Meeting Minutes

Date: March 24, 1998 **Time:** 10:30 AM - 11:25 AM **Place:** Parklawn; Rm. 17B-43

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

Type of Meeting: Pre-Pre-NDA

Sponsor: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Lisa Rarick

Meeting Recorder: Mrs. Diane Moore

FDA Participants:
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Marianne Mann, M.D. - Acting Deputy Director, 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)
Krishan Raheja, D.V.M., Ph.D. - Pharmacologist, DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)

External Participants: none

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 the sponsor's 1.0 mg Estradiol Tablet, USP and their 1.0 Estradiol USP/90 µg Norgestimate Tablet. The proposed indications are for the treatment of vasomotor symptoms and vulvovaginal atrophy, prevention of osteoporosis.

Discussion Items:

- no cholesterol, lipid or metabolic substudies were performed for the drug products
- reference values should be clarified
- a consult was sent to the Cardio-Renal Division and the Division of Metabolic and Endocrine Drug Products to analyze the studies investigating carotid intima-media hyperplasia and peripheral blood flow and carotid intima-media thickness as markers; both Divisions referred to the studies as exploratory; the clinical relevance of changes in these particular endpoints remains uncertain at this time

Decisions:

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:
  - the micronized norgestimate product is a new form of norgestimate; there is no previous data on this form of norgestimate
  - the sponsor should include 3-month and 1-year stability endpoint data in addition to those endpoints provided
  - the change in particle size should be monitored during stability testing
  - although the sponsor has clarified the size of the micronized particles in IND , the size of the partilces 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?
- Answers to question 2:
  - the DMF for this drug substance will be cross-referenced to the previous NDA for the characteristics
  - the polymorphic form of the drug substance to be submitted should be clarified

- 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:
  - the proposed specification for the particle size is acceptable
  - the micronized particles should be monitored for aggregation during stability studies
  - the impurity specifications should be expanded and all should be specified
  - the deletion of the identification test by UV is acceptable
  - the melting point test is important for testing the crystal structure; the rationale for removing this test procedure should be clarified

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:

- specifications for impurities should be justified by stability data
- norgestrel and estrone are listed at no more than % and % (somewhat high) respectively; these must be justified by stability data
- norgestimate normally has other impurities; therefore more information should be provided
- dissolution specifications should be based on dissolution profile data; minutes dissolution appears to be too long; minutes dissolution should be considered

- Question 5: **Drug Product Stability:** RWJPRI intends to provide 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 NDA review period? Is the stability program for our drug product acceptable to assess the stability of this drug product?
- Answer to Question 5:
  - ICH guidelines recommend 12 month room temperature and 6 months 40° C data; however, 6 months of data at the time of the NDA submission is acceptable
  - the expiration date being sought should be clarified

- 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:
  - bioequivalence studies to evaluate the change in shape and color of the tablets are not necessary
  - bioequivalence studies have already been performed between Estrace and the R.W. Johnson estradiol tablet
  - information concerning what happened during development should be disclosed
  - the tablet formulation for marketing should be clarified
  - the commercial process uses the dry formulation; the manufacturing summary is short and uses no solvent—it should be clarified whether this is also the dry formulation
  - the clinical batch used has a % overage, but the commercial batch has a % overage; the overage should be justified

- 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)
  - one batch of each strength of drug product that was used to conduct a bioavailability 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 for each strength of drug product should be submitted
  - although not required by law, batch studies for the clinical study are requested
  - electronic file submissions should be submitted in WORD 7.0

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 CYCLIN and TRI-CYCLEN Tablet NDAs, as listed and summarized in this background dossier (see Backgrounds: Toxicology and Pharmaoclogy). 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; the dose being studied is less than previous doses studied

- 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:
  - acceptable; studies are in progress for 17 β-norgestimate in another IND for a transdermal system
  - mutagenesis tests are undergoing
  - if not already planned, a mouse micronucleus assay should be added

- 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:
  - it must be demonstrated that the bioavailability and the pharmacokinetics of the R.W. Johnson estrogen tablet are the same as for Estrace
  - if an ANDA is approved for the R.W. Johnson estrogen tablet, it must be demonstrated that the bioavailability of estrogen is the same when the norgestimate is added; the sponsor claims to have studies to address this issue
  - it must be shown that the pharmacokinetics of estrogen is dose-proportional
  - the 0.5 mg dose has not been studied as previously requested by the Agency

- it should be clarified whether the manufacturing process will be the wet or dry process
- an abbreviated summary of Studies ESTRNRG-PHI-006 and ESTNRG-PHI-007 should be submitted for review
- a request for a bio-waiver should be made for the 1 mg dose providing the comparative dissolution data for 0.5, 1.0 and 2 mg E2 tablets

- 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:
  - the plan appears to be adequate; it is acceptable to cross-reference the NDA

- 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:
  - No, the draft guidance is not official yet. Ninety percent confidence intervals should be submitted. Goal posts will be decided during the review depending on the guidance that is in effect

- 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:
  - Yes, provided that items in Question 2 above are 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:
  - electronic files to be submitted should include:
    - summary of the pharmacokinetic section
    - data sets in ADCI files
    - synopses of individual study reports in WORD 7.0
    - labeling in WORD 7.0

D. CLINICAL/STATISTICAL

- Question 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 Question 1:
  - the pivotal study for the NDA for relief of vasomotor symptoms contains 36 patients for 18 days
  - 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
  - both single and multiple dose studies should be performed
  - 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

- Question 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 Question 2:
  - the primary analysis should be the absolute change from baseline, not the percent change from baseline as presented
  - the analysis plan should be submitted for review
  - a single VMS study is proposed for the vasomotor indication and is acceptable
  - the lowest effective dose of E_2/NGM for the treatment of osteoporosis is unknown; the NDA will include information on only the 1.0 mg E_2 dose, which will be carefully evaluated for its relative safety and efficacy
  - the following should be provided:
    - details and references for the closed testing procedure intended to apply for multiple comparisons for endometrial hyperplasia analysis
    - counts of the number of subjects per treatment group (the table on page 78 only gives the total per study)
    - the protocols should be submitted for review; although the FDA guidelines are referenced, the study description was not included in the pre-meeting package
    - the counts of the number of subjects for study CHRT 104 per treatment group (not only totals)
  - Study CHRT-104:
    - pooling centers: descriptive statistics should be provided by center for all centers, not just the pooled end result
    - if any pairwise comparisons are planned in the analysis, an appropriate adjustment for multiple comparisons must be performed

- Study CHRT 102/103
  - the intent-to-treat analysis is the primary analysis, not the evaluable subset of patients proposed
  - the study proposal to combine studies 102 and 103 for hyperplasia indication is not acceptable

- Question 3: **Dose Selection:** In correspondence dated August 29, 1994, FDA requested that RWJPRI include a 0.5 mg E2 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.
- Answer to Question 3:
  - the sponsor should determine a plan for the endometrial hyperplasia studies if the 0.5 mg dose is effective for the vasomotor study
  - data from the Phase 3 study should be submitted for review

- Question 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.
- Answer to Question 4:
  - **acceptable** if data from the Phase 3 trials was not used in the decision to stop the 2 mg E_2 dose groups

- Question 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.
- Answer to Question 5:
  - no question was asked pertaining to this issue; the safety and efficacy endpoints should be clarified

- Question 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 Question 6a:
  - the formulation for the commercial batch should be clarified (wet or dry)

- Question 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 Question 6b:
  - demographic data should be presented by center; it is not necessary to separate the U.S. and non-U.S. studies

- Question 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 Question 7:
  - the intent-to-treat analysis should include all randomized patients not just evaluable; these patients should be included in the NDA
  - the data from the bleeding trial may be affected by the inclusion of all patients in the study
  - if all safety data including the last clinical visit for every patient is included in the NDA, the follow-up data could be submitted in the 4-month safety update; however, if clinical data from the study (such as the last visit safety data) is missing, the proposal is unacceptable

- Question 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 Question 8:
  - see question 1 above
  - descriptive statistics by centers should be provided, not pooled data

- Question 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 Question 9:
  - for statistical review, clinical data, SAS data sets with programs used in the analysis and documentation of contents, variables, and formats should be provided; WORD 7.0 is acceptable text program

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:
  - see above

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:
  - no comment

- Question 2: Ongoing Studies: Information for ongoing studies will be daily reported in the NDA, as "ongoing".
- Answer to Question 2:
  - no comment

- Question 3: ANDA Cross-Reference: RWJPRI will cross-refer to the ANDA for the E_2-only tablet to support the claim "prevention of osteoporosis". This cross-reference will appear in the annotated package insert. Does the Agency agree with this proposal?
- Answer to Question 3:
  - no comment

- Question 4: Tabulations: We are aware of the FDA industry guidance entitled; "Electronic Submission of Case Report Forms and Case Report Tabulations (September 1997), which requires CRF tabulations to be submitted to FDA in PDF files, however, CRF tabulations generated by RWJPRI are contained in individual study reports (as "Appendices" to study reports). Therefore, we propose to cross reference tabulations (Item 11) to the location in Item 8 (Clinical Data Section). Is this acceptable to the Agency?
- Answer to Question 4:
  - yes

- Question 5: Case Record Forms: Case record forms (CRFs) for patients who died or discontinued due to an adverse event will be submitted in accordance with 21CFR 314.50 (f) (2). In accordance with the industry guidance for submission of electronic submission of CRFs, we can provide to the Agency all CRFs in PDF files (per patient). Does the Agency accept this proposal?
- Answer to Question 5:
  - paper copies of all serious adverse events, all discontinuations, and all deaths is acceptable

To-do items

Item :	Responsible Person :	Due Date:
• submit a memo to the Nomenclature Committee regarding the drug reference in the tradename	Dr. Rhee	one week

/S/
Signature, recorder

/S/ 4/17/98
Signature, Chair

Post Meeting Addendum:
The Division requested a second review on the tradename "Perfest" by the nomenclature committee on the basis that the tradename should mention both components or neither component, not just one component. The Division felt that the tradename "Perfest" was not acceptable because this name implies reference to estrogens, but not progestins.

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

DATE: September 24, 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: Valerie Donnally
R.W. Johnson Pharmaceutical Research Institute

Background: The sponsor submitted labeling revisions in an amendment to the NDA dated September 2, 1999.

Proposed labeling revisions:

- **DESCRIPTION** section
  - in the fourth sentence that begins, the word, should be deleted
- **CLINICAL PHARMACOLOGY** section
  - the fourth paragraph that begins, "Norgestimate is a progestin with low androgenicity." the remainder of the paragraph after this phrase should be deleted
  - the sponsor can expand on the use of progesterone as a class in the description statement
  - **Pharmacokinetics** subsection
    - **Distribution** subsection
      - the third sentence that begins, should be deleted
      - Table 1 entitled, "Pharmacokinetic parameters of E_2, E_1, E_1S, and 17d-NGM[1] Following Single and Multiple Dosing of ORTHO-PREFEST™" should use baseline unadjusted PK parameters
  - **Clinical Studies** subsection
    - **Efficacy On Postmenopausal Symptoms** subsection
      - the first paragraph that begins, should be replaced with the following:
      - "The effect of the estrogen component of ORTHO-PREFEST was confirmed in a 12-week placebo-controlled trial of healthy postmenopausal women with moderate-to-severe vasomotor symptoms (MSVS). The addition of norgestimate to estrogen (i.e., the ORTHO-Prefest regimen) was studied in two 12-month trials in healthy postmenopausal women (n=1212) for endometrial protection. Results from a subset population (n=119) of these 12-month trials (women with MSVS) are shown in Table X"
      - a table entitled, "Change in the Mean Number of Moderate-to-Severe Vasomotor Symptoms" should be inserted; the table should clarify that this was data from the subset of subjects with ≥ 7 moderate-to-severe hot flushes per day

- Table 2 entitled, ' should be deleted

- **Effects on the Endometrium** subsection
  - Table 3 entitled, "Incidence of Endometrial Hyperplasia At End Of Treatment in Two 12-Month Clinical Trials of ORTHO-PREFEST™" the numbers should be revised to show only data from Study 102 and 103.
  - the title should be revised to read, "Incidence of Endometrial Hyperplasia (ITT population) At End Of Treatment in Two 12-Month Clinical Trials of ORTHO-PREFEST™"
  - "at month 12" should be added to the sub-header entitled, "the Total No. evaluable Biopsies" so that it reads , "the Total No. evaluable Biopsies at month 12"
  - Under the column entitled, "Continuous" (97%) should be added after the number 256 for the Total No. Evaluable Biopsies at month 12
  - under the column entitled, "ORTHO-PREFEST™" should be replaced with 242; should be replaced with 227; (94%) should be added after 227 for the Total No. Evaluable Biopsies at month 12
  - should be replaced with 227 under "ORTHO-PREFEST™" column for "Normal Endometrium"
- **Control of Uterine Bleeding** subsection
  - this section should describe cumulative amenorrhea (as described in the Prempro label, for reference)
  - in the second paragraph, first sentence, the number of 12-month trials should be revised to three so that the sentence reads, "The effect of ORTHO-PREFEST™ on uterine bleeding in three 12-month trials of 432 healthy postmenopausal women was evaluated." since C101 safety data was added to the data from Studies 102 and 103; 432 should be replaced with 429 in this sentence
  - the second sentence that begins, should be deleted
  - the third sentence that begins, should be deleted
  - a new sentence that reads, "Results are shown in Figure 1." should be inserted
- **Metabolic Parameters** subsection
  - Effects on Lipids subsection
  - in the paragraph that begins, "The effect of ORTHO-PREFEST™ on lipids . . ." the first sentence that reads, "The effect of ORTHO-PREFEST™ on lipids was evaluated in a 12-month metabolic trial of healthy postmenopausal women." can be retained; the rest of this paragraph should be deleted
  - a sentence that reads, "Results are shown in Table X" should be added
  - the bar graph should be replaced by a table including data describing % changes from baseline HDL, LDL, total cholesterol and triglycerides after one year of treatment

- **CONTRAINDICATIONS** section
  - active liver disease should be added to the this section
- **WARNINGS** section
  - **Induction of Malignant Neoplasms** subsection
    - the sentence that begins, and the following sentence should be deleted; a new sentence should be added that reads, "Results from two 12-month clinical trials of the effects of ORTHO-PREFEST™ on endometrial hyperplasia are shown in the **Clinical Studies** section of this label."
  - **Venous thromboembolism** subsection
  - the second paragraph that begins, should be deleted

- **PRECAUTIONS** section
  - The title, should be revised to read, "Prevention of Osteoporosis"
  - this label does not include Cardiovascular Risks section under the **PRECAUTIONS** section; although the section is not included in the proposed new estrogens labeling guidance, it may be prudent to discuss including such a section in this label of a combined HRT product
  - **Elevated Blood pressure** subsection
    - in the first sentence that begins, the word, should be replaced by the word, "Occasional"
    - another item that could be requested is a precaution regarding visual problems
  - **Drug/Laboratory Test Interactions** subsection
    - items 8 and 9 that begin,

- **ADVERSE REACTIONS** section should be deleted
  - the number for the healthy postmenopausal women treated with ORTHO-PREFEST™ (579) should be verified by the sponsor
  - the two sentences in the second paragraph that begins, should be deleted; this has not been allowed in any HRT labeling; no trials were set up to demonstrate body weight endpoints
- **DOSAGE AND ADMINISTRATION** section
  - in the second paragraph, the second sentence that begins, should be revised to read, "After all tablets from the blister card have been used, the first tablet from a new blister card should be taken on the following day."
  - the administration of the doses for the HRT indication and osteoporosis indication should be separated into two sections and headers should be added to distinguish the two sections by indication
  - the osteoporosis section should include wording that states that this dose may not be the lowest effective dose for osteoporosis
- **HOW SUPPLIED** section
  - the first part of the sentence that was deleted should be retained except the 2-year expiration should be revised to 18 months; the added sentence is acceptable; the last sentence should read "This product is stable for 18 months. Store at 25°C (77°F); excursions permitted to (15°-30°C), (59°-86°F)."

Concurrence:

cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/Tvan der Vlugt/MRhee/AJordan/DMoore/TRumble
HFD-580/DHoberman/LKammerman/AParekh/JLau
HFD-510/AHakim

Minutes of Telecon

Date: October 19, 1999 **Time:** 12:00 - 1:30 PM **Place:** Parklawn; Room 17B-43

NDA: 21-040 **Drug Name:** ORTHO-Prefest [(cyclophasic, 1.0 mg 17 β-estradiol and 1.0 mg 17 β-estradiol + 90 ug norgestimate (NGM)] Tablets, USP

Type of Meeting: Labeling discussion

Indication: Treatment of vasomotor symptoms, vulvar vaginal atrophy, prevention of osteoporosis

External Constituent: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Shelley Slaughter **External Participant Lead:** Dr. Ramon Polo

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Product (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
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Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

External Participants:
Larry Abrams, Ph.D. – Human PK/Drug Metabolism, R.W. Johnson
Frank van den Ouweland, M.D., Ph.D. – Director, International Project Management and clinical Research, Bassersdorf, Switzerland
Pilar Lim, Ph.D. - Biostatistics, R.W. Johnson
Ramon Polo, Ph.D. – Regulatory Affairs, R.W. Johnson
Gary Shangold, M.D. – Regulatory Affairs, R.W. Johnson
Valeria Donnelly – Regulatory Affairs, R.W. Johnson

Meeting Objective: To discuss the Agency's responses to the sponsor's October 14, 1999, proposed labeling for the physician package insert and patient package insert for NDA 20-040.

Background: On October 14, 1999, the sponsor submitted proposed labeling revisions to the physician and patient package inserts for NDA 21-040. Also included were the sponsor's responses to several recent labeling revisions proposed by the Agency.

Discussion Items:

- theories on the mechanism of action of a drug product are not included in product labeling unless study data supports the conclusions; no data supporting the comments in the **CLINICAL PHARMACOLOGY** section were presented or referenced in the NDA
- the circumstances regarding the administration of the product with or without food during the clinical studies is reflected in the **DOSAGE and ADMINISTRATION** section of the labeling (also see **Food-Drug Interactions** section in approved Prempro labeling)
- either term, "cyclical" or "cyclophasic" may be used in the label providing the chosen term is used consistently throughout the labeling
- in the **CLINICAL PHARMACOLOGY** section, **Pharmacokinetics** subsection, Excretion subsection, the Division requested the sponsor clarify from where the half-life of 37 hours was derived for norgestimate
- Table 1
  - the Division recommended that the number "~~16~~" (that has strikeout marking) in the fourth row under the "E_2" section under the column heading "Multiple Dose E2/NGM" be replaced by the number "16" without strikeout marking; the sponsor explained that the endogenous estrogen has the half-life removed because the data was not baseline corrected; this revision was accepted by the Division
- the only data time points to be referenced in the label are Weeks 4, 8 and 12, the only primary endpoints; no other time points may be included

Decisions:

- Physician's package insert
  - **INTRODUCTION**
    - in the second line that begins, should be deleted and the term, "tablets" should be moved to the right of the parenthesis so that the sentence reads, "ORTHO-PREFEST™ (17β-estradiol/norgestimate) tablets"
  - **DESCRIPTION** section
    - the first paragraph that begins, should be revised to read as follows:
      "The ORTHO-PREFEST™ regimen provides for a single oral tablet to be taken once daily. The pink tablet containing 1.0 mg estradiol is taken on Days 1 through 3. The white tablet containing both 1.0 mg estradiol and 0.09 µg norgestimate is taken on Day 4 through 6 of therapy. This cyclical pattern is repeated continuously throughout therapy."
  - **CLINICAL PHARMACOLOGY** section
    - in the second paragraph, the second sentence that begins, should be replaced by the phrase, "adult women with normal menstrual cycles"
    - the fifth paragraph that begins, should be deleted
    - **Pharmacokinetics** subsection
      - Absorption subsection
        - the third sentence that begins, should be deleted
        - the following sentence should be inserted at the end of the Absorption subsection "Upon coadministration of ORTHO Prefest with a high fat meal, the C_{max} for estrone and estrone sulfate was increased by 14% and 24%, respectively, and the C_{max} for 17-deacetyl norgestimate was reduced by 16%."

- a sentence stating "the clinical relevance of these findings is unknown" is not required for this label
- Distribution subsection
  - in the fourth sentence that begins, [redacted] should be deleted
- **Special Populations** subsection
  - in the Effects of Race, Age, and Body Weight subsection, in the fourth sentence that begins, "No significant difference due to body weight . . . ," the parenthesis including the term, "60-80 kg" should be deleted and the phrase, "in women in the 60-80 kg weight range" should be added after the word "observed." so that the sentence reads, "no significant difference due to body weight was observed in women in the 60-80 kg weight range."
- Table 1
  - the word "Mean" should be added to the title before the word "Pharmacokinetic"
  - the half-life of 37 hours in the fourth row under 17d-NGM under the column entitled, "First Dose E3/NGM" should be confirmed by the sponsor
  - the phrase, "Baseline uncorrected data are reported for E_2, E_1 and E_1S" should be added to the end of footnote 1
  - the term [redacted] should be deleted in both places in footnote 2
- **Drug-Drug Interactions** subsection
  - in the third sentence that begins, [redacted] should be deleted and replaced by the phrase, "the steady-state serum estradiol levels during the estradiol plus norgestimate days of the cyclophasic regimen may be lower by 12-18% as compared to the estradiol alone regimen."
- **Clinical Studies** subsection
  - **Efficacy on Postmenopausal Symptoms** subsection
    - the third paragraph that begins, [redacted] should be deleted; the sponsor may propose text to add data from the clinical trials to describe the effect of ORTHO-PREFEST on vulvar and vaginal atrophy
    - the following text should follow Table 2: "The steady-state serum estradiol levels during the estradiol plus norgestimate days of the cyclophasic regimen may be lower by 12-18% as compared to the estradiol alone regimen. The clinical relevance of this is unknown."
  - **Effects on the Endometrium** subsection
    - the first paragraph of this subsection that begins, [redacted] should be revised to read, "The effect of ORTHO-PREFEST™ on the endometrium was evaluated in two 12-month trials. Combined results are shown in Table 3."
    - The title of Table 3 should be revised to read, "Incidence of Endometrial Hyperplasia after 12 Months of Treatment (ITT population)
    - the sponsor may propose a sentence to insert after Table 3 to reflect the safety data from Study C-101
  - **Control of Uterine Bleeding** subsection
    - the paragraph that begins, [redacted] should be revised to read, "The effect of ORTHO-PREFEST on uterine bleeding was evaluated in two 12-month trials. Combined results are shown in Figure 1."

- Figure 1 should be revised to show the ITT population (not all subjects who completed 12 months)
- in the title to Figure 1, the phrase, should be deleted and replaced with ITT population so that the title reads, "Subjects with Cumulative Amenorrhea Over Time (ITT Population)

- **Metabolic Parameters** subsection
  - in the second sentence, first paragraph that reads, "Results are shown in table 4." the word "table" should be capitalized
  - in Table 4, the word "Total" should be inserted before the term "Cholesterol" and the calculations for ORTHO-PREFEST™ under the column entitled, "Mean % Change" should be clarified
  - the paragraph after Table 4 that begins, should be deleted
  - Figure A entitled, should be deleted; the Agency is consistently limiting the amount of lipid profile data allowed in all estrogen class labeling

- **CONTRAINDICATIONS** section
  - item 7. should be removed as it is not included in the revised guidance document
- **WARNINGS** section
  - **Venous thromboembolism** subsection
    - the previous paragraph that begins, should remain out of the label; this does not reflect standard clinical practice, although it could be advised in some patients; the risk/benefit ratio is based on individual patients and surgery to be done; the Division prefers to have decision-making by the physician rather than to have this statement in the labeling
- **PRECAUTIONS** section
  - under item c., the sentence that begins, should be revised to read, "possible enhancement of mitotic activity in breast epithelial tissue. there is minimal epidemiological data available to address this point."
- **DOSAGE and ADMINISTRATION** section
  - under item 1., the following sentence should be added after the third sentence that begins, "After all tablets from the blister card . . :" "This dose may not be the lowest effective dose for the treatment of vulvar and vaginal atrophy."; the new sentence should be emphasized by bolding or underlining
  - under item 2., in the fourth sentence that begins, "This dose may not . . ." the phrase "prevention of" should be inserted after "for" so the sentence reads, "This dose may not be the lowest effective dose for prevention of osteoporosis."; this sentence should be bolded or underlined
- **HOW SUPPLIED** section
  - the paragraph that begins, should be revised to read, "ORTHO-PREFEST™ is available as two separate, round-shaped tablets for oral administration. It is arranged such that three pink tablets are followed by three white tablets for a total of 30 tablets per blister card."

- Patient Package Insert
  - **USES OF ESTROGEN** section

- the subsections –

should be deleted

- **SIDE EFFECTS** section
  - in the seventh bulleted item, the term "Mental depression" in bullet item 9 should be deleted as it is redundant with
- **USES IN CHILDREN** section
  - the first sentence that begins, deleted should be

Action items:

• **Item:**	**Responsible Person:**	**Due Date:**
• check cholesterol numbers and individual numbers in Table 4	R.W. Johnson	1-2 days
• submit revised labeling	R.W. Johnson	1-2 days

/S/ 11/8/99
Signature, minutes preparer

/S/
Signature, Chair 11/8/99

Post Meeting Addendum:
At 1:05 PM, discussion was continued with the sponsor and Drs. Parekh and Lau of the Clinical Biopharmaceutics discipline regarding data pertinent to the **Drug-Drug Interaction** subsection. The Agency was concerned with the data because no estradiol-alone regimen was included with the sex hormone binding globulin (SHBG) data. The steady-state SHBG data from Day 1/30 was expected to be similar to estradiol alone data. In the August 9, 1999, response, 1/90 from Day 90 was compared to 1/30 of Day 87. It was noted that the package cartons need to be revised to accommodate the revision in the expression from 17β-estradiol and 17β-estradiol/norgestimate to 17β-estradiol/norgestimate as in the original draft. The pink and white tablets should be described separately on the packaging.

drafted: dm/10.28.99/N21040TC101999.doc

Concurrence:
TRumble 10.29.99/AParekh 11.01.99/MMann 11.02.99/Tvan der Vlugt, SSlaughter 11.03.99
cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/Tvan der Vlugt/MRhee/DMoore/TRumble
HFD-580/AParekh/JLau

Minutes of Telecon

Date: October 6, 1999 **Time:** 1:00 - 2:00 PM **Place:** Parklawn; Room 17B-43

NDA: 21-040 **Drug Name:** ORTHO-Prefest (Cyclophasic, 1.0 mg 17 β-estradiol and 1.0 mg 17 β-estradiol + 90 ug Norgestimate (NGM) Tablets, USP

Type of Meeting: Labeling discussion

Indication: Treatment of vasomotor symptoms, vulvar vaginal atrophy, prevention of osteoporosis

External Constituent: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Marianne Mann, M.D. - Deputy Director, Division of Reproductive and Urologic Drug Product (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II (DNDC II) @ DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

External Participants:
Larry Abrams, Ph.D. – Human PK/Drug Metabolism, R.W. Johnson
Greg Axenroth – New Products, R.W. Johnson
Roxanne Beck – Regulatory Affairs, R.W. Johnson
Patrick Caubel, M.D. – Medical Director, R.W. Johnson
Valeria Donnelly – Regulatory Affairs, R.W. Johnson
Angela Falzone, Ph.D. – Analytical Development, R.W. Johnson
Larry Gifford, M.D. – Global Safety and Pharmacovigilance, R.W. Johnson
Tracy Healy – Regulatory Affairs, R.W. Johnson
Rosanne Lane – Biostatistics, R.W. Johnson
Pilar Lim, Ph.D. - Biostatistics, R.W. Johnson
Ramon Polo, Ph.D. – Regulatory Affairs, R.W. Johnson
Gary Shangold, M.D. – Regulatory Affairs, R.W. Johnson
Mike Sinclair – New Products, R.W. Johnson

Meeting Objective: To discuss the proposed physician package insert for NDA 21-040 and the sponsor's October 5, 1999, responses and questions to the Agency letter dated September 22, 1999.

Background: On October 5, 1999, the sponsor submitted a response to the Agency letter dated September 22, 1999, which included nine discussion questions. The labeling text is from the sponsor's revised labeling submitted September 2, 1999, and the Agency memo to the sponsor dated September 24, 1999.

Discussion Items:

- **Question 1:** Regarding the overage of estradiol, instead of using fixed overage %), the overage should be determined for each production batch based on the actual water content analysis data obtained from the batch of estradiol to be used.
  - the sponsor noted that the water content could vary from batch to batch throughout the manufacturing process; that is why the % overage was proposed
  - the Agency proposed that the overage determination be based on the actual water content analysis data from the batch of estradiol used for an interim period of 1-2 years; during this time the water content can be analyzed from the incoming drug substance with data from ten batches; once consistency has been demonstrated, a supplement can be submitted to the NDA for a fixed overage
  - the sponsor proposed to submit data from 40 lots of 17 β-estradiol from for review; the manufacturing dates will be included for each batch
- **Question 3:** Please provide information on the holding time and storage conditions for the drug substance before being used in the manufacturing of the drug product.
  - the holding time of the drug substance is three years; the release testing of the drug substance is being done on a yearly basis
  - a statement regarding the timing of the release testing on the drug substance should be submitted to the NDA
- **Question 5:** Please provide information on the holding time and storage conditions for the bulk drug product before blister packaging.
  - the holding time for the drug product is six months prior to packaging; the expiration date should include the holding time
  - the Agency will contact the sponsor if there are further comments on this question; it was noted that the response to the deficiency letter from the DMF holder for DMF has not been received; the sponsor will follow-up on this issue
- **Question 9:** Please revise the storage statement in the package insert and immediate container and carton labels; it should read: Store at 25°C (77°F) excursion permitted to 15°-30°C (59-86°F). [See USP Controlled Room Temperature]."
  - the sponsor agreed to implement the statement in the package insert and carton and labels; however, there is little room to add additional wording on the immediate container; the sponsor should submit their proposal to include the statement on the front for consideration by the Agency
- for clarification for the F2 similarity factor, the to-be-marketed batches are full scale batches
- in the case of the single center used for conducting the safety readings, there was one laboratory and multiple pathologists who read slides independently from the pathologists who read for efficacy purposes
- the sponsor had no comments regarding the comments conveyed to them in the memo dated October 7, 1999, regarding the Patient Package Insert

Physician's package insert

- **DESCRIPTION** section
  - the fourth sentence that begins, [redacted] should be deleted; the sponsor should propose new wording for review by the Division
  - the Division is concerned regarding the term "pulsed"
- **Effects on the Endometrium** subsection
  - the numbers in Table 3 were proposed based on a head-to-head comparison study with estradiol in Studies 102 and 103; Study C-101 had an inadequate washout period and was not included in the numbers for Table 3 because, although this is a safety issue, the table is making an efficacy claim presentation about the safety issue
  - the inclusion/exclusion criteria intervals in Study C-101 were not in compliance with the guidance for washout periods for previous hormone replacement therapy (HRT) use
  - the sponsor should express the rationale for why all histology data from all the clinical trial experience is relevant and propose text for this point; the washout issue should also be addressed
- **Cumulative amenorrhea** subsection
  - the cumulative amenorrhea graph (figure B) should be revised to show bleeding by days (e.g., the PREMPRO insert)
  - amenorrhea patients are not represented in this graph if they bleed
  - sponsor should submit a day-to-day graph; physicians want to see the percent of patients who will not bleed by a given point in time
  - all estrogen labels have the same type of graph; this graph style gives the most clinically meaningful data
  - the information must be presented in a graph, not as text
  - the graph should include the intent-to-treat population and patient population on the bottom of the graph
- **Metabolic Parameters** subsection, Effects on Lipids subsection
  - most of the text in this section should be deleted; instead, the sponsor may submit a table with the data from the graph
  - LDL/HDL ratio should not be included in the table; a percent change in a ratio is difficult to interpret
- **WARNINGS** section
  - **Venous thromboembolism** subsection
    - the sponsor proposed to retain the paragraph that begins, "Where elective surgery . . ."
    - this paragraph is a hold-over from Oral Contraceptives and is not in other HRT labels
    - additional data to support the paragraph should be submitted for reconsideration
    - the Division is having an Advisory Meeting to discuss the HRT guidance on October 18, 1999; comments from sponsors can be presented at that time on this issue
- **INDICATIONS AND USAGE** section
  - in the Prevention of osteoporosis indication, the limited wording [redacted] can be removed so that is reads, "Prevention of osteoporosis"; the Division Director will be consulted on this issue for concurrence
  - the warning that the ORTHO-PREFEST regimen may not be the lowest effective dose of estrogen for the prevention of osteoporosis indication should be underlined
- **DOSAGE and ADMINISTRATION** section
  - headers should be inserted according to each indication

Decisions:

- Clinical Pharmacology and Biopharmaceutics labeling comments
  - in the **Pharmacokinetics** subsection, Distribution subsection
    - in the fifth sentence that begins,
      should be deleted
    - in the **Special Populations** subsection, Effects of Race, Age, and Body Weight subsection
      - the fifth sentence that begins, "Women with body . . ." references a 40% lower peak serum levels of 17-deacetylnorgestimate; the C_{max} for norgestrel and AUC for 17-deacetylnorgestimate numbers should be included in the text
      - the sixth sentence that begins, should be revised to read, "The clinical relevance of this observation is unknown."
  - in the **Drug-Drug Interactions** subsection
    - the third sentence that begins, "A clinical study . . . " should reflect the multiple-dose study data; Day 87-90 study basis of the statement may not be valid
    - the sponsor agreed to revise the statement after discussion with their management
- a revised label should be submitted

Action items:

• **Item:**	**Responsible Person:**	**Due Date:**
• submit revised labeling	R.W. Johnson	1 week

/S/ 11/6/99
Signature, minutes preparer

/S/ 11/8/99
Signature, Chair

Post Meeting Addendum: the Division Director was consulted on October 6, 1999, regarding broadening the **INDICATION** section to read, "prevention of osteoporosis"; she concurred with the caveat that the **DOSAGE AND ADMINISTRATION** section reads to convey that the ORTHO-PREFEST regimen may not be the lowest effective dose of estrogen for this indication.

drafted: dm/10.17.99/N21040TC10699.doc

Concurrence:
KColangelo, 10.19.99/MMann, JLau 10.27.99/SSlaughter 10.28.99/AParekh 11.01.99
MRhee, 11.04.99/Tvan der Vlugt 11.05.99

cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/Tvan der Vlugt/MRhee/DMoore/TRumble
HFD-580/AParekh/JLau

Meeting Minutes

Date: September 29, 1999 **Time:** 11:00 AM - 12:05 PM **Place:** Parklawn; Room 17B-43

NDA: 21-040 **Drug Name:** ORTHO-Prefest (Cyclophasic, 1.0 mg 17 β-estradiol and 1.0 mg 17 β-estradiol + 90 ug Norgestimate (NGM) Tablets, USP

Type of Meeting: Labeling

Indication: Treatment of vasomotor symptoms, vulvar vaginal atrophy, prevention of osteoporosis

Sponsor: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Shelley Slaughter, M.D., Ph.D. – Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

Meeting Objective: To discuss the proposed patient package insert for NDA 20-040. The labeling text is from the original submission dated December 23, 1999.

Background: Previous labeling discussions for the Physician's Package Insert for ORTHO-Prefest™ were held on September 20 and 29, 1999, from the September 2, 1999, labeling amendment.

Decisions:

- **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
- **PROGESTERONE OR PROGESTERONE-LIKE DRUGS** 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,
    the words, should be deleted and the word, "women" should be capitalized; the term, 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**"
- section
  - the term in this heading should be replaced by the term, "**RISKS**"
  - under **Cancer of the breast** subsection
    - the second sentence that begins, should be deleted
    - the first sentence that begins, 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,
    should be deleted
  - the first sentence that reads,
    should be deleted
  - in the second sentence that begins, the word should be deleted so that the sentence reads, "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, 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, "While you are using . . " 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, 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 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, 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."

Action items:

• **Item:**	**Responsible Person:**	**Due Date:**
• provide sponsor with proposed labeling revisions	Ms. Moore	1-2 weeks

/S/ 10/26/99
Signature, minutes preparer

/S/ 10/27/99
Signature, Chair

drafted: dm/10.04.99/N21040LB92999.doc

Concurrence:
TRumble 10/07/99/Tvan der Vlugt, JLau 10.13.99/SSlaughter 10.21.99

cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/Tvan der Vlugt/MRhee/DMoore/TRumble
HFD-580/AParekh/JLau

Meeting Minutes

Date: September 23, 1999 **Time:** 11:20 AM - 12:30 PM **Place:** Parklawn; Room 17B-43

NDA: 21-040 **Drug Name:** ORTHO-Prefest (Cyclophasic, 1.0 mg 17 β-estradiol and 1.0 mg 17 β-estradiol + 90 ug Norgestimate (NGM) Tablets, USP

Type of Meeting: Labeling

Indication: Treatment of vasomotor symptoms, vulvar vaginal atrophy, prevention of osteoporosis

Sponsor: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Marianne Mann, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580) (via telephone)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)

Meeting Objective: To continue the discussion of the proposed labeling for NDA 20-040. The labeling text is from the September 2, 1999, amendment to the NDA.

Background: A previous labeling discussion for ORTHO-Prefest™ was held on September 20, 1999, from the September 2, 1999, labeling amendment.

Decisions:

- **CLINICAL PHARMACOLOGY** section
  - **Distribution** subsection
    - the third sentence that begins, and the fourth sentence that begins, should be deleted
    - Table 1 entitled, "Pharmacokinetic parameters of E_2, E_1, E_1S, and 17d-NGM[1] Following Single and Multiple Dosing of ORTHO-PREFEST™" should use baseline unadjusted PK parameters; if the sponsor desires to have baseline-adjusted parameters, justification must be submitted for consideration
  - **Drug-Drug Interactions** subsection
    - the hormone replacement therapy (HRT) labeling should be consistent between sponsors; since previous HRT sponsors have not been required to include interactions other than progestins, it was decided to discuss the need for adding this information to estrogen and

progesterone labeling for HRT as a class and including it in the "Labeling Guidance for Estrogen Drug Products" if it is found relevant before addressing the issue with this sponsor

- **Clinical Studies** subsection
  - **Efficacy On Postmenopausal Symptoms** subsection
    - Table 2 should be revised and labeled to reflect relief of VSMS in the 12-month studies (102 and 103) for women with a baseline of 7 MSVS; the title should read, "Change in the Mean Number of Moderate-to-Severe Vasomotor Symptoms During Therapy in Subjects With ≥ 7 Moderate-to-Severe Hot Flushes at Baseline"
  - **Effects on the Endometrium** subsection
    - the first sentence that begins, "The effect of ORTHO-PREFEST™ on . . ." should be combined with the second sentence that begins, " In two 12-month . . . " ; the number should be revised to 507 and the phrase, should be deleted in the second sentence so that the combined sentences read, "The effects of the ORTHO-PREFEST™ regimen was evaluated in two 12-month trials that included 507 healthy postmenopausal women."
    - a second sentence that reads, "Results are shown in Table 3." should be added to the paragraph
    - Table 3 entitled, ' the numbers should be revised to show only data from Study 102 and 103,
      - the title should be revised to read, "Incidence of Endometrial Hyperplasia (ITT population) At the End Of Treatment in Two 12-Month Clinical Trials of ORTHO-PREFEST™"
      - "at month 12" should be added to the sub-header entitled, "the Total No. evaluable Biopsies" so that it reads , "the Total No. evaluable Biopsies at month 12"
      - Under the column entitled, "Continuous" (97%) should be added after the number 256 for the Total No. Evaluable Biopsies at month 12
      - under the column entitled, "ORTHO-PREFEST™" should be replaced with 242; should be replaced with 227; (94%) should be added after 227 for the Total No. Evaluable Biopsies at month 12
      - should be replaced with 227 under "ORTHO-PREFEST™" column for "Normal Endometrium"
  - **Control of Uterine Bleeding** subsection
    - the sponsor submitted uterine bleeding as bleeding; however, bleeding and spotting should be grouped together as bleeding; a graph could be included in the labeling, not the figure presented
    - in the second paragraph, first sentence, the number of 12-month trials should be revised to three so that the sentence reads, "The effect of ORTHO-PREFEST™ on uterine bleeding in three 12-month trials of 432 healthy postmenopausal women was evaluated." since C101 safety data was added to the data from Studies 102 and 103; should be replaced with 429 in this sentence
    - the second sentence that begins, should be deleted
    - the third sentence that begins, should be deleted
    - a new sentence that reads, "Results are shown in Figure 1." should be inserted
    - figure B should be revised to show cumulative amenorrhea (the PREMPRO label could be used as an example)

- **INDICATIONS AND USAGE** section
  - it was noted that item number 3 had wording limiting the prevention of osteoporosis indication to women using ORTHO-PREFEST for relief of menopausal symptoms; this wording will be referred to the Division Director for comment
  - **CONTRAINDICATIONS** section
    - active liver disease should be added to this section
  - **WARNINGS** section
    - **Induction of Malignant Neoplasms** subsection
      - the sentence that begins, and the following sentence should be deleted; a new sentence should be added that reads, "Results from two 12-month clinical trials of the effects of ORTHO-PREFEST™ on endometrial hyperplasia are shown in the **Clinical Studies** section of this label."
    - **Venous thromboembolism** subsection
      - the second paragraph that begins, should be deleted
  - **PRECAUTIONS** section
    - this label does not include a **Cardiovascular Risks** subsection under the **PRECAUTIONS** section; although a **Cardiovascular Risks** section is not included in the proposed new estrogens labeling guidance, it may be prudent to discuss including such a section in this combined HRT product label
    - **Elevated Blood pressure** subsection
      - in the first sentence that begins, the word, should be replaced by the word, "Occasional"
      - another item that could be requested is a precaution regarding visual problems
  - **ADVERSE REACTIONS** section
    - the number for the healthy postmenopausal women treated with ORTHO-PREFEST™ (579) should be verified by the sponsor
    - the two sentences in the second paragraph that begins, should be deleted; this has not been allowed in any HRT labeling; no trials were set up to demonstrate body weight endpoints
  - **DOSAGE AND ADMINISTRATION** section
    - in the second paragraph, the second sentence that begins, "Upon exhaustion of a blister . . " should be revised to read, "After all tablets from the blister card have been used, the first tablet from a new blister card should be taken on the following day."
    - the administration of the doses for the HRT indication and osteoporosis indication should be separated into two sections and headers should be added to distinguish the two sections by indication
    - the prevention of osteoporosis section should include wording that states that this dose may not be the lowest effective dose for the prevention of osteoporosis
- the Patient Package Insert will be discussed at a subsequent meeting; the Medical Officer will compare the patient package insert from this label to the new estrogen labeling guidelines

Action items:

• **Item:**	**Responsible Person:**	**Due Date:**
• provide sponsor with proposed labeling revisions	Ms. Moore	1-2 weeks
• verify remaining data in Biopharmaceutics sections of the labeling	Dr. Johnny Lau	1-2 weeks
• set up labeling meeting to discuss	Ms. Moore	1 week

Patient Package Insert • compare Patient package insert to proposed estrogens labeling guidance	Dr. van der Vlugt	prior to next meeting

/S/ 10/15/99
Signature, minutes preparer

/S/
Signature, Chair

Post Meeting Addendum: The title, in the INDICATIONS section of the labeling should be revised to say, "Prevention of Osteoporosis" per discussions with Drs. van der Vlugt, Slaughter and Mann on September 24, 1999.

drafted: dm/09.23.99/N21040LB92099.doc

Concurrence:

TRumble 09.24.99/MMann, SSlaughter 09.27.99/Tvan der Vlugt 09.29.99/JLau 10.04.99
AParekh 10.15.99

cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/Tvan der Vlugt/MRhee/AJordan/DMoore/TRumble
HFD-580/DHoberman/LKammerman/AParekh/JLau
HFD-510/AHakim

Meeting Minutes

Date: September 20, 1999 **Time:** 10:30 AM - 12:00 PM **Place:** Parklawn; Room 17B-43

NDA: 21-040 **Drug Name:** ORTHO-Prefest (Cyclophasic, 1.0 mg 17 β-estradiol and 1.0 mg 17 β-estradiol + 90 ug Norgestimate (NGM) Tablets, USP

Type of Meeting: Labeling

Indication: Treatment of vasomotor symptoms, vulvar vaginal atrophy, prevention of osteoporosis

Sponsor: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Shelley Slaughter

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Marianne Mann, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Ali Al-Hakim, Ph.D. – Chemist, DNDC II @Division of Gastro-Intestinal and Coagulation Drug Products (DGCDP; HFD-180)
Johnny Lau, R.Ph., Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
David Hoberman, Ph.D. – Statistician @ DRUDP (HFD-580)

Meeting Objective: To discuss the proposed labeling for NDA 20-040. The labeling text is from the September 2, 1999, amendment to the NDA.

Background: Labeling comments from the August 2, 1999, FDA labeling discussion were conveyed to R.W. Johnson via telefacsimile on August 14, 1999. Additional comments were conveyed via Teleconference between DRUDP and representatives of R.W. Johnson. The sponsor incorporated these proposals and included additional comments and labeling revisions in an amendment to the NDA dated September 2, 1999.

Decisions:

- Clinical
  - review pending
  - 11 cases of gallbladder disease occurred during the studies; this safety issue will be further reviewed using the Integrated Summary of Safety (ISS) and the Safety Update
- Chemistry, Manufacturing and Quality Control
  - review complete and approvable; a deficiency letter has been drafted to send to the sponsor
  - the submitted stability data is adequate for a 18-month expiration date for the product

- Clinical Pharmacology and Biopharmaceutics
  - the prevention of osteoporosis claim can be substantiated from the bioequivalence of the estrogen to Estrace (an estrogen that has the osteoporosis claim); a link was made with serum estradiol blood level concentrations from the 1/30 and 1/90 regimens at Day 87 and Day 90, although there was a 12-18% difference in C_{max}
  - the lowest effective dose of estradiol in Estrace for the prevention of osteoporosis is 0.5 mg; the efficacy of the ORTHO-Prefest regimen is based on bioequivalence with Estrace, therefore, the 1.0 mg estradiol dose in the ORTHO-Prefest regimen is not the lowest effective dose for the prevention of osteoporosis indication; this should be reflected in the labeling
  - review completion is targeted for October 8, 1999; a draft of the review will be provided to the Medical Team Leader
  - specific numbers in the labeling in the **CLINICAL PHARMACOKINETICS** section are being verified during the review
- Biometrics
  - a formal review will not be written; statistical comments will be reflected in the clinical review
  - the data submitted regarding triglycerides is not statistically significant
- Regulatory
  - the action package goal date is October 10, 1999; the 10-month goal date is October 24, 1999
- Labeling
  - **DESCRIPTION** section
    - in the fourth sentence that begins, the word, should be deleted
  - **CLINICAL PHARMACOLOGY** section
    - the fourth paragraph that begins, "Norgestimate is a progestin with low androgenicity." the remainder of the paragraph after this phrase should be deleted
    - the sponsor can expand on the use of progesterone as a class in the description statement
    - the fifth paragraph that begins, "Pulsed administration of progestin . . ." is the sponsor's theory for the rationale of the regimen referring to three literature articles; the clinical reviewers will reword this paragraph
    - **Distribution** subsection
      - the data in this section should reflect human rather than animal data
    - Table 1
      - the numbers in the table will be verified by Biopharmaceutics reviewer; unadjusted baseline data should be used
    - **Metabolic Parameters** subsection
      - Effects on Lipids subsection
        - in the paragraph that begins, "The effect of ORTHO-PREFEST™ on lipids . . ." the first sentence that reads, "The effect of ORTHO-PREFEST™ on lipids was evaluated in a 12-month metabolic trial of healthy postmenopausal women." can be retained; the rest of the paragraph should be deleted
        - a sentence that reads, "Results are shown in Table X" should be added
        - the bar graph should be replaced by a table including data for HDL, LDL, total cholesterol and triglycerides
    - **Special Populations** subsection
      - the data in Table 1 should be unadjusted from baseline
    - **Drug-Drug Interactions** subsection
      - this labeling refers to the interaction between estrogens and progestins; this is acceptable since other HRT labeling is similar

- another HRT label has included other drugs that may interact with estrogens and progestins in their **PRECAUTIONS** section; because this is not in the "Labeling Guidance for Estrogen Drug Products", it was decided to discuss this item further internally before recommending this be added to any HRT labeling
- all patient numbers shown in Table 2 should be from patients with MSVS greater than 7 at baseline

- **CLINICAL STUDIES** subsection
  - **Efficacy On Postmenopausal Symptoms** subsection
    - the first paragraph that begins, "ORTHO-PREFEST has demonstrated safety and efficacy . . ." should be replaced with the following:
      - "The effect of the estrogen component of ORTHO-PREFEST on vasomotor symptoms was confirmed in a 12-week placebo-controlled trial of healthy postmenopausal women with moderate-to-severe vasomotor symptoms (MSVS). The addition of norgestimate to estrogen (i.e., the ORTHO-PREFEST regimen) was studied in two 12-month trials in healthy postmenopausal women (n=1212) for endometrial protection. Results from a subset population (n=119) of these 12-month trials (women with MSVS) are shown in Table X"
      - a table entitled, "Change in the Mean Number of Moderate-to-Severe Vasomotor Symptoms during therapy in subjects with ≥7 Moderate-to-Severe Hot Flushes at Baseline" should be inserted
      - Table 2 entitled, should be deleted
  - **Drug/Laboratory Test Interactions** subsection
    - items 8 and 9 that begin, should be deleted
- **HOW SUPPLIED** section
  - the first part of the sentence that was deleted should be retained except the 2-year expiration should be revised to 18 months; the added sentence is acceptable; the last sentence should read "This product is stable for 18 months. Store at 25°C (77°F); excursions permitted to (15°-30°C, (59°-86°F)."

Action item:

Item:	Responsible Person:	Due Date:
• provide sponsor with proposed labeling revisions	Ms. Moore	1-2 weeks
• verify data in Biopharmaceutics sections of the labeling	Dr. Johnny Lau	September 23, 1999

/S/
Signature, minutes preparer

/S/
Signature, Chair

Post meeting addendum: A memorandum containing the Division's labeling comments was sent to R.W. Johnson via telefacsimile on September 24, 1999.
The sponsor has removed the second paragraph under the **CLINICAL STUDIES** section that begins, however, the third paragraph that begins, should also be deleted; this comment will be conveyed to the sponsor by the project manager.

Minutes of Teleconference

Date: September 10, 1999 **Time:** 2:30 - 2:55 PM **Place:** Parklawn; Dr. van der Vlugt's Office

NDA: 21-040 **Drug Name:** Ortho-Prefest™ (Estradiol (E_2)/Norgestimate (NGM) Tablets

Indications: relief of vasomotor symptoms, vulvar and vaginal atrophy and the prevention of osteoporosis

Type of Meeting: Information Request (Statistical)

External Constituent: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Theresa van der Vlugt **External Lead:** Dr. Ramon Polo

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
David Hoberman – Statistician, Division of Biometrics II (DBII) @DRUDP (HFD-580)

External Participants:
Ramon Polo, Ph.D. - Associate Director, Regulatory Affairs, R.W. Johnson PRI
Valerie Donnelly – Associate, Regulatory Affairs, R.W. Johnson PRI
Roseanne Lane – Statistician, R.W. Johnson PRI
Pilar Lim, Ph.D. – Statistician, R.W. Johnson PRI
Mary Gallagher – Clinical Affairs, R.W. Johnson PRI

Meeting Objective: To discuss statistical information needed to continue review of NDA 21-040.

Background: The Agency requested this teleconference to clarify the statistical information in the **CLINICAL PHARMACOLOGY** section, **Clinical Studies** subsection of the label needed in regard to the VMS indication for NDA 21-040.

Discussion Items:

- the total number of patients depicted in Table 3 (Incidence Of Endometrial Hyperplasia At End Of Treatment in Two 12-Month Clinical Trials of ORTHO-PREFEST) is 432 and the number of evaluable patients (with biopsies) depicted in the Table is 409; the sponsor should verify these numbers
  - 432 total patients – 409 evaluable patients = 23 patients with insufficient tissue from the biopsies
- the data that was combined to get 432 should be clarified; the text mentions three clinical trials were pooled
  - the sponsor had treated the pooled patients from Studies 102 and 103 as one clinical trial; 190 patients came from Study C101 and 242 came from Studies 102 and 103 making a total of 432 patients
  - in Table 4 (adverse events table), the sponsor should verify the number of studies contributing to the 579 number of patients; the text in the label refers to four 12-month studies

  - the Integrated Summary of Safety (ISS) table from the 1-year safety group includes patients from Studies 102, 103, C101, and Study N93072; anyone with safety data who received this drug was included (three 12-month studies with Studies 102 and 103 pooled)
- under the **CLINICAL PHARMACOLOGY** section, **Clinical Studies** subsection, **Control of Uterine Bleeding** subsection, the sponsor should verify whether the paragraph that begins, "the effect of ORTHO-PREFEST™ on uterine bleeding . . ." refers to uterine bleeding only, or whether it refers to uterine bleeding and spotting
  - bleeding and spotting data were captured on the diary cards and coded with a bleeding code for hemorrhaging; instead of representing cumulative amenorrhea in the label, the sponsor inserted this paragraph

Decisions:

- the four studies in the text referring to the 579 patients in Table 4 should be revised to say three studies; data from Studies 102 and 103 should be presented as pooled data to be consistent with the rest of the labeling
- the sponsor will confirm the numbers in the **Control of Uterine Bleeding** paragraph including the 3% of patients with vaginal bleeding and the 1% of patients who discontinued
- further discussions regarding cumulative amenorrhea will follow

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• sponsor to verify requested information	R.W. Johnson	1-2 weeks

Signature, minutes preparer 10/7/99

Signature, Chair 10/7/99

drafted: dm/09.20.99/N21040TC91099.doc

Concurrence:
TRumble 09.21.99/Tvan der Vlugt 09.22.99
Concurrence not received from DHoberman
cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/Tvan der Vlugt/DHoberman/TRumble/DMoore

Teleconference Minutes

Date: August 16, 1999 **Time:** 2:00 - 3:00 PM **Location:** Dr. Mann's Office

NDA: 21-040 **Drug Name:** Prefest™ (Estradiol (E2)/Norgestimate (NETA) Tablets,USP

Indication: Treatment of vasomotor symptoms, vulvar vaginal atrophy, prevention of osteoporosis

External Participant: R.W. Johnson Pharmaceutical Research Institute

Type of Meeting: Advice

Meeting Chair: Dr. Shelley Slaughter **External Participant Lead:** Ms. Patricia Johnson

Meeting Recorder: Ms. Eufrecina DeGuia

FDA Attendees:
Shelley Slaughter, M.D., Ph.D., Team Leader, Division of Reproductive and Urologic Drug Products, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Eufrecina DeGuia, Regulatory Project Manager, DRUDP (HFD-580)

External Constituents:
Patricia Johnson – Principal Regulatory Affairs Scientist, Raritan NJ
Ramon Polo, Ph.D. – Associate Regulatory Affairs, Raritan, NJ
Jerry Rudman, Global Director, Reproductive Medicine, Raritan, NJ

Meeting Objectives: To convey some additional changes to the (revised) labeling proposal sent on August 14, 1999, by Ms. Diane Moore.

Discussion Points:

- Labeling
  - in the Clinical Studies subsection, Table 2 should be revised; to include a "No Hyperplasia" heading and a "Hyperplasia" heading after "Insufficient tissue"; the total number of evaluable biopsies should add up to 432
  - bottom of page 11: In the first sentence after Table 1 that begins, "The effect of Ortho-Prefest...," the words, "that included" should be inserted after the word, "trials" and before the number of patients.
  - page 12: Figure A should be revised to demonstrate the "Cumulative Incidence of Amenorrhea over Twelve Months"
  - in the Metabolic Parameters subsection on page 13: Effects on Lipids subsection should be in a Table format rather than text and HDL_2-C should be added as one of the parameters

- in the Breast Cancer subsection, the location or reference (publication) of the meta-analysis should be identified in the text
- in Table 4, the "%" in the title and not each line in Column 2 is acceptable; the number 579 should be verified
- the first sentence after Table 4 that begins, ' and the follow-in sentence should be deleted
- page 21: on **OVERDOSAGE**; the double negative in the statement, "serious....not" should be corrected
- page 21: on **DOSAGE AND ADMINISTRATION:**
  - in the second sentence that begins, the words, should replace the words, "throughout therapy"; and the word should be deleted
  - the second paragraph that begins, "Therapy consists of one..." should be re-written
  - in the Missed Tablets subsection, in the sentence that begins, the phrase should be deleted

Action Items:

Item:	Responsible Person:	Due Date:
• Provide sponsor with the date of the next status meeting	Ms. DeGuia	August 15, 1999

/S/ 9.7.99
Signature, minutes preparer

/S/
Concurrence, Chair
9/7/99

Minutes of Teleconference

Date: August 3, 1999 **Time:** 4:00 - 4:10 PM **Place:** Parklawn; Ms. Moore's Office

NDA: 21-040 **Drug Name:** Ortho-Prefest™ (Estradiol (E_2)/Norgestimate (NGM) Tablets

Type of Meeting: Information Request

External Constituent: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Theresa van der Vlugt **External Lead:** Dr. Ramon Polo

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)

External Participants:
Ramon Polo, Ph.D. - Associate Director, Regulatory Affairs, Raritan, NJ
Valerie Donnelly – Associate, Regulatory Affairs, Raritan, NJ

Meeting Objective: To request information from Studies 102, 103 and 104 and serum pharmacokinetics data.

Background: The proposed NDA will include data for a CYCLOPHASIC hormonal replacement therapy regimen (1.0 mg of 17 β-estradiol daily for three days alternating with 1.0 mg of 17 β-estradiol plus 90 μg of NGM daily for three days, continuously).

Discussion Items:
- comparing the estradiol levels from the 1/0, 1/30, and 1/90 combinations at baseline and Months 7 and 12, the estradiol blood levels from the combination E_2/NGM doses appear to be comparable to estradiol blood levels from estradiol-alone doses at steady-state

Decisions:
- using data from the ITT population from the pivotal efficacy studies (Studies 102 and 103), a table showing the mean number of changes from baseline (in actual numbers) of hot flushes for patients with 7-8 moderate-to-severe vasomotor symptoms (MSVS) per day at Weeks 4, 8 and 12 for each treatment arms should be provided
- in Studies 102 and 103, the sponsor is requested to compare serum estradiol blood level concentrations from the 1/30 and 1/90 regimens at Day 87 and Day 90, i.e., Day 87 to day 90; Day 87 to Day 87; and Day 90 to Day 90
- the bioequivalence evaluation for the estradiol component at Day 87 and Day 90 should have 90% confidence intervals (CI)

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• sponsor to submit requested information	R.W. Johnson	1-2 weeks

/S/ 9/13/99
Signature, minutes preparer

/S/ 9/13/99
Signature, Chair

Post Meeting Addendum: The sponsor submitted the requested information in a submission dated August 9, 1999.

drafted: dm/09.1.99/N21040TC8399.doc

Concurrence:
TRumble 09.03.99/Tvan der Vlugt 09.08.99/AParekh 09.10.99
cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/Tvan der Vlugt/JLau/VJarugula/AParekh/DMoore

Moore

Meeting Minutes

Date: August 2, 1999 **Time:** 11:00 AM - 12:00 PM **Place:** Parklawn; Room 17B-43

NDA: 21-040 **Drug Name:** ORTHO-Prefest (Cyclophasic, 1.0 mg 17 β-estradiol and 1.0 mg 17 β-estradiol + 90 ug Norgestimate (NGM) Tablets, USP

Type of Meeting: 8-month Status (Internal)

Indication: Treatment of vasomotor symptoms, vulvar vaginal atrophy, prevention of osteoporosis

Sponsor: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Marianne Mann

Meeting Recorder: Ms. 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)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Jeanine Best – Project Manager, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
David Hoberman, Ph.D. – Statistician @ DRUDP (HFD-580)

Meeting Objective: To discuss the 8-month review status of NDA 20-040.

Background:

The proposed NDA will include data for a CYCLOPHASIC hormonal replacement therapy regimen (1.0 mg of the 17 β-estradiol daily for three days alternating with 1.0 mg of 17 β-estradiol plus 90 μg of NGM daily for three days, continuously. Three pivotal and three supportive studies are included in the NDA. Protocols 102 and 103 studied endometrial histology. The U.S. Study 104 was a 12-week vasomotor study (VMS).

Decisions:

- Clinical
  - review pending
  - the actual changes from baseline are needed for moderate-to-severe vasomotor symptoms per week for Weeks 4, 8 and 12; no baseline numbers were given in the Study Report 104
  - the sponsor should provide data in actual numbers for the pivotal efficacy study (Study 104); subset analyses were received for efficacy only as supportive data from Study 102 and 103
  - the sponsor should provide data regarding the effects of ORTHO-Prefest on glucose levels and insulin parameters, coagulation results, and any other results that were outside the normal range

- DSI inspections
  - three of the four inspections have been completed with no major deficiencies
- Clinical Pharmacology and Biopharmaceutics
  - although sex hormone binding globulins (SHBG) were measured in Study 102, serum estradiol concentration (E_2) and data for estrone would have been useful
  - a multiple-dose, estradiol-alone arm was included in the endometrial hyperplasia protection study; data from this study may be useful for providing ancillary data to support bioequivalence of ORTHO-Prefest with estradiol alone; additional documentation will be needed to support the bioequivalence of estradiol-alone and estradiol plus progestin, especially upon chronic administration due to interaction with SHBG
  - single-dose E_2 pharmacokinetics (PK) parameters from the fed-fasting study can be used to simulate multiple-dose E_2 PK without taking into account SHBG's effect on E_2 PK
- Chemistry, Manufacturing and Quality Control
  - review complete and approvable
- EER
  - pending
- Pharmacology
  - draft review complete; recommend approval
- Biometrics
  - review pending
- Regulatory
  - the sponsor should request a waiver for the Pediatrics section because this product is not used in pediatric populations
  - the action package goal date is October 10, 1999; the 10-month goal date is October 24, 1999
- Labeling
  - the black box **WARNING** can be removed because this is a combination product; the black box refers to the dangers of giving estrogen without a progestin to women with a uterus
  - because the Premphase product is similar to this one, the Premphase labeling could be used for reference in future labeling discussions
  - **CLINICAL PHARMACOLOGY** section
    - the **CLINICAL PHARMACOLOGY** section should be revised to the standard estrogens labeling format; the text in the **CLINICAL PHARMACOLOGY** section should be moved to the beginning of the section so that it is before the **Clinical Studies** section; the **Clinical Studies** section should follow the **Drug-Drug Interactions** section
    - the sentence that reads,

      should be deleted
    - the next paragraph that begins, should be deleted because no trials have been performed to substantiate the claim; only data from the trials performed should be included in the label; this theory on the mechanism of action does not belong in the label
    - Figure A should be deleted; a table could be inserted to show the data
    - in Table 1 in the **Clinical Studies** section, the sample size should be verified for 1mg E2=48 and placebo =49; this should not be expressed as percent change; only data from Study 104 can be used in the VMS table, not data from the 12-week analysis from the hyperplasia trials; all treatment arms should be described
    - the second paragraph in the **Clinical Studies** section is misleading and should be deleted

- a table from Study 104 could be added to substantiate the sentence that reads, "ORHTO-PREFEST™ was also shown to effectively influence the cytological changes associated with postmenopausal atrophy."
- the sentence that reads, [redacted] should be deleted
- medical references should be provided to substantiate wording in the *Breast Cancer* subsection

Action item:

• **Item:**	**Responsible Person:**	**Due Date:**
• request actual numbers for MSVMS data	Ms. Moore	1-2 weeks
• provide sponsor with proposed labeling revisions	Ms. Moore	1-2 weeks
• request for lipid, carbohydrate and insulin laboratory data	Ms. Moore	1-2 weeks
• remind sponsor to request Pediatric waiver	Ms. Moore	1-2 weeks
• request references for Breast Cancer section	Ms. Moore	1-2 weeks

/S/ 9/16/99
Signature, minutes preparer

/S/ MD 9/16/99
Signature, Chair

Post Meeting Addendum: Ms. Moore requested actual numbers for MSVS, patient laboratory data for lipids, carbohydrates and insulin, a request for Pediatric waiver and references for Breast Cancer section on August 4, 1999. She provided the sponsor with a copy of proposed labeling revisions to the sponsor on August 14, 1999.

drafted: dm/09.1.99/N21040SM8299.doc

Concurrence:
TRumble 09.03.99/Tvan der Vlugt 09.08.99/MMann, JLau 09.09.99/AParekh, JBest 09.10.99
DHoberman 09.16.99

cc:
HFD-580
HFD-580/LRarick/MMann/SSlaughter/Tvan der Vlugt/MRhee/AJordan/DMoore/TRumble
HFD-580/DHoberman/LKammerman/AParekh/JLau
HFD-510/AHakim

Meeting Minutes

Date: July 12, 1999 **Time:** 1:00 - 1:50 PM **Place:** Parklawn; Room 17B-43

NDA: 21-040 **Drug Name:** ORTHO-Prefest (Cyclophasic, 1.0 mg 17 β-estradiol and 1.0 mg 17 β-estradiol + 90 ug Norgestimate (NETA)) Tablets, USP

Type of Meeting: 7-month Status (Internal)

Indication: Treatment of vasomotor symptoms, vulvar vaginal atrophy, prevention of osteoporosis

Sponsor: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Marianne Mann

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Marianne Mann, M.D. – Deputy Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Shelley Slaughter, M.D., Ph.D. – Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
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)
Ali Al-Hakim, Ph.D. – Chemist, DNDC II @Division of Gastro-Intestinal and Coagulation Drug Products (DGCDP; HFD-180)
Johnny Lau, R.Ph., Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)OCPB
David Hoberman, Ph.D. – Statistician @ DRUDP (HFD-580)

Meeting Objective: To discuss the 7-month review status of NDA 20-040.

Background:

The proposed NDA will include data for a CYCLOPHASIC hormonal replacement therapy regimen (1.0 mg of the 17 β-estradiol daily for three days alternating with 1.0 mg of 17 β-estradiol plus 90 μg of NETA daily for three days, continuously. Three pivotal and three supportive studies are included in the NDA. Protocols 102 and 103 studied endometrial histology. The U.S. study 104 was a 12-week vasomotor study (VMS).

Decisions:

- Clinical
  - review pending
  - US study 104 meets the criteria for a VMS study; currently, the NDA could be approved for the 1.0 mg estradiol alone portion for VMS and vulvar vaginal atrophy indications

- the prevention of hyperplasia is a safety issue with long-term use (i.e., prevention of osteoporosis); Studies 102 and 103 provide data showing that the proposed regimen protects the endometrium if the prevention of osteoporosis indication is approved

- DSI inspections
  - inspection reports are pending
- Clinical Pharmacology and Biopharmaceutics
  - Biopharmaceutics issues were discussed in 6-month status meeting
  - the data from the studies performed for Ortho-Prefest may not be comparable to the referenced data reported by Lobo et al.; the estimated serum estradiol concentrations at Day 87 and Day 90 for Ortho-Prefest are average steady-state concentrations whereas, data reported by Lobo et al., at Day 25 are minimum serum estradiol concentrations at steady state; therefore, R.W. Johnson may be overestimating serum estradiol concentrations
  - 0.5 mg serum estradiol concentrations should be requested for 0.5 mg Estrace after multiple doses at steady-state
  - a combination study for osteoporosis has not been performed
  - no data has been submitted to demonstrate that the combination drug product gives the same results as estradiol alone
  - a 30-45 day estradiol-alone study may be needed to demonstrate bioequivalence with that of the cyclic regimen in study ESTNRG-PHI-001
  - a comparison of the requirements for other previously approved combination estrogen-progesterone products that had continuous intermittent administration of progesterone is ongoing
- Chemistry, Manufacturing and Quality Control
  - review complete and approvable
- EER
  - pending
- Pharmacology
  - draft review complete; recommend approval
- Biometrics
  - review pending
- Regulatory
  - the action package goal date is October 10, 1999; the 10-month goal date is October 24, 1999

Action item:

Item:	**Responsible Person:**	**Due Date:**
request multiple-dose serum estradiol data for Estrace	Ms. Moore	1 month

/S/ 8/9/99
Signature, minutes preparer

/S/ 8/9/99
Signature, Chair

Post Meeting Addendum: Additional data for the Biopharmaceutics review was requested on August 4, 1999 (see attached).

drafted: dm/07.16.99/N21040SM71299.doc

NDA 21-040, Ortho-Prefest, R.W. Johnson Pharmaceuticals

Ortho-Prefest consists of a phasic regimen where patients will be on a continuous estradiol treatment with 3-days-on-3-days-off administration of progestin (norgestimate, NGM). Among other studies, a single dose BE study comparing R.W. Johnson's estradiol tablet to the 0.5 and 2 mg Estrace tablets has been submitted in support of the osteoporosis claim. Estradiol binds to sex hormone binding globulin (SHBG) and also induces it, while progestins inhibit the SHBG. As a result, total estradiol concentrations at steady state (of SHBG) in the presence of progestins may be different from those of estradiol alone. The sponsor was informed of these concerns and was requested to submit data or evidence showing that the estradiol concentrations with chronic administration of NGM will be equivalent to the concentrations expected from administration of estradiol alone. The sponsor had provided justification and literature data to address this concern (April, 1999). We have reviewed this information and further request the following analyses for the data from pharmacokinetics study ESTNRG-PHI-001:

From multiple dose regimen with 1:1/30 and 1:1/90, please provide 90% confidence intervals for log transformed AUC and Cmax (bioequivalence testing) for baseline corrected and uncorrected estradiol, estrone and estrone sulfate as follows:

1:1/30		1:1/90
Day 87	vs	day 90
Day 87	vs	Day 87
Day 90	vs	Day 90

We would like to request the results of these analyses sent as soon as possible.

Thanks,

[S]

Ameeta Parekh, Ph.D. 8/4/99
DPEII/OCPB/OPS/CDER

Meeting Minutes

Date: June 14, 1999 **Time:** 10:00 - 10:50 AM **Place:** Parklawn; Room 17B-43

NDA: 21-040 **Drug Name:** ORTHO-Prefest (Cyclophasic, 1.0 mg 17 β-estradiol and 1.0 mg 17 β-estradiol + 90 μg Norgestimate (NETA)) Tablets, USP

Type of Meeting: 6-month Status

Indication: Treatment of vasomotor symptoms, vulvar vaginal atrophy, prevention of osteoporosis

Sponsor: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Lisa Rarick

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Susan Allen, M.D., M.P.H. – Acting Team Leader, DRUDP (HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Brenda Gierhart, M.D. – Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Evelyn Farinas – Project Manager, DRUDP (HFD-580)
Ali Al-Hakim, Ph.D. – Chemist, DNDC II @Division of Gastro-Intestinal and Coagulation Drug Products (DGCDP; HFD-180)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)OCPB
David Hoberman, Ph.D. – Statistician @ DRUDP (HFD-580)

Meeting Objective: To discuss the review status of NDA 20-040 at 6 months.

Background:

The proposed NDA will include data for a CYCLOPHASIC hormonal replacement therapy regimen (1.0 mg of the 17 β-estradiol daily for three days alternating with 1.0 mg of 17 β-estradiol plus 90 μg of NETA daily for three days, continuously). Three pivotal and three supportive studies are included in the NDA. Protocols 102 and 103 studied endometrial histology. The U.S. study 104 was a 12-week vasomotor study (VMS).

Decisions:

- Clinical
  - review pending
  - the ANDA by R.W. Johnson has been withdrawn because of batch size issues and therefore cannot be referenced by this NDA; the US study 104 meets the criteria for a VMS study

- DSI inspections
  - inspections are pending
- Clinical Pharmacology and Biopharmaceutics
  - R.W. Johnson intends to acquire the prevention of osteoporosis indication by demonstrating bioequivalence to Estrace®; however, the lowest effective dose of Estrace for osteoporosis is 0.5 mg and the proposed estradiol dose for Ortho-Prefest is 1.0 mg, therefore, the proposed dose for Ortho-Prefest may not be the lowest effective dose for osteoporosis
  - the single-dose study demonstrates that the R.W. Johnson estradiol is bioequivalent to Estrace®; however, the addition of norgestimate with the estradiol may not result in bioequivalency because norgestimate affects serum human binding globulin (SHBG) opposite from the way estradiol affects SHBG; this difference can affect the PK of the estradiol; a teleconference to discuss this concern was held on April 5, 1999; additional justification regarding this issue was provided on April 30, 1999
  - an estradiol-alone arm was not included in the multiple-dose study 9ESTNRG-PHI-001); this could have supplied steady-state data for the estradiol for comparison to the combination product data at the end of 3 months; consequently, the study is a cross-comparison study which demonstrates merely similarity, not bioequivalence
- Chemistry, Manufacturing and Quality Control
  - review pending
- Pharmacology
  - review complete; approval recommended
- Biometrics
  - review pending
  - the sponsor imputed hyperplasia vs no hyperplasia in the endometrial hyperplasia studies; no hyperplasia was reported for the 90 μg dose; 15% hyperplasia was seen in the 1.0 mg estradiol-alone dose group at 12 weeks
  - the maturation index is improved over 12 months
- Labeling comments
  - the patients from the combined hyperplasia study in the clinical studies section should not be used to discuss the VMS indication
- the action package goal date is October 10, 1999; the 10-month goal date is October 24, 1999

Action item:

Item:	**Responsible Person:**	**Due Date:**
• compare review of similar products such as Prempro for bioequivalence requirements	Biopharmaceutics Reviewer	one month

/S/ 8/9/99
Signature, minutes preparer

/S/ 8/12/99
Signature, Chair

drafted: dm/07.14.99/N21040SM61499.doc

Concurrence:
TRumble 07.20.99/BGierhart, SAllen 07.21.99/AParekh 07.22.99/LRarick 08.02.99
JLau 08.06.99
Concurrence not received from DFarinas/AAlHakim/DHoberman

Minutes of Teleconference

Date: April 5, 1999 **Time:** 1:00 - 2:00 PM **Place:** Parklawn; Room 17B-45

NDA: 21-040 **Drug Name:** Ortho-Prefest™ (Estradiol (E_2)/Norgestimate (NETA) Tablets

Type of Meeting: Advice (Biopharmaceutics)

External Constituent: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Shelley Slaughter **External Lead:** Ms. Patricia Johnson

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Shelley Slaughter, M.D., Ph.D. – Acting Team Leader, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
Theresa van der Vlugt, M.D., M.P.H. - Medical Officer, DRUDP (HFD-580)
Diane Moore – Regulatory Project Manager, DRUDP (HFD-580)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Venkateswar R. Jarugula, Ph.D. - Pharmacokinetic Reviewer, OCPB @ DRUDP (HFD-580)
Johnny Lau, R. Ph., Ph.D. – Pharmacokinetics Reviewer, OCPB @ DRUDP (HFD-580)

External Participants:
Larry Abrams, Ph.D. – Research Fellow, Clinical Drug Metabolism, Raritan, NJ
Patrick Caubel, M.D. – Clinical Director, Reproductive Medicine, Raritan, NJ
Chris Holinka, Ph.D. – Consultant, Raritan, NJ
Patricia Johnson – Principal Regulatory Affairs Scientist, Raritan, NJ
Jaya Natarajan, Ph.D. – Research Fellow, Preclinical Biostatistics, Raritan, NJ
Ramon Polo, Ph.D. - Associate Director, Regulatory Affairs, Raritan, NJ
Jerry E. Rudman – Global Project Director, Reproductive Medicine, Raritan, NJ
Frank van den Ouweland, M.D., Ph.D. – Director, International Project Management and clinical Research, Bassersdorf, Switzerland

Meeting Objective:
To convey to sponsor FDA concerns regarding the data submitted to address the potential interaction between E_2 and NETA steady-state pharmacokinetics (PK).

Discussion Items:
- the Ortho-Prefest estradiol dose is 1.0 mg, whereas, the Estrace doses are 0.5, 1.0 mg and 2.0 mg
- the estradiol PK in the estradiol-alone phase may be affected by the carryover effect of NETA or metabolites from the previous E_2 and NETA administrations
  - in study PHI-001, serum estradiol concentrations on Day 87 may be affected by carryover effects of NETA on sex hormone binding globulin (SHBG)
  - this study does not prove that there is no effect of NETA on estradiol
  - the sponsor cited Study 001 for providing data to support the lack of carryover effect of NETA (see the table in the NDA on page 305, item 6, vol. 9, Attachment #107, listing data for the E_2 + NETA 17-deacetyl norgestimate regimen); serum 17-deacetyl norgestimate (17d-NGM)

concentrations were simulated on Day 87, when the E_2 dose was administered and shown that 17-δ-NGM serum levels were below limits of detection

- however, this does not mean Sex Human Binding Globulin (SHBG) levels are not affected
- the sponsor stated that the justification for the lack of effect of NETA on SHBG could be found in item 8, vol 182, page 11, in the clinical section of the NDA
- estradiol concentrations in study PHI-001 are comparable to the estradiol concentrations in reference 9 (Lobo, et al. J. Reprod. Med. 1992; 37: 77-84) using 1 mg/day Estrace for 25 days; therefore, the sponsor claims that this demonstrates justification that norgestimate and its metabolites do not affect estradiol concentrations
- SHBG levels of both 1 mg E_2 + 0.3 mg NGM and 1 mg E_2 + 0.9 mg NGM were similar
- the sponsor requested a reference to demonstrate that levonorgestrel can suppress SHBG in 20-30 days; the reference that shows that levonorgestrel can inhibit SHBG production is in "Therapeutic Drugs" edited by Sir Colin Dollery

Decisions:

- study data, simulations or summaries from literature sources describing norgestimate alone and E_2/NETA and SHBG levels should be provided to demonstrate that NETA and its metabolites do not affect the PK of estradiol alone
- the Division will review the norgestimate data provided in Clinical section item 8, volume 182 for the justification for the cyclic regimen

Action Items:

• **Item:**	**Responsible Person:**	**Due Date:**
• submit data addressing the potential interaction between E_2 and NETA steady-state PK	R.W. Johnson	April 30, 1999
• fax copy of NDA item 8, vol 182 (justification for osteoporosis claim)	R.W. Johnson	2 days

/S/ 5/5/99
Signature, minutes preparer

/S/
Signature, Chair

drafted: dm/04.8.99/N21040TC4599.doc

Concurrences:

TRumble 04.19.99/Tvan der Vlugt 04.20.99/SSlaughter 04.23.99/AParekh, VJarugula 04.28.99

The Clinical Pharmacology and Biopharmaceutics reviewers briefed the Medical Officers prior to scheduling this teleconference. It was, therefore, agreed that no pre-meeting would be necessary.

cc:
HFD-580
HFD-580(LRarick/MMann/SSlaughter/Tvan der Vlugt/JLau/VJarugula/AParekh/DMoore

Meeting Minutes

Date: February 8, 1999 **Time:** 10:00 - 10:00 AM **Place:** Parklawn; Room 17B-43

NDA: 21-040 **Drug Name:** ORTHO-Prefest (Cyclophasic, 1.0 mg 17 B-estradiol and 1.0 mg 17 B-estradiol + 90 ug Norgestimate (NETA)) Tablets, USP

Type of Meeting: Filing

Indication: Treatment of vasomotor symptoms, vulvar vaginal atrophy, prevention of osteoporosis

Sponsor: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Lisa Rarick

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Lisa Rarick, M.D. - Director, Division of Reproductive and Urologic Drug Products (DRUDP; HFD-580)
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)
Dena Hixon M.D., Ph.D. – Medical Officer, DRUDP (HFD-580)
Terri Rumble – Chief, Project Management Staff, DRUDP (HFD-580)
Diane Moore - Project Manager, DRUDP (HFD-580)
Dornette Spell-LeSane – Project Manager, DRUDP (HFD-580)
Eufrecina Deguia – Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II DNDC II) @ DRUDP (HFD-580)
Ali Al-Hakim, Ph.D. – Chemist, DNDC II @Division of Gastro-Intestinal and Coagulation Drug Products (DGCDP; HFD-180)
Ameeta Parekh, Ph.D. - Pharmacokinetic Team Leader, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)
Johnny Lau, R.Ph., Ph.D. - Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)OCPB
Lisa Kammerman, Ph.D. - Team Leader, Division of Biometrics II (DBII) @ DRUDP (HFD-580)
Lisa Stockbridge, Ph.D. - Regulatory Reviewer, Division of Drug Marketing and Communication (DDMAC; HFD-40)

Meeting Objective: To discuss the fileability of NDA 20-040 by R.W. Johnson.

Background:
The proposed NDA will include data for a CYCLOPHASIC hormonal replacement therapy regimen using the sponsor's 1.0 mg Estradiol Tablet, USP and their 1.0 Estradiol USP/90 ug Norgestimate Tablet.

Decisions:

- Clinical (see filing memo dated February 8, 1999)
  - Fileable (FA)
  - the dosing regimen included 1.0 mg of the 17 B-estradiol daily for three days alternating with 1.0 mg of 17 B-estradiol plus 90 ug of NETA for three days, continuously
  - the clinical rationale for the cyclic method of administration as a new form of administration is to use lower progesterone doses to give endometrial protection throughout drug use, with no withdrawal bleeding
  - three pivotal and three supportive studies are included in the NDA
  - two bioequivalence studies (BE) have been submitted in support of a 505(b)(2) application based on an approved ANDA for osteoporosis
  - Protocols 102 and 103 studied endometrial histology using the dry blend manufacturing method that is proposed for marketing
  - four sites have been identified for DSI audit
- Chemistry, Manufacturing and Quality Control
  - FA
  - a new tradename must be requested for review by the Nomenclature Committee; the ORTHO portion of the name was not previously submitted for comment; Cyclophasic HRT may be problematic
- Pharmacology
  - FA
- Biometrics
  - FA
- Clinical Pharmacology and Biopharmaceutics (see filing memo dated February 11, 1999)
  - FA
  - data for population pharmacokinetic (PK) analysis should be provided on diskette
  - a bioequivalence (BE) study was submitted to link the dry manufacturing product to the wet manufacturing product; the clinically tested formulation differs in color and shape from the to-be-marketed formulation
  - the sponsor submitted an ANDA for their 0.5 and 2.0 mg estradiol tablets to reference Estrace®
  - PK study ESTNRG-PHI-001 showed that NETA and its metabolites do not affect the PK of estradiol and its metabolites
  - the estradiol dose for the proposed osteoporosis indication is 1.0 mg, while the lowest Estrace dose is 0.5 mg of estradiol; the discrepancy in estradiol doses may cause the labeling to be complex
  - the sponsor may be required to make a Phase 4 commitment to study the 0.5 mg estradiol and NETA dose
  - a waiver should be requested to bracket the 1.0 mg estradiol dose between the 0.5 mg and 2 mg estradiol doses
- the 10-month goal date is October 24, 1999

Action items: none

/S/ 3/12/99
Signature, minutes preparer

/S/ 3/15/99
Signature, Chair

Moore

Minutes of Telecon

Date: November 19, 1998 **Time:** 10:15 - 10:40 AM **Place:** Parklawn; Rm. 17B-43

IND: **Drug Name:** CYCLOPHASIC HRT (17β-Estradiol and Norgestimate)

Type of Meeting: Pre-NDA

Indication: The treatment of vasomotor symptoms (VMS) and vulvovaginal atrophy, prevention of osteoporosis.

Sponsor: R.W. Johnson Pharmaceutical Research Institute

FDA Lead: Dr. Lisa Rarick **External Lead:** Ms. Patricia M. Johnson

Meeting Recorder: Ms. Diane Moore

FDA Participants:
Lisa Rarick, 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)
Diane Moore - Project Manager, DRUDP (HFD-580)
Moo-Jhong Rhee, Ph.D. - Chemistry Team Leader, Division of New Drug Chemistry II
Ameeta Parekh, Ph.D. - Team Leader, Pharmacokinetic Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB) @ DRUDP (HFD-580)OCPB

External Participants:
Patricia M. Johnson - Principal Regulatory Affairs Scientist
David Goldberger, MS., R.Ph. – Manager, Regulatory Affairs
Frank van den Ouweland, M.D., Ph.D. - Director, International Project Management and Clinical Research, Global Research and Development
Chris Olinka, Ph.D. - Consultant, Clinical Research

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

Background:

The proposed NDA will submit data for a CYCLOPHASIC hormonal replacement therapy regimen using the sponsor's 1.0 mg Estradiol Tablet, USP and their 1.0 Estradiol USP/90 ug Norgestimate Tablet. On November 4, 1998, the sponsor submitted a letter requesting that their drug interaction study be considered as a 505 (b)(2) submission in support of an osteoporosis indication.

Discussion Items:

- the issue is whether the R.W. Johnson estradiol dose is equivalent to Estrace; an equivalence claim with Estrace must show that the norgestimate does not affect the pharmacokinetics of the 17β-estradiol .

- the lowest effective dose of Estrace for the osteoporosis indication is 0.5 mg; the 0.5 mg dose was not studied in the clinical vasomotor (VMS) trial using Norgestimate plus estradiol
- there is no patent problem with the Office of Generic Drug Products
- fasted studies show bioequivalence between Estrace and the estradiol in the R.W. Johnson product
- a food effect study has been performed with the new combination product
- serum PK levels for the 17β-norgestimate metabolite are below quantitative levels (20-30 hour half-life)
- the sponsor chose to study the 1.0 mg 17β-Estradiol dose over the 0.5 mg dose because the 1.0 mg dose was more effective for the VMS indication
- because this is not the lowest effective dose combination for osteoporosis, there may be many clarification clauses in the label
- FDA recommended that the 0.5 mg dose be studied in a letter dated August 29, 1994
- the sponsor seeks to discuss other NDA issues such as the layout of the NDA, the clinical section and the format for the Biopharmaceutics section

Decisions:

- data from the single-dose bioequivalence studies that were submitted as part of the ANDA can be referenced in the NDA as a 505(b)(2) to support equivalence between the estradiol and Estrace
- the data from the food-effect study using the combination product should be submitted for review; the labeling proposal from the food-effect should be submitted
- in order to state that norgestimate does not interfere with the effect of estradiol, the data from day 87 in the bioequivalence study must show only estradiol; there should be no carryover from day 84
- the sponsor will construct an argument to clarify that data at day 87 is the steady-state level of estradiol alone
- the appropriate study has not been performed with the 0.5 mg dose of estrogen combined with the norgestimate
- labeling statements should be proposed for an osteoporosis indication
- ASCII data sets will be provided with the NDA for the Biopharmaceutics reviewer
- clinical trial data should be provided as ASCII files for the statistical reviewer
- the label can be provided on diskette in WORD
- clarification must be made in the label to indicate that 0.5 mg of estradiol is appropriate for the osteoporosis indication
- a Phase 4 hyperplasia study to test the 0.5 mg estradiol dose in combination with the norgestimate dose may be required

To-do items

Item :	Responsible Person :	Due Date:
• schedule statistics teleconference	Ms. Moore	2 weeks
• discuss technical NDA questions	Ms. Moore and Ms. Johnson	2 weeks

/S/ 12/29/98
Signature, minutes preparer

/S/ 1/5/99
Signature, Chair

drafted: dm/12.02.98/i44227pm.111998.doc