella group, from lung cancer. Of some interest, 23% of placebo patients discontinued due to an adverse event compared with 17% of the Activella-treated women. Two placebo and 3 Activella-treated subjects discontinued because of breast pain; 1 placebo and 0 Activella-treated woman discontinued because of endometrial hyperplasia; 0 placebo and 3 Activella subjects discontinued because of bleeding; and 4 placebo and 0 Activella women discontinued due to hot flushes. Of note, of the approximately 74% of subjects in the placebo and Activella groups who had evaluable endometrial biopsies, 1 placebo patient and none of the Activella-treated women developed endometrial hyperplasia. As assessed by vaginal ultrasound, the mean increases in endometrial thickness from baseline to Endpoint were 0.2 mm and 0.6 mm in the placebo and Activella groups, respectively (p=ns). No differences between the placebo and Activella treatment groups were noted for changes in cervical cytology.

The second primary study was conducted in France and was designed as a multicenter, randomized, double-blind study of 24 months duration in which a total of 135 women were randomized (in equal fashion) to one of 3 doses: placebo, E2 1.0mg + NETA 0.25mg, or E2 1.0mg + NETA 0.5mg. Relevant inclusion criteria included age 45-65 years, > 1 year since last menses, endometrial thickness $\leq$ 4mm, and LS BMD T-score of +2.0 to –1.9. Exclusion criteria included history of CHF, MI, angina, CVA, DVT, and diabetes. Subjects were also excluded if they had a BMI > 30 kg/m^2, smoked more than 40 cigarettes per day, or had hypertension.

The primary efficacy variable for this study was the change in LS BMD as measured using a logarithm of BMD at the end of the study divided by the baseline BMD. Comparison of the change in LS BMD was assessed using a regression model which included values for bone markers, baseline BMD, BMI, menopausal age, and treatment center as covariates. Secondary endpoints included measurement of BMD at the hip, distal radius, and total body. Special safety assessments included measurement of endometrial thickness and vaginal bleeding (using a daily diary).

Baseline demographics were similar among the groups. The mean age of the women upon entry into the study was 58 years and the vast majority of subjects were Caucasian. Baseline LS BMD was 0.97 g/cm^2 in the placebo group and 0.99 g/cm^2 in the Activella group; this difference was not statistically significant. A total of 73% of the placebo participants completed the study compared with 63% of the Activella women. Twenty-eight percent of the Activella subjects discontinued early because of an adverse event vs. 13% of placebo-treated women.

Efficacy was clearly demonstrated in the Activella group. Compared with a mean decrease in LS BMD of 0.9% in the placebo group, the Activella group had a 5.4% increase from baseline to Endpoint ($p<0.001$). The change seen in the 1.0mg E2 + 0.25mg NETA group was nearly identical to that observed in the Activella group. In the group of subjects who completed the study, the mean increase in LS BMD was 5.9% in the Activella group vs. –1.1% in the placebo group. Importantly, statistically and clinically

significant increases in BMD at the distal radius (cortical bone) and total body were seen in the Activella group relative to the placebo group. The effect of Activella on BMD at the hip was variable: although BMD at the femoral neck and Ward's triangle increased in the Activella group relative to the placebo group, the differences were not statistically significant. There was however, a statistically significant increase in BMD at the femoral trochanter in the Activella group. The increases in BMD at the various skeletal sites examined were, in general, similar for the two doses of active treatment.

Two subjects died in this study. One subject treated with Activella died from a MI 4 months into the study. The second woman, treated with placebo, was found dead and presumed to have suffered sudden cardiac death. Of note, both of these women had histories of coronary artery disease and should not have been enrolled into the study (as per the exclusion criteria). Over twice as many subjects in the Activella group (28%) discontinued treatment early because of an adverse event than in the placebo group (13%). No placebo and 2 Activella subjects discontinued because of vaginal bleeding; no placebo and 5 Activella women discontinued because of breast pain; no placebo and 2 Activella women discontinued because of breast neoplasm/fibroadenosis (neoplasm reported as benign) and 2 placebo and no Activella subjects discontinued because of vertebral fractures.

Comment

Novo Nordisk has submitted data from two studies that clearly demonstrate a LS BMD-preserving effect of Activella relative to placebo when taken over a two-year period (drug-placebo difference of 6%). It is also clear from the submitted data that women who took lower doses of estradiol had relative preservations of LS BMD when compared with placebo. However, the magnitude of the differences between active drug and placebo were smaller for the lower doses of estradiol, and the studies were not designed to compare efficacy among active-treatment groups. No unusual or unexpected safety issues emerged from review of this application.

As alluded to in Dr. Zawadski's review, although there is an inverse relationship between the change in LS BMD and risk for vertebral fracture, this correlation is not large for drugs currently approved for the prevention and treatment of postmenopausal osteoporosis. Matters are further complicated by the absence of fracture data from a large randomized trial of estrogen (± progestin) in women with, or at risk for, postmenopausal osteoporosis. In essence, we do not know what the optimal estrogen-induced change in BMD is for fracture prevention. Do the relative increases in LS BMD observed with the lower doses of estradiol confer the same change in risk for fracture as that seen with Activella?

Based in large part on the Guidance for Clinical Evaluation of Combination Estrogen/Progestin-Containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women, Dr. Zawadski has deemed this application approvable pending an additional study of lower estradiol/norethindrone acetate combination doses. This is a reasonable suggestion. However, because Activella is currently approved for the treatment of vasomotor symptoms and vaginal atrophy in postmenopausal women, I think that it is equally rationale to approve Activella for the prevention of postmenopausal osteoporosis based on the submitted data. The labeling for the drug will clearly indicate that the doses of estrogen and progestin in Activella may not be the lowest effective doses for the prevention of postmenopausal osteoporosis. Health care providers can then make the decision about whether to use this drug in women solely for the purpose of preventing osteoporosis, or treat with another agent.

In addition to seeking an indication for the prevention of postmenopausal osteoporosis, the Sponsor has also requested an indication for [redacted] No data were submitted to substantial an indication [redacted]

Regulatory Recommendation

Approve Activella for the **prevention of postmenopausal osteoporosis.**

/S/ 1/10-00

Eric Colman, MD
Medical Team Leader

cc: NDA file

MEMORANDUM TO FILE

To: **HFD 510 file/ NDA 21103**
RE: **NDA 21103**
Questions to Sponsor
From: Joanna K. Zawadzki, M.D., F.A.C.P.
Medical Reviewer
Date: 4/11/00

On 4/7/00, the sponsor was asked about protocol violations listings in the NDA for the pivotal studies, KLIM/PD/11/USA and KLIM/PD/7/USA. The sponsor cited the references (Vol. 1.8, p. 50 and p.339 and Vol. 1.13 p.66). No other references were cited. This question was the last outstanding question addressed to the sponsor.

APPEARS THIS WAY
ON ORIGINAL

Meeting Date: March 16, 2000 Time: 4:00 - 4:45 PM Location: 14-56

NDA 21-103 Activella (estradiol/norethindrone)

Type of Meeting: Status Meeting

External participant: None

Meeting Chair: Dr. Eric Colman

External participant lead: None

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Eric Colman, Medical Team Leader, DMEDP
Dr. Joanna Zawadzki, Medical Reviewer DMEDP
Dr. Jopo Choudhury, Statistical Reviewer, DOB II
Mr. Bill Koch, CSO, DMEDP
Mr. Randy Hedin, CSO, DMEDP

External participant Attendees and titles:

None

Meeting Objectives:

Internal meeting requested by the project manager to discuss the status of the reviews of Activella, and labeling issues.

Discussion Points and Decisions (agreements) reached:

Clinical: The review will be finished by the goal date. The medical officer presented labeling changes to the group (see attached comments), and will send an electronic version of the label to the project manager. The group discussed if the estrogen dose proposed by the firm is the lowest effective dose for the prevention of postmenopausal osteoporosis, and if it is not, should Activella be approved. Also, the trade name Activelle has been changed to Activella.

Statistics: The review will be finished on time. However, there are labeling comments. The project manager will send an electronic version of the label for comments when the medical review comments are incorporated in it.

DDMAC: The Division of Drug Marketing, Advertising, and Communications (DDMAC) did not attend the meeting. However, Ms. Kober informed the project manager that DDMAC would provide comments on the label to the Division.

Unresolved or issues requiring further discussion:

- None

Action Items:

- Send draft labeling comments to the firm.

Signature, minutes preparer: /S/

Concurrence Chair: /S/

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD-511/RHedin/3.17.00/N21103.MN1
Concurrences: JZawadzki/3.17/EColman/3.22/JChoudhury/3.22/BKoch/3.22.00

Meeting Date: July 29, 1999 Time: 1:00 - 1:45 PM Location: 14-56

NDA Activelle (estradiol/norethindrone acetate) Tablets

Type of Meeting: Filing Meeting

External participant: None

Meeting Chair: Dr. Sobel

External participant lead: None

Meeting Recorder: Mr. Randy Hedin

FDA Attendees and titles:

Dr. Solomon Sobel, Division Director DMEDP
Dr. Joanna Zawadzki, Medical Reviewer DMEDP
Dr. Todd Sahlroot, Team Leader, Division of Biostatistics
Dr. Joppo Choudhury, Reviewer, Division of Biostatistics
Dr. Ronald Steigerwalt, Pharmacology Team Leader
Mr. Randy Hedin, Project Manager, DMEDP

External participant Attendees and titles:

None

Meeting Objectives:

To determine if NDA 21-103 will be filed, and discuss plans for the review of the NDA.

Discussion Points:

Pharmacology : The application is fileable.

Biostatistics: The application is fileable. See attached screening memo.

Clinical: The application is fileable. The firm should be asked to submit all electronic data that is available, and an electronic label.

Decisions (agreements) reached:

- The application will be filed.

- The review will be done as a standard review. The goal to finish the reviews will be March 1, 2000.
- A labeling meeting will be scheduled for March 11, 2000.
- There will be DSI inspections; the two largest centers should be selected.
- There will not be an Advisory Committee meeting.

Unresolved or issues requiring further discussion:

- None

Action Items:

- Schedule status meetings as appropriate.

Signature, minutes preparer: /S/

Concurrence Chair: /S/

cc: NDA Arch
HFD-510
Attendees
HFD-510/EGalliers
HFD-511/RHedin/9.13.99/N21103.MN1
Concurrences: JZawadzki/RSteigerwalt/9.14/SSobel/TSahlroot/JChoudhury/9.20.99

Screening of New NDAs
(Japobrata Choudhury)

NDA #: 21-103

Priority Classification: S

Trade Name: Activelle

Sponsor: Novo Nordisk Pharmaceuticals

Generic Name: estradiol/norethindrone acetate

Indication: Osteoporosis

No. of Controlled Studies: 5 (2 main)

Date of Submission: June 10, 1999

User Fee Goal Date: April 11, 2000

Volume numbers in statistical section: 1.24 to 1.40

Date of 45 Day Meeting:

Anticipated Review Completion Date: Feb. 11, 2000

CHECKLIST

Item	Check (NA if not applicable)
Index sufficient to locate necessary reports, tables, etc.	Not in one place
Original protocols & subsequent amendments available in the NDA	Yes
Designs utilized appropriate for the indications requested	Yes
Endpoints and methods of analysis spelled out in the protocols	Not quite satisfactory
Interim analyses (if present) planned in the protocol and appropriate adjustments in significance level made	NA
Appropriate references included for novel statistical methodology (if present)	NA
Sufficient data listings and intermediate analysis tables to permit a statistical review	Yes
Data from primary studies on diskettes and/or CANDA submitted	Don't see
Intent-to-treat analyses	Yes
Effects of dropouts on primary analyses investigated	Don't see
Gender, racial, and geriatric subgroups investigated	No

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

(1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	SEE ATTACHED	

(2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

(3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Barry Reit PhD	Vice President, Regulatory Affairs
FIRM/ORGANIZATION	
Novo Nordisk Pharmaceuticals,Inc	
SIGNATURE	DATE
	June 10, 1999

Paperwork Reduction Act Statement

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Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

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information

OFFICES OF DRUG EVALUATION
ORIGINAL NDA/NDA EFFICACY SUPPLEMENT
ACTION PACKAGE CHECKLIST

NDA 21-103 Drug: Actiq/Fe

Applicant: Novo Nordisk Chem/Ther/other Types: _____

CSO/PM: R Hedin Phone: 7-6392 MailCode: HFM-510

ACTION PERF. GOAL DATE: 4/11/00 DATE CKLIST CMPLTD: _____

Arrange package in the following order (include a completed copy of this CHECKLIST): Check or Comment

1. ACTION LETTER with supervisory signatures — AP____ AE____ NA✓
   Are there any Phase 4 commitments? — Yes____ No✓
2. Have all disciplines completed their reviews? — Yes✓ No____
   If no, what review(s) is/are still pending? — NA
3. LABELING (package insert and carton and container labels). — Draft✓
   (If final or revised draft, include copy of previous version with ODE's comments and state where in action package the Division's review is located. If Rx-to-OTC switch, include current Rx Package insert and HFD-312 and HFD-560 reviews of OTC labeling.) — Revised Draft____ Final____
4. PATENT INFORMATION ✓
5. EXCLUSIVITY CHECKLIST ✓
6. PEDIATRIC PAGE ✓
7. DEBARMENT CERTIFICATION (Copy of applicant's certification for all NDAs submitted on or after June 1, 1992). ✓
8. Statement on status of **DSI's AUDIT OF PIVOTAL CLINICAL STUDIES** ✓
   If AE or AP ltr, explain if not satisfactorily completed. Attach a COMIS printout of DSI status.
   If no audits were requested, include a memo expaining why.

9. REVIEWS & MEMORANDA:

DIVISION DIRECTOR'S MEMO	If more than 1 review for any	✓
GROUP LEADER'S MEMO	1 discipline, separate reviews	✓
MEDICAL REVIEW	with a sheet of colored paper.	✓
SAFETY UPDATE REVIEW	Any conflicts between reviews	✓
STATISTICAL REVIEW	must have resolution documented	✓
BIOPHARMACEUTICS REVIEW		
PHARMACOLOGY REVIEW (Include pertinent IND reviews)		✓
Statistical Review of Carcinogenicity Study(ies)		NA
CAC Report/Minutes		NA
CHEMISTRY REVIEW		✓
Labeling and Nomenclature Committee Review Memorandum		NA
Date EER completed _____ (attach signed form or CIRTS printout)		OK✓ No____
FUR needed _____ FUR requested _____		
Have the methods been validated?		Yes (attach)✓ No____
Environmental Assessment Review / FONSI		Review✓ FONSI____
MICROBIOLOGY REVIEW		NA
What is the status of the monograph?		NA

10. **CORRESPONDENCE, MEMORANDA OF TELECONS, and FAXes** _____
11. **MINUTES OF MEETINGS** _____
    Date of End-of-Phase 2 Meeting None
    Date of pre-NDA Meeting None IND # [redacted]
12. **ADVISORY COMMITTEE MEETING MINUTES** — Minutes____ Info Alert____
    or, if not available, 48-Hour Info Alert or pertinent section of transcript. — Transcript____ No mtg✓
13. **FEDERAL REGISTER NOTICES; OTC or DESI DOCUMENTS** None
14. If approval letter, has **ADVERTISING MATERIAL** been reviewed? — Yes____ No____
    If no and this is an AP with draft labeling letter, has advertising material already been requested? — Yes, documentation attached____ No, included in AP ltr ✓

ACTION PACKAGE CHECKLIST

16. **INTEGRATED SUMMARY OF SAFETY** (from NDA) ✓

17. **FDA LETTERS & MEMOS** ✓

18. **APPLICANT'S LETTERS** ✓

19. **CHARGE AND HISTORY CARD** ✓

revision:1/16/98