CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER(S)
NDA 20-729/S-010

Trade Name: Uniretic Tablets, 15/12.5 mg

Generic Name(s): (Moexipril hydrochloride/ hydrochlorothiazide)

Sponsor: Schwarz Pharma, Inc.

Approval Date: February 14, 2002

Indication: Provides for a new dosage strength tablet, 15/12.5 mg, including final printed labeling

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

NDA 20-729/S-010

Approval Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-729/S-010

Schwarz Pharma, Inc.
Attention: Ms. Donna K. Multhauf
P. O. Box 2038
Milwaukee, WI 53201-2038

Dear Ms. Multhauf:

Please refer to your supplemental new drug application dated August 30, 2001 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uniretic (moexipril hydrochloride/hydrochlorothiazide) 7.5/12.5 and 15/25 mg Tablets.

We acknowledge receipt of your submission dated December 27, 2001 that constituted a complete response to our December 18, 2001 action letter.

This supplemental new drug application provides for a new dosage strength tablet, 15/12.5 mg, including final printed labeling that incorporated this change.

We have completed the review of this supplemental application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the submitted final printed labeling (package insert submitted December 27, 2001). Accordingly, the supplemental application is approved effective on the date of this letter.

We also refer to conversations between and Ms. Carol Holquist, Office of Drug Safety (ODS, formerly the Office of Post-Marketing Drug Risk Assessment, OPDRA) and Schwarz Pharma, Inc. on December 20, 2001. We note the corrections to the labeling listed in your letter and agree with your point-by-point responses to our comments and requests in our December 18, 2001 approvable letter, as follows:

1. Schwarz Pharma, Inc. will revise the labels and labeling to include "Tablets" in the established name.
2. The current corporate logo size is acceptable.
3. The strength of the drug product will be centered under the established name and color coded in red, as below:

   15 mg / 12.5 mg
4. The underline will be removed from beneath the proprietary name and strength, and brackets will be added to the product's established name.
5. No other changes will be made to the bottle label or professional sample labeling.

These changes to the labeling should be included in your next annual report.

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

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

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

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

If you have any questions, please contact:

Ms. Sandra Birdsong
Regulatory Project Manager
(301) 594-5334

Sincerely,

{See appended electronic signature page}

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Raymond Lipicky
2/14/02 11:00:38 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 20-729/S-010

Approvable Letter

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-729/SCF-010

Schwarz Pharma, Inc.
Attention: Ms. Donna K. Multhauf
P. O. Box 2038
Milwaukee, WI 53201

Dear Ms. Multhauf:

Please refer to your August 30, 2001supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Uniretic (moexipril hydrochloride and hydrochlorothiazide).

This supplement proposes an additional strength of the combination of Uniretic (moexipril hydrochloride and hydrochlorothiazide) Tablets; no moexipril hydrochloride 15 mg and hydrochlorothiazide 12.5 mg tablet is currently approved or proposed.

Included in your application is labeling with the following proposed changes:

1. The third paragraph in the **DESCRIPTION** section has been changed from:

/

to:

uniretic® is available for oral administration in three tablet strengths. The inactive ingredients in all strengths are lactose, magnesium oxide, crospovidone, magnesium stearate and gelatin. The film coating in all strengths contains hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol 6000, magnesium stearate and titanium dioxide. In addition, the film coating for uniretic® 15/25 contains ferric oxide.

2. Under the **Pharmacodynamics and Clinical Effects** section , the following has been changed from:

/

to:

By blocking the renin-angiotensin-aldosterone axis, administration of moexipril tends to reduce the potassium loss associated with hydrochlorothiazide. In UNIRETIC controlled clinical trials, the average change in serum potassium was near zero in subjects who received 3.75/6.25 mg or 7.5/12.5 mg, but subjects who received 15/12.5 mg or 15/25 mg experienced a mild decrease in serum potassium, similar to that experienced by subjects who received hydrochlorothiazide 25 mg monotherapy.

3. In the section under **Drug Interactions**/*Potassium Supplements and Potassium-Sparing Diuretics*, the first sentence has been changed from:

to:

As noted above *(Serum Electrolyte Imbalance*) the net effect of Uniretic may be to elevate a patient's serum potassium, to reduce it, or to leave it unchanged.

4. The subsection **Geriatric Use** has been changed from:

to:

Hydrochlorothiazide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

5. The **Dosage and Administration** section, has been changed from:

to:

In uniretic® controlled clinical trials, the average change in serum potassium was near zero in subjects who received 3.75/6.25 mg or 7.5/12.5 mg, but subjects who received 15/12.5 mg or 15/25 mg experienced a mild decrease in serum potassium, similar to that experienced by subjects who received hydrochlorothiazide 25 mg monotherapy.

6. Under **Dosage and Administration**/ *Dose Titration Guided by Clinical Effect*, the labeling has been changed from:

to:

A patient whose blood pressure is not adequately controlled with either moexipril or hydrochlorothiazide monotherapy may be given uniretic® 7.5/12.5 mg, uniretic® 15/12.5 mg or uniretic® 15/25 mg one hour before a meal. Further increases in moexipril, hydrochlorothiazide or both depend on clinical response. The hydrochlorothiazide dose should generally not be increased until 2-3 weeks have passed.

7. The following has been added under **How Supplied (Added Strength Information):**

uniretic® (moexipril hydrochloride/ hydrochlorothiazide) 15/12.5 tablets are white, oval, film-coated and scored with engraved code 720 on the unscored side and S and P on either side of the score. They are supplied as follows: Bottles of 100 NDC 0091-3720-01.

We have completed the review of this application, as amended, and it is approvable. In addition, we have reviewed the dissolution information provided in this supplement and are granting a bio-waiver for the newly proposed strength of uniretic® 15/12.5 mg Tablets.

We have also reviewed the physician sample container labels and carton labeling, container labels, and package insert labeling. We provide recommendations for labeling revisions that might minimize potential user error. Before this application may be approved it will be necessary for you to submit final printed labeling (FPL) revised as follows:

1. The dosage form "Tablets" should be included in the established name.

2. The corporate name appears larger and more prominent than the proprietary and established names. Increase the prominence of the proprietary and established names.

3. The strength of the drug product should be revised to include the dosage unit of measure (mg). In addition, add a space preceding and following the dash (see below). Additionally, the strength should be relocated so it appears prominently beneath the established name as follows:

15 mg / 12.5 mg

This strength should be color coded (red) in the same manner as for the approved strengths.

4. We note you have underlined the proprietary name and strength. The underscoring makes the name and strength difficult to read. Additionally, 21 CFR 201.10 (a) states that the ingredient information shall appear together, without any intervening written, printed, or graphic matter. Therefore, we request that the underline be deleted.

6. The addition of the colored circle background highlights the net quantity statement providing a more prominent appearance than the product strength. Medication errors have resulted from this type of label presentation as the net quantity has been misinterpreted as the product strength when given more prominence on the labels. We recommend relocating the net quantity on the bottles of 100 so it does not appear in this highlighted area. However, the professional samples will only be dispensed by the physician and decreases the likelihood of this type of error occurring in this setting. Therefore, from a medication error perspective the label format as presented does not pose a problem for the physician sample package.

We also note that the proprietary name UNIRETIC™ has been changed to uniretic® throughout the package insert.

All previous revisions as reflected in the most recently approved labeling must be included. To facilitate review of your submission, please provide a highlighted or marked-up copy that shows the changes that are being made.

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL, ten of which individually mounted on heavy weight paper or similar material.

If additional information relating to the safety or effectiveness of this drug becomes available, revision of the labeling may be required.

Within 10 days after the date of this letter, you are required to amend the supplemental application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major

amendment nor will the review clock be reactivated until all deficiencies have been addressed.

This product may be considered to be misbranded under the Federal Food, Drug, and Cosmetic Act if it is marketed with these changes prior to approval of this supplemental application.

If you have any questions, please contact:

Ms. Sandra Birdsong
Regulatory Health Project Manager
(301) 594-5334

Sincerely,

{See appended electronic signature page}

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Raymond Lipicky
12/18/01 03:35:02 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 20-729/S-010

Chemistry Review(s)

CHEMIST'S REVIEW	1. ORGANIZATION HFD-810/110	2. NDA Number 20-729
3. Name and Address of Applicant (City & State) Schwarz Pharma, Inc. 6140 W. Executive Drive, Mequon, WI 53092 P.O. Box 2038 Milwaukee, WI 53201		4. Supplement(s) Number(s) Date(s) SCF-010 August 30, 2001
5. Drug Name Uniretic® Tablets	6. Nonproprietary Name Moexipril hydrochloride /hydrochlorothiazide	7. Amendments & Other (reports, etc) – Dates
8. Supplement Provides For Line extension of an additional strength tablet containing 15-mg moexipril HCl and 12.5 mg hydrochlorothiazide (15/12.5 mg).		
9. Pharmacological Category ACE inhibitor/Diuretic	10. How Dispensed Rx ☒ OTC	11. Related IND(s)/ NDA(s)/DMF(s)
Dosage Form(s) Tablets	13. Potency(ies) 7.5/12.5 mg and 15/25 mg Moexipril HCl /hydrochlrothiazide	
14. Chemical Name and Structure Moexipril HCl - Mol. Formula : $C_{27}H_{35}N_2O_7Cl$ Mol. Weight: 535.04 Hydrochlorothiazide – Mol. Formula: $C_7H_8ClN_3O_4S_2$ Mol. Wt. 297.73		15. Records/Reports Current Yes ☒ No Reviewed Yes ☒ No

16. Comments: Prior Approval Supplement

The following information is provided.
Qualitative and quantitative formulations, Master and Executive batch records, In- process and fininished Drug Product specifications and analytical methods.
Three months accelerated and long-term stability on batches of Uniretic 15/12.5 Tablets in different packages.
Dissolution profiles, and Draft labeling.

17. Conclusions and Recommendations

Dissolution data using 5 different media required according to SUPAC-IR, has been provided.
Biopharmaceutist has reviewed the data and is satisfactory (dated 9/14/01).
Draft package insert and container labeling for proposed Uniretic 15/12.5 mg Tablets have been submiitted for consult review to OPDRA and Clinical Division.
Chemistry data is satisfactory. This supplement may be approved.as far as CMC data is concerned
APPROVAL letter with request for FPL is recommended from chemistry perspective..

18. REVIEWER

Name JV Advani	Signature /S/	Date Completed 11/29/01

Distribution: Original Jacket ☒ Reviewer ☒ Division File ☒ PM ☒

JVA File NameFirm has c:\ sup-rev\20729s07 R/D init: K. Srinivasachar

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/s/

J. V. Advani
12/11/01 04:49:14 PM
CHEMIST

Kasturi Srinivasachar
12/12/01 06:31:52 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 20-729/S-010

Clinical Pharmacology and Biopharmaceutics Review

CLINICAL PHARMACOLOGY and BIOPHARMACEUTICS REVIEW
Division of Pharmaceutical Evaluation I

NDA 20-729 **SUBMISSION DATE:** August 30, 2001
Supplement SCF-010

UNIRETIC™ Tablets
(Moexipril HCl/HCTZ)
Schwarz Pharma
Milwaukee, WI **REVIEWER:** Angelica Dorantes, Ph.D.

TYPE OF SUBMISSION: NDA Supplement: Product Line Extension – Additional Strength of Uniretic Tablets

BACKGROUND:

NDA 20-729 for UNIRETIC™ (moexipril HCl/HCTZ) 7.5/12.5 mg and 15/25 mg Tablets were approved by the Agency on June 27, 1997 for the treatment of hypertension.

SUBMISSION:

Supplement SCF-010 to NDA 20-729 dated August 30, 2001 provides information to support a drug product line extension of an additional strength tablet containing 15 mg moexipril HCl and 12.5 mg hydrochlorothiazide (15/12.5 mg). Uniretic 15/12.5 mg Tablets have been produced utilizing the current approved manufacturing process, equipment and container/closure systems for bottles of 100 and blister samples.

This supplement provides the following information:

- Qualitative and quantitative formulation, master and executed batch records, in process and finished drug product specifications and analytical methods;
- Three months accelerated and long-term stability on one batch of Uniretic 15/12.5 Tablets,
- Dissolution profiles, and
- Draft labeling

ISSUE:

In this submission the sponsor is requesting a bio-waiver for the new Uniretic 15/12.5 mg formulation. To support their request the sponsor provided dissolution data in five different media for 3720 Uniretic 15/12.5 mg, Lot X10046 versus 3725 Uniretic Tablets, 15/25 mg, lot B03050 (The 3725 profile was performed on 05/00 and 01/01). Twelve tablets were tested in 900 mL 0.1 N

Hydrochloric acid, 900 mL USP pH 4.5 Acetate Buffer, 900 mL USP pH 6.5 Phosphate Buffer, 900 ml, USP pH 7.5 Phosphate Buffer and 900 mL Water per DAP-3720-00 using Apparatus II at 50 rpm, withdrawing samples at 5, 10 and 15 minutes.

Please note that the SUPAC-IR guidance suggests the use of 15, 30, 45, 60 and 120 minutes as sampling points, or until an asymptote is reached. Schwarz Pharma determined that the more appropriate sampling timepoints for this product are 5, 10, and 15 minutes, since these timepoints have been previously submitted and approved for previous changes to this application.

The percent dissolved (mean and range) of moexipril HCl and HCTZ in the different media and the similarity factors (f_2) values are listed in Table 1.

TABLE 1

Dissolution Medium	UNIRETIC TABLETS													
	*Percent Dissolved of Moexipril HCl							*Percent Dissolved of Hydrochlorohiazide						
	5/25 mg Tablets (Lot B03050)			15/12.5 mg Tablets (Lot X10046)				5/25 mg Tablets (Lot B03050)			15/12.5 mg Tablets (Lot X10046)			
	5 min	10 min	15 min	5 min	10 min	15 min	f_2	5 min	10 min	15 min	5 min	10 min	15 min	f_2
Water	77	92	95	84	100	101		69	88	94	73	89	92	
0.1N HCl	75	90	93	72	94	98		68	89	96	64	85	92	
Buff pH 4.5	76	93	96	73	94	96		66	87	93	67	88	93	
Buff pH 6.5	80	94	96	92	102	103		69	87	92	75	90	92	
Buff pH 7.5	80	93	96	93	102	104		67	86	91	76	89	91	

*Mean & Range

REVIEWER COMMENTS:

1. It should be noted that Uniretic (moexipril HCl/HCTZ) Tablets are currently approved for the following 2 strengths: 7.5/12.5 mg and 15/25 mg. On January 24, 2001, OCPB/DPEI was consulted by Dr. Advani, (reviewing chemist of DCRDP) regarding the OCPB's requirements that were needed for the approval of a new formulation of Uniretic Tablets containing 15mg moexipril HCT and 12.5 mg HCTZ.

2. According to the SUPAC Guidance for IR products, the sponsor needs to conduct a bioequivalence-study to support the approval of the new formulation. However, OCPB was of

the opinion that a bio-waiver could be granted if the sponsor provided appropriate dissolution data using 5 different media (i.e., water, 0.1 N HCl, acetate buffer pH 4.5, phosphate buffer pH 6.5, and phosphate buffer pH 7.5).

3. It should be noted that OCPB's decision to grant a bio-waiver for the new formulation of Uniretic Tablets was based on the following considerations:
   - There are appropriate clinical data that support the moexipril HCL and HCTZ dosage range.
   - The composition of the new formulation is similar to the 15 mg moexipril HCl part of the 15/25 mg approved tablets and to the HCTZ 12.5 mg part of the approved 7.5/12.5 mg tablets.
   - There are appropriate dissolution data for the 7.5/12.5 and 15/25 mg tablets that show that both strengths dissolve very fast in different media — % of moexipril HCL and HCTZ in 15 minutes.

RECOMMENDATION:

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation I (OCPB/DPEI) has reviewed the dissolution information provided in NDA 20-729, Supplement SCF-010 submitted on August 30, 2001. OCPB/DPEI considers that Schwarz Pharma has provided appropriate dissolution information to support their bio-waiver request for the submission of in vivo bioequivalence data. Therefore, a bio-waiver is granted for the newly proposed strength 15/12.5 mg of UNIRETIC Tablets.

With respect to the revised labeling incorporating information for the new strength of Uniretic 15/12.5 mg Tablets, from the OCPB's viewpoint the proposed changes appear to be appropriate and are acceptable.

Please convey the Recommendation as appropriate to the sponsor.

Angelica Dorantes, Ph.D.
Division of Pharmaceutical Evaluation I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FT Initialed by Patrick J. Marroum, Ph.D. /S/

cc: NDA 20-729, HFD-110 (Advani), HFD-860 (Dorantes, Mehta), and CDR (Biopharm).

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/s/

Angelica Dorantes
9/14/01 04:51:47 PM
BIOPHARMACEUTICS

Patrick Marroum
9/14/01 05:17:30 PM
BIOPHARMACEUTICS

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

DATE RECEIVED:	**DUE DATE:**	**OPDRA CONSULT #:**
December 10, 2001	December 13, 2001	01-0237

TO: Raymond Lipicky, M.D.
Director, Division of Cardio-Renal Drug Products
HFD-110

THROUGH: Sandra Birdsong, Project Manager
HFD-110

PRODUCT NAME:	**MANUFACTURED BY:**
Uniretic (Moexipril hydrochloride and Hydrochlorothiazide Tablets) **7.25 mg/12.5 mg, 15 mg/25 mg, and 15 mg/12.5 mg** **NDA #: 20-729/S-010**	Schwarz Pharma, Inc.

SAFETY EVALUATOR: Carol Holquist, R.Ph.

SUMMARY: In response to a consult from the Division of Cardio-Renal Drug Products (HFD-110), OPDRA evaluated the proposed container labels and package insert labeling as requested.

OPDRA RECOMMENDATION:
OPDRA recommends the labels and labeling be revised as outlined in section III of this review.

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment
Phone: (301) 827-3242
Fax: (301) 443-5161

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

Office of Post-Marketing Drug Risk Assessment
HFD-400; Rm 15B-32
Center for Drug Evaluation and Research

Labels and Labeling Review

DATE OF REVIEW: December 11, 2001

NDA: 20-729/S-010

NAME OF DRUG: Uniretic
(Moexipril Hydrochloride and Hydrochlorothiazide Tablets)
7.5 mg/12.5 mg, 15 mg/25 mg and 15 mg/12.5 mg

NDA HOLDER: Schwarz Pharma, Inc.

I. INTRODUCTION

This consult is in response to a December 10, 2001, request from the Division of Cardio-Renal Drug Products (HFD-110), for evaluation of the proposed container labels and package insert labeling. The labels and labeling were revised to reflect a new corporate logo design and an additional strength of 15 mg/12.5 mg. The Division requests our opinion on the new labels and labeling in general and with respect to weather or not they will contribute to medication errors.

PRODUCT INFORMATION
Uniretic has been marketed since June 27, 1997, by Schwarz Pharma, Inc. Uniretic is a combination of an angiotensin-converting enzyme (ACE) inhibitor, moexipril hydrochloride, and a diuretic, hydrochlorothiazide. Uniretic is indicated for the treatment of patients with hypertension and is not indicated for initial therapy. The product was first supplied in 7.5 mg/12.5 mg and 15 mg/25 mg combination tablets. This supplement allows for an additional strength of 15 mg/12.5 mg. A patient whose blood pressure is not adequately controlled with either moexipril or hydrochlorothiazide monotherapy may be given Uniretic at any strength one hour before meals. The dose is dependent on clinical response.

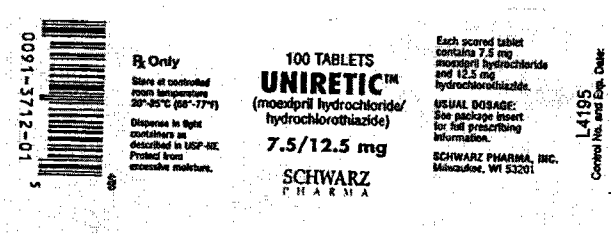
II. RISK ASSESSMENT

The FDA Adverse Event Reporting System *(AERS)* database was searched for all post-marketing safety reports of medication errors reported for the active ingredient terms "hydrochloro%" and "moexipril%, trade name "Uniretic%", and verbatim for all, using the Meddra Preferred Term, DRUG MALADMINISTRATION to determine if there are any existing problems relating the packaging and labeling of this drug product. This search strategy retrieved sixty-seven medication error reports, one of which was related to Uniretic. However, the report described an error that involved the misadministration of Uniretic for the intended drug, Univasc. The error was not related to the labeling or packaging of Uniretic.

The sponsor submitted proposed labels and labeling for the new strength 15 mg/12.5 mg that included a physician sample size containing 7 tablets, bottle of 100, and revised package insert labeling that reflects the new strength. The revised container labels of the originally marketed strengths (7.5 mg/12.5 mg and 15 mg/25 mg) were not supplied for review and comment. However, the sponsor stated that the new design elements are being incorporated into the labeling for all Schwarz Pharma products.

The Division requested our review and comments on the new labeling in general in addition to any concerns with regard to their contribution to medication errors. The sponsor has revised the appearance of the container label as follows:

Approved Label



Proposed Label

Upon completion of our review, we have identified areas of improvement that might minimize the risk of potential user error. See section III of this review for the comments that can be provided to the sponsor.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES

OPDRA has reviewed the physician sample container labels and carton labeling, container labels, and package insert labeling. We provide the following recommendations for labeling revisions, which might minimize potential user error.

1. The dosage form "Tablets" should be included in the established name.

2. The corporate name appears larger and more prominent than the proprietary and established names. Increase the prominence of the proprietary and established names.

3. The strength of the drug product should be revised to include the dosage unit of measure (mg). In addition, add a space preceding and following the dash (see below). Additionally, the strength should be relocated so it appears prominently beneath the established name as follows:

   15 mg / 12.5 mg

4. We note you have underlined the proprietary name and strength. The underscoring makes the name and strength difficult to read. Additionally, 21 CFR 201.10 (a) states that the ingredient information shall appear together, without any intervening written, printed, or graphic matter. Therefore, we request the underline be deleted.

5. Since the labeling for the currently marketed product strengths were not provided for review, it is difficult to determine if the multiple product strengths have been differentiated by color, boxing or some other means. In particular, we are concerned with possible confusion between the 15 mg / 25 mg and 15 mg /12.5 mg strengths. We recommend differentiating all product strengths to help distinguish the containers from one another.

6. The addition of the colored circle background highlights the net quantity statement providing a more prominent appearance than the product strength. Medication errors have resulted from this type of label presentation as the net quantity has been misinterpreted as the product strength when given more prominence on the labels. We recommend relocating the net quantity on the bottles of 100 so it does not appear in this highlighted area. However, the professional samples will only be dispensed by the physician and decreases the likelihood of this type of error occurring in this setting. Therefore, from a medication error perspective the label format as presented does not pose a problem for the physician sample package.

IV. RECOMMENDATIONS

OPDRA recommends the labeling revisions outlined in section III of this review be implemented upon approval of this supplement.

OPDRA would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Carol Holquist at (301) 827-0915.

/S/

Carol Holquist, RPh.
Safety Evaluator
Office of Post-Marketing Drug Risk Assessment

Concur: /S/

Jerry Phillips, RPh
Associate Director for Medication Error Prevention
Office of Post-Marketing Drug Risk Assessment

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/s/

Carol Holquist
12/14/01 11:24:28 AM
PHARMACIST

Jerry Phillips
12/14/01 11:35:16 AM
DIRECTOR

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 20-729/S-010

Administrative Documents

RHPM Review of Final Printed Labeling

Application:	NDA 20-729/SCF-010 Uniretic (moexepril
Sponsor:	Schwarz Pharma, Inc.
Date of Supplement:	August 30, 2001
Type of Supplement:	Formulation Revision with Labeling

Background

This supplement proposes a new formulation that provides for a new strength of moexipril 15 mg/hydrochlorothiazide (HCTZ)12.5 mg. Currently, two strengths are approved: moexipril 7.5 mg/HCTZ 12.5 mg and moexipril 15 mg/HCTZ 25 mg.

Dr. J. V. Advani, the chemist assigned to this application, requested a consultation with the Office of Post-Marketing Drug Risk Assessment (OPDRA) regarding the changes in carton labels, particularly the new logo. OPDRA recommended approval of the labeling revisions as described in their review. These revisions will be included in our letter to the sponsor.

The Medical Officer, Dr. Throckmorton, and Biopharm reviewer, Dr. Dorantes, also recommended approval of the revisions listed in this supplement. Additionally, a bio-waiver for this supplement has been granted and will be included in our letter.

Evaluation

This supplement proposes the following labeling changes in the package insert:

1. The third paragraph in the **DESCRIPTION** section has been changed from:

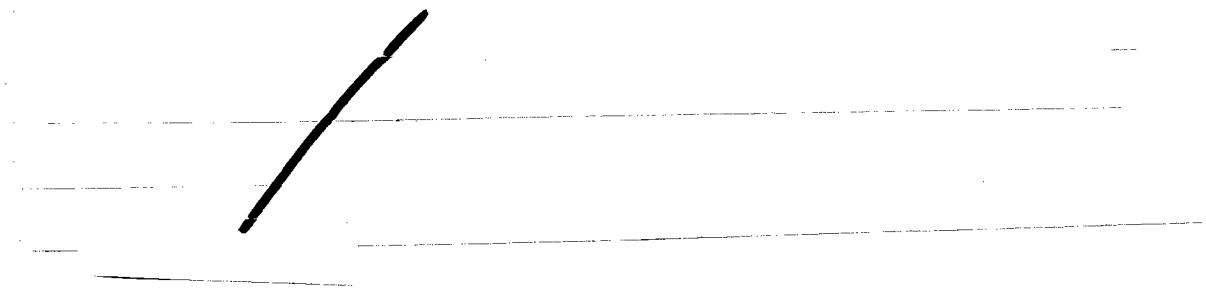
[redacted]

to:

> uniretic® is available for oral administration in three tablet strengths. The inactive ingredients in all strengths are lactose, magnesium oxide, crospovidone, magnesium stearate and gelatin. The film coating in all strengths contains hydroxypropyl methylcellulose, hydroxypropyl cellulose, polyethylene glycol

6000, magnesium stearate and titanium dioxide. In addition, the film coating for uniretic® 15/25 contains ferric oxide.

2. Under the **Pharmacodynamics and Clinical Effects** section , the following has been changed from:



to:

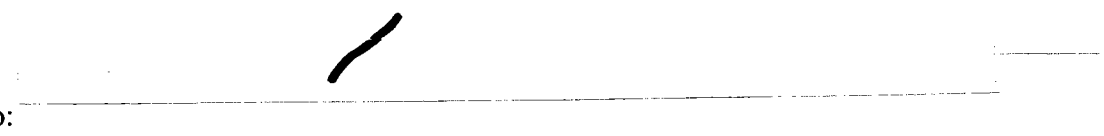
By blocking the renin-angiotensin-aldosterone axis, administration of moexipril tends to reduce the potassium loss associated with hydrochlorothiazide. In UNIRETIC controlled clinical trials, the average change in serum potassium was near zero in subjects who received
3.75/6.25 mg or 7.5/12.5 mg, but subjects who received **15/12.5 mg or** 15/25 mg experienced a mild decrease in serum potassium, similar to that experienced by subjects who received hydrochlorothiazide 25 mg monotherapy.

3. In the section under **Drug Interactions**/*Potassium Supplements and Potassium-Sparing Diuretics*, the first sentence has been changed from:

to:

As noted above *(Serum Electrolyte Imbalance*) the net effect of **Uniretic** may be to elevate a patient's serum potassium, to reduce it, or to leave it unchanged.

4. The subsection **Geriatric Use** has been changed from:



to:

Hydrochlorothiazide is known to be substantially excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function.

5. The **Dosage and Administration** section, has been changed from:

to:

In uniretic® controlled clinical trials, the average change in serum potassium was near zero in subjects who received 3.75/6.25 mg or 7.5/12.5 mg, but subjects who received **15/12.5 mg or** 15/25 mg experienced a mild decrease in serum potassium, similar to that experienced by subjects who received hydrochlorothiazide 25 mg monotherapy.

6. Under **Dosage and Administration**/ *Dose Titration Guided by Clinical Effect*, the labeling has been changed from:

to:

A patient whose blood pressure is not adequately controlled with either moexipril or hydrochlorothiazide monotherapy may be given uniretic® 7.5/12.5 mg, **uniretic® 15/12.5 mg** or uniretic® 15/25 mg one hour before a meal. Further increases in moexipril, hydrochlorothiazide or both depend on clinical response. The hydrochlorothiazide dose should generally not be increased until 2-3 weeks have passed.

7. The following has been added under **How Supplied (Added Strength Information):**

uniretic® (moexipril hydrochloride/ hydrochlorothiazide) 15/12.5 tablets are white, oval, film-coated and scored with engraved code 720 on the unscored side and S and P on either side of the score. They are supplied as follows: Bottles of 100 NDC 0091-3720-01.

Additionally, the proprietary name UNIRETIC™ has been changed to uniretic® throughout the package insert.

The following are recommendations for labeling revisions that might minimize potential user error, as per the OPDRA consultation dated December 13, 2001:

1. The dosage form "Tablets" should be included in the established name.

2. The corporate name appears larger and more prominent than the proprietary and established names. Increase the prominence of the proprietary and established names.

3. The strength of the drug product should be revised to include the dosage unit of measure (mg). In addition, add a space preceding and following the dash (see below). Additionally, the strength should be relocated so it appears prominently beneath the established name as follows:

   15 mg / 12.5 mg

4. We note you have underlined the proprietary name and strength. The underscoring makes the name and strength difficult to read. Additionally, 21 CFR 201.10 (a) states that the ingredient information shall appear together, without any intervening written, printed, or graphic matter. Therefore, we request the underline be deleted.

5. Since the labeling for the currently marketed product strengths were not provided for review, it is difficult to determine if the multiple product strengths have been differentiated by color, boxing or some other means. In particular, we are concerned with possible confusion between the 15 mg /25 mg and 15 mg /12.5 mg strengths. We recommend differentiating all product strengths to help distinguish the containers from one another.

6. The addition of the colored circle background highlights the net quantity statement providing a more prominent appearance than the product strength. Medication errors have resulted from this type of label presentation as the net quantity has been misinterpreted as the product strength when given more prominence on the labels. We recommend relocating the net quantity on the bottles of 100 so it does not appear in this highlighted area. However, the professional samples will only be dispensed by the physician and decreases the likelihood of this type of error occurring in this setting. Therefore, from a medication error perspective the label format as presented does not pose a problem for the physician sample package.

Recommendation

As recommended by Drs. Srinivasachar and Throckmorton, an approvable letter will be drafted for Dr. Lipicky's signature.

/s/

Sandra Birdsong

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/s/

Sandra Birdsong
12/17/01 05:33:12 PM
CSO

Memo to File

Date: January 24, 2002

From: Sandra Birdsong, RHPM

To: NDA 20-729/SCF-010

Subject: Correction to RHPM review signed on December 17, 2001

This is a correction to the RHPM Review of labeling for Supplement 010, signed by Sandra Birdsong, RHPM on December 17, 2001. The Review should read "RHPM Review of Draft Labeling", instead of "RHPM Review of Final Printed Labelint".

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/s/

Sandra Birdsong
1/24/02 04:29:55 PM
CSO

RHPM Review of Final Printed Labeling

Application:	NDA 20-729/S-010 Uniretic® (moexipril hydrochloride/hydrochlorothiazide)
Sponsor:	Schwarz Pharma, Inc.
Date of Submission:	August 30, 2001
Date of Receipt:	August 31, 2001
Approvable Letter:	December 18, 2001
Type of Submission:	Final Printed Labeling
Date of this Submission:	December 27, 2001

Background

An approvable letter issued December 18, 2001 for this supplement that proposes a product line extension of an additional strength tablet, uniretic® 15/12.5 mg Tablets. The ODS (Office of Drug Safety, formerly the Office of Post-Marketing and Drug Risk Assessment-OPDRA) reviewer's comments, as well as those of the Division chemist, and a biowaiver were included in the approvable letter. The sponsor submitted Amendment 001 to Supplement 010 that responded to the requests listed in our approvable letter on December 28, 2001. Dr. Lipicky reviewed this amendment on January 24, 2002.

The sponsor conferred with Carol Holquist, the ODS reviewer, on December 20, 2001, and reached agreement on their responses to the items in our approvable letter. Dr. Lipicky agreed to the responses of the sponsor in the amendment, as noted in this review.

Evaluation

I reviewed the final printed labeling in its entirety and it is identical to the draft labeling submitted on December 28, 2001.

Dr. Lipicky agreed to each of the sponsor's responses in Amendment 001. This amendment responds to each item in our December 18, 2001 approvable letter (shown in bold), as follows:

1. **The dosage form "Tablets" should be included in the established name.**

   While it was agreed that this is not a regulatory requirement since uniretic® is not a USP item, SPInc will revise the labels and labeling to include "Tablets"

in the established name as this will provide further clarification of the product dosage form.

2. **The corporate name appears larger and more prominent than the proprietary and established names. Increase the prominence of the proprietary and established names.**

   The font size of the current corporate logo is smaller than the size of the proprietary and established names. In addition, the size of the corporate logo meets regulatory requirements by not using up more than one-third of the space of the container labeling. It was agreed that the current logo size is acceptable.

3. **The strength of the drug product should be revised to include the dosage unit of measure (mg). In addition, add a space preceding and following the dash (see below). Additionally, the strength should be relocated so it appears prominently beneath the established name as follows:**

   15 mg / 12.5 mg

   This strength should be color-coded (red) in the same manner as for the approved strengths.

   The strength of the drug product will be revised as requested. If necessary due to space limitations, the strength will also be relocated to appear beneath the established name. As discussed with Ms. Holquist, SPInc is using contrasting colors to format each of the Uniretic product strengths.

4. **We note you have underlined the proprietary name and strength. The underscoring makes the name and strength difficult to read. Additionally, 21 CFR 201.10(a) states that the ingredient information shall appear together, without any intervening written, printed, or graphic matter. Therefore, we request that the underline by deleted.**

   The underline will be removed from beneath the proprietary name and strength, and brackets will be added to the product's established name.

5. **The addition of the colored circle background highlights the net quantity statement providing a more prominent appearance than the product strength. Medication errors have resulted from this type of label presentation as the net quantity has been misinterpreted as the product strength when given more prominence on the labels. We recommend relocating the net quantity on the bottles of 100 so it does not appear in this highlighted area. However, the professional samples will only be dispensed by the physician and decreases the likelihood of this type of error occurring in this setting. Therefore, from a medication error**

perspective the label format as presented does not pose a problem for the physician sample package.

It was agreed that the inclusion of the net quantity within the colored sphere, as currently formatted on the bottle label, is acceptable as it does not interfere with identification of the product strength. Therefore, no changes will be made to this sphere or its contents on either bottle label or professional sample labeling.

The sponsor also noted in Amendment 001 that a follow-up conversation held between the sponsor and the Division resulted in agreement that the revisions noted in comments #1,3 and 4 to the bottle label, package circular and physician sample container and carton labeling will be made within three months of initial distribution of the product approved in S-010 for packaging of launch supplies. Therefore, the final printed labeling included in Amendment 001 represents the labeling as proposed in S-010.

Recommendation

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

/S/

Sandra Birdsong, RPM

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/s/

Sandra Birdsong
2/15/02 10:54:02 AM
CSO

CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
NDA 20-729/S-010

Correspondence

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 20-729/S-010

Schwarz Pharma, Inc.
Attention: Ms. Donna K. Multhauf
P.O. Box 2038
Milwaukee, WI 53201-2308

Dear Ms. Multhauf:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Uniretic (moexipril hydrochloride/hydrochlorothiazide) Tablets

NDA Number: 20-729

Supplement number: S-010

Date of supplement: August 30, 2001

Date of receipt: August 31, 2001

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, this application will be filed under section 505(b) of the Act on October 30, 2001 in accordance with 21 CFR 314.101(a).

All communications concerning this supplement should be addressed as follows:

U.S. Postal Service:
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Ms. Sandra Birdsong
Regulatory Project Manager
(301) 594-5334

Sincerely yours,

Natalia A. Morgenstern
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Natalia Morgenstern
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