CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-268

Administrative Documents

14.0 PATENT CERTIFICATION

A. Eprosartan

The undersigned declares that US Patent Number 5,185,351 covers the composition and method of use of Eprosartan for the treatment of hypertension. This product is currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

B. Hydrochlorothiazide

The undersigned declares there are no patents that claim Hydrochlorothiazide nor a method of using said drug with respect to which a claim of patent infringement could reasonably be asserted.

8/22/00

Kirk Rosemark, R.A.C. Date

Director, Regulatory Affairs

Unimed Pharmaceuticals, Inc.

13.0 PATENT INFORMATION

A. Eprosartan

In accordance with 21 CFR 314.53, Unimed Pharmaceuticals, Inc. submits the following patent information on Eprosartan:

Patent Number	Expiration Date	Type of Patent	Patent Owner	Representative
5,185,351	09 Feb 2010	Drug, Composition & Method of Use	SmithKline Beecham Corporation	Mary E. McCarthy Corporate Intellectual Property SmithKline Beecham Corporation

B. Hydrochlorothiazide

The Applicant declares there are no patents that claim Hydrochlorothiazide nor a method of using said drug with respect to which a claim of patent infringement could reasonably be asserted.

EXCLUSIVITY SUMMARY FOR NDA # 21-268

Trade Name: Teveten HCT **Generic Name:** eprosartan/hydrochlorothiazide

Applicant Name: Unimed Pharmaceuticals, Inc. **HFD #** 110

Approval Date If Known:

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) Is it an original NDA?
YES /_X__/ NO /___/

b) Is it an effectiveness supplement?

YES /___/ NO /__X_/

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

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_X__/ NO /___/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

_____

_____

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

_____

_____

Form OGD-011347 Revised 10/13/98
cc: Original NDA Division File HFD-93 Mary Ann Holovac

d) Did the applicant request exclusivity?

YES /___/ NO /__X_/

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

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

No

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

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /__X_/

If yes, NDA # Drug Name

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

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

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

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

YES /___/ NO /___/

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

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES / X / NO / ___ /

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

NDA# 20-738 Teveten

NDA# _____ _____

NDA# _____ _____

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

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

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

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /_X_/ NO /___/

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

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

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /_X_/ NO /___/

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

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /_X_/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X_/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 148
Study 088

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

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 #148 **IND #_____** **YES /___/** **NO /__X__/**

Investigation #2 #088 **IND #_____** **YES /___/** **NO /__X__/**

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

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 #148 **YES /___/** **NO /__X__/**

Investigation #2 #088 **YES /___/** **NO /__X__/**

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

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

___Study 148_____

___Study 088_____

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

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

Investigation #1

IND #[_____] **YES /_X_/** **NO /___/ Explain: _____**

Investigation #2

IND #[_____] **YES /_X_/** **NO /___/ Explain: _____**

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

Investigation #1

YES /___/ Explain _____ **NO /___/ Explain _____**

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ **NO /___/ Explain _____**

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /__/ NO /__X__/

If yes, explain: _____

_____

S

_____ _____
Signature **Date**
Title: Consumer Safety Officer

S

Raymond Lipicky, M.D. _____
Signature of **Date**
Division Director
Cardio-Renal Drug Products
HFD-110

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

Put in DFS
at time of
AP ltr.
Kit Dunbar

PEDIATRIC PAGE (Complete for all original application and all efficacy supplements)

View as Word Document

NDA Number:	021268	**Trade Name:**	TEVETEN EPROSARTAN MESYLATE/HYDROCH
Supplement Number:	000	**Generic Name:**	EPROSARTAN MESYLATE/HYDROCHLOROTHIAZIDE
Supplement Type:	N	**Dosage Form:**	
Regulatory Action:	OP	**COMIS Indication:**	REPLACEMENT THERAPY FOR THE FREE COMBINATION OF EPROSARTAN HYDROCHLOROTHIAZIDE/FOR PATIENTS WHOSE HYPERTENSION IS NOT ADEQUATELY CONTROLLED BY THE 600MG/12.5MG
Action Date:	8/30/00		

Indication # 1 Hypertension

Label Adequacy: Does Not Apply

Formulation Needed: NO NEW FORMULATION is needed

Comments (if any): 03 May 2001: Sponsor requested a waiver of the pediatric requirement for this supplement on 8/23/00. Waiver granted by Dr. Lipicky per telephone conversation with PM on 03 May 2001.

Ranges for This Indication

Lower Range	Upper Range	Status	Date
1 years	16 years	Waived	6/30/01

Comments: 1) The combination product with its indication for replacement therapy does not represent a meaningful therapeutic benefit over existing single drug therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients. 2) Necessary studies are highly impractical because the number of such patients is so small.

This page was last edited on 5/9/01

Signature

Date 5/9/01

20.0 OTHER

Pediatric Use

In accordance with 21 CFR 314.55(c)(2), Unimed Pharmaceuticals, Inc. requests a waiver for assessment of this combination product in the pediatric population. Unimed Pharmaceuticals certifies that:

i. The combination product with its indication for replacement therapy does not represent a meaningful therapeutic benefit over existing single drug therapies for pediatric patients and is not likely to be used in a substantial number of pediatric patients

ii. Necessary studies are highly impractical because the number of such patients is so small

8/23/00

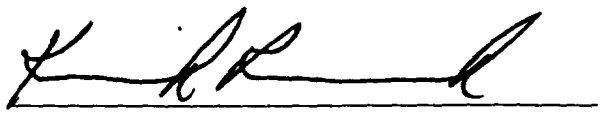
Kirk Rosemark, R.A.C. Date

Director, Regulatory Affairs

Unimed Pharmaceuticals, Inc.

16.0 DEBARMENT CERTIFICATION

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



3/22/00

Kirk Rosemark, R.A.C. Date

Director, Regulatory Affairs

Unimed Pharmaceuticals, Inc.

17.0 FIELD COPY CERTIFICATION

Pursuant to 21 CFR 314.50(k)(3), Unimed Pharmaceuticals, Inc. has submitted a complete copy of Section 3.0 (Application Summary) and Section 4.0 (Chemistry, Manufacturing and Controls) of this submission to the FDA's Chicago District Field Office. A copy of the application form FDA 356(h) accompanied this field office copy.

Unimed Pharmaceuticals, Inc. certifies that the field copy is a true copy of sections 3.0 and 4.0 contained in the archival and review copies of this application.

8/24/00

Kirk Rosemark, R.A.C. Date

Director, Regulatory Affairs

Unimed Pharmaceuticals, Inc.

CONSULTATION RESPONSE
Office of Post-Marketing Drug Risk Assessment
(OPDRA; HFD-400)

DATE RECEIVED: 10/ 23/ 2000	DUE DATE: 12/ 15/ 2000	OPDRA CONSULT #: 00-0297

TO:

Raymond Lipicky
Director, Division of Cardio-Renal Drug Products
(HFD-110)

THROUGH:

Sandy Birdsong
Project Manager
(HFD-110)

PRODUCT NAMES:	**NDA HOLDER:** Unimed Pharmaceuticals, Inc.
Teveten (eprosartan and hydrochlorothiazide tablets) *Teveten HCT [alternate name]* **NDA #**: 21-268	

SAFETY EVALUATOR: Lauren Lee, Pharm.D.

OPDRA RECOMMENDATION: OPDRA does not recommend the use of the proprietary name, Teveten. However, we have no objections to the use of the alternate name, Teveten HCT, at this time.

FOR NDA/ANDA WITH ACTION DATE BEYOND 90 DAYS OF THIS REVIEW

This name must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from the signature date of this document. A re-review request of the name should be submitted via e-mail to "OPDRAREQUEST" with the NDA number, the proprietary name, and the goal date. OPDRA will respond back via e-mail with the final recommendation.

☐ FOR NDA/ANDA WITH ACTION DATE WITHIN 90 DAYS OF THIS REVIEW

OPDRA considers this a final review. However, if the approval of the NDA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary names/NDA's from this date forward.

☐ FOR PRIORITY 6 MONTH REVIEWS

OPDRA will monitor this name until approximately 30 days before the approval of the NDA. The reviewing division need not submit a second consult for name review. OPDRA will notify the reviewing division of any changes in our recommendation of the name based upon the approvals of other proprietary names/NDA's from this date forward.

Jerry Phillips, R.Ph.
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 480-8173

Martin Himmel, MD
Deputy Director
Office of Post-Marketing Drug Risk Assessment
Center for Drug Evaluation and Research
Food and Drug Administration

Minutes of a Teleconference

Date of Meeting: July 10, 2001

Application: NDA 21-268
Teveten HCT (eprosartan/hydrochlorothiazide)

Sponsor: Unimed Pharmaceuticals, Inc.

Subject: Proposed Labeling

Meeting Chair: Raymond Lipicky, M.D.

Meeting Recorder: Sandra Birdsong

Participants:

FDA

Raymond Lipicky, M.D., Director, Division of Cardio-Renal Drug Products (HFD-110)
Norman Stockbridge, M.D., Medical Team Leader, HFD-110
Kasturi Srinivasachar, Ph.D., Team Leader/Chemist, HFD-810
Sandra Birdsong, Regulatory Health Project Manager, HFD-110

Unimed Pharmaceuticals, Inc.

Judy Athey, Unimed Pharmaceuticals, Inc.

Henk Pluim, Ph.D., Solvay BV
Claus Steinborn, M.D., Solvay BV
Frans Coenen, Ph.D., Solvay BV

Background

This new combination product was submitted on August 30, 2000 as replacement therapy for the individual components of eprosartan mesylate and hydrochlorothiazide. An approvable letter issued June 27, 2001, accompanied by marked-up draft labeling. The approvable letter stated that the Teveten HCT tablets should be scored to support the option of twice a day dosing.

The sponsor requested this teleconference to discuss the labeling and dosing issue.

Meeting

The discussion focused on the **DOSAGE AND ADMINISTRATION** section of the labeling and the Division's rationale for a scored tablet.

Dr. Lipicky stated that the labeling should be consistent with that of other combination antihypertensive products. He emphasized the importance of dosing that is logical in terms of progression from monotherapy to the addition of a second drug.

In addition, Dr. Lipicky noted that the ambulatory blood pressure monitoring data from the monotherapy application concludes that the antihypertensive effect of eprosartan wanes during the 24 hour period, and it is not as effective when administered daily as twice-daily. Thus, the recommendation for eprosartan monotherapy is to progress from once- to twice-daily prior to the addition of a second drug. Scoring of the tablet would allow the prescribing physician to adhere to this dosing pattern.

The sponsor suggested the addition of subheadings for *Monotherapy* and *Combination Therapy* under **DOSAGE AND ADMINISTRATION** section to be consistent with other antihypertensive combinations. They plan to revise the labeling under this section and confer with the Division further.

Conclusions

1. The sponsor plans to submit proposals for clarifying the **DOSAGE AND ADMINISTRATION** section.

2. Dr. Lipicky offered another teleconference or face-to-face meeting, if needed.

Signature, Meeting Recorder: [ ]

Signature, Meeting Chair: [ ]

RHPM Review of Final Printed Labeling
NDA 21-268 Teveten/Hydrochlorothiazide

Date of Submission:	September 28, 2001
Date Received:	October 1, 2001
Applicant Name:	Unimed Pharmaceuticals, Inc.
Product Name:	Teveten/HCTZ
Date Reviewed:	October 15, 2001

Evaluation

This submission provides for final printed labeling (FPL) and mock-ups of container labels as requested in the Agency's June 27, 2001 approvable letter. The FPL contains changes contained in marked-up draft labeling and changes negotiated during teleconferences and faxes between Unimed and the Agency August 23-26 and August 29, 2001.

The approvable letter stated that the tablets should be scored to provide for once or twice daily dosing. In the above negotiations between the Agency and the sponsor, it was agreed that Unimed would make available a 300 mg eprosartan tablet (approved December 22, 1997, but not manufactured previously) that may be added to provide for additional dosing options.

When compared with the marked-up draft labeling contained in the approvable letter, the following changes were noted:

1. The positions of the double bonds in the imidazole ring of the eprosartan mesylate structure have been corrected in the package insert.

2. Under **DOSAGE AND ADMINISTRATION/Replacement Therapy**, the following paragraph has been added:

   > If the patient under treatment with Teveten® HCT requires additional blood pressure control at trough, or to maintain a twice a day dosing schedule of monotherapy, 300 mg TEVETEN® may be added as evening dose.

3. In the table under the **HOW SUPPLIED** section, we recommend that the complete NDC code be placed in the appropriate column at the time of your next printing, as follows:

Eprosartan (mg)	HCTZ (mg)	Color	NDC
600	12.5	Butterscotch	NDC 0051-5147-01
600	25	Brick red	NDC 0051-5150-01

Comments/Recommendations

The final printed labeling for NDA 21-268 was reviewed and found to be in accordance with changes negotiated between Unimed and the Division.

An approval letter will be drafted for Dr. Lipicky's signature.

[S]

Sandra Birdsong, RHPM