CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 21040

ADMINISTRATIVE DOCUMENTS

GROUP LEADER MEMORANDUM
ORTHO-PREFEST™ ORIGINAL NDA

NDA: 21-040

Drug: Ortho-Prefest™

Dosage Form/Route: Tablet/Oral

Strength: 1mg 17β-Estradiol
1mg 17β-Estradiol plus 90 μg Norgestimate

Applicant: The R.W. Johnson Pharmaceutical Research Institute

Original Submission Date: December 23, 1998

Date of Memorandum: October 20, 1999

In NDA 21-040, the Sponsor seeks approval of the Ortho-Prefest™ Regimen [continuous Estradiol (E_2) and intermittent norgestimate (NGM) administered in a continuous cycle of three days without NGM and three days with NGM] for the indications of treatment of moderate to severe vasomotor symptoms, treatment of vulvovaginal atrophy and prevention of osteoporosis as well as protection of the endometrium (during long term treatment for the prevention of osteoporosis). The dosage proposed for marketing is 1mg E_2/1 mg E_2 + 90 μg NGM. The weight of the evidence for approval of the osteoporosis prevention and the vasomotor symptom treatment indication is based on biopharmaceutics data. The remainder of this memorandum will discuss the evidence for approval of each indication as follows:

Treatment of moderate-to-severe vasomotor symptoms

Studies ESTNRG-PHI-006 and –007 showed that the Sponsor's 0.5 and 2 mg E_2 tablets are bioequivalent to 0.5 mg and 2 mg Estrace® tablets [the ratio of the test to reference (uncorrected for baseline) tablets are within 80% - 125% of the 95% confidence interval (CI)]. The strength of the Sponsor's 1 mg E_2 tablet is bracketed within their 0.5 mg and 2 mg E_2 Tablet. The formulation of the 1 mg tablets is proportionally similar to the formulations of the 0.5 and 2 mg E_2 tablets and the dissolution profile for the 1 mg E_2 tablet is similar to the dissolution profiles for the 0.5 mg and 2 mg E_2 tablets. Therefore, the reviewing team has accepted the Sponsor's request for a Bioequivalence (BE) study waiver for their 1 mg E_2 tablet to the 1 mg Estrace® tablet.

Study ESTNRG-CHRT-104 is the primary clinical study submitted in support of efficacy of the 1mg E_2 for the treatment of vasomotor symptoms. This was a double-blind, placebo-controlled study in which 251 subjects received either placebo, 0.5mg E_2 or 1 mg E_2 for 12 weeks. The 1 mg E_2 dose was shown to be efficacious in reducing the mean

number of moderate to severe vasomotor symptoms and the difference between the 1 mg E_2 dose and placebo was significant at 4 weeks and sustained to week 12. The 0.5 mg E_2 dose (for which approval is not sought) demonstrated a significant difference versus placebo in the reduction of the mean number of moderate to severe vasomotor symptoms only at week 8 sustained to week 12.

There was no clinical trial of the cyclophasic E_2/ E_2+ NGM regimen which was designed to look at relief of vasomotor symptoms as the primary clinical outcome. Studies ESTNRG-CHRT-102/103 which were analyzed together in one report (with Agency agreement) were designed to evaluate the efficacy of the cyclophasic regimen for prevention of endometrial hyperplasia (protection of the endometrium), however, data was collected for the first 12 study weeks by diary card on vasomotor symptoms. There were no requirements for symptoms at baseline and there was no placebo arm in these studies. At the Division's request a post-hoc analysis was performed for those subjects who retrospectively met enrollment criteria per the HRT guidance document (i.e. 7-8 moderate to severe hot flushes per day or 60 per week). This analysis demonstrated no statistical difference in the reduction of the mean number of moderate to severe vasomotor symptoms between the 1 mg E_2/ 1 mg E_2+ 90µg NGM group and 1 mg E_2 alone group. This analysis was viewed as supportive but not definitive for the efficacy of the 1mg E_2/ 1mg E_2+ 90µg NGM regimen for the relief of vasomotor symptoms. Therefore, pharmacokinetic data was relied upon to make the link.

Study ESTNRG-PHI-001 is a single-dose and multiple dose parallel pharmacokinetic (PK) study in which the cyclophasic regimens (1 mg E_2/1 mg E_2+30 µg NGM vs. 1 mg E_2/ 1 mg E_2+90 µg NGM vs. 1 mg E_2/1 mg E_2+180 µg NGM) were compared. No continuous E_2 alone group was included for comparison, and, therefore, no direct assessment of the effect of the administration of intermittent norgestimate with continuous E_2 (drug interaction) on the steady state PK of E_2 could be made from this study alone. Norgestimate is expected to decrease SHBG leading to an increased free fraction of estradiol. However, an increased free fraction is expected to have a more rapid systemic clearance. Therefore, the steady state PK of E_2 could be affected with the addition of norgestimate to continuous E_2 when compared to continuous E_2 alone.

Given the fact that a multidose BE study was not included in this NDA, the Agency requested that the Sponsor provide point estimate and 90% confidence interval information for the ratio of E_2 C_{max} and AUC $_{0\text{-}24h}$ in order to evaluate the effect of the addition of intermittent norgestimate to the continuous E_2 regimen (drug interaction). This request was based on information from the Sponsor that SHBG levels reached steady state after 30 days of treatment with the 1 mg E_2/ 1mg E_2+ 90µg NGM regimen (study ESTNRG-PHI-001) and SHBG levels were not significantly different after treatment with 1mg E_2/ 1mE_2 + 30 µg NGM as compared to treatment with continuous 1mg E_2 alone (ESTNRG-CHRT-102). The analysis submitted by the Sponsor demonstrated that the E_2 C_{max} and AUC $_{0\text{-}24h}$ following administration of the1mg E_2/ 1mg E_2+ 90µg NGM regimen was 12-18% lower than that following administration of the 1mg E_2/ 1mg E_2 + 30 µg NGM regimen. Clinically this means that the E_2 serum level during the E_2 + NGM days of the cyclophasic regimen may be lower by 12-18% than the

levels during the E_2 only days of the regimen and efficacy during the days of intermittent norgestimate administration could potentially be reduced.

The results from clinical trial ESTNRG-CHRT-104 on the efficacy of the 0.5mg E_2 and the 1 mg E_2 dose in reducing vasomotor symptoms, the post hoc analysis of vasomotor symptom relief for the 1mg E_2/ 1mg E_2+ 90µg NGM regimen from studies ESTNRG-CHRT-102/103 as well as the PK finding of potentially reduced steady state E_2 levels following norgestimate administration were all discussed with the Division Director. The decision was made that approval for the 1mg E_2/ 1mg E_2+ 90µg NGM regimen could be granted based on the single dose BE study (bioequivalency of 1 mg E_2 to 1 mg of Estrace®) and that the label would include language in both the clinical pharmacology and clinical studies section addressing the steady state E_2 levels during intermittent progestin administration.

Treatment of Vulvovaginal Atrophy (VVA)

Studies ESTNRG-CHRT-104 and Studies ESTNRG-CHRT-102/103 are the primary clinical trials submitted to support an indication for the treatment of vulvovaginal atrophy. Study ESTNRG-CHRT-104 was a 12 wk trial which did not have symptomatic inclusion criteria for vaginal atrophy nor did it include pre- or post-treatment assessments for severity of symptoms. Baseline and end of treatment maturation indices were assessed. Both the 0.5 mg and the 1mg continuous E_2 doses in ESTNRG-CHRT-104 were similarly efficacious in decreasing the number of parabasal cells and increasing the numbers of superficial cells, i.e. "shift to the right". Study ESTNRG-CHRT-102 also did not have symptomatic inclusion criteria nor did it evaluate for any change in symptoms throughout treatment. The maturation index was evaluated at baseline (pre-treatment) and at month 7. The three cyclophasic regimens (1 mg E_2 /1mg E_2 + 30 µg NGM, 1 mg E_2 /1mg E_2 + 90 µg NGM and 1 mg E_2 /1mg E_2 + 180 µg NGM) all demonstrated an increase in superficial cells and a decrease in parabasal cells. No statistically significant difference between any of the cyclophasic E_2/E_2+NGM doses and continuous E_2 was seen.

The 1 mg E_2 /1mg E_2 + 90 µg NGM dose is clearly efficacious in the treatment of vulvovaginal atrophy. However, in clinical trial ESTNRG-CHRT-104, the 0.5 mg continuous E_2 only dose was shown to be effective for the treatment of vulvovaginal atrophy. A clinical trial to look at 0.5mg E_2 in a cyclophasic regimen with NGM was not conducted. Therefore, the 1mg E_2/ 1mg E_2+ 90 µg NGM regimen might not represent the lowest effective dose of the estrogen component for this indication and this should be reflected in the labeling.

Prevention of osteoporosis

No clinical trials were conducted to assess the safety and efficacy of the Ortho-Prefest™ 1mg E_2/ 1mg E_2+ 90 µg NGM regimen for the prevention of osteoporosis. Rather pharmacokinetic data was relied upon to link the efficacy of Ortho-Prefest™ to estradiol.

The same assessment that steady state E_2 levels following treatment with the 1 mg E_2/ 1 mg E_2+ 90 µg NGM regimen might be 12 %– 18% lower than the steady state E_2 levels following treatment with continuous 1 mg E_2 alone (considered under treatment for VMS) also applies to the indication for the prevention of osteoporosis. However, since the lowest effective dose of Estrace® for prevention of osteoporosis is 0.5mg, a decrease of 12% - 18 % in the steady state serum E_2 levels during intermittent 90 µg NGM administration is expected to have little effect on the efficacy for this indication. Therefore, the prevention of osteoporosis indication for the 1mg E_2/ 1mg E_2+ 90 µg NGM regimen is approved.

Protection of the Endometrium.

Studies ESTNRG-CHRT-102/103 are the primary studies submitted in support of a claim for prevention of estrogen-induced endometrial hyperplasia (protection of the endometrium). These were 12 month studies in a total of 1,264 subjects who were treated with one of the three cyclophasic E_2/E_2+NGM regimens (1mg E_2/1 mg E_2+30 µg NGM, 1 mg E_2/ 1 mg E_2+90 µg NGM or 1 mg E_2/1 mg E_2+180 µg NGM) or continuous 1 mg E_2. Endometrial biopsies were obtained prior to treatment and at the end-of-study. Biopsy slides were evaluated by two pathologists for the presence or absence of hyperplasia. If there was a discrepancy in the two evaluations, a third pathologist served as the adjudicator. In cases were two of the three pathologists differed as to the severity of the hyperplasia, the most severe type of pathology was recorded. According to this schematic for judging hyperplasia, no cases of endometrial hyperplasia were recorded in the 1 mg E_2/1 mg E_2+90 µg NGM group or the 1 mg E_2/1 mg E_2+180 µg NGM group. Hyperplasia was diagnosed in 28.9% and 6.5% of the continuous 1 mg E_2 group and the 1 mg E_2/1 mg E_2+30 µg NGM group, respectively. Clearly the 1 mg E_2/1 mg E_2+90 µg NGM dose contains the lowest dose of NGM (of those evaluated) that adequately protects the endometrium.

Clinical Safety

The safety of three cyclophasic E_2/E_2+NGM regimens (1 mg E_2/1 mg E_2+30 µg NGM vs. 1 mg E_2/ 1 mg E_2+90 µg NGM vs. 1 mg E_2/1 mg E_2+180 µg NGM) was evaluated in six Phase II and III trials in a total of 1,657 subjects. Five Hundred Seventy Nine (579) subjects received the to be marketed formulation, 1 mg E_2/ 1 mg E_2+ 90µg NGM, for up to 1 year of treatment and 150 subjects received this formulation for up to two years of treatment. The most frequently reported adverse events were endometrial hyperplasia, breast pain, upper respiratory infection, abdominal pain, dysmenorrhea, and vaginal bleeding. These were consistent with adverse events usually seen following HRT.

The non-fatal serious adverse events included 18 malignancies: 7 cases of breast cancer, 1 case of an uncertain diagnosis between atypical intraductal hyperplasia and cribriform intraductal carcinoma, 1 multiple myeloma, 1 basal cell carcinoma, 1 metastatic adenocarcinoma (lung primary), 1 cervical carcinoma, 1 colon cancer, 1 thyroid cancer, 1 pulmonary carcinoma and 1 non-Hodgkins lymphoma. This was not an unusually large number of malignant cases for large 1 –2 year HRT trials. There were two myocardial

infarctions in subjects with pre-existing cardiovascular disease. There were 11 cases of cholelithiasis/cholecystitis. Five of these cases were clustered in the 1 mg E_2/ 1 mg E_2+ 90µg NGM group. While these 11 cases of cholelithiasis/cholecystitis do not represent a higher incidence of these events relative to those reported in previous large HRT clinical trials, the clustering in the 1 mg E_2/ 1 mg E_2+ 90 µg NGM group may represent a signal which should be scrutinized in post-marketing experience.

There were a total of three deaths during trial duration for the six completed trials. One (1) death occurred during study drug treatment and two subjects died after study medications were discontinued. The deaths did not appear to be causally related to the study drug.

Overall, the to-be-marketed regimen, 1mg E_2/ 1mg E_2+ 90µg NGM Ortho-Prefest™, has an adverse events profile which is consistent with that seen for other estrogen only or estrogen/progestin regimens.

Chemistry

The drug substance 17β-estradiol is manufactured and supplied by and the CMC information was reviewed through their DMF Norgestimate is manufactured and supplied by and its CMC information was reviewed through their DMF The CMC information on the drug substances is considered to be satisfactory. The drug substance and drug product manufacturing facilities are in compliance with cGMP regulations. The NDA is acceptable for approval from a Chemistry, Manufacturing and Controls point of view.

Pharmacology (Pre-clinical)

There were no significant pharmacology/toxicology issues raised with this application and the pharmacology reviewing team recommended approval.

Biopharmaceutics

The decreased steady state serum E_2 levels following treatment with E_2 + NGM as compared to those levels following treatment with E_2 alone has been discussed in the sections on the osteoporosis and VMS indications.

One additional point to consider is the difference in the drug formulations used in the previously mentioned clinical pharmacology and clinical trials. The primary clinical trials (ESTNRG-CHRT-104 and ESTNRG-CHRT-102/103) as well as 5 of the clinical pharmacology trials (ESTNRG-PHI-001, ESTNRG-PHI –004, ESTNRG-PHI –006, ESTNRG-PHI –007, and ESTNRG-PHI –008) were all conducted with the to-be-marketed formulation (utilizing a "dry manufacturing process"). A "wet manufacturing" process was used in 2 clinical pharmacology and 2 supportive clinical trials. Study ESTNRG-PHI-008 showed that the dry- and wet-manufacturing process tablets were BE in estrone, estrone sulfate and norgestimate serum levels. The two formulations did not

show equivalent rates of absorption of E_2 and 17d-NGM (the wet-manufacturing process reached C_{max} faster and had a higher C_{max} than did the dry-manufacturing process), but did show equivalent systemic exposure (AUC) for E_2 and 17d-NGM. The product intended for marketing is the dry formulation.

Nomenclature:

The tradename "Prefest" was agreed upon by the Labeling and Nomenclature Committee on June 23, 1998.

Conclusions:

The 1 mg E_2/ 1 mg E_2+ 90 µg NGM Ortho-Prefest™ regimen should be approved for the prevention of osteoporosis indication in women with a uterus. The labeling should reflect that this dose might not be the lowest effective dose for the prevention of osteoporosis. The 1 mg E_2/ 1 mg E_2+ 90µg NGM Ortho-Prefest™ regimen should be approved for the prevention of estrogen-induced endometrial hyperplasia.

The 1 mg E_2/ 1 mg E_2+ 90 µg NGM Ortho-Prefest™ regimen should be approved for the treatment of vulvovaginal atrophy in women with a uterus. The labeling should reflect that this dose may not be the lowest effective dose for this indication.

1 mg E_2/ 1 mg E_2+ 90 µg NGM Ortho-Prefest™ regimen can be approved for the treatment of vasomotor symptoms in women with a uterus. The labeling should reflect that steady state serum E_2 levels during the E_2 + NGM days of the cyclophasic regimen may be lower by 12-18% and that the efficacy for the treatment of vasomotor symptoms during the days of intermittent norgestimate administration could potentially be reduced.

/S/ 10/21/99

Shelley R. Slaughter, MD, Ph.D.
Reproductive Medical Team Leader

cc: NDA 21-040
HFD-580/L.Rarick/M.Mann/S.Slaughter/T.vanderVlugt/A.Parekh/D.Moore

Addendum
Group Leader Memorandum
Ortho-Prefest™

NDA 21-040
Drug: Ortho-Prefest™
Date of Memorandum: October 22, 1999

Upon the advice of the Division of Drug Marketing, Advertising and Communications (DDMAC) we sought and obtained from the company a Phase 4 commitment to revise the Patient Package Insert to be consistent with a plain English language format. DDMAC will assist the sponsor in revising patient labeling according to a format that has been used with several previously approved drugs. The final approved label is included in this action package.

/S/

10/22/99

Shelley R. Slaughter, MD, Ph.D.
Reproductive Medical Team Leader

NDA 21-040
ORTHO-Prefest™ (17β-estradiol and 17β-estradiol/norgestimate tablets)
R.W. Johnson Pharmaceutical Research Institute

Division Director's Memo

The application will be signed off at the Division level. No memo is necessary.

Estradiol Tablets U. S. P.

PATENT INFORMATION

Listed Drug: ESTRACE Tablets, Bristol-Meyers Squibb

Patent Status: In the opinion and to the best knowledge of The Robert Wood Johnson Pharmaceutical Research Institute, a division of Ortho-McNeil Pharmaceutical, Inc., there are no patents that claim the listed drug referred to in this application or that claim a use of the listed drug.

Date: June 30 98

Signature:

John Harbour
Assistant Secretary/
Patent Attorney
Ortho-McNeil Pharmacutical, Inc.

EXCLUSIVITY SUMMARY for NDA # _21-040_____ SUPPL #_____

Trade Name: ORTHO-Prefest™ Generic Name: (17β-estradiol and norgestimate) Tablets, USP

Applicant Name R.W. Johnson Pharmaceutical Research Institute___ **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:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/ Sponsor plans to request exclusivity within 60 days of approval.

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 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__/ OTC Switch /___/

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# __19-697_____ _ORTHO-Tri-Cyclen_____

NDA# __19-653_____ _ORTHO-Cyclen_____

NDA# _____ _____

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:

_____

YES /___/ NO /___/

(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 /___/

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:

Study 102 and Study 103 (prevention of endometrial hyperplasia)

Study 104 (relief of vasomotor symptoms)

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__/

Investigation #3 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__/
Investigation #3	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"):

_Studies 102, 103 and 104_____

_____

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/ 9/30/99

Signature Date
Diane Moore,
Regulatory Project Manager

/S/ 10/5/99

Signature of Division Director Date
Dr. Lisa Rarick

cc: Original NDA 21-040 Division File HFD-93 Mary Ann Holovac
HFD-580/DMoore/TRumble

PEDIATRIC PAGE

(Complete for all original application and all efficacy supplements)

NDA/BLA Number:	21040	**Trade Name:**	ORTHO-PREFEST (17B-ESTRADIOL/NORGESTIMAT
Supplement Number:		**Generic Name:**	17B-ESTRADIOL/NOREGESTIMATE 1MG ESTRADIO
Supplement Type:		**Dosage Form:**	TAB
Regulatory Action:	PN	**Proposed Indication:**	1. Treatment of moderate-to-severe vasomotor symptoms associated with the menopause. 2. Treatment of vulvar and vaginal atrophy. 3. Prevention of osteoporosis in women using ORTHO-PREFEST for relief of menopausal symptoms.

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	Does Not Apply
Formulation Status	
Studies Needed	
Study Status	

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

COMMENTS:

Pediatric studies are not applicable for this indication. October 18, 1999.

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

/S/

Signature

10/18/99

Date

ITEM 16: DEBARMENT CERTIFICATION

The R.W. Johnson Pharmaceutical Research Institute 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 application.

Graham Burton, MD
Vice President, Regulatory Affairs
The R.W. Johnson Pharmaceutical Research Institute
Route 202, P.O. Box 300
Raritan, NJ 08869-0602

Johnson & Johnson

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October 9, 1998

Re: Estradiol/Norgestimate HRT Regimen NDA No. 21-040
Information Required in Accordance with 21 CFR § 314.53

Pursuant to the provisions of 21 CFR § 314.53, attached hereto please find patent information for the above identified application.

Attached item 13 lists 2 patents. The undersigned declares that U.S. Patent No. 5,108,995 and owned by Jencap Research Ltd. and licensed to the applicant, covers the method of use of the product which is the subject of this application for which approval is being sought. The undersigned further declares that U.S. Patent No. 5,382,573 and owned by Jencap Research Ltd. and licensed to the applicant, covers the pack of doses of the product which is the subject of this application for which approval is being sought.

A claim of patent infringement could be asserted if a person not licensed by the owner of the patents listed above engaged in the manufacture, use or sale of the drug product of this application for which approval is sought.

Respectfully submitted,

John W. Harbour
Registered Patent Attorney
Reg. No. 31,365

Item 13: Patent Information
Estradiol/Norgestimate HRT Regimen NDA No. 21-040
Information Required in Accordance with 21 CFR § 314.53

Estradiol/Norgestimate HRT Regimen is protected by the following:

U.S. Patent No.	Patent Type	Expiration Date	Owner
5,108,995	Method of Use	April 28, 2009	Jencap Research Ltd.
5,382,573	Pack of Doses	January 17, 2012	Jencap Research Ltd.

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Date:

From: David Hoberman, Ph.D., HFD-715

Subject: Ortho-Prefest for menopausal symptoms

To: File (NDA# 21-040)

The sponsor submitted two randomized, controlled trials: 104 (N≈50/group) which evaluated hot flushes in patients with moderate to severe flushes at baseline, and 102/103 (N≈250/group) which evaluated hyperplasia.

Trial 104, 1 mg Estradiol was statistically better than placebo at both weeks 4 and 12. In the 1 mg Estradiol arm, the baseline mean # of hot flushes was approximately 15 and the mean # at week 12 was approximately 2. In the placebo arm, the respective numbers were 15 and 6.

In Trial 102/103, each treatment group containing norgestimate (30 μg, 90 μg , and 180 μg) was compared to 1 mg of continuous Estradiol. The 90 μg and 180 μg groups were found to be adequate to suppress hyperplasia. The only statistical issue in this application was the fact that the only trial to have a treatment arm using the marketed product was study 102/103 in which the required entrance criterion of at least 7 hot flushes at baseline was not used. Instead, the sponsor enrolled by far most patients with fewer than 7 hot flushes at baseline. A restrospective analysis by the sponsor using a two-sided 95% confidence interval for the difference between the 90 μg and the Estradiol groups was provided in which the sponsor culled approximately 30 patients per group with the required inclusion criteria. The result indicated that, **at worst**, the mean change from baseline for the number of hot flushes using Ortho-Prefest would be 1 less than that using Estradiol, alone.

/S/

David Hoberman, Ph.D.

NDA 21-040
ORTHO-Prefest (17β-estradiol and 17β-estradiol/norgestimate tablets)
R.W. Johnson Pharmaceutical Research Institute

Carcinogenicity Studies

No carcinogenicity studies are required for this product per Dr. Jordan October 6, 1999.

NDA 21-040
ORTHO-Prefest™ (17β-estradiol and 17β-estradiol/norgestimate tablets)
R.W. Johnson Pharmaceutical Research Institute

Methods Validation

The Methods Validation is pending. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated

NDA 21-040
ORTHO-Prefest™ (17β-estradiol and 17β-estradiol/norgestimate tablets)
R.W. Johnson Pharmaceutical Research Institute

Statistical Review of drug stability

No statistical review of drug stability was performed for this product.

NDA 21-040
ORTHO-Prefest™ (17β-estradiol and 17β-estradiol/norgestimate tablets)
R.W. Johnson Pharmaceutical Research Institute

Environmental Assessment

A categorical exclusion is claimed for this NDA in accordance with 21 CFR part 25.31 (b), and it is accepted (see Chemistry Review #1).

6. ENVIRONMENTAL ASSESSMENT

THE R.W. JOHNSON PHARMACEUTICAL RESEARCH INSTITUTE
RARITAN, NJ 08869

CATEGORICAL EXCLUSION

New Drug Application, No. 21-040 for 1.0 mg Estradiol Tablet, USP and 1.0 mg Estradiol/90 µg Norgestimate Tablet

The R.W. Johnson Pharmaceutical Research Institute (RWJPRI), Raritan, NJ certifies that the above referenced action meets the criteria for categorical exclusion defined in the regulations [21 CFR 25.31(b)], and that to RWJPRI's knowledge no extraordinary circumstances exist. Thus, no environmental assessment need be performed per 21 CFR 25.30.

Signature: _____

Christopher A. DeSantos

Title: Sr. Environmental Engineer

Date: December 1, 1998

NDA 21-040
ORTHO-Prefest™ (17β-estradiol and 17β-estradiol/norgestimate tablets)
R.W. Johnson Pharmaceutical Research Institute

Microbiology Review

No microbiology review is required for oral tablets.

NDA 21-040
ORTHO-Prefest™ (17β-estradiol and 17β-estradiol/norgestimate tablets)
R.W. Johnson Pharmaceutical Research Institute

Advisory Committee Meeting Minutes

This application was not the subject of an Advisory Committee Meeting.

NDA 21-040
ORTHO-Prefest™ (17β-estradiol and 17β-estradiol/norgestimate tablets)
R.W. Johnson Pharmaceutical Research Institute

Federal Register Notices

This application was not the subject of any Federal Register Notices.

NDA 21-040
ORTHO-Prefest™ (17β-estradiol and 17β-estradiol/norgestimate tablets)
R.W. Johnson Pharmaceutical Research Institute

Advertising Material

No advertising material has been submitted.

NDA 21-040
ORTHO-Prefest™ (17β-estradiol and 17β-estradiol/norgestimate tablets)
R.W. Johnson Pharmaceutical Research Institute

Abuse Liability Review

This product does not require an abuse liability review.

NDA 21-040
ORTHO-Prefest™ (17β-estradiol and 17β-estradiol/norgestimate tablets)
R.W. Johnson Pharmaceutical Research Institute

Foreign Labeling

This product has not been approved in any foreign country. There is no foreign market labeling for this product.

MEMORANDUM

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

DATE: October 7, 1999

FROM: Diane Moore
Division of Reproductive and Urologic Drug Products (HFD-580)
FAX: (301) 827-4267

SUBJECT: Labeling Comments for NDA 21-040
Drug Name: ORTHO-Prefest (17 β-estradiol and Norgestimate (NGM) Tablets, USP

TO: Ramon Polo
R.W. Johnson Pharmaceutical Research Institute

The following labeling comments for the Patient Package Insert for ORTHO-Prefest™ are in response to the December 23, 1998, label.

INTRODUCTION section

- in the third section that begins, "**ESTROGENS INCREASE THE RISK . . .**" the black box around the text should be removed; the text should remain
  section
- this heading should be deleted
- the first five paragraphs should be deleted; the first paragraph begins with,
  and the fifth paragraph begins,
- the sixth paragraph that reads, "If you take ORTHO-PREFEST™ and later find you were pregnant when you took it, be sure to discuss this with your doctor as soon as possible." should be retained in the labeling with the previous section

USES OF ESTROGEN section

- the fifth paragraph that reads,
  should be deleted
- the sixth paragraph that reads,
  should be deleted

WHO SHOULD NOT USE ESTROGENS section

- in the second subsection that reads,
  should be deleted
- under the subsection, in the fourth paragraph, in the sentence that begins, the words, should be deleted and the word, "women" should be capitalized; the term, "**DANGERS**" should be replaced by the term, "**RISKS**"
- under the subsection, "**After childbirth or when breast-feeding a baby**" in the second sentence that begins, "Such treatment may . . ." the term should be replaced by the term "**RISKS**"

DANGERS OF ESTROGENS AND/OR PROGESTINS section

- the term . in this heading should be replaced by the term, "**RISKS**"

- under **Cancer of the breast** subsection
  - the second sentence that begins, [redacted] should be deleted
  - the first sentence that begins, " Studies suggest a higher . . " should be revised to include the following: "(especially more than 10 years), or who use higher doses for shorter time periods" so that the sentence reads, "Studies suggest a higher risk of breast cancer in women who have used estrogens for long periods of time (especially more than 10 years), or who use higher doses for shorter time periods."
  - an additional sentence should follow that reads, "The effects of added progestin on the risks of breast cancer are unknown."

SIDE EFFECTS section

- in the first sentence that begins, "In addition to the risks . . . ," the phrase, "and/or progestin" should be inserted between "estrogen" and "use" so that the sentence reads, "In addition to the risks listed above, the following side effects have been reported with estrogen and/or progestin use:"
- the additional bullets under this heading should be added
  - irregular vaginal bleeding or spotting
  - headache, depression, migraine, dizziness, faintness or change in vision including intolerance to contact lenses
  - mental depression
  - vaginal yeast infections
- possible additional bullets could include
  - scalp hair loss
  - involuntary muscle spasms
  - changes in sex drive
  - possible change in blood sugars

USE IN CHILDREN section

- in the first sentence that begins, [redacted] should be deleted and in the second sentence that begins, [redacted] should be deleted so that the two sentences read, "Estrogens may be prescribed for certain girls whose ovaries do not work normally. Estrogen treatment has not been shown either effective or safe for use by infants, children or adolescent boys or girls."

REDUCING THE RISKS OF ESTROGEN USE section

- the sentence that begins, [redacted] should be deleted; the phrase, "While you are using ORTHO-Prefest:" should be inserted keeping the headings "**See your doctor regularly**", "**Reassess your need for treatment**" and "**Be alert for signs of trouble**"
- under the heading "**See your doctor regularly**" the paragraph that begins, [redacted] . " should be revised to read, "Visit your doctor regularly for a check-up. If you develop vaginal bleeding, you may need further evaluation."
- under "**Reassess your need for treatment**" subsection, the term, [redacted] should be replaced by "ORTHO-Prefest" so that the sentence reads, " You and your doctor should reevaluate whether or not you still need ORTHO-Prefest every six months"
- under "**Be alert for signs of trouble**" subsection, the term [redacted] should be replaced by "ORTHO-Prefest" so that the sentence reads, "If any of these warning signals (or any other unusual symptoms) happen while you are using ORTHO-Prefest, call your doctor immediately:"

HOW SUPPLIED section

- in the first paragraph, second sentence that begins, "The three-day phases. . ." the phrase, [redacted] should be replaced by the phrase, "three days of pink tablets followed by 3-days of

white tablets" and the term, ' should be replaced by the term, "repeated" so that the sentence reads, "The three days of pink tablets followed by 3-days of white tablets are repeated continuously during treatment."

/S/ 10/5/99

Diane Moore, Regulatory Project Manager

Meeting Minutes

Date: March 31, 1998 **Time:** 1:15 - 2:45 PM **Place:** Parklawn; Chesapeake Room

IND: **Drug Name:** CYCLOPHASIC HRT (Norgestimate and Ethinyl Estradiol)

Type of Meeting: Pre-NDA

Sponsor: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Marianne Mann **External Lead:** Ms. Patricia M. Johnson

Meeting Recorder: Mrs. Diane Moore

FDA Participants:

Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Tatiana Pavlova M.D., Ph.D. - Clinical Pharmacology Fellow
Diane Moore - Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II DNDC II) @ DRUDP (HFD-580)
David Lin, Ph.D. - Chemist, DNDC II @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)OCPB
Kate Meaker - Statistician, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Participants:

Joseph Etse, Ph.D. - Principal Scientist, Analytical Development
Angela Falzone, Ph.D. - Principal Scientist, Process Development Technical Services
Karen Futterknecht, R.Ph. - Senior Regulatory Affairs Associate
Mary Gallagher - Clinical Trials Team Leader
Lee Gisclon, Ph.D. - Research Fellow, Clinical Drug Metabolism
Patricia M. Johnson - Principal Regulatory Affairs Scientist
Pilar Lim, Ph.D. - Principal Biostatistician, Global Clinical Biostatistics and Data management
Phoebe Lohmar, Ph.D. - Principal Medical Writer, Medical Writing/Regulatory Affairs
Donna Panasewicz - Manager, Regulatory Affairs
Dibakar Panigrahi, Ph.D. - Research Fellow, Preclinical Development
Patrick Rojas, Ph.D. - Senior Biostatistician, Global Clinical Biostatistics and Data Management
Daniel Schaufelberger, Ph.D. - Director, Analytical Development/Product Development Technical Service
Frank van den Ouweland, M.D., Ph.D. - Director, International Project Management and Clinical Research, Global Research and Development

Meeting Objective:
To discuss R.W. Johnson's proposals for a new drug application for submission in December 1998.

Background:

The proposed NDA will include data for a CYCLOPHASIC hormonal replacement therapy regimen using a 1.0 mg Estradiol Tablet, USP and a 1.0 mg Estradiol USP/90 µg Norgestimate Tablet. The proposed indications are for the treatment of vasomotor symptoms and vulvovaginal atrophy, prevention of osteoporosis,

Discussion Items:

- the sponsor plans to market the formulation; the results were more bioequivalent to the Estrace® tablets using the formulation
- a compliance issue is linked to the shape of the tablet; the sponsor seeks to market a round tablet
- the estradiol/norgestimate tablet will be white; the estradiol tablet will be pink
- there has not been a change in the norgestimate supplier
- minutes dissolution data should be considered for dissolution studies
- the sponsor is seeking a 2-year expiration date

Decisions:

B. NONCLINICAL PHARMACOLOGY AND TOXICOLOGY

- Question 1: **Cross-referencing:** RWJPRI plans to cross-reference relevant nonclinical pharmacology, toxicology and ADME study information previously submitted to the Ortho CYCLEN and TRI-CYCLEN Tablet NDAs, as listed and summarized in this background dossier (see Backgrounds: Toxicology and Pharmacology). Additional study information not previously submitted to the two NDAs (Cyclen and Tricyclen) will be submitted to the HRT NDA. Does the Agency agree with this proposal?
- Answer to Question 1:
  - acceptable

- Question 2: The nonclinical program for the HRT product will be comprised of the relevant previous study information and the new studies which are listed as "in progress". It is felt that the combination of previously submitted and approved information with newer studies summarized in this dossier, is sufficient to support the proposed NDA. Does the Agency agree with the nonclinical development program proposed for the NDA? Does the Agency foresee a refusal to file issue based upon a lack of adequate nonclinical information for the proposed NDA?
- Answer to Question 2:
  - the nonclinical development program appears to be adequate; no other studies are needed
  - the information appears to be adequate for filing

- Question 3: **Electronic files:** The Agency will be provided with the Nonclinical Technical Summaries (Pharmacology, Toxicology and ADME) in WORD 7.0, in addition to the NDA paper copy. No other files from this section of the NDA are planned for electronic submission.
- Answer to Question 3:
  - acceptable

C. HUMAN PHARMACOKINETICS AND BIOAVAILABILITY

- Question 1: **Multiple-dose Pharmacokinetics**: RWJPRI has conducted a single- and multiple-dose pharmacokinetic study (ESTNRG-PHI-001) in 36 post-menopausal female subjects. This was a parallel, three group study design of once-daily dosing for 90 consecutive days with the cycling E2, E2/NGM regimen across three dose levels. The study provides single- and multiple-dose pharmacokinetic information for E2, E1, E1S, 17d-norgestimate and norgestrel. Does this study satisfy the Agency's requirement for multiple-dose pharmacokinetic information?
- Answer to Question 1:
  - Yes

- Question 2: Bioequivalence Data: Data from the bioequivalence studies ESTNRG-PHI-006 and -007 are not planned for inclusion in the Human Pharmacokinetics section of the proposed NDA. These studies were conducted primarily to demonstrate bioequivalence of two strengths of the RWJPRI estradiol tablets to two strengths of the marketed ESTRACE tablets. The study reports are planned for inclusion in the ANDA. We anticipate submitting to the Division of Generic Drug Products in July 1998. Does the Agency concur with this proposal?
- Answer to Question 2:
  - the NDA should contain the following:
    - abbreviated summaries of Studies ESTRNRG-PHI-006 and ESTNRG-PHI-007 containing bioequivalence data; the study data should include the formulation used
    - comparative dissolution data for 0.5, 1.0 and 2.0 mg E_2 tablets
    - request for a bio-waiver for the 1 mg dose; bracketing for the 1.0 mg dose is acceptable providing the 0.5 mg dose and the 2.0 mg dose are shown to be bioequivalent
    - comparative dissolution data before and after color and shape changes
    - pharmacokinetic data on the estrogen/norgestimate combination formulation; the data should demonstrate that there is no difference between the combination drug product and Estrace® for estrogen bioavailability when the norgestimate is added to the formulation

- Question 3: **Cross-referencing:** RWJPRI plans to cross-reference relevant Human Pharmacokinetic and Bioavailability data previously submitted to Ortho CYCLEN and Ortho TRI-CYCLEN Tablets NDAs, as listed and summarized in this submission (see Background; Human Pharmacokinetics and Bioavailability). Additional study information not previously submitted to the two NDAs will be submitted to the HRT NDA. Does the Agency agree with this proposal?
- Answer to Question 3:
  - Yes

- Question 4: **Food Effect**: With reference to the FDA draft guidance entitled: "Food-Effect Bioavailability and Bioequivalence Studies", published in the Federal Register December 30, 1997, RWJPRI plans to apply the revised C_{max} confidence interval stated in the guidance, to our Food Effect study ESTNRG-PHI-004. Does the Agency concur with this proposal?
- Answer to Question 4:
  - the current approved Guidelines should be followed
  - 90% confidence intervals should be included

- Question 5: Does the Agency agree that the Pharmacokinetic program for CYCLOPHASIC E2/NGM hormone replacement therapy, as described in the background document, is adequate and supportive of the proposed indication for the NDA?
- Answer to Question 5:
  - an abbreviated summary of Studies ESTRNRG-PHI-006 and ESTNRG-PHI-007 should be submitted for review
  - items in Question 2 under Human Pharmacokinetics and Bioavailability should also be addressed

- Question 6: **Electronic files:** In addition to the NDA paper copy, we will provide the Human Pharmacokinetics and Bioavailability Technical Summary on diskette in WORD 7.0. This file will also include ASCII datasets for relevant patient information from only the new human PK/Bio studies; datasets from references cross-referenced to Ortho CYCLEN and Ortho TRI-CYCLEN Tablet NDAs will not be provided. Is this acceptable to the Agency?
- Answer to Question 6:
  - Yes

D. CLINICAL/STATISTICAL

- Item 1: **Osteoporosis Indication:** We would like confirmation from the Division indicating concurrence with the previously agreed-upon approach for obtaining the claim for "prevention of osteoporosis". This approach is to file an ANDA for the E_2-only tablet, a generic version of Estrace®, which is indicated for the prevention of osteoporosis. If RWJPRI's ANDA is approved, we could then claim "prevention of osteoporosis" and "treatment of vasomotor symptoms" for the E_2/NGM Cyclophasic HRT regimen. This approach was previously discussed at the End-of-Phase 2 Meeting We wish to note that the ANDA bioequivalence studies were conducted utilizing the 0.5 and 2 mg E_2 tablets, however, the NDA will contain information for a 1 mg E_2 dose. This is briefly mentioned in the Clinical background provided.
- Answer to Item 1:
  - the estradiol dose must be shown to be proportional to the 0.5 and 2.0 mg doses
  - FDA will clarify whether the filing of the NDA would be in jeopardy if the R.W. Johnson estradiol-only product ANDA has not been approved by the time of the NDA filing
  - the proposal for the osteoporosis claim is acceptable provided the ANDA is approved for Estrace and the R.W. Johnson combination estrogen/norgestimate tablet is also shown to be bioequivalent to Estrace for estrogen bioavailability when the norgestimate is added to the formulation

- Item 2: **Efficacy:** The primary efficacy for the NDA, as summarized in this background dossier, is comprised of the following clinical study information:
  - 1 endometrial hyperplasia study with metabolic sub-study
  - 2 vasomotor studies
    - 1 placebo controlled
    - 2 Phase 3 studies (ESTNRG-CHRT-102 and -103)

The proposal for the vasomotor study was previously discussed with FDA and subsequently agreed to. The endometrial hyperplasia study was developed and conducted in accordance with the FDA Guideline entitled FDA's Guidance for Evaluation of Combination Estrogen/Progestin-Containing Drug Products for Hormone Replacement Therapy of Post Menopausal Women (June 1995)". Does the Agency agree that the proposed efficacy program is sufficient to support an NDA for hormone replacement therapy in which the indication is for treatment of vasomotor symptoms and vulvovaginal atrophy; and the prevention of osteoporosis?

- Answer to Item 2:
  - the primary analysis should be the absolute change from baseline, not the percent change from baseline, as presented
  - Study CHRT-1[redacted]
    - descriptive statistics should be provided by center for all centers, not just the pooled end results
    - if any pair/wise comparisons are planned in the analysis, an adjustment to p-values for multiple comparisons should be applied
  - Study CHRT 102/103
    - the intent-to-treat analysis is the primary analysis variable, not the evaluable subset of patients proposed
    - the study proposal to combine studies 102 and 103 for hyperplasia indication is acceptable
  - the following should be submitted:
    - the Phase 3 protocols
    - list of laboratory values including metabolic values
    - details and references for the closed testing procedure intended to apply for multiple comparisons for endometrial hyperplasia analysis
    - the counts of the number of subjects per treatment group for study CHRT 104

- Item 3: **Dose Selection:** In correspondence dated August 29, 1994, FDA requested that RWJPRI include a 0.5 mg E_2 dose in the Phase 2 study, N93-072. We are awaiting results of our Phase 3 study ESTNRG-CHRT-104 to determine if further clinical investigation is warranted.
- Response to Item 3:
  - the sponsor plans to market the 1 mg dose only; this is a statement of the status of the Phase 3 study in which the 0.5 mg dose is being studied
  - the sponsor should determine a plan for the endometrial studies if the 0.5 mg dose is effective for the vasomotor study
  - data from the Phase 3 study should be submitted for review

- Item 4: **Interim Analysis:** A planned interim analysis of the Phase 2 study N93-072 resulted in the discontinuation of the 2 mg E_2 dose in the pivotal Phase 3 studies.
- Response to Item 4:
  - Acceptable as long as data from the Phase 3 trials was not used in the decision to stop the 2 mg E2 dose groups

- Item 5: **Bleeding Data:** Results from studies N93-072 and CC2636-C-101 indicate that there is an acceptable level of bleeding in the 1 mg E2 dose combinations. We are awaiting results from our ongoing Phase 3 studies to draw final conclusions regarding vaginal bleeding.
- Response to Item 5:
  - the sponsor plans to market the 1 mg dose only; this is a statement of the status of the Phase 3 studies in which bleeding will be assessed

- Item 6a: **ISS/ISE:** The ISS will include pooled safety data across all subjects who were treated with E2/NGM tablets, with specific attention to the proposed regimen of 1 mg E2/90 ug NGM. The wet formulation studies (CC2636-C-101, ENTNRG-CHRT-105 and N93-072 will be pooled with the dry formulation studies (ESTNRG-CHRT-102 and -103). The individual safety summaries by formulation will also be provided as "Attachments" in the ISS. Does the Agency agree with our proposals?
- Answer to Item 6a:
  - Yes

Item 6b: **Demographic Data:** Will the Agency require separate US and non-US analyses of the data for presentation in the integrated summaries for Safety and for Efficacy?

- Answer to Item 6b:
  - No

Item 7: **Four Month Safety Update:** Follow-up data for those subjects whose limiting adverse events persisted at their last clinical visit, and those subjects who had markedly abnormal laboratory analyte values at their last clinical visit will not be evaluated in the NDA, but will be included in the Four Month Safety Update. Is this proposal acceptable to the Agency?

- Answer to Item 7:
  - Yes, providing that the studies are completed and patient results are followed up
  - intent-to-treat analysis should include all randomized patients not just evaluable; patients with abnormal laboratory values should be provided

Item 8: **Statistics:** Does the agency agree with our proposed analysis plans to show safety and efficacy of the proposed regimen as described in the Clinical Background provided?

- Answer to Item 8:
  - Metabolic values should also be included
  - the number of subjects in the study should be provided
  - the primary analysis should be the absolute change from baseline, not the percent change from baseline as depicted in the background package
  - descriptive statistics by centers should be provided, not pooled data

Item 9: **Electronic Files:** The following summaries and reports will be provided to FDA as WORD 7.0 files:

  - Clinical Pharmacology Summary
  - Phase 3 study reports only (report text; not appendices or attachments)
  - ISE
  - ISS
  - Integrated Summary of Risk/benefit
- We will provide data files of the primary Phase 3 studies, in a mutually agreeable format, for the Statistical Reviewers.
- Answer to Item 9:
  - the proposed electronic files are acceptable for submission
  - Biometrics requires SAS data sets and copies of the software programs used in the data analyses
  - a copy of the label in WORD 7.1 should be submitted
  - Clinical Pharmacology and Biopharmaceutics requires ASCII files

E. CANDA

- Question 1: RWJPRI plans to provide electronic files for specific Technical Summaries, clinical study reports and statistical data (see "Electronic Files" issues stated in the various Issues for Discussion categories above) in order to satisfy FDA's requirement for a computer assisted NDA. Are the proposals presented for Electronic Files sufficient to meet this FDA requirement?

- Answer to Question 1:
  - yes

A. CHEMISTRY

- Question 1: **Drug Substance Stability**: Does the Agency agree with our proposal for the amount and content of stability data to be provided in the NDA for 17B-estradiol USP (micronized) and norgestimate (micronized)? Please refer to item 2.3 of the Chemistry Background provided in this submission for further details.
- Answers to question 1:
  - yes
  - 3-month stability data is lacking; 1-year stability endpoint data should be available during the review clock
  - the change in particle size will be monitored during stability
  - although the sponsor has clarified the size of the micronized particles in their IND the size of the particles should also be clarified in this IND

- Question 2: **Drug Substance Physical and Chemical Characteristics**: As described in item 2.1 of the Chemistry Background, does the Agency consider the physiochemical information to be provided in the NDA sufficient for review of the drug substances?
- Answer to question 2:
  - Yes

- Question 3: **Drug Substance Specifications**: Are the proposed tests for the drug substances, as described in item 2.2 of the Chemistry Background, adequate for review by the Agency? Does the Agency agree with our request to delete the identification test by UV and the melting point determination?
- Answer to Question 3:
  - yes; the deletion of the identification test by UV is acceptable
  - the impurity specifications should be expanded and all should be described in the specifications
  - the justification for removing the melting point determination procedure should be submitted for review

Question 4: **Drug Product Specifications:** Does the Agency consider the drug product specifications described in the background document to be sufficient for the NDA? (Refer to item 3.4 of the Chemistry Background.)
Answer to Question 4:

- yes, however the following information should be provided:
  - a list of specific norgestimate impurities
  - justification by stability data for overage for estrone

- Question 5: **Drug Product Stability:** RWJPRI intends to provide in the NDA, primary stability data on three batches of each strength of CYCLOPHASIC HRT Tablets. Data at the initial, 1, 3 and 6 month sampling intervals will be provided for tablets that have been stored at both the long term condition of 25 C/60% RH and at accelerated conditions. Stability data for the 9 and 12 month sampling intervals will be submitted within six months following submission of the NDA. Does the Agency accept our request to provide additional stability data (9 and 12 months) during the DNA review period. Is the stability program for our drug product acceptable to assess the stability of this drug product?
- Answer to Question 5:
  - yes

- Question 6: **Drug Product Comparability Testing:** As described in item 3.7 of the Chemistry Background, several changes have been incorporated into the method of manufacture between the clinical product and the commercial product. RWJPRI will provide dissolution profile and batch analysis data to establish comparability of the products. Will dissolution profile data and batch analysis data be adequate (to) establish comparability?
- Answer to Question 6:
  - yes

- Question 7: Batch Documentation will be provided in the NDA as follows:
  - One pilot scale batch of each strength of drug product that was used to conduct a primary stability study (total of 2 batches); the documentation for the four individual batches will be provided in separate appendices in the Chemistry section of the NDA. Is the amount of data proposed acceptable to the Agency?
- Answer to Question 7:
  - one batch of each strength tablet from the clinical pivotal trial in each shape should be submitted

F. NDA Format

- Question 1: **Reviewer's Guides:** These guides briefly highlight to the individual Reviewers any codes, page numbering schemes, legends and notable items specific to the NDA item for which they are prepared; a Reviewer Guide is prepared for each NDA Item. Does the Agency wish to comment on this proposal?
- Answer to Question 1:
  - Acceptable

- Question 2: **Ongoing Studies:** Information for ongoing studies will be daily reported in the NDA, as "ongoing".
- Answer to Question 2:
  - Acceptable provided the last clinical visit is completed by the time of the NDA submission