CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-907/S-003

Trade Name:	Activella 1mg/0.5mg Tablets
Generic Name:	estradiol / norethindrone acetate
Sponsor:	Novo Nordisk
Approval Date:	April 11, 2000

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-003

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-003

APPROVAL LETTER

NDA 20-907/S-003

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Dear Dr. Reit:

We acknowledge receipt of your supplemental new drug application dated April 10, 2000, received April 10, 2000, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Activella®, (estradiol 1mg/northindrone acetate 0.5mg).

We also acknowledge receipt of your submission dated April 11, 2000.

This supplement proposes label changes to include the indication of prevention of osteoporosis.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical, to the submitted draft labeling (package insert submitted April 10, 2000).

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplement NDA 20-907/S-003." Approval of this submission by FDA is not required before the labeling is used.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Practitioner" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Susan Allen, M.D., M.P.H.
Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

cc:
Archival NDA 20-907
HFD-580/Div. Files
HFD-580/D.Spell-LeSane
HFD-580/Mann/Slaughter/Price/Rhee/Lin/Parekh/Jarugula/Jordan/Rumble
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-103/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFI-20/Press Office (with labeling)
HFD-400/OPDRA (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling)
HFD-095/DDMS-IMT (with labeling)
HFD-820/DNDC Division Director
DISTRICT OFFICE

Drafted by: dsl/April 11, 2000
Initialed by:Rumble, 4.11.00/Allen, 4.11.00
final: Spell-LeSane, 4.11.00
filename: NDA/20907/letter/AP003

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-003

ADMINISTRATIVE DOCUMENTS

Internal Meeting Minutes

Date: July 5, 2000 **Time:** 10:00 a.m.-11:10 a.m. **Location:** Parklawn; 17B-43

NDA: 20-907 **Drug:** Activella (estradiol/norethindrone acetate) 1 mg/0.5 mg) tablets

Sponsor: Novo Nordisk Pharmaceuticals, Inc.

Indication: Treatment of menopausal symptoms

Type of Meeting: Labeling

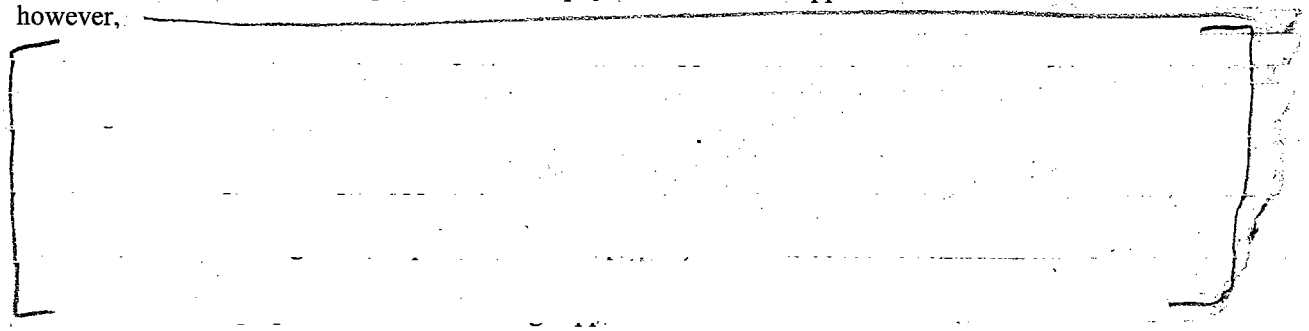
Meeting Chair: Shelley Slaughter, M.D., Ph.D.

Meeting Recorder: Dornette Spell-LeSane, NP-C

FDA Attendees
Shelley Slaughter, M.D., Ph.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Phill Price, M.D. - Medical Officer, DRUDP (HFD-580)
Lisa Stockbridge, Ph.D., Regulatory Reviewer, Division of Drug Marketing Advertising and Communications (DDMAC; HFD-42)
Margaret Kober, R. Ph., Project Manager, DDMAC (HFD-42)
Diane Moore, Project Manager, DRUDP (HFD-580)
Dornette Spell-LeSane, NP-C, Project Manager, DRUDP (HFD-580)

Meeting Objectives:
To discuss proposed changes to the label

Background:
This NDA was originally approved for the treatment of moderate to severe vasomotor symptoms associated with the menopause and treatment of vulvar vaginal atrophy, on Nobember18, 1998. The sponsor did not market the product until this year when a supplemental NDA was approved for the prevention of postmenopausal osteoporosis April 11, 2000. A physician insert was approved with the new indication however,



Discussion:

The following are proposed changes to the Activella label:

1. In the **CLINICAL STUDIES** section,

   a. VASOMOTOR SYMPOTOMS subsection, figure 3, titled "Percentage of Women Bleeding at each month in a 12-month study" should be deleted and replaced with a figure that depicts the cumulative percentage of women who experience amenorrhea over time during the 12-month study. The analysis to create this figure should include all randomized patients. A woman should only be considered amenorrheic at a given timepoint if she has not bled during that month or any subsequent month(s) of follow-up.

   b. INFORMATION REGARDING LIPID EFFECTS subsection, Table 3, "Percentage change from baseline in selected lipid parameters with Activella in a 12-month placebo-controlled study" the forth column "LDL: HDL Ratio" should be deleted.

   Conclusion: This is acceptable.

2. In the **WARNINGS** section,

   a. Number 1. Induction of malignant neoplasms, Endometrial cancer, second paragraph, second sentence reads:
   There is no evidence that "natural" estrogens are more or less hazardous than "synthetic" estrogens at equivalent doses.

b. Number 3. Cardiovascular disease reads:

3. *Cardiovascular disease.* Large doses of estrogens (5 mg conjugated estrogen per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women or from unopposed estrogen to combination estrogen/progestin therapy. However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose.

The draft HRT guidance reads: Large doses of estrogens (5 mg conjugated estrogen per day), comparable to those used to treat cancer of the prostate and breast, have been shown in a large prospective clinical trial in men to increase the risk of nonfatal myocardial infarction, pulmonary embolism, and thrombophlebitis. These risks cannot necessarily be extrapolated from men to women or from unopposed estrogen to combination estrogen/progestin therapy.

DRUDP:
The paragraph on cardiovascular risk proposed by the Sponsor is consistent with the Draft labeling guidance with the exception of the last sentence.

Conclusion: The statement proposed by the Sponsor regarding cardiovascular disease which reads: *"However, to avoid the theoretical cardiovascular risk to women caused by high estrogen doses, the dose for estrogen replacement therapy should not exceed the lowest effective dose."* **is acceptable; this statement should also be considered for inclusion in the guidance document to apply to all HRT labels. Further discussion is needed with DRUDP to make recommendations to the draft guidance document.**

c. Number 8, *Thromboembolic disorders*, which currently reads:

8. *Thromboembolic disorders.* The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drugs should be discontinued immediately. In a one-year study where 295 women were exposed to Activella™, there were two cases of deep vein thromboses reported.

Should be replaced with:

7. *Venous Thromboembolism.* Five epidemiologic studies have found an increased risk of venous thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions for VTE, such as a past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The risk appeared to be higher in the first year of use and decreased thereafter. The findings were similar for ERT alone or with added progestin and pertain to commonly used oral and transdermal doses, with a possible dose-

dependent effect on risk. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2-3 cases per 10,000 women per year.

Conclusion: This is acceptable.

4. In the **DOSAGE AND ADMINISTRATION** section, the second paragraph reads:

"For the treatment of moderate to severe vasomotor symptoms associated with the menopause, and treatment of vulvar and vaginal atrophy, and the prevention of postmenopausal osteoporosis- Activella™ 1 mg E2/ 0.5 mg norethisterone acetate daily. The doses of 17 beta-estradiol and norethindrone acetate in Activella may not be the lowest effective dose-combination for the prevention of osteoporosis."

Should be replaced with:

"For the treatment of moderate to severe vasomotor symptoms associated with the menopause, and treatment of vulvar and vaginal atrophy, one Activella™ 1 mg E2/0.5 mg NETA tablet should be taken daily. Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary."

"For the prevention of postmenopausal osteoporosis, one Activella™ 1 mg E2/ 0.5 mg norethindrone acetate tablet should be taken daily. The doses of 17 beta-estradiol and norethindrone acetate in Activella™ may not be the lowest effective dose-combination for the prevention of osteoporosis.

Conclusion: This is acceptable.

5. In the **PRECAUTIONS** section,

   a. The title CARCINOGESIS, MUTAGENESIS, and IMPAIRMENT OF INFERTILITY

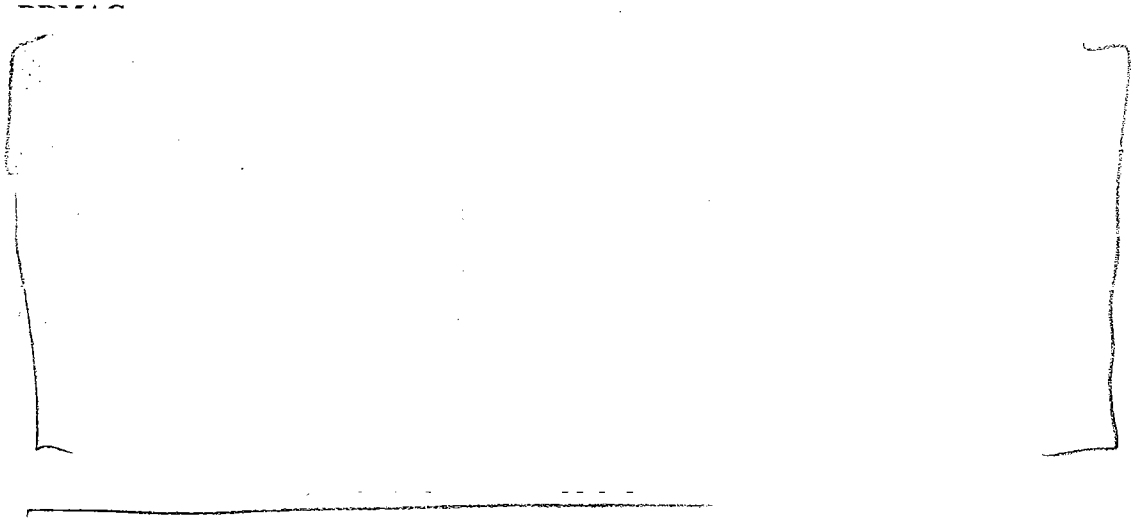
   should be changed to:

   CARCINOGENISIS, MUTAGENESIS, and IMPAIMENT OF FERTILITY

   Conclusion: This is acceptable.

b. In the NURSING MOTHERS section, the second sentence reads:

"As a general principle, the administration of any drug to nursing mothers should be done only when clearly necessary since many drugs are excreted in human milk"



6. In the GERIATRIC USE section, the statement:

"clinical studies of Activella did not include sufficient number of subjects aged 65 and over to determine if they responded differently from younger subjects."

and in the **DOSAGE AND ADMINISTRATION** section, the 3rd sentence states:

"The doses of 17-beta-estradiol and norethindrone acetate in Activella may not be the lowest effective dose-combination for the prevention of osteoporosis.

[redacted]

7. No discontinuations are discussed in the Package insert even though the number is strikingly large (44% discontinuation due to bleeding; 9% due to breast pain) The sponsor provided overall safety summaries and individual study safety summaries with the launch.

   Conclusion: Dr. Price will review discontinuation rates and make recommendations for labeling changes.

Decisions Reached:

1. Agreed upon labeling changes will be included in the "Request for Labeling Changes" letter to the Sponsor.
2. [redacted]
3. [redacted]

[redacted]

5. Additional recommended changes to the Patient Package Insert will be included in the request letter to the Sponsor.

APPEARS THIS WAY
ON ORIGINAL

Action Items:

1. [ ]

2. Project Manager to obtain any additional comments from DMEDP regarding the label and incorporate comments into the label review.

3. Project Manager to circulate label review for signature.

4. Package Insert and Patient Package Insert labeling changes will be conveyed to the sponsor via a "Request for Labeling Supplement".

5. Label review and minutes from this meeting will be discussed with DRUDP Director.

Minutes Preparer

Meeting Chair

cc:
Original NDA 20-907
HFD-580/Div. Files
HFD-580/Allen/Slaughter/Price/
HFD-42/Stockbridge/Kober
Drafted by: ds-l, 7.11.00

Concurrence: Rumble, Stockbridge, 7.11.00/Kober, Price, 7.12.00/Slaughter,7.20.00,

final: Spell-LeSane, 9.29.00

MEETING MINUTES

Division of Reproductive and Urologic Drug Products

Regulatory Project Manager Review

Application Number: NDA 20-907/S-003

Name of Drug: Activella™ (1.0 mg estradiol/ 0.5 mg norethindrone acetate)

Sponsor: Novo Nordisk Pharmaceuticals, Inc.

Material Reviewed:
FPL for Approved SNDA 20-907/S-003

- Package Insert

Submission Date: December 14, 2000

Receipt Date: December 15, 2000

Background and Summary Description: Final Printed Labeling for approved SNDA 20-907/S-003.

Review:
The Package Insert is identical to the April 11, 2000, approved labeling, with exception to minor editorial revisions that were reported in the Annual Report dated January 19, 2001.

Conclusions:
The editorial revisions are acceptable, an Acknowledge and Retain Letter will be issued for this FA submission containing FPL.

Jeanine A. Best, M.S.N., R.N.
Senior Regulatory Associate

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeanine Best
12/11/01 03:00:58 PM
CSO

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-907/S-003

CORRESPONDENCE

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-907

SUPPLEMENT REQUEST

Novo Nordisk Pharmaceuticals, Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Dear Dr. Reit:

Please refer to your new drug application (NDA) for Activella™ (1 mg/0.5mg).

We also refer to our letter dated January 18, 2000, in which we proposed changes to the Activella™ label.

We have reviewed your labeling supplement, S-003 dated April 10, 2000, approved April 11, 2000, in conjunction with your NDA 21-103 for the osteoporosis indication.

In addition, we have reviewed your proposed changes to the Patient Package Insert submitted April 12, 2000.

We request that the following changes be made to your labeling within 2 months from the date of this letter, so as to furnish adequate information for the safe and effective use of the drug:

The following are the requested changes to the Activella Physician Package Insert:

1. **CLINICAL STUDIES** section,

   a. In the VASOMOTOR SYMPTOMS subsection, Figure 3, titled "Percentage of Women Bleeding at each month in a 12-month study" should be deleted and replaced with a figure that depicts the cumulative percentage of women who experience amenorrhea over time during the 12-month study. The analysis to create this figure should include all randomized patients. A woman should only be considered amenorrheic at a given timepoint if she has not bled during that month or any subsequent month(s) of follow-up.

   b. In the INFORMATION REGARDING LIPID EFFECTS subsection, Table 3, "Percentage change from baseline in selected lipid parameters with Activella in a 12-month placebo-controlled study", the forth column "LDL: HDL Ratio" should be deleted.

2. **WARNINGS** section,

a. Number 8, *Thromboembolic disorders*, which currently reads:

8. *Thromboembolic disorders*. The physician should be alert to the earliest manifestations of thrombotic disorders (thrombophlebitis, cerebrovascular disorders, pulmonary embolism, and retinal thrombosis). Should any of these occur or be suspected, the drugs should be discontinued immediately. In a one-year study where 295 women were exposed to Activella™, there were two cases of deep vein thromboses reported.

should be replaced with:

Venous Thromboembolism. Five epidemiologic studies have found an increased risk of venous thromboembolism (VTE) in users of estrogen replacement therapy (ERT) who did not have predisposing conditions for VTE, such as a past history of cardiovascular disease or a recent history of pregnancy, surgery, trauma, or serious illness. The increased risk was found only in current ERT users; it did not persist in former users. The risk appeared to be higher in the first year of use and decreased thereafter. The findings were similar for ERT alone or with added progestin and pertain to commonly used oral and transdermal doses, with a possible dose-dependent effect on risk. The studies found the VTE risk to be about one case per 10,000 women per year among women not using ERT and without predisposing conditions. The risk in current ERT users was increased to 2-3 cases per 10,000 women per year.

3. **DOSAGE AND ADMINISTRATION** section, the second paragraph which reads:

"For the treatment of moderate to severe vasomotor symptoms associated with the menopause, and treatment of vulvar and vaginal atrophy, and the prevention of postmenopausal osteoporosis-Activella™ 1 mg E2/ 0,5 mg norethisterone acetate daily. The doses of 17 beta-estradiol and norethindrone acetate in Activella may not be the lowest effective dose-combination for the prevention of osteoporosis."

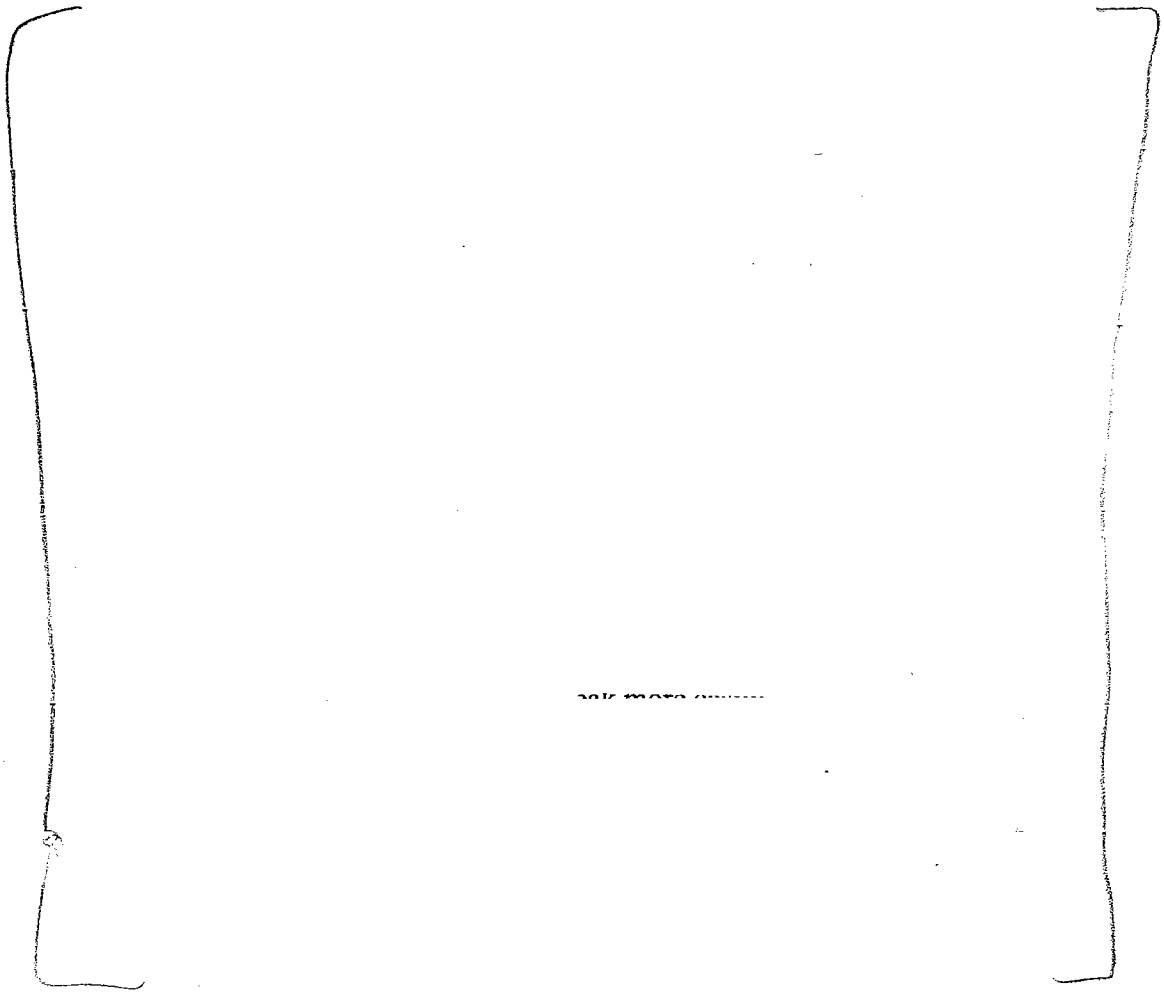
Should be replaced with:

"For the treatment of moderate to severe vasomotor symptoms associated with the menopause, and treatment of vulvar and vaginal atrophy, one Activella™ 1 mg E2/0.5 mg NETA tablet

should be taken daily. Patients should be reevaluated at 3 to 6 month intervals to determine if treatment is still necessary."

"For the prevention of postmenopausal osteoporosis, one Activella™ 1 mg E2/ 0.5 mg norethisterone acetate tablet should be taken daily. The doses of 17 beta-estradiol and norethindrone acetate in Activella™ may not be the lowest effective dose-combination for the prevention of osteoporosis.

4. The **INFORMATION FOR THE PATIENT** section, in the Patient Package Insert, was not changed in the approved label of April 11, 2000. We are requesting the following changes (strike through for delete and underline for additions) be made.



c.

Turn the outer transparent dial one space clockwise as indicated by the arrow. Tip out the next tablet.

Note: The ~~transparent~~ clear dial can only be turned after you remove the tablet in the opening ~~has been removed.~~

APPEARS THIS WAY
ON ORIGINAL

Please submit twenty copies of the final printed labeling, ten of which are individually mounted on heavy weight paper or similar material, exactly as specified above as a "Supplement - Changes Being Effected". Please incorporate class labeling revisions (see FDA letter dated October 11, 2000) as well as previous revisions as reflected in the most recently approved package insert. Alternatively, you may submit the FPL electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDAs* (January 1999). To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

This supplement should be submitted within 2 months.

If you have any questions, call Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

Susan Allen, M.D., M.P.H.
Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

/s/

Daniel A. Shames
1/5/01 01:52:34 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-907/S-003

Novo Nordisk Pharmaceuticals Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
100 College Road West
Princeton, NJ 08540-7810

Dear Dr. Reit:

We acknowledge receipt of your December 14, 2000, submission containing final printed labeling in response to our April 11, 2000, letter approving your supplemental new drug application for Activella™ (estradiol/norethindrone acetate tablets).

We have reviewed the labeling that you submitted in accordance with our April 11, 2000, letter and we find it acceptable.

If you have any questions, call Dornette Spell-LeSane, NP-C, Regulatory Project Manager, at (301) 827-4260.

Sincerely,

{See appended electronic signature page}

Daniel Shames M.D.
Acting Director
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Terri F. Rumble
12/13/01 09:55:46 AM
for Daniel Shames