CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-907

ADMINISTRATIVE DOCUMENTS

Division Director Memo

NOV 12 1998

NDA: 20-907

Sponsor: Novo Nordisk Pharmaceuticals

Drug: Activelle (1.0 mg estradiol and 0.5 mg norethindrone acetate)
Oral tablet for once daily dosing

Indication: Moderate to severe vasomotor symptoms in women with a uterus

Date received: November 12, 1997 (User Fee received Nov. 19, 1997)

Date of Memo: November 12, 1998

I agree with the review team's conclusion that the sponsor has provided adequate data to establish the combination of 1.0 mg estradiol plus 0.5 mg norethindrone acetate given as a once daily oral tablet as an effective, safe and quality product for treatment of moderate to severe vasomotor symptoms in postmenopausal women with a uterus.

Estradiol (E2) alone is a currently approved drug in various dosages for the treatment of various conditions in postmenopausal women as both oral and transdermal preparations.

Norethindrone (NET) and norethindrone acetate (NETA) are well-known progestogenic compounds used alone in certain brands of oral contraceptives (progestin-only oral contraceptive products at a dose of .35 mg per day) and also found in combination with ethinyl estradiol in various combined oral contraceptive (COC) products (used at a dose range of 0.4 to 1 mg per day)—used for the prevention of pregnancy in reproductive age women. NETA is also the active ingredient of "Aygestin", a 5mg oral tablet intended for short term use as a treatment of secondary amenorrhea, endometriosis and abnormal uterine bleeding in premenopausal women

As is the case for hormone replacement therapy (HRT) in women with a uterus, the progestin component of oral contraceptives is also meant to prevent the unwanted consequence of unopposed estrogen therapy—specifically the known association of estrogen use and increases in both endometrial hyperplasia and endometrial carcinoma.

The appropriate doses and ratios of estrogen to progestin in combined oral contraceptive products is a complex discussion and has been a result of the evolution of theoretical arguments, established findings, historical developments, and increased knowledge in terms of risks and benefits. The development of similar entities for post-menopausal hormone replacement therapy is somewhat more straightforward.

The use of estrogen products to prevent the unwanted side effects of either natural or surgical menopause is long established. Because of the known benefits of estrogen therapy in post-menopausal women, the development of an estrogen product with the addition and impact of a progestin component has been addressed through both verbal discussion and written guidance. The recognized need to develop the lowest effective and acceptable dose for its primary intent (to prevent the unwanted endometrial stimulation) while addressing the potential impact on other likely beneficial effects of estrogen-alone therapy is addressed in a 1995 guidance document[1].

This sponsor has provided ~~the~~ trials submitted in support of Activelle's approval in accordance with the 1995 guidance.

The main study to support the combination product--the one year, endometrial hyperplasia-prevention trial (KLIM/PD/7/USA)--was adequately performed and described and supports the approval of the highest dose of NETA studied (the combination of 1.0 mg E2 with 0.5 mg NETA).

Although the sponsor presents three studies to support Activelle's use in vasomotor symptoms, not all are required to support this portion of the indication. One 12-weeek study (KLIM/PD/8/USA) in 333 women established that both 1.0 and 2.0mg estradiol were superior to placebo in reducing moderate to severe hot flushes at all preset time points.

Since the studies supporting the biopharmaceutical portion of the NDA revealed that no effect on the pharmacokinetics of the E2 component is seen with the addition of the NETA, this one vasomotor symptom study could likely have sufficed to support the estradiol-based indication.

If the pharmacokinetics of E2 had changed with the addition of the NETA, the second vasomotor symptom reduction trial (KLIM/PD/9/USA) performed in 92 subjects would have been pivotal. This study supports both the E2 alone and the Activelle product as superior to placebo for this indication. Although the sponsor suggests that the study shows that the NETA component of Activelle appears to be additive to the E2 component in terms of reduction of vasomotor symptoms, this study was not powered to answer this question and the data is not adequate to support this conclusion.

A third study in 113 women with less severe vasomotor symptoms failed to show a significant difference between placebo and two doses of Activelle products (1.0mg E2 with either 0.25mg or 0.5 mg NETA) in reducing vasomotor symptoms. These results confirm the need for further discussion and study of women with mild vasomotor symptoms if this potential indication is to be developed.

The labeling for this product was developed from various sources--the clinical trial data presented in the NDA, a need for consistency with other combination HRT products, as well as through application of the 1992 estrogen class labeling guidance document[2]. This class labeling guidance document has recently been revised and the new draft is currently published for review and comment prior to finalization. As for other approved products in this class, a label based on the revised guidance will be expected once the final guidance document is issued.

The 1992 class labeling calls for the assignment of pregnancy category "X" for postmenopausal estrogen products. This was based on the fact that there is no indication for use of these products during pregnancy and on concerns based on findings for one estrogenic product—diethylstilbestrol. The 1998 guidance currently published for comment removes the "X" category and would allow for the following statement which I would favor for this label:

As for other estrogens products in this class, the labeling includes indications for both reduction in vasomotor symptoms and treatment of vulvar and vaginal atrophy. Historically, products distributed systemically and established for vasomotor symptom reduction have been granted the second indication. This appears from the earliest days of regulation of estrogen products and follows from both logic and early data supporting the alleviation of vaginal dryness and atrophic symptoms through adequate systemic estrogen replacement. Certainly the converse is not allowed--products intended and established as safe and effective for vaginal or vulvar atrophy based on local delivery are not granted the vasomotor symptom reduction indication.

Please refer to the various discipline reviews for specifics in regards to more complete quality, safety and effectiveness evaluations.

Recommendation: Approval with change to the pregnancy use statement in the "Precautions" section of the label (pending ODE II agreement).

/S/ 1/12/98

Lisa Rarick, MD
Director
DRUDP, HFD-580

cc: NDA 20-907
HFD-580/Price/Mann
HFD- /Houn/Bilstad

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[1] Guidance for Clinical Evaluation of Combination Estrogen/Progestin-containing Drug Products Used for Hormone Replacement Therapy of Postmenopausal Women. March, 1995.
[2] Labeling Guidance for Estrogen Drug Products, Physician Labeling and Labeling Guidance for Estrogen Drug Products, Patient Package Insert, August, 1992.

NOV 10 1998

Group Leader Memorandum

NDA:	**20-907**
Drug:	**Activelle™** **1.0 mg estradiol and 0.5 mg norethindrone acetate (combined as a single tablet)**
Dose:	**one tablet daily for continuous use**
Indication:	**Hormone Replacement Therapy (control of vasomotor symptoms)** **Endometrial protection**
Sponsor:	**Novo Nordisk Pharmaceuticals**
Date Submitted:	**November 12, 1997**
Date of Memorandum:	**November 10, 1998**

Background

There are several approved combination estrogen/progesterone drug products available for hormone replacement therapy (HRT). These include:

- Prempro®: oral tablets composed of 0.625 mg conjugated estrogen and 2.5 mg or 5 mg medroxyprogesterone acetate to be taken once daily continuously. Patients are instructed to use the lowest effective dose. Prempro® is indicated for the treatment of moderate to severe vasomotor symptoms and for the prevention of osteoporosis;
- Premphase®: two separate tablets, one of which is composed of 0.625 mg conjugated estrogens taken days 1-14 and a second tablet containing 0.625 mg conjugated estrogens with 5 mg medroxyprogesterone acetate taken days 15-28. Premphase® is indicated for the treatment of moderate to severe vasomotor symptoms and the prevention of osteoporosis;
- Combipatch®: a patch consisting of 0.05 mg estradiol in combination with either 140, 250, or 400 mcg/day norethindrone acetate to be taken either continuously or sequentially. Combipatch® is indicated for the treatment of moderate to severe vasomotor symptoms.

Activelle™ is a new combined hormone replacement therapy made as a tablet for continuous oral use. It is composed of 1 mg estradiol combined with 0.5 mg norethindrone acetate (NETA). This combination has never been marketed in the United States, but in Europe and other countries, Kliogest® (composed of 2 mg estradiol and 1 mg norethindrone acetate) is marketed as a continuous HRT regimen. Thus, there is world-wide experience with an oral product containing two times the dosages (but same ratio) of estradiol and NETA present in Activelle™.

Indication

The sponsor seeks to provide Activelle™ as a product to be used in a fixed, continuous, once daily dosing regimen for the management of moderate to severe vasomotor symptoms (VMS), and to obtain the safety claim for prevention of endometrial hyperplasia.

Vasomotor Symptom Trials

Three multicenter, double-blind, randomized, placebo-controlled studies were submitted in support of the efficacy of Activelle™ for the management of VMS.

1. KLIM/PD/8/USA

This first study was an estrogen dose ranging study to determine the lowest effective dose of estrogen in combination with 0.5 mg norethindrone acetate for relief of VMS. The results of this study revealed that women receiving 2 mg of estradiol were twice as likely to experience adverse events as placebo patients. Bleeding and breast pain were the most frequent adverse events. A total of 16% of patients discontinued the study prematurely: 8% due to adverse events (again, most common in the 2 mg estradiol arm), 5% due

to noncompliance (evenly distributed among treatment arms), and 1% due to ineffective results (two placebo patients).

Results revealed that doses of estradiol of 0.5 mg, 1.0 mg, and 2.0 mg were all superior to placebo in reducing the mean number of VMS/week at week 12, while the 0.25 mg doses of estradiol showed no effect. Only the 1.0 and 2.0 mg doses of estradiol showed significant differences in the reduction of mean weekly VMS compared to placebo at all three timepoints: week 4, 8, and week 12.

Conclusions

This study was primarily designed to determine the correct dose of estradiol for the final Activelle™ formulation. There was no additional benefit to the highest dose of 2.0 mg estradiol and side effects were noticeably worse at this dose. The lowest dose of 0.25 mg estradiol was clearly ineffective. This leaves the 0.5 and 1.0 mg estradiol dosages, where a choice of optimal dose is less clear. Significant reductions in VMS were noted at week 4 and were sustained throughout weeks 8 and 12 in the 1.0 mg estradiol arm whereas significant relief was not noted until weeks 8 and 12 for the 0.5 mg estradiol arm. The sponsor's predefined primary endpoint assessment at week 4 supports the selection of the 1.0 mg estradiol dose as the optimal dose for efficacy.

Adverse reactions leading to study discontinuation occurred in 5% versus 9% of the 0.5 and 1.0 mg arms, respectively. Treatment emergent adverse events occurred with an almost identical frequency of 67% and 66% in each group. Postmenopausal bleeding occurred in 6% of patients in the 0.5 mg versus 21% of the 1.0 mg estradiol group. Endometrial biopsies obtained at the end of 12 weeks of treatment revealed one patient in each arm with hyperplasia, although seven patients in the 2.0 mg arm had hyperplasia detected, supporting a direct dose-response relationship for this important risk factor.

The 1.0 mg estradiol dose therefore was a reasonable choice for optimal efficacy, and tolerability of this dosage was acceptable.

2. KLIM/PD/9/USA

The second study compared Activelle ™(1.0 mg estradiol with 0.5 mg NETA) to estradiol 1.0 mg alone and to placebo for the control of vasomotor symptoms. A total of 92 subjects from the United States were enrolled: 34 received placebo, 29 received estrogen alone, and 29 received Activelle™. Only two subjects discontinued prematurely: one estrogen alone subject due to a protocol violation and one Activelle™ subject due to noncompliance.

A significant reduction in mean number of VMS/week was noted at week 4, 8, and 12 in both active treatment arms compared to placebo. Of note, the mean reduction in symptoms in the Activelle™ arm tended to be slightly greater than that obtained in the estrogen only arm at week 4, week 8, and week 12 observations. While the sponsor concluded that NETA added to the efficacy of estradiol alone in controlling VMS, the data is not adequate to support this conclusion. Adverse events were reported in 65% of placebo patients, 41% of estradiol alone patients, and 62% of Activelle™ patients. The most common events in the Activelle™ arm were breast pain (21%), headache (17%), nausea (10%) and post-menopausal bleeding (10%). Bleeding or spotting during the 3 month trial were reported by 24% of Activelle™ patients compared to only 3% of placebo and 7% of estradiol alone patients. Endometrial biopsies were available in 25 of 29 enrolled Activelle™ subjects, and revealed no hyperplasia.

Conclusions

This study confirmed that Activelle™ was superior to placebo in relieving VMS. Claims of superiority of Activelle™ compared to estradiol alone for relieve of VMS are not supported.

3. KLIM/PD/1/N

This study was performed in Norway, and enrolled menopausal women with a minimum of 20 moderate to severe hot flushes per week. This entry criterion is much lower than the FDA requirement of 56 moderate to severe hot flushes per week. The study compared two dose formulations of Activelle™ (1mg estradiol

with 0.25 and 0.5 mg NETA, respectively) to placebo. The number of patients enrolled was relatively low (n=37 placebo and n=36 and 40 for the 0.25 and 0.5 mg doses of NETA, respectively). Not surprisingly, due to the relatively low number of baseline vasomotor symptoms, this trial failed to show any significant differences between the two active treatment groups and placebo at weeks 4, 8, and 12.

Conclusions

This trial was not powered to detect a significant decrease in VMS in these women who had very mild VMS at baseline. Thus, it is not surprising that the results of this trial were not significant. While not supportive of the VMS indication, therefore, this trial does not raise any concerns about the use of Activelle™ in women with truly moderate-severe VMS.

Prevention of Endometrial Hyperplasia Trial

1. KLIM/PD7/USA

A single study was performed to support this indication. The study was designed to determine the lowest effective dose of NETA (0.1, 0.25, or 0.50 mg/day) should be given with 1.0 mg estradiol to substantially reduce the incidence of endometrial hyperplasia compared to estradiol (1.0 mg) alone after 12 months of therapy. A total of 1176 subjects were randomized into four arms: n=296 (estradiol 1.0 mg alone); n=294 (estradiol/0.1 mg NETA); n=291 (estradiol/0.25 mg NETA); n=295 (estradiol/0.5 mg NETA). A normal endometrial biopsy or a normal pelvic ultrasound (endometrial thickness $\leq$ 4mm) was required for entry. Approximately 90% of patients had biopsies, while 10% (distributed evenly throughout study arms) required pelvic ultrasound since an endometrial biopsy was not obtained due to patient refusal or technical difficulties.

Approximately 85% of enrolled subjects had biopsies obtained at month 12 (again evenly distributed among treatment arms). The incidence of endometrial hyperplasia in these patients at one year was:

1.0 mg estradiol unopposed	34 of 246 subjects (13.8%)	28 simple/6 complex
1.0 mg estradiol/0.1 mg NETA	2 of 249 subjects or 0.8% (0.097-2.8%)	1 simple/1 complex
1.0 mg estradiol/0.25 mg NETA	1 of 251 subjects or 0.4% (0.01-2.3%)	1 complex
1.0 mg estradiol/0.5 mg NETA	1 of 241 subjects or 0.4% (0.01-2.2%)	1simple

Hyperplasia was clearly diminished with all three doses of NETA . The 0.25 and 0.5 mg NETA arms had the best results and were quite comparable. Although two cases of complex hyperplasia occurred at the 0.1mg and 0.25 mg doses of NETA, the absence of this finding at the 0.5 mg dose of NETA does not imply that the 0.5 mg doses of NETA is optimal. A much larger trial would be required in order to detect a meaningful difference in rates of complex versus simple hyperplasia.

Approximately 80% of subjects receiving NETA completed the study versus 72% of those receiving unopposed estrogen. This difference primarily related to more frequent bleeding in the unopposed estrogen group. The incidence of bleeding/spotting during cycle was not substantially different between the three NETA groups (ranging from 23.4 to 28%), although by cycle 4 bleeding/spotting was 24.3% in the low dose NETA group, 19% in the mid-dose NETA group, and only 13.8% in the 0.5 mg NETA group. Adverse experiences were reported in 80-85% of patients in each arm. Most of the adverse events were comparable between treatment arms, but breast pain was more common with increasing NETA doses (as expected).

Conclusions:

This study supports either the 0.25 and 0.5 mg NETA dosages as providing protection regarding endometrial hyperplasia. Tolerability of these two NETA doses was fairly comparable (with a slight tendency for more bleeding and breast pain at the 0.5 mg dose). The truly lowest effective dose of NETA, in this reviewer's opinion, would be the 0.25 mg NETA dose. Nonetheless, the sponsor's choice of the 0.5 mg NETA dose does not appear to entail any safety concerns, and is acceptable. It is also rational to consider that the sponsor may have wished to maintain the ratio of estradiol/NETA found in the currently marketed product, Kliogest®.

Summary

This NDA application provides sufficient data to support the approval of Activelle™ (1.0 mg estradiol with 0.5 mg NETA) for the treatment of moderate-severe vasomotor symptoms and supports the claim of endometrial protection.

/S/ 4/10/08

Marianne Mann, M.D.
Deputy Director, HFD-580

Patent Certification
Nuvera

Pursuant to CFR 314.53(c)(3), the undersigned declares that there are no patents held by Novo Nordisk which claim Nuvera (1 mg estradiol and 0.5 mg norethindrone acetate) or which claim a method of using Nuvera with respect to which a claim of patent infringement could reasonably be asserted against a non-licensed person.

Date: 16 October 1997

By: _____

Torsten Nørgaard
Corporate Patents
Novo Nordisk

EXCLUSIVITY SUMMARY FOR NDA # 20-907 SUPPL #____

Trade Name **Estradiol/Norethindrone Acetate** Generic Name **Activelle ™**

Applicant Name **Novo Nordisk Pharmaceuticals** HFD # **580**

Approval Date If Known _____

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 question about the submission.

a) Is it an original NDA?

YES /_X_/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /_X_/

If yes, what type? (SE1, SE2, etc.) _____

c) 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 /_X_/ 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.

_____

_____

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:

_____

_____

Form OGD-011347 Revised 10/13/98

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

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /_X_/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X_/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (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.

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).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

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 any one 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 /_X_/ NO /___/

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

NDA# 20-538 **Estradiol Transdermal System**

NDA# 20-527 **Prempro/Premphase**

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. 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 /_X_/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

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.

(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 /_X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(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 /_X_/

(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 /_X_/

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 /_X_/

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:

KLIM/PD/7/USA
KLIM/PD/8/USA
KLIM/PD/9/USA

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

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 /_X_/

Investigation #2 YES /___/ NO /_X_/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) 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"):

KLIM/PD/7/USA **KLIM/PD/8/USA**

KLIM/PD/9/USA

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

IND # YES /_X_/ ! NO /___/ Explain: _____

Investigation #2

IND # YES /_X_/ ! NO /___/ Explain: _____

Investigation #3

IND# YES/_X_/ ! NO/___/ 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 /___/ Explain _____ ! NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ ! NO /___/ 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 /_X_/

If yes, explain: _____

_____

/S/ 11/12/98

Signature Date

Title: PM

/S/ 11/13/98

Signature of Office/ Date
Division Director

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

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	20907	**Trade Name:**	NUVERA(ESTRADIOL 1MG/NORETHINDRONE ACETA
Supplement Number:		**Generic Name:**	ESTRADIOL 1MG/NORETHINDRONATE ACETATE 0.
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:	AP	**Proposed Indication:**	

IS THERE PEDIATRIC CONTENT IN THIS SUBMISSION? NO

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 Status -
Formulation Status -
Studies Needed -
Study Status -

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

COMMENTS:

This Page was completed based on information from a PROJECT MANAGER/CONSUMER SAFETY OFFICER, JENNIFER MERCIER .

Signature /S/ Date 11/6/98

Debarment Statement

Novo Nordisk 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 the application.

Barry Reit, PhD
Vice President
Regulatory Affairs

DF

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUTION AND RESEARCH

DATE: November 7, 1997
FROM: Venkateswar R. Jarugula, Ph.D. (HFD-870) VR Jarugula 12/11/97
THROUGH: Angelica Dorantes, Ph.D., Team Leader (HFD-870) for 12/11/97
TO: HFD-580
RE: Filing Meeting for NDA 20-907, 1mg Estradiol/0.5 mg Norethindrone (Nuvera™) Acetate Tablets

SUMMARY

Novo Nordisk submitted NDA 20-907 for 1 mg Estradiol/0.5 mg Norethindrone Acetate (NuveraTM) tablets on 11/07/97. Nuvera™ is a continuous oral hormone replacement therapy product intended for the treatment of moderate to severe vasomotor symptoms associated with the menopause and the treatment of vulvar and vaginal atrophy in women with intact uterus.

In support of the pharmacokinetics and human bioavailability section of the NDA, six clinical pharmacology studies were conducted including two supportive trials in Japanese women. The six trials involved a total of 135 healthy postmenopausal women, including 35 Japanese women. These trials were designed to provide information on the pharmacokinetics of estradiol (E_2), estrone (E_1), etrone sulfate (E_1S) and norethindorne acetate (NETA) following single and multiple dose administration; relative bioavailability compared to oral solution; effect of food; and bioequivalence of two different tablet formulations used in the clinical program. The following table summarizes the design and objectives of the various Clinical Pharmacology studies submitted to the NDA:

Protocol No.	Objective	Design	No. of subjects Enrolled/completed	Dose
KLIM/PD/3/S	Single & Multiple dose PK	Open label, randomized, crossover	25/24	1mg E_2/0.5 mg NETA; 0.5 mg NETA
KLIM/PD/24/D	Relative bioavailability	Open-label, three period, cross over	27/25	1mg E_2/0.5 mg NETA, 1mg E_2/ 0.25 mg NETA tablets, 1mg E_2/ 0.5 mg NETA solution
KLIM/PD/25/USA	Bioequivalence	Open-label, two-period,randomized, crossover	24/23	Gelatin formulation Vs. Povidone formulation
KLIM/PD/26/USA	Effect of Food	Open-label, randomized, two-way crossover	24/23	1mg E_2/0.5 mg NETA
KLIM/PD/12/J	Safety, tolerability & PK of ascending single dose (Dose proportionality)	Single blind, placebo controlled trial	18/14	1 mg E_2/0.25mg NETA, 1 mg E_2/0.5 mg NETA 2 mg E_2/0.5 mg NETA 4 mg E_2/0.5 mg NETA
KLIM/PD/13/J	Safety, tolerability & multiple dose PK (Dose proportionality)	Single blind, randomized, placebo controlled, parallel group, 14 day multiple dose study	17/16	1 mg E_2/0.5 mg NETA; 2 mg E_2/1 mg NETA

In addition, information on steady-state plasma levels of E_2, E_1 and E_1S were also provided from two phase III trials (KLIM/7/USA and KLIM/PD/8/USA).

According to the sponsor, during the clinical development of this product, a formulation change occurred. Early trials (KLIM/PD/3/S, KLIM/PD/12/J, KLIM/PD/13/J), formulation was used. Because of the stability problems with this formulation, a new tablet formulation containing copolyvidone was developed and was used in all Clinical Pharmacology trials in the US including the two main phase III studies supporting efficacy (KLIM/PD/7/USA and KLIM/PD/9/USA). To support the formulation change, bioequivalence between the gelatin and the copolyvidone (to be marketed) formulations was evaluated in the study KLIM/PD/25/USA.

It should be noted that only synopses were submitted for the Japanese studies KLIM/PD/12/J and KLIM/PD/13/J; and for the two phase III studies KLIM/PD/7/USA and KLIM/PD/8/USA. The validation data of analytical methods for the determination of E_2, E_1, E_1S and NETA was submitted along with individual study reports. No drug-drug interaction or special population studies were submitted in the NDA

The summary of proposed dissolution method and the recommended specifications are given below:

Apparatus:	USP II (Paddle method)
Medium:	500 ml water + %
Temp:	37^0C
Speed:	100 ± 2
Sampling Times:	minutes
Specifications:	

Reviewer Comments:

1. To support the proposed dissolution specifications, the sponsor included only mean dissolution data for the batches used in clinical trials KLIM/PD/24/D and KLIM/PD/25/USA. The dissolution data including the individual tablet data for the batches used in all the clinical pharmacology as well as adequate and well controlled clinical trials should be submitted.

2. To facilitate the review process, the sponsor is encouraged to submit the individual summary of all the clinical pharmacology study reports including the Japanese trails and the two clinical trials (KLIM/PD/7/USA and KLIM/PD/8/USA); and the draft of the physician's package insert in electronic format preferably in 'Word'. Additionally, the raw data of these studies should be submitted in ASCI format.

3. It should be noted that according to the sponsor's conclusion, the bioequivalence between the two formulations was demonstrated only for AUC_{0-72} of norethindrone (NET) and the C_{max} of E_2. The other pharmacokinetic parameters were slightly out of

the passing range, 80-125% CI. The sponsor claims that these findings could be due to one outlier skewing the results and that the borderline findings are not considered to have any clinically relevant impact. However this would be a review issue rather than a filing issue.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation II has reviewed the NDA for its fileability and is of the opinion that the NDA is fileable, provided the sponsor addresses the Reviewer Comment 1 and 2 appropriately.

cc: NDA 20-947, HFD-580 (Jolson, Markow), HFD-870 (M.Chen, Dorantes, Jarugula), CDR (B.Murphy for Drug).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-907

CORRESPONDENCE

NOV – 6 1998

NDA 20-907

Novo Nordisk Pharmaceuticals
Attention: Mary Anne McElligott, Ph.D.
Regulatory Affairs
100 Overlook Center, Suite 200
Princeton, NJ 08540-7810

Dear Dr. McElligott:

Please refer to your pending November 12, 1997 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Estradiol/Norethindrone acetate Tablets (activelle) Tablets.

We also refer to your submission dated October 14, 1998.

We have completed our review of the Biopharmaceutics section of your submission and have the following comments and information requests:

The proposed dissolution method for Activelle is USP paddle method

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

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Jennifer Mercier, Project Manager at (301) 827-4260.

Sincerely,

/S/

11/6/98

Terri Rumble, B.S.N.
Chief, Project Management Staff (Acting)
Division of Reproductive and Urologic Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

cc:
Archival NDA 20-907
HFD-580/Div. Files
HFD-580/JM
HFD-820/DNDC Division Director (only for CMC related issues)
DISTRICT OFFICE

Drafted by: /November 6, 1998
Initialed by:
final:
filename: 20907IR.WPD

INFORMATION REQUEST (IR)

DF

OCT - 2 1998

NDA 20-907

Novo Nordisk
Attention: Mary Anne McElligott, Ph.D.
Director, Regulatory Affairs
100 Overlook Center, Suite 200
Princeton, NJ 08540-7810

Dear Dr. McElligott:

Please refer to your pending November 20, 1997, new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Activelle™ (estradiol/norethindrone acetate) Tablets .

We also refer to your submissions dated March 19 and July 8, 1998.

We have completed our review of the chemistry section of your submission and have the following comments and information requests:

Manufacturing:

1. Please clarify the number of individual drug product samples that are to be analyzed in each test described in the proposed batch formula.

2. Please specify the storage conditions and duration for the drug substances being used in the manufacture of the drug product.

3. The specifications for the total sum of estradiol-related impurities should be tightened to % and norethindrone acetate-related impurities should be tightened to %.

4. Please tighten the dissolution specification to Q % at minutes. The proposed specifications are not supported by the actual data.

5. Please provide updated detailed batch records clarifying the operation conditions and equipment that will be used. Clearly specify the Standard Operating Procedures used for the in-process testing and other pertinent information.

Stability:

1. The hardness values presented in the twelve-month interim report show that hardness values for the tablets seem to drop to one-half at nine months, but recover at twelve months. Please explain this observation.

2. The impurity values for the sum of estradiol and sum of norethindrone acetate values at nine months are higher and then decrease at twelve months. Please explain this observation.

Labeling:

Phase IV Commitment:

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

These comments are being provided to you prior to completion of our review of the application to give you preliminary notice of issues that have been identified. Per the user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and are subject to change as the review of your application is finalized. In addition, we may identify other information that must be provided prior to approval of this application. If you choose to respond to the issues raised in this letter during this review cycle, depending on the timing of your response, as per the user fee reauthorization agreements, we may or may not be able to consider your response prior to taking an action on your application during this review cycle.

If you have any questions, contact Jennifer Mercier, Project Manager, at (301) 827-4260.

Sincerely,

/S/ 10/1/98

Moo-Jhong Rhee, Ph.D.
Chemistry Team Leader for the
Division of Reproductive and Urologic Drug Products, (HFD-580)
DNDC II, Office of New Drug Chemistry
Center for Drug Evaluation and Research

cc:
Original NDA 20-870
HFD-580/Div. Files
HFD-580/CSO/JMarkow
HFD-580/LRarick, HJolson, LPauls, AJordan, MRhee, ADorantes, LKammerman, GTurner, LStockbridge.
DISTRICT OFFICE

Drafted by: JMarkow/November 25, 1997/wpfiles/nda/letters/20907ac.nnd
Concurrence: LPauls 12.2.97

ACKNOWLEDGMENT (AC)

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

DF

Food and Drug Administration
Rockville MD 20857

NDA 20-907

DEC - 3 1997

Novo Nordisk Pharmaceuticals Inc.
Attention: Barry Reit, Ph.D.
Vice President, Regulatory Affairs
Suite 200
100 Overlook Center
Princeton, NJ 08540-8710

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:	estradiol/norethindrone acetate tablets
Therapeutic Classification:	Standard
Date of Application:	November 7, 1997
Date of Receipt:	November 19, 1997
Our Reference Number:	20-907

Please note that the user fee for this application was not posted until November 19, 1997. The user fee goal date will be one calender year from the date of receipt of the user fee payment.

Unless we notify you within 60 days of our receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on January 18, 1998, in accordance with 21 CFR 314.101(a).

If you have any questions, please contact Mr. John C. Markow at (301) 827-4260.

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

Sincerely,

/S/ 12/2/97

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

cc:
Original NDA 20-870
HFD-580/Div. Files
HFD-580/CSO/JMarkow
HFD-580/LRarick, HJolson, LPauls, AJordan, MRhee, ADorantes, LKammerman, GTurner, LStockbridge.
DISTRICT OFFICE

Drafted by: JMarkow/November 25, 1997/wpfiles/nda/letters/20907ac.nnd
Concurrence: LPauls 12.2.97

ACKNOWLEDGMENT (AC)

NDA AMENDMENT

November 18, 1998

Novo Nordisk

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

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

Re: Activelle™ (1 mg estradiol/0.5 mg norethindrone acetate tablets)
NDA 20-907
Activelle Labeling Revision 4

Dear Dr. Rarick:

Reference is made to NDA 20-907 and to Labeling Revision 3, submitted November 18, 1998. We also refer the fax of November 18, 1998 with requested revisions for the package insert.

We have made all changes as requested and have enclosed a revised copy.

If you have any questions, please contact Mary Ann McElligott Ph.D. at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Mary Ann McElligott for Barry Reit

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

cc: Field Office, Certified Field Copy

NDA AMENDMENT

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

November 18, 1998

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

Re: Activelle™ (1 mg estradiol/0.5 mg norethindrone acetate tablets)
NDA 20-907
Activelle Labeling Revision 3

Dear Dr. Rarick:

Reference is made to NDA 20-907 and to Labeling Revision 2, submitted November 11, 1998. We also refer to a telephone conversation of November 17, 1998 with Dr. Mann and Terri Rumble in which we were requested to revise the patient insert wording (page 30) regarding the section to be consistent with the contraindications section of the package insert. The following is our proposed revision:

We have attached the revised page. If you have any questions, please contact Mary Ann McElligott Ph.D. at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Mary Ann McElligott for Barry Reit

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

cc: Field Office, Certified Field Copy

NDA AMENDMENT
SAFETY UPDATE

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

November 6, 1998

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

Re: NDA 20-907, 1mg Estradiol/0.5 mg Norethindrone Acetate Tablets

Dear Dr. Rarick:

We refer to NDA 20-907 for 1mg Estradiol/0.5 mg norethindrone acetate tablets. We also refer to the request from the medical reviewer for a Safety Update, transmitted by Jennifer Mercier on October 29, 1998.

Enclosed is a safety update of the serious adverse events in the clinical development program for Activelle (1 mg E2 + 0.5 mg NETA) reported after the 120-day safety update through November 4, 1998. Additionally, serious adverse events previously reported in a blinded fashion in the 120-day update are identified by treatment group.

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

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

NDA AMENDMENT

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

November 6, 1998

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

Re: Activelle™ (1 mg estradiol/0.5 mg norethindrone acetate tablets)
NDA 20-907
Activelle Labeling Revision 1

Dear Dr. Rarick:

Reference is made to NDA 20-907 and to the fax of October 30, 1998 providing Division labeling revisions for the package insert.

We have revised the labeling of the Package Insert according to the recommendations of October 30, 1998 with some modifications and editorial changes. For ease of review, all changes to the October 30 document are indicated by number in the October 30 document margin, as well as in this Revision 1 document. The revisions are listed by page location, item number, change and reason for change in the attached table. All reference superscripts have been removed as requested.

We are also submitting the following revisions to the dispenser and carton labels for Activelle: replacement of Nuvera with Activelle, new wording for storage conditions (these two changes in response to CMC review comments of October 1, 1998), replacement of Caution statement with . and the addition of to the generic name. Since we are in the process of negotiation with a marketing partner, the language may be altered; however, it will be one of the defined phrases in 21 CFR, Part 201, Subpart A, 201.1 (h) (5). The NDC code has not yet been finalized.

Enclosed are copies of: the October 30, 1998 recommended labeling; printed copy of the revised label with all changes inserted and identified by number; an electronic version of the revised label with the file name of Draft Package Insert, Revision 1; the dispenser label and carton label marked with the indicated changes as well as copies of the original versions.

If you have any questions, please contact Mary Ann McElligott Ph.D. at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

MA Mc Elligott for Barry Reit

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

cc: Field Office, Certified Field Copy

NDA Amendment

November 3, 1998

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

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

Re: NDA 20-907, 1mg Estradiol/0.5 mg Norethindrone Acetate Tablets
NDA CMC Amendment
Response to review comments

Dear Dr. Rarick:

We refer to NDA 20-907 for 1mg Estradiol/0.5 mg Norethindrone Acetate Tablets, and to the teleconference we had with Drs. Ysern and Jarugula to discuss our response to the review comment for Manufacturing No. 4 (fax of October 1, 1998).

We were asked to tighten our dissolution specifications from our proposal. We hereby agree to the interim specification limit of Q % at minutes (both Estradiol and NETA) discussed yesterday with the above reviewers.

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

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

cc: Ms. Jennifer Mercier
Dr. Maria Ysern
Dr. Venkat Jarugula

ORIGINAL

ORIG AMENDMENT

General Correspondence

October 28, 1998

Novo Nordisk

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

Ms. Jennifer Mercier
Div. of Reproductive and
Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Response to request for electronic Patient Package Insert
NDA 20-907 Activelle [1mg Estradiol/0.5mg Norethindrone Acetate Tablets]

Dear Jennifer,

As requested, here is another electronic and hard copy of the patient insert for Activelle.

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,

Mary Ann McElligott, Ph. D.
Director, Regulatory Affairs

Enclosures

ORIGINAL

September 14, 1998

DRUG AMENDMENT

BL

Mr. John Markow
Div. of Reproductive and
Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Novo Nordisk

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

Re: Response to request for electronic Package Inserts
Activelle NDA 20-907

Dear John,

Enclosed are the following files for the Package Insert and the Information for Patients:

- Patient Package Insert
- Unannotated Package Insert

We have removed the annotations column from the Package Insert as requested.

If you have any questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,

Mary Ann McElligott

Mary Ann McElligott, Ph. D.
Director, Regulatory Affairs

Enclosures

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

ORIGINAL

General Correspondence

AJ 8/3/98

noted JTC 8/4/98 NEW CORRESP

July 22, 1998

Dr. Lisa Rarick
Director, Research and Evaluation
Division of Reproductive and Urologic Drug Products
Food & Drug Administration
5600 Fishers Lane - HFD-580
Rockville, MD 20857-1706

Noted Meeting Date 8-27 August OK 7/30/98

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

Re: NDA 20-907 1 mg Estradiol/0.5mg Norethindrone Acetate Tablets
Meeting Request

Dear Dr. Rarick,

We refer to NDA 20-907 for 1 mg Estradiol/0.5mg Norethindrone Acetate Tablets (Activelle).

We are requesting a meeting to discuss Activelle data in support of an osteoporosis indication, as an amendment to the NDA. We are interested in meeting August 26, 27 or 28, 1998. We will provide a briefing document with specific discussion items three weeks in advance of a meeting.

If you have any questions, please contact Mary Ann McElligott, Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

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

cc: John Markow

CENTER FOR DRUG EVALUATION AND RESEARCH
REC'D
JUL 23 1998
HFD-580

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☐ N.A.I. ☐ MEMO

CSO INITIALS DATE 8/4/98

AJ 4/21/98

ORIGINAL

noted submission to LNC 3/26/98 DTC 4/11/98

General Correspondence

Noted To Nomenclature committee 4/6/98

Novo Nordisk

Novo Nordisk Pharmaceuticals Inc.

Suite 200
100 Overlook Center
Princeton, NJ 08540-7810

Tel. 609-987-5800
Fax 609-921-8082

March 25, 1998

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D MAR 26'1998

Mr. John Markow
Div. of Reproductive and
Urologic Drug Products, HFD-580
Office of Drug Evaluation II
Center for Drug Evaluation & Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

NEW CORRESP

RE: NDA 20-907 1mg Estradiol/0.5 mg Norethindrone Acetate Tablets Tradename

Dear John,

As discussed, we are resubmitting the tradename Activelle for consideration as the replacement for Nuvera. Our company will be using this name worldwide and it is desirable to have only one tradename.

If you have any further questions, please contact Mary Ann McElligott, Ph. D., Director, Regulatory Affairs at (609) 987-5831.,

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

Mary Ann McElligott

Mary Ann McElligott, Ph. D.
Director, Regulatory Affairs

CENTER FOR DRUG EVALUATION AND RESEARCH REC'D MAR 26 1998 HFD-580

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

CSO INITIALS 4/21/98 DATE

DUPLICATE

NDA AMENDMENT
Chemistry, Manufacturing & Controls

ORIG AMENDMENT

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

March 19, 1998

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

Re: NDA 20-907 1mg Estradiol/0.5mg Norethindrone Acetate Tablets

Dear Dr. Rarick,

Reference is made to original NDA 20-907 submitted on November 7, 1997 and a telephone conference with the Division on December 12, 1997. During the teleconference, the chemistry reviewer requested that we submit 12 month stability data to update the 6 month data for 3 pilot scale batches provided in the NDA. We also refer to our letter dated December 16, 1997 where we commit to providing 12 month stability data when available.

At this time we are amending NDA 20-907 to provide the requested 12 month interim stability data which includes the statistical report on the shelf-life for the pilot scale batches at 12 months.

If you need further information, please contact Mary Ann McElligott, Ph.D., Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS, INC.

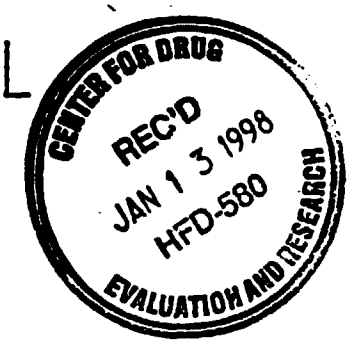
Barry Reit, Ph.D.
Vice President, Regulatory Affairs

cc: FDA field office

General Correspondence

January 9, 1998

ORIGINAL



Novo Nordisk

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

John Markow
Div. of Metabolic and
Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Parklawn Bldg. Room 17B-31
5600 Fishers Lane
Rockville, MD 20857

RE: NDA 20,907 Trademark Name for 1mg Estradiol/0.5mg Norethindrone Acetate Tablets

NEW CORRESP AJ 1/14/98

H Johnson MD 1/14/98

Dear John,

The original trademark name of "Nuvera" was considered unacceptable. The following are six candidates we have identified:

Juvifem

Activelle

Fematesse

Carest 1/14/98 DTL

Advita
Stelest } submitted to the LNC (1/9/98) MJ

REVIEWS COMPLETED
CSO ACTION:
☐ LETTER ☑ N.A.I ☐ MEMO
CSO INITIALS 1/14/98 DATE

Please submit these to the trademark committee. As discussed, we would appreciate initial feedback because we would like to have one worldwide name and by January 19th we will need to choose for Europe.

Sincerely,

M A Mc Elligott

Mary Ann McElligott
Director, Regulatory Affairs

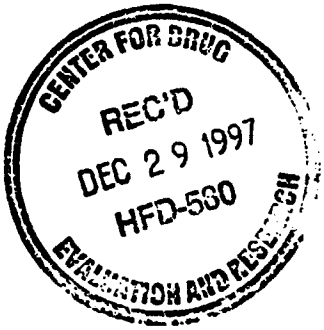
20-907

ORIGINAL

GENERAL CORRESPONDENCE

NEW CORRESP

December 16, 1997



Dr. Lisa D. Rarick
Supervisory Medical
CDER/ODEII/DMEDP (HFD-580
Parklawn Bldg. Room 17B45
5600 Fishers Lane
Rockville, MD 20857

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

Dear Dr. Rarick,

We refer to the teleconference of December 12, 1997. Based on that discussion, it is our understanding that we need to submit the following information by January 10, 1998 for the NDA to be acceptable for filing:

- The primary analysis for Study 8 and 9 will be revised based on the mean percentage (and mean absolute number) reduction in the weekly frequency of moderate to severe hot flushes.

- We will submit descriptive statistics and analyses of Studies KLIM/PD/7/USA, KLIM/PD/8/USA and KLIM/PD/9/USA by center; summaries of the number of dropouts, the percentage change and absolute change from baseline in the number of moderate to severe hot flushes for weeks 4, 8 and 12; means, standard deviations and ranges will be included when describing changes from baseline.

- For studies KLIM/PD/8/USA and KLIM/PD/9/USA, we will discuss the impact of dropouts on the analyses for the absolute and relative change from baseline in moderate to severe hot flushes. We will include a description of the number of dropouts over time and a comparison of the results between those who were losses and those who continued in the study.

Although the following were not filing issues, we understood that this information was also needed for review:

Chemistry: Twelve month stability data for three pilot scale batches in the NDA to be submitted when available (studies initiated February 1997). The new trade name will also be submitted when available for consideration by the trademark committee.

Biopharm: Individual tablet data for all batches in the clinical pharmacology and adequate and well controlled trials, with raw data in will be submitted by January 10, 1998.
Electronic summary of reports (individual synopses) for Clinical Pharmacology Studies and Japanese studies and PD7 and 8 to be submitted by January 10, 1998.

Statistics: SAS PROC CONTENTS outputs for data sets for Studies 8, 9, 1, 7 to be submitted by January 10, 1998.

If you have any questions, please contact Mary Ann McElligott, Director, Regulatory Affairs at (609) 987-5831.

Sincerely,
NOVO NORDISK PHARMACEUTICALS

Mary Ann McElligott for Barry Reit

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

REVIEWS COMPLETED

CSO ACTION:
☐ LETTER ☑ N.A.I. ☐ MEMO

CSO INITIALS 12/5/98 DATE