CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

76-204

Generic Name:	Moexipril Hydrochloride Tablets, 7.5mg and 15mg
Sponsor:	TEVA Pharmaceuticals USA
Approval Date:	May 8, 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 76-204

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CENTER FOR DRUG EVALUATION AND RESEARCH

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APPROVAL LETTER

ANDA 76-204

MAY 8 2003

TEVA Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454-1090

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated July 16, 2001, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (Act), for Moexipril Hydrochloride Tablets, 7.5 mg and 15 mg.

Reference is also made to your amendments dated January 29, and May 31, 2002; and January 23, and February 26, 2003. We also acknowledge receipt of your correspondence dated November 26, 2001, and March 27, 2003 pertaining to patent and litigation issues noted below.

The listed drug product referenced in your application, Univasc Tablets of Schwarz Pharma, Inc., is subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. patent 4,743,450 (the '450 patent) is due to expire on February 24, 2007. Your application contains a paragraph IV certification to the '450 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the '450 patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Moexipril Hydrochloride Tablets under this ANDA. Section 505(j)(5)(B)(iii) of the Act provides that approval of an ANDA may be made effective immediately, unless an action is brought against TEVA Pharmaceuticals USA (TEVA) for infringement of the '450 patent. This action must be brought against TEVA prior to the expiration of 45 days from the date the notice you provided under paragraph (2)(B)(i) was received by the NDA/patent holder(s). You have notified the agency that TEVA complied with the requirements of Section 505(j)(2)(B) of the Act, and that a patent infringement action against you in United States District Court for the

Southern District of New Jersey (Schwarz Pharma, Inc., Schwarz Pharma AG, and Warner-Lambert Company v. TEVA Pharmaceuticals USA, Civil Action No. 01-4995(DRD). You have informed us that in a summary judgement decision entered on March 25, 2003, the District Court ruled that TEVA's Moexipril Hydrochloride Tablets do not infringe the '450 patent.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Moexipril Hydrochloride Tablets, 7.5 mg and 15 mg, to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Univasc Tablets, 7.5 mg and 15 mg, respectively, of Schwarz Pharma, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

We note that TEVA was the first ANDA applicant to submit a substantially complete ANDA containing a paragraph IV certification to the '450 patent for Moexipril Hydrochloride Tablets, 7.5 mg and 15 mg. With this approval, TEVA is eligible for 180-days of generic drug market exclusivity for this drug product. TEVA's exclusivity commenced on March 25, 2003 upon the entry of the district court's decision.

Under Section 506A of the Act, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FDA 2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 5/8/03
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

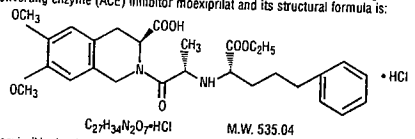
76-204

FINAL PRINTED LABELING(S)

USE IN PREGNANCY
When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury and even death to the developing fetus. When pregnancy is detected, Moexipril Hydrochloride Tablets should be discontinued as soon as possible. **See WARNINGS, Fetal/Neonatal Morbidity and Mortality.**

DESCRIPTION

Moexipril hydrochloride, the hydrochloride salt of moexipril, is chemically described as [3S-[2[R*(R*)],3R*]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, monohydrochloride. It is a non-sulfhydryl containing precursor of the active angiotensin-converting enzyme (ACE) inhibitor moexiprilat and its structural formula is:



$C_{27}H_{34}N_2O_7 \cdot HCl$ M.W. 535.04

Moexipril hydrochloride is a fine white to off-white powder. It is soluble (about 10% weight-to-volume) in distilled water at room temperature.

Moexipril hydrochloride tablets are supplied as bisected, coated tablets containing 7.5 mg and 15 mg of moexipril hydrochloride for oral administration. In addition to the active ingredient, moexipril hydrochloride, the tablet core contains the following inactive ingredients: crospovidone, lactose monohydrate, magnesium stearate, pregelatinized starch and sodium bicarbonate. The film coating of the 7.5 mg tablet contains: hydroxypropyl methylcellulose, iron oxide red, lactose monohydrate, titanium dioxide and triacetin. The film coating of the 15 mg tablet contains: hydroxypropyl methylcellulose, iron oxide red, lactose monohydrate, titanium dioxide and triacetin.

CLINICAL PHARMACOLOGY

Mechanism of Action

Moexipril hydrochloride is a prodrug for moexiprilat, which inhibits ACE in humans and animals. The mechanism through which moexiprilat lowers blood pressure is believed to be primarily inhibition of ACE activity. ACE is a peptidyl dipeptidase that catalyzes the conversion of the inactive decapeptide angiotensin I to the vasoconstrictor substance angiotensin II. Angiotensin II is a potent peripheral vasoconstrictor that also stimulates aldosterone secretion by the adrenal cortex and provides negative feedback on renin secretion. ACE is identical to kininase II, an enzyme that degrades bradykinin, an endothelium-dependent vasodilator. Moexiprilat is about 1000 times as potent as moexipril in inhibiting ACE and kininase II. Inhibition of ACE results in decreased angiotensin II formation, leading to decreased vasoconstriction, increased plasma renin activity, and decreased aldosterone secretion. The latter results in diuresis and natriuresis and a small increase in serum potassium concentration (mean increases of about 0.25 mEq/L were seen when moexipril was used alone, see **PRECAUTIONS**).

Whether increased levels of bradykinin, a potent vasodepressor peptide, play a role in the therapeutic effects of moexipril remains to be elucidated. Although the principal mechanism of moexipril in blood pressure reduction is believed to be through the renin-angiotensin-aldosterone system, ACE inhibitors have some effect on blood pressure even in apparent low-renin hypertension. As is the case with other ACE inhibitors, however, the antihypertensive effect of moexipril is considerably smaller in black patients, a predominantly low-renin population, than in non-black hypertensive patients.

Pharmacokinetics and Metabolism

Pharmacokinetics: Moexipril's antihypertensive activity is almost entirely due to its deesterified metabolite, moexiprilat. Bioavailability of oral moexipril is about 13% compared to intravenous (I.V.) moexipril (both measuring the metabolite moexiprilat), and is markedly affected by food, which reduces the peak plasma level (C_{max}) and AUC (see *Absorption*). Moexipril should therefore be taken in a fasting state. The time of peak plasma concentration (T_{max}) of moexiprilat is about $1\frac{1}{2}$ hours and elimination half-life ($t_{1/2}$) is estimated at 2 to 9 hours in various studies, the variability reflecting a complex elimination pattern that is not simply exponential. Like all ACE inhibitors, moexiprilat has a prolonged terminal elimination phase, presumably reflecting slow release of drug bound to the ACE. Accumulation of moexiprilat with repeated dosing is minimal, about 30%, compatible with a functional elimination $t_{1/2}$ of about 12 hours. Over the dose range 7.5 to 30 mg, pharmacokinetics are approximately dose proportional.

Absorption: Moexipril is incompletely absorbed, with bioavailability as moexiprilat of about 13%. Bioavailability varies with formulation and food intake which reduces C_{max} and AUC by about 70% and 40% respectively after the ingestion of a low-fat breakfast or by 80% and 50% respectively after the ingestion of a high-fat breakfast.

Distribution: The clearance (CL) for moexipril is 441 mL/min and for moexiprilat 232 mL/min with a $t_{1/2}$ of 1.3 and 9.8 hours, respectively. Moexiprilat is about 50% protein bound. The volume of distribution of moexiprilat is about 183 liters.

Metabolism and Excretion: Moexipril is relatively rapidly converted to its active metabolite moexiprilat, but persists longer than some other ACE inhibitor prodrugs, such that its $t_{1/2}$ is over one hour and it has a significant AUC. Both moexipril and moexiprilat are converted to diketopiperazine derivatives and unidentified metabolites. After I.V. administration of moexiprilat, about 40% of the dose appears in urine as moexiprilat, about 26% as moexipril, with small amounts of the metabolites; about 20% of the I.V. dose appears in feces, principally as moexiprilat. After oral administration, only about 7% of the dose appears in urine as moexiprilat, about 1% as moexipril, with about 5% as other metabolites. Fifty-two percent of the dose is recovered in feces as moexiprilat and 1% as moexipril.

Special Populations:

Decreased Renal Function: The effective elimination of $t_{1/2}$ and AUC of both moexipril and moexiprilat are increased with decreasing renal function. There is insufficient information available to characterize this relationship fully, but at creatinine clearances in the range of 10 to 40 mL/min, the $t_{1/2}$ of moexiprilat is increased by a factor of 3 to 4.

Decreased Hepatic Function: In patients with mild to moderate cirrhosis given single 15 mg doses of moexipril, the C_{max} of moexipril was increased by about 50% and the AUC increased by about 120%, while the C_{max} for moexiprilat was decreased by about 50% and the AUC increased by almost 300%.

Elderly Patients: In elderly male subjects (65-80 years old) with clinically normal renal and hepatic function, the AUC and C_{max} of moexiprilat is about 30% greater than those of younger subjects (19-42 years old).

Pharmacokinetic Interactions With Other Drugs:

No clinically important pharmacokinetic interactions occurred when moexipril hydrochloride was administered concomitantly with hydrochlorothiazide, digoxin, or cimetidine.

Pharmacodynamics and Clinical Effect

Single and multiple doses of 15 mg or more of moexipril hydrochloride tablets gives sustained inhibition of plasma ACE activity of 80-90%, beginning within 2 hours and lasting 24 hours (80%).

In controlled trials, the peak effects of orally administered moexipril increased with the dose administered over a dose range of 7.5 to 60 mg, given once a day. Antihypertensive effects were first detectable about 1 hour after dosing, with a peak effect between 3 and 6 hours after dosing. Just before dosing (i.e., at trough), the antihypertensive effects were less prominently related to dose and the antihypertensive effect tended to diminish during the 24-hour dosing interval when the drug was administered once a day.

In multiple dose studies in the dose range of 7.5 to 30 mg once daily, moexipril hydrochloride tablets lowered sitting diastolic and systolic blood pressure effects at trough by 3 to 6 mmHg and 4 to 11 mmHg, more than placebo, respectively. There was a tendency toward increased response with higher doses over this range. These effects are typical of ACE inhibitors but, to date, there are no trials of adequate size comparing moexipril with other antihypertensive agents.

The trough diastolic blood pressure effects of moexipril were approximately 3 to 6 mmHg in various studies. Generally, higher doses of moexipril leave a greater fraction of the peak blood pressure effect still present at trough. During dose titration, any decision as to the adequacy of a dosing regimen should be based on trough blood pressure measurements. If diastolic blood pressure control is not adequate at the end of the dosing interval, the dose can be increased or given as a divided (BID) regimen.

During chronic therapy, the antihypertensive effect of any dose of moexipril hydrochloride is generally evident within 2 weeks of treatment, with maximal reduction after 4 weeks. The antihypertensive effects of moexipril hydrochloride have been proven to continue during therapy for up to 24 months.

Moexipril hydrochloride, like other ACE inhibitors, is less effective in decreasing trough blood pressures in blacks than in non-blacks. Placebo-corrected trough group mean diastolic blood pressure effects in blacks in the proposed dose range varied between +1 to –3 mmHg compared with responses in non-blacks of -4 to -6 mmHg.

The effectiveness of moexipril hydrochloride was not significantly influenced by patient age, gender, or weight. Moexipril hydrochloride has been shown to have antihypertensive activity in both pre- and postmenopausal women who have participated in placebo-controlled clinical trials.

Formal interaction studies with moexipril have not been carried out with antihypertensive agents other than thiazide diuretics. In these studies, the added effect of moexipril was similar to its effect as monotherapy. In general, ACE inhibitors have less than additive effects with beta-adrenergic blockers, presumably because both work by inhibiting the renin-angiotensin system.

INDICATIONS AND USAGE

Moexipril hydrochloride tablets are indicated for treatment of patients with hypertension. It may be used alone or in combination with thiazide diuretics.

In using moexipril hydrochloride, consideration should be given to the fact that another ACE inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen-vascular disease. Available data are insufficient to show that moexipril hydrochloride does not have a similar risk (see **WARNINGS**).

In considering use of moexipril hydrochloride, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in non-blacks. In addition, ACE inhibitors (for which adequate data are available) cause a higher rate of angioedema in black than in non-black patients (see **WARNINGS, *Angioedema***).

CONTRAINDICATIONS

Moexipril hydrochloride tablets are contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an ACE inhibitor.

WARNINGS

Anaphylactoid and Possibly Related Reactions

Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors, including moexipril hydrochloride, may be subject to a variety of adverse reactions, some of them serious.

Angioedema: Angioedema involving the face, extremities, lips, tongue, glottis, and/or larynx has been reported in patients treated with ACE inhibitors, including moexipril hydrochloride. Symptoms suggestive of angioedema or facial edema occurred in <0.5% of moexipril-treated patients in placebo-controlled trials. None of the cases were considered life-threatening and all resolved either without treatment or with medication (antihistamines or glucocorticoids). One patient treated with hydrochlorothiazide alone experienced laryngeal edema. No instances of angioedema were reported in placebo-treated patients.

In cases of angioedema, treatment should be promptly discontinued and the patient carefully observed until the swelling disappears. In instances where swelling has been confined to the face and lips, the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms.

Angioedema associated with involvement of the tongue, glottis, or larynx, may be fatal due to airway obstruction. Appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 to 0.5 mL) and/or measures to ensure a patent airway, should be promptly provided (see **ADVERSE REACTIONS**).

Anaphylactoid Reactions During Desensitization: Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions did not occur when ACE inhibitors were temporarily withheld, but they reappeared when the ACE inhibitors were inadvertently readministered.

Anaphylactoid Reactions During Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes and treated concomitantly with an ACE inhibitor. Anaphylactoid reactions have also been reported in patients undergoing low-density lipoprotein apheresis with dextran sulfate absorption.

Hypotension

Moexipril hydrochloride can cause symptomatic hypotension, although, as with other ACE inhibitors, this is unusual in uncomplicated hypertensive patients treated with moexipril hydrochloride alone. Symptomatic hypotension was seen in 0.5% of patients given moexipril and led to discontinuation of therapy in about 0.25%. Symptomatic hypotension is most likely to occur in patients who have been salt- and volume-depleted as a result of prolonged diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. Volume- and salt-depletion should be corrected and, in general, diuretics stopped, before initiating therapy with moexipril hydrochloride. (see **PRECAUTIONS, Drug Interactions**, and **ADVERSE REACTIONS**).

In patients with congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension, which may be associated with oliguria or progressive azotemia, and rarely, with acute renal failure and death. In these patients, moexipril hydrochloride therapy should be started under close medical supervision, and patients should be followed closely for the first two weeks of treatment and whenever the dose of moexipril or an accompanying diuretic is increased. Care in avoiding hypotension should also be taken in patients with ischemic heart disease, aortic stenosis, or cerebrovascular disease, in whom an excessive decrease in blood pressure could result in a myocardial infarction or a cerebrovascular accident.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, treated with an intravenous infusion of normal saline. Moexipril hydrochloride treatment usually can be continued following restoration of blood pressure and volume.

Neutropenia/Agranulocytosis

Another ACE inhibitor, captopril, has been shown to cause agranulocytosis and bone marrow depression, rarely in patients with uncomplicated hypertension, but more frequently in hypertensive patients with renal impairment, especially if they also have a collagen-vascular disease such as systemic lupus erythematosus or scleroderma. Although there were no instances of severe neutropenia (absolute neutrophil count <500/mm^3) among patients given moexipril hydrochloride, as with other ACE inhibitors, monitoring of white blood cell counts should be considered for patients who have collagen-vascular disease, especially if the disease is associated with impaired renal function. Available data from clinical trials of moexipril hydrochloride are insufficient to show that moexipril hydrochloride does not cause agranulocytosis at rates similar to captopril.

Fetal/Neonatal Morbidity and Mortality

ACE inhibitors can cause fetal and neonatal morbidity and death when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ACE inhibitors should be discontinued as soon as possible.

The use of ACE inhibitors during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these were caused by the ACE inhibitor exposure.

Fetal and neonatal morbidity do not appear to have resulted from intrauterine ACE inhibitor exposure limited to the first trimester. Mothers who have used ACE inhibitors only during the first trimester should be informed of this. Nonetheless, when patients become pregnant, physicians should make every effort to discontinue the use of moexipril as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to ACE inhibitors will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intraamniotic environment.

If oligohydramnios is observed, moexipril should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not be detected until after the fetus has sustained irreversible injury.

Infants with histories of *in utero* exposure to ACE inhibitors should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion or peritoneal dialysis may be required as means of reversing hypotension and/or substituting for disordered renal function.

Theoretically, the ACE inhibitor could be removed from the neonatal circulation by exchange transfusion, but no experience with this procedure has been reported.

No embryotoxic, fetotoxic, or teratogenic effects were seen in rats or in rabbits treated with up to 90.9 and 0.7 times, respectively, the Maximum Recommended Human Dose (MRHD) on a mg/m^2 basis.

Hepatic Failure

Rarely, ACE inhibitors have been associated with a syndrome that starts with cholestatic jaundice and progresses to fulminant hepatic necrosis and sometimes death. The mechanism of this syndrome is not understood. Patients receiving ACE inhibitors who develop jaundice or marked elevations of hepatic enzymes should discontinue the ACE inhibitor and receive appropriate medical follow-up.

PRECAUTIONS

General

Impaired Renal Function: As a consequence of inhibition of the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. There is no clinical experience of moexipril hydrochloride in the treatment of hypertension in patients with renal failure.

Some hypertensive patients with no apparent preexisting renal vascular disease have developed increases in blood urea nitrogen and serum creatinine, usually minor and transient, especially when moexipril hydrochloride has been given concomitantly with a thiazide diuretic. This is more likely to occur in patients with preexisting renal impairment. There may be a need for dose adjustment of moexipril hydrochloride and/or the discontinuation of the thiazide diuretic.

Evaluation of hypertensive patients should always include assessment of renal function (see **DOSAGE AND ADMINISTRATION**).

Hypertensive Patients With Congestive Heart Failure: In hypertensive patients with severe congestive heart failure, whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with ACE inhibitors, including moexipril hydrochloride, may be associated with oliguria and/or progressive azotemia and, rarely, acute renal failure and/or death.

Hypertensive Patients With Renal Artery Stenosis: In hypertensive patients with unilateral or bilateral renal artery stenosis, increases in blood urea nitrogen and serum creatinine have been observed in some patients following ACE inhibitor therapy. These increases were almost always reversible upon discontinuation of the ACE inhibitor and/or diuretic therapy. In such patients, renal function should be monitored during the first few weeks of therapy.

Hyperkalemia: In clinical trials, persistent hyperkalemia (serum potassium above 5.4 mEq/L) occurred in approximately 1.3% of hypertensive patients receiving moexipril hydrochloride. Risk factors for the development of hyperkalemia with ACE inhibitors include renal insufficiency, diabetes mellitus, and the concomitant use of potassium-sparing diuretics, potassium supplements, and/or potassium-containing salt substitutes, which should be used cautiously, if at all, with moexipril hydrochloride (see **PRECAUTIONS, Drug Interactions**).

Surgery/Anesthesia: In patients undergoing major surgery or during anesthesia with agents that produce hypotension, moexipril may block the effects of compensatory renin release. If hypotension occurs in this setting and is considered to be due to this mechanism, it can be corrected by volume expansion.

Cough: Presumably due to the inhibition of the degradation of endogenous bradykinin, persistent nonproductive cough has been reported with all ACE inhibitors, always resolving after discontinuation of therapy. ACE inhibitor-induced cough should be considered in the differential diagnosis of cough. In controlled trials with moexipril, cough was present in 6.1% of moexipril patients and 2.2% of patients given placebo.

Information for Patients

Food: Patients should be advised to take moexipril one hour before meals (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Angioedema: Angioedema, including laryngeal edema, may occur with treatment with ACE inhibitors, usually occurring early in therapy (within the first month). Patients should be so advised and told to report immediately any signs or symptoms suggesting angioedema (swelling of the face, extremities, eyes, lips, tongue, difficulty in breathing) and to take no more moexipril hydrochloride until they have consulted with the prescribing physician.

Symptomatic Hypotension: Patients should be cautioned that lightheadedness can occur with moexipril hydrochloride, especially during the first few days of therapy. If fainting occurs, the patient should stop taking moexipril hydrochloride and consult the prescribing physician.

All patients should be cautioned that excessive perspiration and dehydration may lead to an excessive fall in blood pressure because of reduction in fluid volume. Other causes of volume depletion such as vomiting or diarrhea may also lead to a fall in blood pressure; patients should be advised to consult their physician if they develop these conditions.

Hyperkalemia: Patients should be told not to use potassium supplements or salt substitutes containing potassium without consulting their physician.

Neutropenia: Patients should be told to report promptly any indication of infection (e.g., sore throat, fever) that could be a sign of neutropenia.

Pregnancy: Female patients of childbearing age should be told about the consequences of second- and third-trimester exposure to ACE inhibitors and should also be told that these consequences do not appear to have resulted from intrauterine ACE inhibitor exposure that has been limited to the first trimester. Patients should be asked to report pregnancies to their physicians as soon as possible.

Drug Interactions

Diuretics: Excessive reductions in blood pressure may occur in patients on diuretic therapy when ACE inhibitors are started. The possibility of hypotensive effects with moexipril hydrochloride can be minimized by discontinuing diuretic therapy for several days or cautiously increasing salt intake before initiation of treatment with moexipril hydrochloride. If this is not possible, the starting dose of moexipril should be reduced. (See **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Potassium Supplements and Potassium-Sparing Diuretics: Moexipril hydrochloride can increase serum potassium because it decreases aldosterone secretion. Use of potassium-sparing diuretics (spironolactone, triamterene, amiloride) or potassium supplements concomitantly with ACE inhibitors can increase the risk of hyperkalemia. Therefore, if concomitant use of such agents is indicated, they should be given with caution and the patient's serum potassium should be monitored.

MOEXIPRIL HYDROCHLORIDE TABLETS, 7.5 mg and 15 mg

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JUL 18 2003

icoagulants: Interaction studies with warfarin failed to identify any clinically t effect on the serum concentrations of the anticoagulant or on its anticoagulant

Increased serum lithium levels and symptoms of lithium toxicity have been in patients receiving ACE inhibitors during therapy with lithium. These ıould be coadministered with caution, and frequent monitoring of serum evels is recommended. If a diuretic is also used, the risk of lithium toxicity ncreased.

ients: No clinically important pharmacokinetic interactions occurred when il hydrochloride was administered concomitantly with hydrochlorothiazide, or cimetidine.

l hydrochloride has been used in clinical trials concomitantly with calcium-blocking agents, diuretics, H_2 blockers, digoxin, oral hypoglycemic agents, lesterol-lowering agents. There was no evidence of clinically important interactions.

genesis, Mutagenesis, Impairment of Fertility

nce of carcinogenicity was detected in long-term studies in mice and rats up to 14 or 27.3 times the Maximum Recommended Human Dose on a mg/m^2 basis.

genicity was detected in the Ames test and microbial reverse mutation ith and without metabolic activation, or in an *in vivo* nucleus anomaly test. increased chromosomal aberration frequency in Chinese hamster ovary detected under metabolic activation conditions at a 20-hour harvest time.

ction studies have been performed in rabbits at oral doses up to 0.7 times D on a mg/m^2 basis, and in rats up to 90.9 times the MRHD on a mg/m^2 lo indication of impaired fertility, reproductive toxicity, or teratogenicity erved.

cy

cy Categories C (first trimester) and D (second and third trimesters). TNINGS, Fetal/Neonatal Morbidity and Mortality.

Mothers

known whether moexipril hydrochloride is excreted in human milk. many drugs are excreted in human milk, caution should be exercised ıexipril hydrochloride is given to a nursing mother.

Use

ıd effectiveness of moexipril hydrochloride in pediatric patients have not ıblished.

Use

tudies of moexipril hydrochloride did not include sufficient numbers of aged 65 and over to determine whether they respond differently from subjects. Other reported clinical experience has not identified differences ıses between the elderly and younger patients. In general, dose selection lerly patient should be cautious, usually starting at the lower end of the nge, reflecting the greater frequency of decreased hepatic, renal, or cardiac and of concomitant disease or other drug therapy.

E REACTIONS

l hydrochloride has been evaluated for safety in more than 2500 patients ertension; more than 250 of these patients were treated for approximately The overall incidence of reported adverse events was only slightly greater s treated with moexipril hydrochloride than patients treated with placebo.

adverse experiences were usually mild and transient, and there were no es in adverse reaction rates related to gender, race, age, duration of therapy, ily dosage within the range of 3.75 mg to 60 mg. Discontinuation of therapy of adverse experiences was required in 3.4% of patients treated with hydrochloride and in 1.8% of patients treated with placebo. The most reasons for discontinuation in patients treated with moexipril hydrochloride gh (0.7%) and dizziness (0.4%).

se experiences considered at least possibly related to treatment that at any dose in placebo-controlled trials of once-daily dosing in more than tients treated with moexipril hydrochloride alone and that were at least as in the moexipril hydrochloride group as in the placebo group are shown owing table:

ADVERSE EVENTS IN PLACEBO-CONTROLLED STUDIES

VERSE VENT	MOEXIPRIL HYDROCHLORIDE (N=674)	PLACEBO (N=226)
	N (%)	N (%)
gh Increased	41 (6.1)	5 (2.2)
ness	29 (4.3)	5 (2.2)
hea	21 (3.1)	5 (2.2)
yndrome	21 (3.1)	0 (0)
ue	16 (2.4)	4 (1.8)
yngitis	12 (1.8)	2 (0.9)
ling	11 (1.6)	0 (0)
	11 (1.6)	2 (0.9)
gia	9 (1.3)	0 (0)

erse events occurring in more than 1% of patients on moexipril that were frequent on placebo include: headache, upper respiratory infection, pain, spepsia, nausea, peripheral edema, sinusitis, chest pain, and urinary frequency. **NINGS** and **PRECAUTIONS** for discussion of anaphylactoid reactions, na, hypotension, neutropenia/agranulocytosis, second and third trimester natal morbidity and mortality, hyperkalemia, and cough.

ntially important adverse experiences reported in controlled or uncontrolled als in less than 1% of moexipril patients or that have been attributed to inhibitors include the following:

icular: Symptomatic hypotension, postural hypotension, or syncope were 1750 (0.51%) patients; these reactions led to discontinuation of therapy lled trials in 3/1254 (0.24%) patients who had received moexipril ride monotherapy and in 1/344 (0.3%) patients who had received moexipril ride with hydrochlorothiazide (see **PRECAUTIONS** and **WARNINGS**). Other ents included angina/myocardial infarction, palpitations, rhythm disturbances, rovascular accident.

hypertensive patients with no apparent preexisting renal disease, 1% of eceiving moexipril hydrochloride alone and 2% of patients receiving hydrochloride with hydrochlorothiazide experienced increases in serum to at least 140% of their baseline values (see **PRECAUTIONS** and **AND ADMINISTRATION**).

estinal: Abdominal pain, constipation, vomiting, appetite/weight change, , pancreatitis, hepatitis.

ry: Bronchospasm, dyspnea, eosinophilic pneumonitis.

t: Renal insufficiency, oliguria.

gic: Apparent hypersensitivity reactions manifested by urticaria, rash, s, pruritus, photosensitivity, alopecia.

al and Psychiatric: Drowsiness, sleep disturbances, nervousness, mood anxiety.

gioedema (see **WARNINGS**), taste disturbances, tinnitus, sweating, malaise, hemolytic anemia.

aboratory Test Findings

and Blood Urea Nitrogen: As with other ACE inhibitors, minor increases ea nitrogen or serum creatinine, reversible upon discontinuation of therapy, rved in approximately 1% of patients with essential hypertension who were treated with moexipril hydrochloride. Increases are more likely to occur in patients receiving concomitant diuretics and in patients with compromised renal function (see **PRECAUTIONS, General**).

Other (causal relationship unknown): Clinically important changes in standard laboratory tests were rarely associated with moexipril hydrochloride administration.

Elevations of liver enzymes and uric acid have been reported. In trials, less than 1% of moexipril-treated patients discontinued moexipril hydrochloride treatment because of laboratory abnormalities. The incidence of abnormal laboratory values with moexipril was similar to that in the placebo-treated group.

Serum Electrolytes: Hyperkalemia (See **PRECAUTIONS**), hyponatremia.

OVERDOSAGE

Human overdoses of moexipril have not been reported. In case reports of overdoses with other ACE inhibitors, hypotension has been the principal adverse effect noted. Single oral doses of 2 g/kg moexipril were associated with significant lethality in mice. Rats, however, tolerated single oral doses of up to 3 g/kg.

No data are available to suggest that physiological maneuvers (e.g., maneuvers to change the pH of the urine) would accelerate elimination of moexipril and its metabolites. The dialyzability of moexipril is not known.

Angiotensin II could presumably serve as a specific antagonist-antidote in the setting of moexipril overdose, but angiotensin II is essentially unavailable outside of research facilities. Because the hypotensive effect of moexipril is achieved through vasodilation and effective hypovolemia, it is reasonable to treat moexipril overdose by infusion of normal saline solution. In addition, renal function and serum potassium should be monitored.

DOSAGE AND ADMINISTRATION

Hypertension

The recommended initial dose of moexipril hydrochloride tablets in patients not receiving diuretics is 7.5 mg, one hour prior to meals, once daily. Dosage should be adjusted according to blood pressure response. The antihypertensive effect of moexipril hydrochloride may diminish towards the end of the dosing interval. Blood pressure should, therefore, be measured just prior to dosing to determine whether satisfactory blood pressure control is obtained. If control is not adequate, increased dose or divided dosing can be tried. The recommended dose range is 7.5 to 30 mg daily, administered in one or two divided doses one hour before meals. Total daily doses above 60 mg a day have not been studied in hypertensive patients.

In patients who are currently being treated with a diuretic, symptomatic hypotension may occasionally occur following the initial dose of moexipril hydrochloride. The diuretic should, if possible, be discontinued for 2 to 3 days before therapy with moexipril hydrochloride is begun, to reduce the likelihood of hypotension (see **WARNINGS**). If the patient's blood pressure is not controlled with moexipril hydrochloride alone, diuretic therapy may then be reinstituted. If diuretic therapy cannot be discontinued, an initial dose of 3.75 mg of moexipril hydrochloride tablets should be used with medical supervision until blood pressure has stabilized (see **WARNINGS** and **PRECAUTIONS, Drug Interactions**).

Dosage Adjustment in Renal Impairment

For patients with a creatinine clearance ≤40 mL/min/1.73 m^2, an initial dose of 3.75 mg once daily should be given cautiously. Doses may be titrated upward to a maximum daily dose of 15 mg.

HOW SUPPLIED

Moexipril hydrochloride tablets, 7.5 mg, are pink, film-coated, oval, convex tablets debossed "17" on one side and bisected on the other. They are available in bottles of 100 and 1000.

Moexipril hydrochloride tablets, 15 mg, are pink, film-coated, oval, convex tablets debossed "5150" on one side and "93" to the left of a bisect on the other side. They are available in bottles of 100 and 1000.

Store at controlled room temperature, between 15° and 30°C (59° and 86°F). [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

Manufactured By:
TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

Printed in U.S.A.
Iss: 6/2002

Ap 5-8-03
76-204

NDC 0093-0017-10

MOEXIPRIL HYDROCHLORIDE Tablets
7.5 mg APPROVED

Each tablet contains:
Moexipril Hydrochloride 7.5 mg

℞ only

1000 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature, between 15° and 30°C (59° and 86°F). [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

PG Iss. 10/2000

N 3 0093-0017-10 0

MAY - 8 2003

NDC 0093-0017-01

MOEXIPRIL HYDROCHLORIDE Tablets
7.5 mg

Each tablet contains:
Moexipril Hydrochloride 7.5 mg

℞ only

100 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature, between 15° and 30°C (59° and 86°F). [See USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

PG Iss. 10/2000

0093-0017-01

APPROVED

MAY - 8 2003

NDC 0093-5150-10

MOEXIPRIL HYDROCHLORIDE Tablets
15 mg

Each tablet contains:
Moexipril Hydrochloride 15 mg

℞ only

1000 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature, between 15° and 30°C (59° and 86°F). [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

PG Iss. 10/2000

N 3 0093-5150-10 9

APPROVED

MAY - 8 2003

NDC 0093-5150-01

MOEXIPRIL HYDROCHLORIDE Tablets
15 mg

Each tablet contains:
Moexipril Hydrochloride 15 mg

APPROVED

℞ only

100 TABLETS

TEVA

Usual Dosage: See package insert for full prescribing information.

Store at controlled room temperature, between 15° and 30°C (59° and 86°F). [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required).

KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

TEVA PHARMACEUTICALS USA
Sellersville, PA 18960

PG Iss. 10/2000

0093-5150-01

MAY - 8 2003

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-204

CSO LABELING REVIEW(S)

APPROVAL SUMMARY
REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76-204
Date of Submission: July 19, 2002
Applicant's Name: Teva Pharmaceuticals USA
Established Name: Moexipril Hydrochloride Tablets, 7.5 mg and 15 mg

---

APPROVAL SUMMARY

1. **Do you have 12 Final Printed Labels and Labeling? Yes**

2. **CONTAINER** - Bottles of 100 and 1000 tablets
   Satisfactory in **final print** as of the July 19, 2002 submission.
   (See blue jackets volume 3.1)

3. **PROFESSIONAL PACKAGE INSERT**
   Satisfactory in **final print** as of the July 19, 2002 submission.
   (See blue jacket volume 3.1)

4. **Revisions needed post-approval:** None

5. **Patent/ Exclusivities:**
   Patent Data – NDA 20-312

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4743450	Feb 24, 2007	None		Paragraph IV	None

Exclusivity Data– NDA 20-312

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

BASIS OF APPROVAL:
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Univasc®
NDA Number: 20-312
NDA Drug Name: Univasc®
NDA Firm: Schwarz Pharma, Inc.
Date of Approval of NDA Insert and supplement #: 20-312/S-016: Approved April 11, 2001.
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved container labels for the reference listed drug.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	

Error Prevention Analysis	Yes	No	N.A.
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			

Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. The labeling submitted by the firm was based on the most recently approved labeling for Univasc. Labeling was recently approved on April 11, 2001/S-016 for the RLD.
2. **Patent/ Exclusivities:**

Patent Data – NDA 20-312

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4743450	Feb 24, 2007	None		Paragraph IV	None

Exclusivity Data– NDA 20-312

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. Storage/Dispensing Conditions:
   NDA: Store, tightly closed, at controlled room temperature. Protect from excessive moisture.
   ANDA: Store at controlled room temperature, between 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].
   NDA: Dispense in tight containers as described in USP-NF. Protect from excessive moisture.
   ANDA:Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

   We will not ask the firm to revise.
4. Product Line:
   The innovator markets their product in two strengths (7.5mg and 15mg). They are packaged in unit of use bottles of 90 tablets and bottles of 100 tablets.

The applicant proposes to market their product as 7.5mg and 15mg strength tablets packages in bottles of 100 and 1000 tablets.

5. The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95. (See pg.8789 and 8796 in volume B. 1.4)
6. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components appearing on page** 7727, Vol B. 1.2.
7. Container/Closure(See page 8427 in Vol B. 1.4)
   Containers: HDPE
   Closure: Non-CRC closures for both 100 and 1000 count bottles.
8. All manufacturing will be done by Teva Pharmaceuticals, USA. (See pg. 7960 in vol. B. 1.3)

Date of Review: 8/28/02 Date of Submission: 7/19/02

Primary Reviewer: Jim Barlow Date: 8/29/02

Team Leader: John Grace Date:

John J Grace 8/29/2002

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cc:

ANDA: 76204
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
V:\FIRMSNZ\TEVA\LTRS&REV\76204ap.s
Review

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	76-204
Date of Submission:	April 2, 2002
Applicant's Name:	Teva Pharmaceuticals USA
Established Name:	Moexipril Hydrochloride Tablets, 7.5 mg and 15 mg

---

Labeling Deficiencies:

1. **CONTAINER** – Bottles of 100 and 1000 tablets
   Satisfactory in **draft** as of the July 16, 2001 submission.

2. **PACKAGE INSERT**
   ADVERSE REACTIONS

   Clinical Laboratory Test Findings
   Relocate the following to be the last subsection in the ADVERSE REACTIONS section and to read as follows –

   ....in the placebo-treated group.

   Serum Electrolytes: Hyperkalemia (See PRECAUTIONS), hyponatremia.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	**Yes**	**No**	**N.A.**
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. The labeling submitted by the firm was based on the most recently approved labeling for Univasc. Labeling was recently approved on April 11, 2001/S-016 for the RLD.
2. **Patent/ Exclusivities:**

Patent Data – NDA 20-312

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4743450	Feb 24, 2007	None		Paragraph IV	None

Exclusivity Data– NDA 20-312

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. Storage/Dispensing Conditions:
   NDA: Store, tightly closed, at controlled room temperature. Protect from excessive moisture.
   ANDA: Store at controlled room temperature, between 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].
   NDA: Dispense in tight containers as described in USP-NF. Protect from excessive moisture.
   ANDA:Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

   We will not ask the firm to revise.
4. Product Line:
   The innovator markets their product in two strengths (7.5mg and 15mg). They are packaged in unit of use bottles of 90 tablets and bottles of 100 tablets.

   The applicant proposes to market their product as 7.5mg and 15mg strength tablets packages in bottles of 100 and 1000 tablets.
5. The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95. (See pg.8789 and 8796 in volume B. 1.4)
6. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components appearing on page** 7727, Vol B. 1.2.
7. Container/Closure(See page 8427 in Vol B. 1.4)
   Containers: HDPE
   Closure: Non-CRC closures for both 100 and 1000 count bottles.
8. All manufacturing will be done by Teva Pharmaceuticals, USA. (See pg. 7960 in vol. B. 1.3)

Date of Review: 6/24/02 Date of Submission: 4/2/02
Primary Reviewer: Jim Barlow Date: 6/25/02

Team Leader: John Grace Date: John D Grace 6/25/2002

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cc:
ANDA: 76-204
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number:	76-204
Date of Submission:	July 16, 2001
Applicant's Name:	Teva Pharmaceuticals USA
Established Name:	Moexipril Hydrochloride Tablets, 7.5 mg and 15 mg

---

Labeling Deficiencies:

1. **CONTAINER** – Bottles of 100 and 1000 tablets
   Satisfactory in **draft** as of the July 16, 2001 submission.

2. **PACKAGE INSERT**
   a. GENERAL COMMENTS
   Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or on the title of the package insert

   b. INDICATIONS AND USAGE
   Revise the first sentence to read as follows-

   Moexipril hydrochloride tablets are indicated...

   d. CONTRAINDICATIONS
   Revise the first sentence to read as follows -

   Moexipril hydrochloride tablets are contraindicated in...

   e. WARNINGS
   i. Relocate the "Geriatric Use" subsection to directly <u>follow</u> the "Pediatric Use" subsection.

   ii. Revise the "Geriatric Use" subsection to read as follows -

   Clinical studies of moexipril hydrochloride did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. Other reported clinical experience has not identified differences in responses between the elderly and younger patients. In general, dose selection for an elderly patient should be cautious, usually starting at the lower end of the dosing range, reflecting the greater frequency of decreased, renal, or cardiac function, and of concomitant disease or other drug therapy.

   f. ADVERSE REACTIONS
   i. *Dermatologic:* Revise to include "alopecia" as and adverse reaction-

   ...pruritis, photosensitivity, alopecia.

   ii. Clinical Laboratory Test Findings
   Include the following directly above the "*Creatinine and Blood Urea Nitrogen*" subsection -

   Serum Electrolytes: Hyperkalemia (See PRECAUTIONS), hyponatremia.

Please revise your labels and labeling, as instructed above, and submit in final print or draft if you prefer.

Prior to approval, it may be necessary to further revise your labeling subsequent to approved changes for the reference listed drug. We suggest that you routinely monitor the following website for any approved changes-http://www.fda.gov/cder/ogd/rld/labeling_review_branch.html

To facilitate review of your next submission, and in accordance with 21 CFR 314.94(a)(8)(iv), please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

Wm. Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

APPEARS THIS WAY
ON ORIGINAL

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		X	
Is this product a USP item? If so, USP supplement in which verification was assured. USP 24		X	
Is this name different than that used in the Orange Book?		X	
If not USP, has the product name been proposed in the PF?		X	
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		X	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			X
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			X
Packaging			
Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR.		X	
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC.		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			X
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			X
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
Labeling			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		X	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Labeling(continued)	Yes	No	N.A.
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		X	

Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR			
Is the scoring configuration different than the RLD?		X	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		X	
Inactive Ingredients: (FTR: List page # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?			X
Do any of the inactives differ in concentration for this route of administration?		X	
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?		X	
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?			
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		X	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		X	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?			X
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?			
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?		X	
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.			
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?		X	
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues?: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.			

FOR THE RECORD:

1. The labeling submitted by the firm was **NOT** based on the most recently approved labeling for Univasc. Labeling was recently approved on April 11, 2001/S-016 for the RLD. Revisions were requested.
2. **Patent/ Exclusivities:**

Patent Data – NDA 20-312

Patent No.	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4743450	Feb 24, 2007	None		Paragraph IV	None

Exclusivity Data– NDA 20-312

Code	Reference	Expiration	Labeling Impact
None	There is no unexpired exclusivity for this product in the Orange Book Database.	N/A	None

3. Storage/Dispensing Conditions:
   NDA: Store, tightly closed, at controlled room temperature. Protect from excessive moisture.
   ANDA: Store at controlled room temperature, between 15 to 30°C (59 to 86°F) [see USP Controlled Room Temperature].
   NDA: Dispense in tight containers as described in USP-NF. Protect from excessive moisture.
   ANDA:Dispense in a tight, light-resistant container as defined in the USP, with a child-resistant closure (as required). KEEP THIS AND ALL MEDICATIONS OUT OF THE REACH OF CHILDREN.

   We will not ask the firm to revise.
4. Product Line:
   The innovator markets their product in two strengths (7.5mg and 15mg). They are packaged in unit of use bottles of 90 tablets and bottles of 100 tablets.

   The applicant proposes to market their product as 7.5mg and 15mg strength tablets packages in bottles of 100 and 1000 tablets.
5. The tablet imprinting have been accurately described in the HOW SUPPLIED section as required by 21CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95. (See pg.8789 and 8796 in volume B. 1.4)
6. Inactive Ingredients:
   The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the **statement of components appearing on page** 7727, Vol B. 1.2.
7. Container/Closure(See page 8427 in Vol B. 1.4)
   Containers: HDPE
   Closure: Non-CRC closures for both 100 and 1000 count bottles.
8. All manufacturing will be done by Teva Pharmaceuticals, USA. (See pg. 7960 in vol. B. 1.3)

Date of Review: 11/19/01 Date of Submission: 7/16/01

Primary Reviewer: Jim Barlow Date: 11/19/01

Team Leader: John Grace Date:

John J. Grace 11/27/2000

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cc:

ANDA: 76-204
DUP/DIVISION FILE
HFD-613/JBarlow/JGrace (no cc)
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Review

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-204

CHEMISTRY REVIEW(S)

1. CHEMISTRY REVIEW NO: 1

2. ANDA: 76-204

3. NAME AND ADDRESS OF APPLICANT:
Teva Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
Telephone: 215-591-3000
Facsimile: 215-591-8812

4. LEGAL BASIS for ANDA SUBMISSION:
Univasc Tablets (7.5 mg and 15 mg), the reference listed drug held by Schwarz Pharma (NDA 20-312).

Teva certifies that a single U.S. Patent 4,743,450 has been listed for this drug product (Orange Book). The applicant claims that the listed patent is invalid, unenforceable, and will not be infringed (Paragraph IV Certification).

Teva certifies that there are no listed exclusivities for the referenced product.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Moexipril Hydrochloride Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original Submission: July 16, 2001
Amendment: July 20, 2001
Amendment: August 3, 2001

10. PHARMACOLOGICAL CATEGORY: Antihypertensive

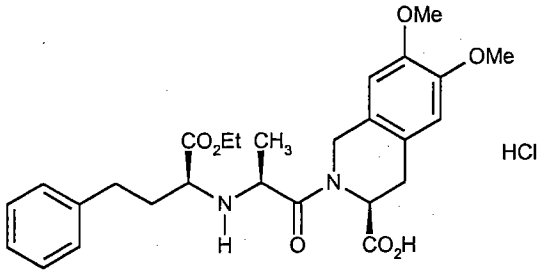
11. OTC/R_x: R_x

12. RELATED IND/NDA/DMF(s): See DMF Checklist

13. DOSAGE FORM: Coated Tablets

14. STRENGTH: 7.5 mg and 15 mg

15. CHEMICAL NAMES AND STRUCTURE:
[3S-[2[R*(R*)],3R*]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, monohydrochloride;
$C_{27}H_{34}N_2O_7 \cdot HCl$, MW = 535.04; CAS 82586-52-5;
Angiotensin-Converting Enzyme (ACE) Inhibitor.



16. RECORDS AND REPORTS: N/A

17. COMMENTS: **First Generic**

18. CONCLUSIONS AND RECOMMENDATIONS: **Not Approvable (Minor)**

19. REVIEWER: ARaw

DATE COMPLETED: 10/31/01
Revised: 12/19/01

cc: ANDA 76-204
DIV FILE

Endorsements:
HFD-623/ARaw, Ph.D./ Anne Raw 12/19/01
HFD-623/AMueller, Ph.D./ AMueller 12-19-01

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F/T by:

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Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO: 2

2. ANDA: 76-204

3. NAME AND ADDRESS OF APPLICANT:
Teva Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
Telephone: 215-591-3000
Facsimile: 215-591-8812

4. LEGAL BASIS for ANDA SUBMISSION: See Chemistry Review #1

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Moexipril Hydrochloride Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original Submission: July 16, 2001
Amendment: July 20, 2001
Amendment: August 3, 2001
Amendment: August 14, 2001
Amendment: November 26, 2001
Amendment: January 29, 2002
Amendment: April 2, 2002
Amendment (Bioequivalence): May 31, 2002

10. PHARMACOLOGICAL CATEGORY: Antihypertensive

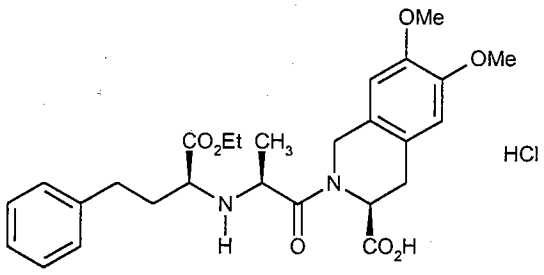
11. OTC/R_x: R_x

12. RELATED IND/NDA/DMF(s): See DMF Checklist

13. DOSAGE FORM: Coated Tablets

14. STRENGTH: 7.5 mg and 15 mg

15. CHEMICAL NAMES AND STRUCTURE:
[3S-[2[R*(R*)],3R*]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, monohydrochloride;
$C_{27}H_{34}N_2O_7 \cdot HCl$, MW = 535.04; CAS 82586-52-5;
Angiotensin-Converting Enzyme (ACE) Inhibitor.



16. RECORDS AND REPORTS: N/A

17. COMMENTS: **First Generic**

18. CONCLUSIONS AND RECOMMENDATIONS: **Not Approvable - Minor**

19. REVIEWER: ARaw

DATE COMPLETED: 4/29/02
REVISED: 7/18/02, 8/23/02

cc: ANDA 76-204
DIV FILE

Endorsements:
HFD-623/ARaw, Ph.D./ Andre' Raw 8/23/02
HFD-623/AMueller, Ph.D./
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Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO: 3

2. ANDA: 76-204

3. NAME AND ADDRESS OF APPLICANT:
Teva Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
Telephone: 215-591-3000
Facsimile: 215-591-8812

4. LEGAL BASIS for ANDA SUBMISSION: See Chemistry Review #1

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Moexipril Hydrochloride Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original Submission: July 16, 2001
Amendment: July 20, 2001
Amendment: August 3, 2001
Amendment (Bioequivalence): August 14, 2001
Amendment (Patent): November 26, 2001
Amendment (Bioequivalence): January 29, 2002
Amendment (CMC): April 2, 2002
Amendment (Bioequivalence): May 31, 2002
Amendment (Labeling): July 19, 2002
Amendment (CMC): October 7, 2002
Telephone Amendment (CMC): January 23, 2003

10. PHARMACOLOGICAL CATEGORY: Antihypertensive

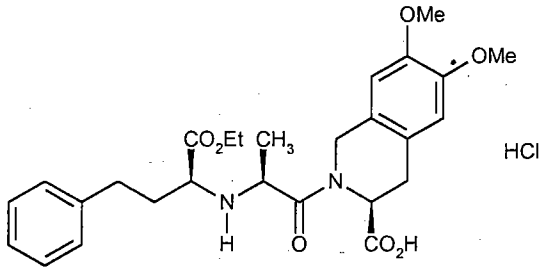
11. OTC/R_x: R_x

12. RELATED IND/NDA/DMF(s): See DMF Checklist

13. DOSAGE FORM: Coated Tablets

14. STRENGTH: 7.5 mg and 15 mg

15. CHEMICAL NAMES AND STRUCTURE:
[3S-[2[R*(R*)],3R*]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, monohydrochloride;
$C_{27}H_{34}N_2O_7 \cdot HCl$, MW = 535.04; CAS 82586-52-5;
Angiotensin-Converting Enzyme (ACE) Inhibitor.



16. RECORDS AND REPORTS: N/A

17. COMMENTS: **First Generic**

18. CONCLUSIONS AND RECOMMENDATIONS: **Not Approvable.**

19. REVIEWER: ARaw

DATE COMPLETED: 10/23/02
REVISED: 1/23/03, 2/07/03

cc: ANDA 76-204
DIV FILE

Endorsements:
HFD-623/ARaw, Ph.D./ 1/10/03
HFD-623/AMueller, Ph.D./ 2-11-03
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F/T by:

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Page(s) of trade secret and /or confidential commercial information

1. CHEMISTRY REVIEW NO.: 4

2. ANDA: 76-204

3. NAME AND ADDRESS OF APPLICANT:
Teva Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454
Telephone: 215-591-3000
Facsimile: 215-591-8812

4. LEGAL BASIS for ANDA SUBMISSION: See Chemistry Review #1
Court decision (March 24, 2003) ruled Patent US4,743,450 is not infringed by TEVA.

5. SUPPLEMENT(s): N/A

6. PROPRIETARY NAME: N/A

7. NONPROPRIETARY NAME: Moexipril Hydrochloride Tablets

8. SUPPLEMENT(s) PROVIDE(s) FOR: N/A

9. AMENDMENTS AND OTHER DATES:
Original Submission: July 16, 2001
Amendment: July 20, 2001
Amendment: August 3, 2001
Amendment (Bioequivalence): August 14, 2001
Amendment (Patent): November 26, 2001
Amendment (Bioequivalence): January 29, 2002
Amendment (CMC): April 2, 2002
Amendment (Bioequivalence): May 31, 2002
Amendment (Labeling): July 19, 2002
Amendment (CMC): October 7, 2002
Telephone Amendment (CMC): January 23, 2003
Amendment (CMC): February 26, 2003
New Correspondence: Court Decision Notification (March 26, 2003)

10. PHARMACOLOGICAL CATEGORY: Antihypertensive

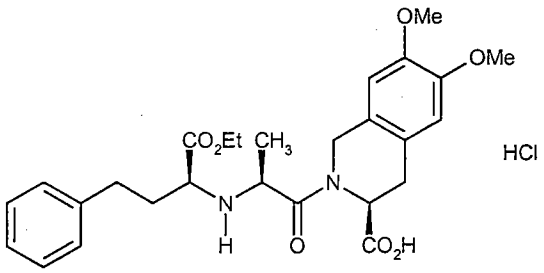
11. OTC/R_x: R_x

12. RELATED IND/NDA/DMF(s): See DMF Checklist

13. DOSAGE FORM: Coated Tablets

14. STRENGTH: 7.5 mg and 15 mg

15. CHEMICAL NAMES AND STRUCTURE:
[3S-[2[R*(R*)],3R*]]-2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]amino]-1-oxopropyl]-1,2,3,4-tetrahydro-6,7-dimethoxy-3-isoquinolinecarboxylic acid, monohydrochloride;
$C_{27}H_{34}N_2O_7 \cdot HCl$, MW = 535.04; CAS 82586-52-5;
Angiotensin-Converting Enzyme (ACE) Inhibitor.



16. RECORDS AND REPORTS: N/A

17. COMMENTS: **First Generic**

18. CONCLUSIONS AND RECOMMENDATIONS: **Approvable.**

19. REVIEWER: S. Dhanesar DATE COMPLETED: 03/28/03

cc: ANDA 76-204
DIV FILE

Endorsements:
HFD-623/SDhanesar, Ph.D./ 3/31/03
HFD-623/AMueller, Ph.D./ 4-2-03
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-204

BIOEQUIVALENCE REVIEW(S)

Tim 8-31-01

1-1

NOV 21 2001

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-204 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Moexipril HCl Tablets, 7.5 mg and 15 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The dissolution testing of the test and reference tablets should be repeated taking samples at early time points (5, 10, 15, 20 and 30 minutes).
2. The data submitted in orange jackets vol. 1.5, 1.6 and 1.7 are repeated in orange jackets 1.8, 1.9 and 1.10 respectively. Please explain.
3. Please submit complete failed fasting bioequivalence study data including potency, content uniformity, and dissolution results.
4. Please note that in future, you should submit the chromatograms from 20% of serially selected subjects. Also, the subjects whose chromatograms are to be submitted should be defined prior to the analysis of the study samples.

Sincerely yours,

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Team 1

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-204 SPONSOR : Teva

DRUG AND DOSAGE FORM : Moexipril Hydrochloride Tablets

STRENGTH(S) : 7.5 mg and 15 mg

TYPES OF STUDIES : Fasting and Fed

CLINICAL STUDY SITE(S) : ———

ANALYTICAL SITE(S) : ——— (DSI REPORT)

STUDY SUMMARY : The fasting and fed studies are acceptable.

DISSOLUTION : The dissolution testing should be conducted in ———
——— The test products meet specification of NLT — (Q) in 20 minutes.

DSI INSPECTION STATUS

Inspection needed: YES	Inspection status:	Inspection results:
First Generic __Yes__	Inspection requested: 1/25/02	Acceptable
New facility _____	Inspection completed: 11/27/02	
For cause _____		
Other _____		

PRIMARY REVIEWER : Kuldeep R. Dhariwal, Ph.D. BRANCH : II

INITIAL : KRD DATE : 12/4/02

TEAM LEADER : S. Nerurkar, Ph. D. BRANCH : II

INITIAL : SN DATE : 12/9/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 12/10/02

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-204 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Moexipril Hydrochloride Tablets
7.5 mg, 15 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in [redacted] The test product should meet the following specifications:

Not less than [redacted] (Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

DEC 10 2002

Craig

Moexipril HCl Tablets	Teva Pharmaceuticals USA
7.5 mg, 15 mg	1090 Horsham Road, PO Box 1090
ANDA 76-204	North Wales, PA 19454
Reviewer: Kuldeep R. Dhariwal	DSI Inspection Report Date: 11/27/02
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Review of DSI Report

The Division of Scientific Investigations (DSI) conducted audits of the following bioequivalence studies submitted in this ANDA:

Protocol #B006539: A relative bioavailability study of moexipril HCl 15 mg tablets under fasting conditions.
Protocol #B016502: A relative bioavailability study of moexipril HCl 15 mg tablets under non-fasting conditions.
Protocol #B006501: A relative bioavailability study of moexipril HCl 15 mg tablets under fasting conditions.

The clinical portions of studies B016502 and B006501 were conducted at [redacted]. The clinical portion of the study B006539 was conducted at [redacted]. The analytical portions of all the three studies were conducted at [redacted].

Form 483 was not issued at [redacted]

The analytical portion of the audit at [redacted] focussed on studies B006539 and B016502. Form 483 was issued to [redacted] at the conclusion of the inspection.

Issue 1: Failure to assure accuracy of subject moexipril concentrations in Run 7 (study B006539) and Run 15 (B016502). An interfering peak in the chromatograms of the subject samples affected the quantitation of moexipril in the runs. The chromatograms for the calibration standard and quality control samples in the runs did not exhibit such interference.

An unknown merging peak significantly interfered with the integration of moexipril peak in many chromatograms for subject 20 (Run 7) of study B006539. Similar interference also affected the integration of moexipril peak in chromatograms for subject 32 (Run 15) of study B016502. Specifically, the chromatograms for subject samples 32,0.5,1 and 32,1.25,2 correspond to C_{max} levels for subject 32. In contrast, the chromatograms for calibration standards and quality controls in Runs 07 and 15 did not exhibit the interference found in the subject chromatograms. The DSI recommends that the bioequivalence should be reestimated following deletion of moexipril data for:

a. subject 20 in study B006539
b. subject 32 in study B016502

Reviewer's comments: The firm in its original submission included the chromatograms from 20% subjects for both the studies. However, the chromatograms from subject 20 in study B006539 and subject 32 in study B016502 were not included. Therefore this reviewer could not see the peak interference observed by the DSI.

As per DSI suggestion, this reviewer deleted the data from these two subjects and repeated statistical analyses.

Study #B006539: The statistical analysis was repeated deleting subject #12 due to pre-dose moexipril levels greater than 5% and subject #20 due to above reasons. The results are given in figure 1 and tables 1 and 2. The study remains acceptable.

Study # B016502: The statistical analysis was repeated deleting subject #32 due to above reasons. The results are given in figure 2 and tables 3 and 4. The study remains acceptable.

Issue 2. Integration of chromatographic peaks was not consistent in Run 8 (study B006539). For example, automatic integration of moexiprilat peak in the 1/0.2 ng/mL calibration standard was different from the manual integration of subject samples 485, 494 and 497.

[redacted] automatically integrated moexiprilat peaks by excluding the shoulder on the peaks in the chromatograms for standard 1/0.2 and QC 2.5/0.5. In contrast, [redacted] included the shoulder when integrating moexiprilat peaks in chromatograms for subject samples 12,10,1; 12,12,2; 12,48,1; 12,48,2; and 12,96,1. The DSI concludes that this finding is not likely to significantly affect the accuracy of moexiprilat concentrations.

Reviewer's comments: No action is necessary.

Conclusion: The analytical results submitted by the firm are acceptable.

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Teva on its moexipril 15 mg tablets, lot #1127-005 comparing it to Univasc® 15 mg tablets, lot #0070801 manufactured by Schwarz Pharma has been found acceptable to the Division of Bioequivalence. The study demonstrates that Teva's moexipril 15 mg tablets are bioequivalent to the reference product, Univasc® 15 mg tablets manufactured by Schwarz Pharma.
2. The bioequivalence study conducted under non-fasting conditions by Teva on its moexipril 15 mg tablets, lot #1127-005 comparing it to Univasc® 15 mg tablets, lot #0070801 manufactured by Schwarz Pharma is acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of moexipril 15 mg tablets manufactured by Teva is similar to the reference product, Univasc® 15 mg tablets manufactured by Schwarz Pharma.
3. The dissolution testing conducted by the firm on its 7.5 mg and 15 mg tablets is acceptable. The formulation for 7.5 mg tablets is proportionally similar to the 15 mg tablet, which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements

for 7.5 mg tablets of the test product is granted. The 7.5 mg test tablets are therefore deemed bioequivalent to Univasc® 7.5 mg tablets manufactured by Schwarz Pharma.

4. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in [redacted] The test products should meet the following specifications:
   NLT [redacted] (Q) in 20 minutes.

K Dhariwal 12/4/02

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR _____ Date 12/9/2002

Concur _____ Date 12/10/02
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

Table 1

MEAN PLASMA MOEXIPRIL LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS IN FASTING STUDY (#B006539)
N=48 (EXCLUDING SUBJECT #12 AND 20)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.167	0.20	0.75	0.61	1.05	0.33
0.333	4.88	4.15	8.41	8.33	0.58
0.5	14.79	8.53	18.05	12.58	0.82
0.75	22.30	11.64	20.24	10.17	1.10
1	20.93	12.61	18.48	10.18	1.13
1.25	16.31	9.78	15.10	9.87	1.08
1.5	12.31	7.65	12.13	8.61	1.01
1.75	9.70	6.24	9.38	6.81	1.03
2	7.89	5.57	7.52	5.70	1.05
2.5	4.99	3.78	4.75	4.18	1.05
3	3.16	2.62	3.04	2.66	1.04
4	1.35	1.74	1.24	1.42	1.09
5	0.56	0.84	0.47	0.74	1.20
6	0.35	0.68	0.18	0.47	2.00
7	0.07	0.34	0.04	0.21	1.62
8	0.02	0.15	0.00	0.00	.
10	0.00	0.00	0.00	0.00	.
12	0.00	0.00	0.00	0.00	.
24	0.00	0.00	0.00	0.00	.
48	0.00	0.00	0.00	0.00	.
72	0.00	0.00	0.00	0.00	.
96	0.00	0.00	0.00	0.00	.
144	0.00	0.00	0.00	0.00	.
192	0.00	0.00	0.00	0.00	.

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

APPEARS THIS WAY
ON ORIGINAL

Table 2

MOEXIPRIL ARITHMETIC MEANS AND RATIOS FOR TEST (1) AND REFERENCE (2) PRODUCTS IN FASTING STUDY (#B006539)
N=48 (EXCLUDING SUBJECT #12 AND 20)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	35.56	18.21	34.91	17.16	1.02
AUCT	33.81	17.81	32.81	16.82	1.03
CMAX	25.09	11.97	25.33	10.80	0.99
KE	0.88	0.35	0.87	0.31	1.01
LAUCI	31.21	0.53	31.03	0.50	1.01
LAUCT	29.39	0.56	28.89	0.52	1.02
LCMAX	22.47	0.48	23.16	0.44	0.97
THALF	0.95	0.48	0.92	0.41	1.04
TMAX	0.91	0.32	0.89	0.45	1.02

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	36.35	34.91	1.04	94.12	114.17
AUCT	34.12	32.92	1.04	93.31	113.95
CMAX	25.25	25.62	0.99	91.39	105.74
LAUCI	31.77	31.10	1.02	92.29	113.07
LAUCT	29.52	29.02	1.02	91.72	112.81
LCMAX	22.57	23.43	0.96	88.93	104.30

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Table 3

MEAN PLASMA MOEXIPRIL LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS IN FED STUDY (#B016502)
N=54 (EXCLUDING SUBJECT #32)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.167	0.00	0.00	0.09	0.52	0.00
0.333	0.52	1.25	1.13	2.86	0.46
0.5	2.10	2.65	2.68	4.62	0.79
0.75	5.61	4.18	4.90	5.70	1.15
1	7.43	4.25	6.23	5.62	1.19
1.25	8.10	5.42	6.73	5.20	1.20
1.5	6.96	4.26	6.19	3.98	1.12
1.75	6.11	3.76	5.31	3.15	1.15
2	5.24	3.20	4.98	2.72	1.05
2.5	4.14	2.80	4.35	2.75	0.95
3	3.02	2.16	3.38	2.71	0.89
4	1.44	1.48	1.51	1.81	0.96
5	0.26	0.56	0.34	0.67	0.75
6	0.04	0.21	0.02	0.14	2.17
7	0.00	0.00	0.00	0.00	.
8	0.00	0.00	0.00	0.00	.
10	0.00	0.00	0.00	0.00	.
12	0.00	0.00	0.00	0.00	.
24	0.00	0.00	0.00	0.00	.
48	0.00	0.00	0.00	0.00	.
72	0.00	0.00	0.00	0.00	.
96	0.00	0.00	0.00	0.00	.
144	0.00	0.00	0.00	0.00	.
192	0.00	0.00	0.00	0.00	.

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

Table 4

MOEXIPRIL ARITHMETIC MEANS AND RATIOS FOR TEST (1) AND REFERENCE (2) PRODUCTS IN FED STUDY (#B016502)
N=54 (EXCLUDING SUBJECT #32)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	18.90	7.75	17.96	7.46	1.05
AUCT	16.38	7.52	15.75	7.04	1.04
CMAX	10.54	4.85	10.22	4.69	1.03
KE	0.85	0.39	0.92	0.38	0.92
LAUCI	17.53	0.39	16.59	0.40	1.06
LAUCT	14.96	0.42	14.45	0.42	1.04
LCMAX	9.65	0.41	9.38	0.41	1.03
THALF	0.98	0.50	0.85	0.29	1.15
TMAX	1.39	0.65	1.56	0.77	0.89

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	18.95	17.95	1.06	100.35	110.87
AUCT	16.38	15.75	1.04	98.85	109.14
CMAX	10.54	10.22	1.03	96.99	109.15
LAUCI	17.61	16.64	1.06	99.67	112.35
LAUCT	14.96	14.45	1.04	98.03	109.36
LCMAX	9.65	9.38	1.03	96.65	109.65

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

APPEARS THIS WAY
ON ORIGINAL

FIG 1. PLASMA MOEXIPRIL LEVELS

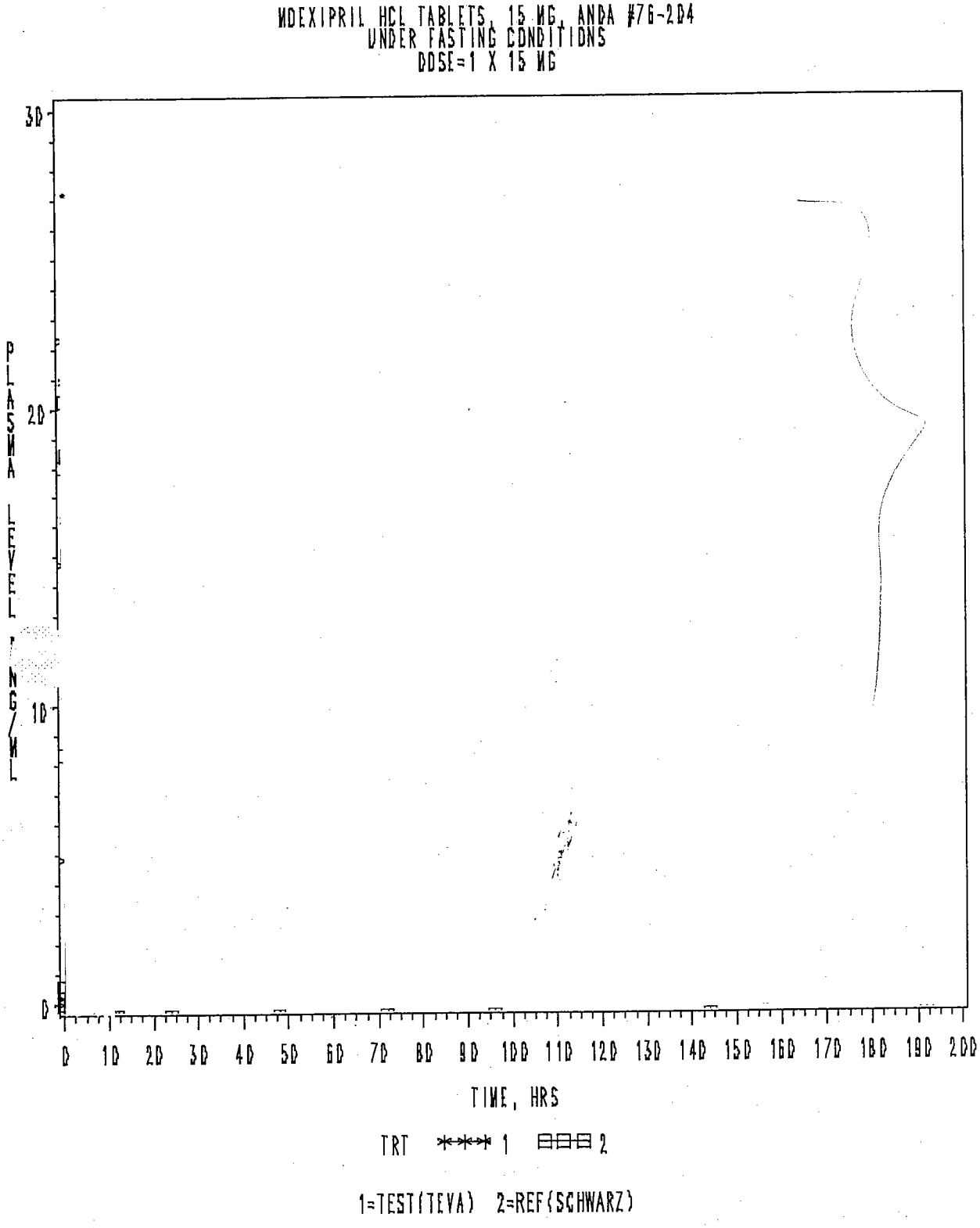
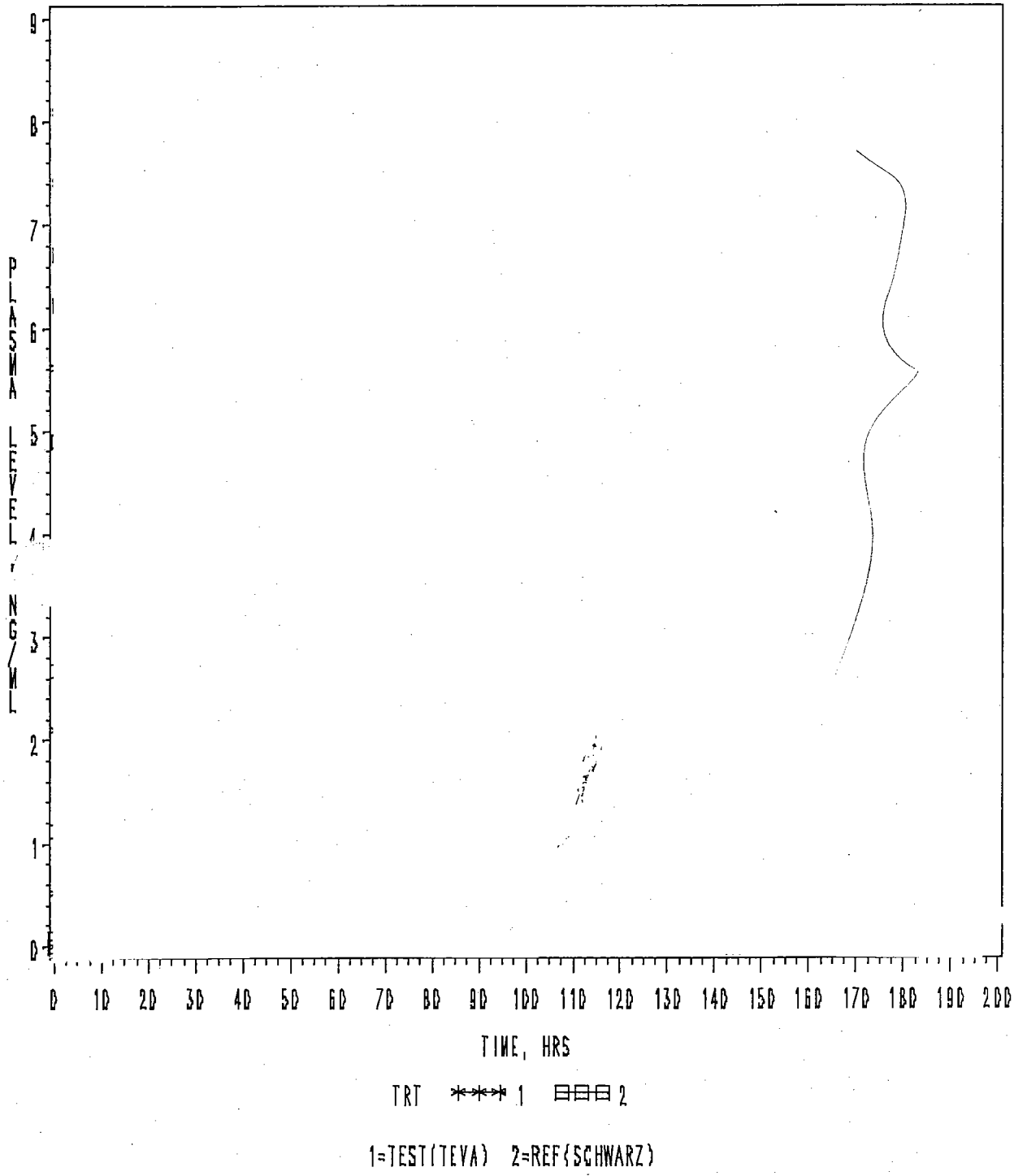


FIG 2. PLASMA MOEXIPRIL LEVELS

MOEXIPRIL HCL TABLETS, 15 MG, ANDA #76-204
UNDER FED CONDITIONS
DOSE=1 X 15 MG



BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-204 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Moexipril Hydrochloride Tablets
7.5 mg, 15 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in _____ The test product should meet the following specifications:

Not less than ~(Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-204
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Dhariwal

Printed in final on 12/04/2002

Endorsements: (Final with Dates)
HFD-655/ Dhariwal 12/4/02
HFD-655/ Nerurkar
HFD-650/ D. Conner 12/10/02

BIOEQUIVALENCY - ACCEPTABLE DSI Report Date: 11/27/02

US Document

1. **OTHER** (OTH)
DSI report date 11/27/02

Strengths: 7.5 mg, 15 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

APPEARS THIS WAY
ON ORIGINAL

3.1 DEC 10 2002 Sept. 16, 02 Craig

Moexipril HCl Tablets	Teva Pharmaceuticals USA
7.5 mg, 15 mg	1090 Horsham Road, PO Box 1090
ANDA 76-204	North Wales, PA 19454
Reviewer: Kuldeep R. Dhariwal	Submission Dates: 01/29/02
V:\Firmsnz\Teva\Ltrs&rev\76204A0102.doc	05/31/02

Review of Amendment

On 07/16/01, the firm submitted fasting and non-fasting studies on 15 mg strength, dissolution data on 7.5 mg and 15 mg tablets and a waiver request for 7.5 mg tablet. The submission was reviewed by the DBE and the deficiencies were communicated to the firm on November 21, 2001. This amendment is response to those deficiencies.

Deficiency 1. The dissolution testing of the test and reference tablets should be repeated taking samples at early time points (5, 10, 15, 20 and 30 minutes).

Response: The dissolution testing of the test and reference tablets was repeated with samples taken at 5, 10, 15, 20 and 30 minutes.

Dissolution (Not to be released under FOI)

Dissolution Medium: [redacted]
Volume: [redacted]
Dissolution Apparatus: [redacted]
Speed: [redacted]

Mean Dissolution Data

Test				Reference		
Lot No.: 1127-005				Lot No.: 0070801		
Strength: 15 mg				Strength: 15 mg		
No. of Units: 12				No. of Units: 12		
Time (min)	Mean	Range	%CV	Mean	Range	%CV
5	12	[redacted]	55.9	83	[redacted]	6.0
10	47	[redacted]	29.5	95	[redacted]	0.8
15	77	[redacted]	12.3	94	[redacted]	0.9
20	91	[redacted]	5.8	94	[redacted]	0.8
30	98	[redacted]	0.40	94	[redacted]	0.6

Mean Dissolution Data

Test				Reference		
Lot No.: 1127-103				Lot No.: 0062701		
Strength: 7.5 mg				Strength: 7.5 mg		
No. of Units: 12				No. of Units: 12		
Time (min)	Mean	Range	%CV	Mean	Range	%CV

DP

5	13	[redacted]		34.2	67	[redacted]	17.8
10	52	[redacted]		9.9	94	[redacted]	3.3
15	76	[redacted]		7.5	95	[redacted]	1.4
20	91	[redacted]		3.5	95	[redacted]	1.3
30	97	[redacted]		1.6	96	[redacted]	1.2

F_2 calculations:

Test 15 mg vs. Test 7.5 mg: 79.51
Test 15 mg vs. Reference 15 mg: 20.36 using all data points
29.59 using 10, 15, 20 and 30 minutes' data points
Test 7.5 mg vs. Reference 7.5 mg: 24.86 using all data points
31.75 using 10, 15, 20 and 30 minutes' data points

Reviewer's comments: The test products dissolve slower than the reference products. A F_2 value of 79.5 is obtained when the test 7.5 mg tablets are compared to the test 15 mg tablets. However, F_2 comparison of the test and reference tablets suggests that the two products are not similar (F_2 values less than 50). The current practice of the DBE is to compare within a product line and not across (test vs. reference). The FDA specifications for this drug product are NLT [redacted] (Q) in 15 minutes. The test products do not meet these specifications. The test products may be given specifications of NLT [redacted] % (Q) in 20 minutes.

The waiver of in vivo bioequivalence study requirements for the test 7.5 mg tablets may be granted because:

a. The firm has conducted an acceptable bioequivalence study on 15 mg tablets.
b. 7.5 mg tablets are proportionally similar in their active and inactive ingredients to the 15 mg tablets. The total weight and amount of ingredients in 7.5 mg tablets are exactly half that of 15 mg tablets.
c. Dissolution profiles of the test 7.5 mg and 15 mg tablets are similar.
d. As per the labeling of the RLD, pharmacokinetics are approximately dose proportional over the dose range of 7.5 to 30 mg.

Deficiency 2: The data submitted in orange jackets 1.5, 1.6 and 1.7 are repeated in orange jackets 1.8, 1.9 and 1.10 respectively. Please explain.

Response: We confirm that the data submitted in orange jackets vol. 1.5, 1.6 and 1.7 are identical to the data submitted in orange jackets vol. 1.8, 1.9 and 1.10. Please disregard this repeated data.

Reviewer's comments: The response is satisfactory.

Deficiency 3: Please submit complete failed fasting bioequivalence study data including potency, content uniformity, and dissolution results.

Response: The failed fasting bioequivalence study data including potency, content uniformity, and dissolution results are included.

Reviewer's comments:
Drug products used in the study:

Test drug: Lot number: 1127-005
Manufacture date: 5/16/00
Batch size: [redacted] tablets
Assay: 102.0%
Uniformity of dosage units: 100.4%
Dissolution: [redacted] in 30 minutes
Description: Pink film-coated, oval, convex tablet debossed "5150" on one side, "93" to the left of a bisect on the other side.

Ref drug: Lot number: 1388800A
Expiry date: 02/01
Assay: 99.2%
Uniformity of dosage units: 97.2%
Dissolution: [redacted] in 30 minutes
Description: Circular salmon tablet marked 715 on one side, scored and marked SP 15 on other side.

The firm has submitted failed bioequivalence study data except the assay validation. The analytical method used in the failed study was the same as used in the other bioequivalence study and therefore it is not necessary to ask for assay validation data from the failed study.

Deficiency 4: Please note that in future, you should submit the chromatograms from 20% of serially selected subjects. Also, the subjects whose chromatograms are to be submitted should be defined prior to the analysis of the study samples.

Response: We acknowledge that in future, we should submit the chromatograms from 20% of serially selected subjects and the subjects whose chromatograms are to be submitted should be defined prior to the analysis of study sample.

Reviewer's comments: The response is satisfactory.

May 31, 2002 submission:
On May 31, 2002 the firm submitted experimental dissolution profiles generated using various media and parameters. In its original submission, the firm stated that the reference product manufactured in the U.S. has a faster dissolution rate at early time points and closely matches the Teva's formulation in a discriminating dissolution system than the reference product manufactured in Germany. The dissolution testing was conducted in simulated gastric fluid without enzymes using paddles at 25 rpm:

Time	% dissolved		
	Ref. (Germany)	Ref. (US)	Test (lot 1127-005)
5	45	68	54
10	74	93	100
15	86	95	102
20	92	96	102

The firm stated that since the US manufactured lot of the reference product closely matched the Teva's formulation in the discriminating dissolution system, Teva performed another bioequivalence study comparing the test product with the reference product manufactured in the US. This study met the bioequivalence criteria. It is noted that AUC and C_{max} values obtained on the reference product manufactured in Germany were about 10% lower than those obtained on the test product. The differences in AUC and C_{max} values between the test product and the reference product manufactured in the US were less than 4%.

However, the dissolution profiles of these reference products are similar in water:

Time	% dissolved		
	Ref. (Germany)	Ref. (US)	Test (lot 1127-005)
5	79	83	12
10	95	95	47
15	98	94	77
20	98	94	91

Comments:

1. The firm conducted two fasting bioequivalence studies on its test product. In the first study, which did not meet bioequivalence criteria, the test product was compared with the reference drug manufactured in Germany. In the second study, the test drug was compared with the reference drug manufactured in U.S.A.
2. Schwarz Pharma (manufacturer of the RLD) submitted a supplement on July 23, 1999 for additional manufacturing site/process changes to its NDA 20-312. The old site was Monheim, Germany and the new site was Seymour, Indiana, USA. In addition to the proposed site change, the firm also proposed manufacturing process and equipment changes. The formulation was not changed. The firm performed a bioequivalence study on the 15 mg tablet to compare the currently approved tablets with the tablets manufactured at the new site. In addition, dissolution profiles of both the drug products manufactured at the currently approved site and the drug product manufactured at the proposed site were submitted and analyzed for similarity.

   Dr. Thomas Parmelee reviewed the supplement and the review is available on RetrievalWare (Clinical Pharmacology/Biopharmaceutics Review dated September 8, 1999). The bioequivalence study showed the tablets produced at the new facility (USA)

to be bioequivalent to the tablets produced at the currently approved manufacturing site (Germany).

3. Since the reference listed drug manufactured in Germany and in U.S. are bioequivalent, it is not clear why Teva's product is bioequivalent to the reference drug manufactured in USA but not to the reference drug manufactured in Germany.
4. The moexipril AUC and C_{max} values reported in the ANDA are much lower than the values reported in the NDA reviews. The moexiprilat AUC values reported in the ANDA are much higher than the values reported in the NDA reviews. Moexipril values are higher than moexiprilat in NDA reviews whereas in the ANDA a reverse pattern is observed. Samples in the NDA studies were collected up to 24 or 36 hours but the samples in the ANDA study were collected up to 192 hours.

   An elimination half-life of 2-9 hours has been reported for moexiprilat in the labeling of the RLD. However, Clinical Pharmacology/Biopharmaceutics reviews of this NDA report half-life of 8.9 h, 20.9 h, 241 h and 204.7 h.
5. The test products dissolve slower than the reference products and do not meet the specifications of NLT [redacted]% (Q) in 15 minutes. There is a similarity in the dissolution profiles of the test 7.5 and 15 mg tablets (F_2 value >50). However, F_2 values of less than 50 are obtained when the test tablets are compared with the reference tablets.
6. The Guidance for Industry entitled "Dissolution Testing of Immediate Release Solid Oral Dosage Forms" recommends that "if the dissolution of the generic product is substantially different compared to that of the reference listed drug and the *in vivo* data remain acceptable, a different dissolution specification for the generic product may be set." The test tablets may be given the following specifications: NLT [redacted]% (Q) in 20 minutes.
7. The bioequivalence studies conducted by the firm are acceptable provided the DSI inspections of the clinical and analytical sites reveal no objectionable findings.
8. The waiver of in vivo bioequivalence study requirements for test 7.5 mg tablets may be granted because:
   a. The firm has conducted an acceptable bioequivalence study on 15 mg tablets.
   b. 7.5 mg tablets are proportionally similar in their active and inactive ingredients to the 15 mg tablets. The total weight and amount of ingredients in 7.5 mg tablets are exactly half of 15 mg tablets.
   c. Dissolution profiles of test 7.5 mg and 15 mg tablets are similar.
   d. As per the labeling of the RLD, pharmacokinetics are approximately dose proportional over the dose range of 7.5 to 30 mg.
9. At the request of the DBE, the Division of Scientific Investigations (HFD-48) conducted an audit of the clinical sites used in this ANDA. Following the inspections at Novum and [redacted] no Form FDA-483 was issued. No significant problem in the studies audited was found. The inspection of the analytical site [redacted] is pending.

Recommendations:

1. The bioequivalence study conducted under fasting conditions by Teva on its moexipril 15 mg tablets, lot #1127-005 comparing it to Univasc® 15 mg tablets, lot #0070801 manufactured by Schwarz Pharma has been found acceptable to the Division of Bioequivalence. The study demonstrates that Teva's moexipril 15 mg tablets are bioequivalent to the reference product, Univasc® 15 mg tablets manufactured by Schwarz Pharma.
2. The bioequivalence study conducted under non-fasting conditions by Teva on its moexipril 15 mg tablets, lot #1127-005 comparing it to Univasc® 15 mg tablets, lot #0070801 manufactured by Schwarz Pharma is acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of moexipril 15 mg tablet manufactured by Teva is similar to the reference product, Univasc® 15 mg tablets manufactured by Schwarz Pharma.
3. The dissolution testing conducted by the firm on its 7.5 mg and 15 mg tablets is acceptable. The formulation for 7.5 mg tablets is proportionally similar to the 15 mg tablet, which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for 7.5 mg tablets of the test product is granted. The 7.5 mg test tablets are therefore deemed bioequivalent to Univasc® 7.5 mg tablets manufactured by Schwarz Pharma.
4. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in [redacted] The test products should meet the following specifications:
   NLT [redacted] (Q) in 20 minutes.

Dhariwal

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Division of Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR _____ Date 9/5/2002

Concur: _____ Date 9/16/02
Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-204 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Moexipril Hydrochloride Tablets
7.5 mg, 15 mg

The Division of Bioequivalence has completed its review and has no further questions at this time.

The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be conducted in [redacted] The test product should meet the following specifications:

Not less than [redacted] Q) of the labeled amount of the drug in the dosage form is dissolved in 20 minutes.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-204
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Dhariwal

Printed in final on 09/03/2002

Endorsements: (Final with Dates)
HFD-655/ Dhariwal 9/3/02
HFD-655/ Nerurkar
HFD-650/ D. Conner 9/16/02

9/5/02

BIOEQUIVALENCY - ACCEPTABLE

Submission dates: 1/29/02
5/31/02

1. **STUDY AMENDMENT** (STA)
1/29/02
Strengths: 7.5 mg, 15 mg
Outcome: AC

2. **STUDY AMENDMENT** (STA)
5/31/02
Strengths: 7.5 mg, 15 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

APPEARS THIS WAY
ON ORIGINAL

Moexipril HCl Tablets	**Teva Pharmaceuticals USA**
7.5 mg, 15 mg	**1090 Horsham Road, PO Box 1090**
ANDA 76-204	**North Wales, PA 19454**
Reviewer: Kuldeep R. Dhariwal	**Submission Date: 07/16/01**
V:\Firmsnz\Teva\Ltrs&rev\76204SDW.701	

Review of Bioequivalence Studies, Dissolution Data and Waiver Request (Electronic Submission)

Introduction

First Generic: Yes
Indication: It is indicated for treatment of patients with hypertension. It may be used alone or in combination with thiazide diuretics.
Type of Submission: Original
Contents of Submission: Fasting and non-fasting studies on 15 mg strength. Dissolution data on 7.5 mg and 15 mg tablets. Waiver request for 7.5 mg tablet.
RLD: Univasc® (Schwarz) 15 mg tablet
Recommended Dose: The recommended initial dose of moexipril in patients not receiving diuretics is 7.5 mg, one hour prior to meals, once daily. Dosage should be adjusted according to blood pressure response. The recommended dose range is 7.5 to 30 mg daily, administered in one or two divided doses one hour before meals. Total daily doses above 60 mg a day have not been studied in hypertensive patients.
Financial Disclosure: Form FDA 3454 was submitted. The clinical investigators have no financial interests in the firm.

Background

Moexipril's antihypertensive activity is almost entirely due to its deesterified metabolite, moexiprilat. Bioavailability of oral moexipril is about 13% compared to intravenous moexipril (both measuring the metabolite moexiprilat), and is markedly affected by food, which reduces the peak plasma level (C_{max}) and AUC. Moexipril should therefore be taken in a fasting state. The time of peak plasma concentration (T_{max}) of moexiprilat is about 1½ hours and elimination half-life (t½) is estimated at 2 to 9 hours in various studies, the variability reflecting a complex elimination pattern that is not simply exponential. Like all ACE inhibitors, moexiprilat has a prolonged terminal elimination phase, presumably reflecting slow release of drug bound to the ACE. Accumulation of moexiprilat with repeated dosing is minimal, about 30%, compatible with a functional elimination t½ of about 12 hours. Over the dose range of 7.5 to 30 mg, pharmacokinetics are approximately dose proportional.

Moexipril is incompletely absorbed, with bioavailability as moexiprilat of about 13%. Bioavailability varies with formulation and food intake which reduces C_{max} and AUC by about 70% and 40% respectively after the ingestion of a low-fat breakfast or by 80% and

50% respectively after the ingestion of a high-fat breakfast. Moexiprilat is about 50% protein bound.

Moexipril is relatively rapidly converted to its active metabolite moexiprilat, but persists longer than some other ACE inhibitor prodrugs, such that its t½ is over one hour and it has a significant AUC. Both moexipril and moexiprilat are converted to diketopiperazine derivatives and unidentified metabolites. After I.V. administration of moexipril, about 40% of the dose appears in urine as moexiprilat, about 26% as moexipril, with small amounts of the metabolites; about 20% of the I.V. dose appears in feces, principally as moexiprilat. After oral administration, only about 7% of the dose appears in urine as moexiprilat, about 1% as moexipril, with about 5% as other metabolites. Fifty-two percent of the dose is recovered in feces as moexiprilat and 1% as moexipril.

Protocol No.: B006539, A Relative Bioavailability Study of Moexipril HCl 15 mg Tablets Under Fasting Conditions

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Principal Investigator:	[redacted]
Sub-investigators:	[redacted]
Clinical Study Dates:	Period I 04/07/01 Period II 04/28/01
Analytical Facility	[redacted]
Principal Investigator:	[redacted]
Analytical Study Dates:	05/16/01 to 06/19/01
Storage Period:	72 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	MOEXIPRIL HCl	UNIVASC®
Manufacturer:	Teva Pharmaceuticals USA	Schwarz Pharma, Inc.
Manufacture Date:	5/16/00	N/A
Expiration Date:	N/A	10/02
ANDA Batch Size:	[redacted] tablets	N/A
Batch/Lot Number:	1127-005	0070801
Potency:	102.0%	98.9%
Content Uniformity:	100.4%	98.1%
Strength:	15 mg	15 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	15 mg	15 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	10 hours	10 hours

RANDOMIZATION		DESIGN	
Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	N
No. of Treatments:	2	**Washout Period:**	21 days

AB: 2,3,4,5,10,12,13,15,16,19,21,24,25,27,28,29,30,31,33,34,37,38,42,43,44,45,51,52,57,59
BA: 1,6,7,8,9,11,14,17,18,20,22,23,26,32,35,36,39,40,41,46,47,48,49,50,53,54,55,56,58,60

DOSING		SUBJECTS	
Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	60
Route of Administration:	Oral	**No. of Subjects Completing:**	50
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	50
Number of Doses:	N/A	**No. of Dropouts:**	10
Loading Dose:	N/A	**Sex(es) Included:**	Both
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	36

Subject Demographics:

Race:	Caucasian 37, African American 19, Asian 2, Hispanic 1, Biracial 1
Height:	Mean 69 inches, range 62-74 inches
Weight:	Mean 164 lbs, range 106-212 lbs
Sex:	Male 48, Female 12
Age group:	<18 0 18-40 48 41-64 12 65-75 0 >75 0 Mean age 30 years, range 18-47 years

Dietary Restrictions:	No alcohol, grapefruit or caffeine/xanthine containing products for 48 hours prior to dosing and throughout the periods of blood collection
Activity Restrictions:	Subjects remained sitting upright or standing for 4 hours after each dosing, except as required for study procedures. No strenuous physical exercise was permitted during confinement
Drug Restrictions:	No prescribed medications for at least 14 days or OTC medications (including herbal medications) for at least 7 days prior to initial dosing and throughout the time of sample collection. No medications were permitted during confinement except those administered.
Blood Sampling:	Blood samples (10 mL) were collected in Vacutainers containing EDTA prior to dosing and at 0.167, 0.333, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, 72, 96, 144 and 192 hours after dosing.

Study Results

1) Clinical

Adverse Events: The common events were headache, lightheaded, elevated glucose. The events were fairly comparable on the two products.

Protocol Deviations: There were a few sampling time deviations. Corrections were made in the calculations for the deviations that were more than ±5% from the target times.

Dropouts:

SUBJECT NO.:	10	15	2	21
REASON:	Personal	Personal	positive drug screen	Personal
PERIOD:	Prior to Period 2 dosing	10 minutes after Period 1 dose	at Period 2 check-in	Prior to Period 2 dosing
REPLACEMENT:	N	N	N	N

SUBJECT NO.:	23	25	31	32
REASON:	Headache	Personal	Personal	Heart palpitations
PERIOD:	At Period 2 check-in	Prior to Period 2 dosing	prior to Period 2 dosing	After Period 1, 144-hour sample
REPLACEMENT:	N	N	N	N

SUBJECT NO.:	50	59		
REASON:	Personal	Personal		
PERIOD:	Prior to Period 2 dosing	After Period 2 2-hour sample		
REPLACEMENT:	N	N		

Comments:

2) Analytical (Not to be Released Under FOI)

Pre-Study Assay Validation:

Redacted 1

Page(s) of trade secret and /or confidential commercial information

3) Pharmacokinetic:

Moexipril:		
Mean Plasma Concentration:	Table 1, Figure 1	
Pharmacokinetic Parameters:	Table 2	
90% Confidence Intervals:	$LAUC_{0-t}$	93.05-113.65%
	$LAUC_{0-inf}$	93.57-113.80%
	LC_{max}	90.95-107.08%
AUC_{0-t} /AUC_{0-inf} ratios:	Test	0.94 (0.81-0.98)
	Reference	0.94 (0.85-0.98)
Root MSE:	$LAUC_{0-t}$	0.297213
	$LAUC_{0-inf}$	0.285514
	LC_{max}	0.242530
Moexiprilat:		
Mean Plasma Concentration:	Table 3, Figure 2	
Pharmacokinetic Parameters:	Table 4	
90% Confidence Intervals:	$LAUC_{0-t}$	100.40-107.65%
	$LAUC_{0-inf}$	100.70-110.77%
	LC_{max}	87.02-117.52%
AUC_{0-t} /AUC_{0-inf} ratios:	Test	0.64 (0.50-0.88)
	Reference	0.65 (0.42-0.85)
Root MSE:	$LAUC_{0-t}$	0.099297
	$LAUC_{0-inf}$	0.134097
	LC_{max}	0.428292

Comments:

1. The reviewer recalculated pharmacokinetic parameters and 90% confidence intervals. The reported values are in good agreement with those obtained by the reviewer.
2. The 90% confidence intervals for moexipril and moexiprilat are within acceptable limits. There was no significant period, treatment or sequence effect for any of the moexipril PK parameters. However, significant period effect was observed for moexiprilat $LAUC_{0-t}$, $LAUC_{0-inf}$ and LC_{max}.
3. Moexipril: Pre-dose drug concentration in subject #12 was more than 5% of C_{max} value in both the periods (10% of C_{max} in period 1 and 16% of C_{max} in period 2). No other subject had pre-dose drug concentration in either period. The following 90% confidence intervals were obtained after deleting this subject from the analysis:
   $LAUC_{0-t}$ 92.24-113.06%
   $LAUC_{0-inf}$ 92.81-113.27%
   LC_{max} 89.78-105.45%
4. Moexiprilat: None of the subjects had pre-dose drug concentration in period 1. However, in period 2, twenty-four subjects had pre-dose drug concentration on test product and twenty-two subjects had pre-dose drug concentration on reference product. The pre-dose drug concentration was more than 5% of C_{max} in three subjects on test product and one

subject on reference product. The data from these four subjects were not included in the results given above for moexiprilat.

5. The elimination rate constant and therefore AUC_{0-inf} could not be calculated for following subjects:
   Moexipril: #53 (test drug) and 58 (reference drug)
   Moexiprilat: #26, 42 and 43 (test drug), 42 (reference drug).
   The reviewer agrees with this observation.

6. **NOT TO BE RELEASED UNDER FOI:**
   The moexipril AUC and C_{max} values reported in this study are much lower than the values reported in the NDA reviews. The moexiprilat AUC values reported in this study are much higher than the values reported in the NDA reviews. Moexipril values are higher than moexiprilat in NDA reviews whereas in this study and in the failed study (see below) a reverse pattern is observed. Samples in the NDA studies were collected up to 24 or 36 hours but the samples in this study were collected up to 192 hours.

   An elimination half-life of 2-9 hours has been reported for moexiprilat in the labeling of the RLD. However, Clinical Pharmacology/Biopharmaceutics reviews of this NDA report half-life of 8.9 h, 20.9 h, 241 h and 204.7 h.
7. The data submitted in orange jackets vol. 1.5, 1.6 and 1.7 are repeated in orange jackets 1.8, 1.9 and 1.10 respectively. The firm should explain why the data are submitted in duplicate.
8. The firm submitted chromatograms from subject #3,4,14,16,34,35,48,49,57 and 58. In future, the firm should submit the chromatograms from 20% of serially selected subjects. Also, the subjects whose chromatograms are to be submitted should be defined prior to the analysis of the study samples.
9. Prior to conducting this study, the firm had conducted another fasting study and the results showed that the test product is not bioequivalent to the reference drug. The firm submitted partial data from the failed study, which are summarized at the end of this review. The firm should be asked to submit complete data of the failed study.

Conclusion: The fasting study is incomplete due to comment #7 and 9.

Protocol No.: B016502, A Relative Bioavailability Study of Moexipril HCl 15 mg Tablets Under Non-Fasting Conditions.

Study Information

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Principal Investigator:	[redacted]
Clinical Study Dates:	Period 1 04/07/01 Period 2 05/05/01
Analytical Facility	[redacted]
Principal Investigator:	[redacted]

Analytical Study Dates:	06/09/01 to 07/05/01
Storage Period:	90 days

TREATMENT INFORMATION

Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Moexipril HCl	Univasc®
Manufacturer:	Teva Pharmaceuticals USA	Schwarz Pharma, Inc.
Manufacture Date:	5/16/00	N/A
Expiration Date:	N/A	10/02
ANDA Batch Size:	[redacted] tablets	N/A
Batch/Lot Number:	#1127-005	0070801
Potency:	102.0%	98.9%
Content Uniformity:	100.4%	98.1%
Strength:	15 mg	15 mg
Dosage Form:	Tablet	Tablet
Dose Administered:	15 mg	15 mg
Study Condition:	Fed	Fed
Length of Fasting:	10.5 hours	10.5 hours
Standardized Breakfast:	Y, 30 min. before dosing	Y, 30 min. before dosing
Breakfast Specifics:	1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 2.45 oz. of hash brown potatoes, 6 fl. oz. of orange juice, 8 fl. oz. Of whole milk	1 buttered English muffin, 1 fried egg, 1 slice of American cheese, 1 slice of Canadian bacon, 2.45 oz. of hash brown potatoes, 6 fl. oz. of orange juice, 8 fl. oz. of whole milk

RANDOMIZATION **DESIGN**

Randomized:	Y	**Design Type:**	Crossover
No. of Sequences:	2	**Replicated Treatment Design:**	N
No. of Periods:	2	**Balanced:**	N
No. of Treatments:	2	**Washout Period:**	28 days

AB: 2,3,4,5,10,12,13,15,16,19,21,24,25,27,28,29,30,31,33,34,37,38,42,43,44,45,51,52,57,59
BA: 1,6,7,8,9,11,14,17,18,20,22,23,26,32,35,36,39,40,41,46,47,48,49,50,53,54,55,56,58,60
Subject numbers 18, 24, 34, 36 and 51 did not complete the study.

DOSING **SUBJECTS**

Single or Multiple Dose:	Single	**IRB Approval:**	Y
Steady State:	N	**Informed Consent Obtained:**	Y
Volume of Liquid Intake:	240 mL	**No. of Subjects Enrolled:**	60
Route of Administration:	Oral	**No. of Subjects Completing:**	55
Dosing Interval:	N/A	**No. of Subjects Plasma Analyzed:**	55
Number of Doses:	N/A	**No. of Dropouts:**	5
Loading Dose:	N/A	**Sex(es) Included:**	Both
Steady State Dose Time:	N/A	**Healthy Volunteers Only:**	Y
Length of Infusion:	N/A	**No. of Adverse Events:**	22

Subject Demographics:

Race:	Caucasian 51, African American 4
Height:	Male: Mean 70 inches, range 67-74 inches Female: Mean 65 inches, range 60-68 inches
Weight:	Male: Mean 184.7 lbs., range 148-240 lbs. Female: Mean 142.8 lbs., range 102-185 lbs.
Sex:	Male 29, Female 26
Age group:	<18 0 18-41 47 42-65 8 65-76 0 >75 0 Male: Mean age 29.4 years, range 21-45 years Female: Mean age 34 years, range 18-62 years

Dietary Restrictions:	No alcohol, grapefruit or caffeine/xanthine containing products for 48 hours prior to dosing and throughout the periods of blood collection
Activity Restrictions:	Subjects remained sitting upright or standing for 4 hours after each dosing, except as required for study procedures. No strenuous physical exercise was permitted during confinement
Drug Restrictions:	No prescribed medications for at least 14 days or OTC medications (including herbal medications) for at least 7 days prior to initial dosing and throughout the time of sample collection. No medications were permitted during confinement except those administered.
Blood Sampling:	Blood samples (10 mL) were collected in Vacutainers containing EDTA prior to dosing and at 0.167, 0.333, 0.50, 0.75, 1, 1.25, 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 7, 8, 10, 12, 24, 48, 72, 96, 144 and 192 hours after dosing.

Study Results

1) Clinical

Adverse Events: The most common event was headache, which was comparable on both products.

Protocol Deviations: One subject received prescription medicine during the wash-out period and two subjects received OTC medications during the study. There were a few sampling time deviations. Corrections were made in the calculations for the deviations that were more than ±5% from the target times.

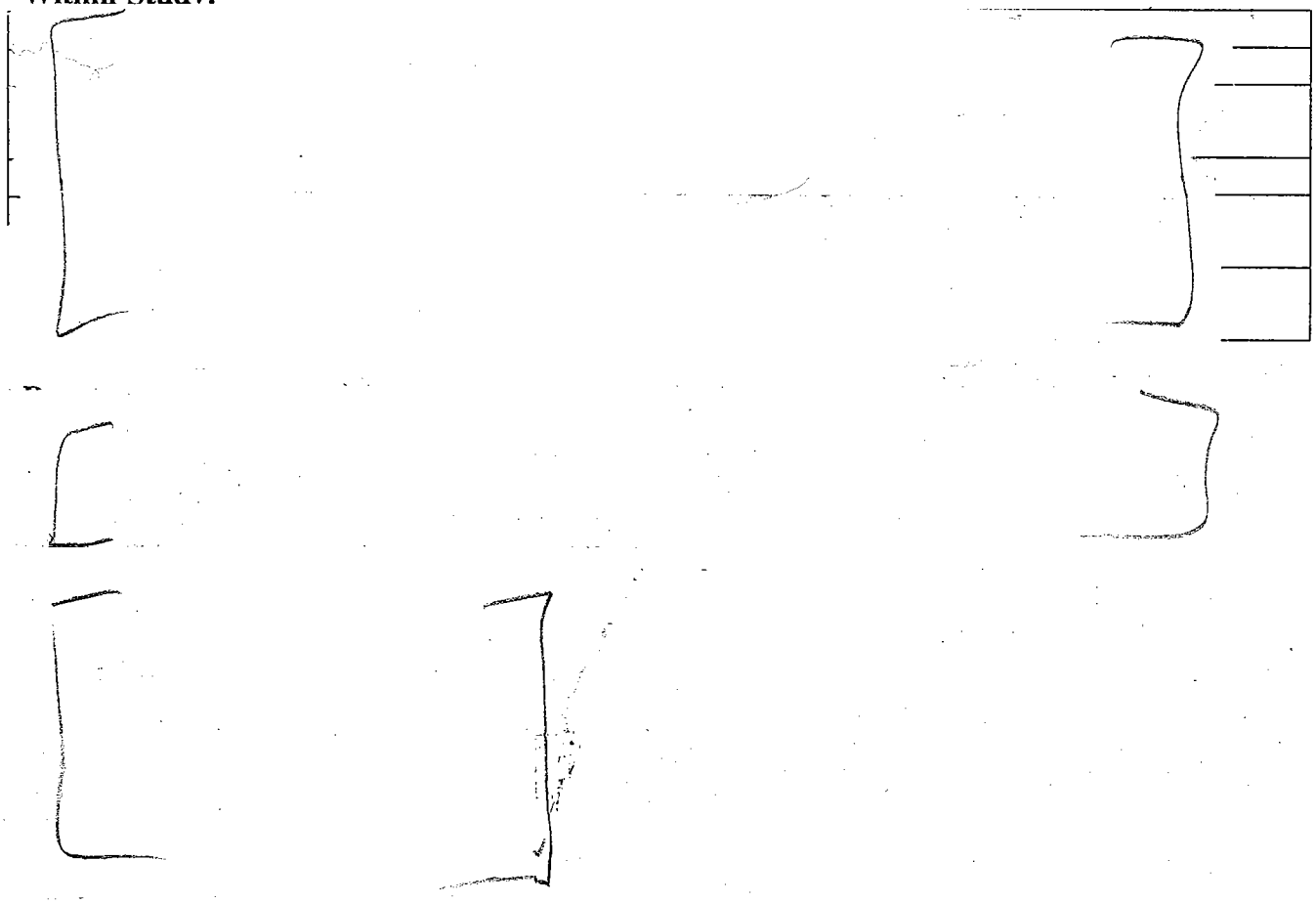
Dropouts:

SUBJECT NO.:	18	24	34	36
REASON:	personal	Personal	Subject received same medication as period 1	Subject received same medication as period 1
PERIOD:	prior to Period 2	prior to Period 2	Period 2	Period 2

	dosing	dosing		
REPLACEMENT:	N	N	N	N
SUBJECT NO.:	51			
REASON:	personal			
PERIOD:	prior to Period 2 dosing			
REPLACEMENT:	N			

2) Analytical (Not to be Released Under FOI)

Within-Studv:



Comments: The analytical method is acceptable.

3) Pharmacokinetic:

Moexipril:

Mean Plasma Concentration:	Table 5, Figure 3	
Pharmacokinetic Parameters:	Table 6	
Ratios of Means:	Table 6	
AUC_{0-t} /AUC_{0-inf} :	Test-fed	0.87 (0.57-0.96)
	Ref-fed	0.88 (0.59-0.96)

Moexiprilat:

Mean Plasma Concentration:	Table 7, Figure 4	
Pharmacokinetic Parameters:	Table 8	
Ratios of Means:	Table 8	
AUC_{0-t} /AUC_{0-inf} :	Test-fed	0.61 (0.48-0.76)
	Ref-fed	0.62 (0.46-0.74)

Comments:

1. The reviewer recalculated pharmacokinetic parameters and ratios of means. The reported values are in good agreement with those obtained by the reviewer.
2. Low (less than 5% of C_{max}) plasma moexiprilat levels were seen in many period 2 pre-dose samples. In fifteen cases (subject # 1,2,3,5,7,9,11,15,20,27,28,35,43,47 and 49) the period 2 pre-dose samples had plasma moexiprilat levels greater than 5% of C_{max}. The data from these fifteen subjects were not included in the results given above for moexiprilat.
3. The elimination rate constant and therefore AUC_{0-inf} could not be calculated for following subjects:
   Moexipril: #21 and 27 (test-fed), 27, 33 and 44 (reference-fed)
   Moexiprilat: #21 and 27 (test-fed), 27, 33 and 44 (reference-fed)
   The reviewer agrees with this observation.
4. The ratios of means are within acceptable limits.
5. The firm submitted chromatograms from subject #1,2,3,4,15,29,30,47,48,59 and 60. In future, the firm should submit the chromatograms from 20% of serially selected subjects. Also, the subjects whose chromatograms are to be submitted should be defined prior to the analysis of the study samples.

Conclusion: The non-fasting study is acceptable.

Formulation (Not to be released under FOI)

INGREDIENT	AMOUNT (mg) PER TABLET	
	7.5 mg TABLETS	**15 mg TABLETS**
Moexipril	7.5*	15.0*
Sodium Bicarbonate USP	[redacted]	[redacted]
Lactose Monohydrate, NF	[redacted]	[redacted]
Crospovidone, NF	[redacted]	[redacted]

INGREDIENT	AMOUNT (mg) PER TABLET	
	7.5 mg TABLETS	**15 mg TABLETS**
Pregelatinized Starch, NF		
Magnesium Stearate, NF		
Total Theoretical Weight	**104**	**208**

Test tablets:
7.5 mg: Pink film-coated, oval, convex tablet debossed "17" on one side, bisected on the other.
15 mg: Pink film-coated, oval, convex tablet debossed "5150" on one side, "93" to the left of a bisect on the other side.
Reference tablets:
Univasc® (moexipril hydrochloride) 7.5 mg tablets are pink colored, biconvex, film-coated and scored with engraved code **707** on the unscored side and **SP** above and **7.5** below the score.
Univasc® (moexipril hydrochloride) 15 mg tablets are salmon colored, biconvex, film-coated, and scored with engraved code **715** on the unscored side and **SP** above and **15** below the score.

Formulation Comments: All ingredients are within IIG limits.

Dissolution (Not to be released under FOI)

Dissolution Medium:
Volume:
Dissolution Apparatus:
Speed:

Mean Dissolution Data

Test				Reference		
Lot No.: 1127-005				Lot No.: 0070801		
Strength: 15 mg				Strength: 15 mg		
No. of Units: 12				No. of Units: 12		
Time (min)	Mean	Range	% CV	Mean	Range	%CV
10	41.72		15.6	97.76		2.54
20	91.85		3.74	98.42		2.02
30	101.32		0.76	98.15		2.06
45	101.39		0.99	97.79		1.99

Mean Dissolution Data

Test				Reference		
Lot No.: 1127-103				Lot No.: 0062701		
Strength: 7.5 mg				Strength: 7.5 mg		
No. of Units: 12				No. of Units: 12		
Time(min)	Mean	Range	%CV	Mean	Range	%CV
10	51.82		12.84	96.47		2.95
20	92.37		3.47	97.69		1.97
30	99.08		0.66	97.56		1.95
45	99.21		0.72	97.61		2.05

Dissolution Comments: Not to be released under FOI

The firm has used the same method as recommended by the FDA. The FDA specifications for this drug product are: NLT Q) in 15 minutes. The test products dissolve slower than the reference products. The firm should be asked to repeat dissolution testing and take samples at 5, 10, 15, 20 and 30 minutes. Additional samples at early time points should provide better comparative profiles of the two products.

Waiver Request

The firm is requesting waiver of in vivo bioequivalence study requirements for its 7.5 mg tablets. The 7.5 mg tablets are proportionally similar in their active and inactive ingredients to 15 mg tablet. However, the firm should be asked to repeat the dissolution testing and take samples at 5, 10, 15, 20 and 30 minutes.

Review of Failed Fasting Bioequivalence Study:

Before conducting the fasting bioequivalence study reviewed above (protocol #B006539), Teva had conducted another fasting bioequivalence study on moexipril tablets, 15 mg. The test drug (lot #1127-005) was tested against Univasc® (lot # 1388800A). The study did not pass. The results suggested that the Teva product was more rapidly available and more bioavailable than the reference product. As a result Teva began a reformulation and at the same time investigated different dissolution media in an effort to find one that would correlate with the in vivo data collected from the biostudy. During the reformulation process, Teva obtained a new lot of Univasc® since the lot used in the original study would expire before a new study could be completed. Using the more discriminating dissolution method, the new lot of innovator (#0070801) was found to have a faster dissolution rate than the previous lot and more closely resembled Teva's original formulation at the early time points. Additionally, further investigation revealed that the two lots of reference product were manufactured at different sites. The original lot (#1388800A) was manufactured in Germany and the new lot (#0070801) was manufactured in the U.S. Since the U.S. manufactured lot of reference product closely matched the original Teva formulation in the discriminating dissolution system, Teva performed another bioequivalence study using the original Teva lot (#1127-005) and the new Univasc® lot (#0070801) under both the fasting and non-fasting conditions. Both the studies passed the bioequivalence criteria (reviewed above).

Details of failed bioequivalence study: The firm has provided only the partial data from this study.

STUDY FACILITY INFORMATION

Clinical Facility:	[redacted]
Principal Investigator:	[redacted]
Clinical Study Dates:	Period I 08/19/2000 Period II 09/16/2000
Analytical Facility	[redacted]
Principal Investigator:	[redacted]
Analytical Study Dates:	Not provided
Storage Period:	Not provided

Test drug: Moexipril tablet, 15 mg (Teva), Manufacture date: 5/16/00, lot # 1127-005
Reference drug: Univasc® 15 mg tablet (Schwarz), Expiry date: 02/01, lot #1388800A

Subjects:
Forty-seven male subjects began the study and all forty-seven completed the study.

Study design: Single-dose, randomized, two-period, two-treatment, two-sequence crossover study under fasting conditions comparing equal doses of the test and reference products.

Sampling time: Samples were collected in Vacutainers containing EDTA at 0, 0.083, 0.167, 0.333, 0.50, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 24, 36 and 48 hours.

Analytical Method: LC/MS/MS
The details of the method validation are not provided. The firm also did not provide within-study accuracy, precision and sample reassay data. The firm states that although all samples from all subjects that completed clinical portion of the study were assayed for moexipril and moexiprilat, there were a number of samples for which no concentration value was reported due to various reasons related to the chromatography.

Low but measurable plasma moexiprilat levels were seen in many period 2 pre-dose samples.

Results:
Moexipril:

PK Parameters, Arithmetic means:

	Test	Reference
AUC_{0-t}	50.03	44.64
AUC_{0-inf}	52.06	46.78
C_{max}	34.68	31.51
T_{max}	1.05	0.97
T_{half}	0.94	1.12

90% Confidence Intervals:	$LAUC_{0-t}$	104-130%
	$LAUC_{0-inf}$	103-127%
	LC_{max}	102-128%

Moexiprilat:

PK Parameters, Arithmetic means:

	Test	Reference
AUC_{0-t}	163.62	149.24
AUC_{0-inf}	279.79	292.86
C_{max}	27.04	21.41
T_{max}	1.89	1.91
T_{half}	45.99	54.36

90% Confidence Intervals:	$LAUC_{0-t}$	104-117%
	$LAUC_{0-inf}$	95.5-103%
	LC_{max}	110-157%

Comments:

1. The following differences are noted in the two fasting bioequivalence studies:
   a. Reference listed drug used in the failed study was manufactured in Germany.

b. Samples in the failed study were collected only up to 48 hours. This, in part, attributes to lower moexiprilat AUC values in the failed study compared to the study, which met bioequivalence criteria. The moexiprilat C_{max} values in the two studies are comparable.
c. Higher values for moexipril PK parameters and lower values for moexiprilat AUC were observed in the failed study compared to the other study, which met bioequivalence criteria.

2. Schwarz Pharma (manufacturer of the RLD) submitted a supplement on July 23, 1999 for additional manufacturing site/process changes to NDA 20-312. The old site was Monheim, Germany and the new site is Seymour, Indiana, USA. In addition to the proposed site change, the firm also proposed manufacturing process and equipment changes. The formulation was not changed. The firm performed a bioequivalence study on 15 mg tablet to compare the currently approved tablets with the tablets manufactured at the new site. In addition, dissolution profiles of both the drug products manufactured at the currently approved site and the drug product manufactured at the proposed site were submitted and analyzed for similarity.

   The supplement was reviewed by Dr. Thomas Parmelee and the review is available on RetrievalWare (Clinical Pharmacology/Biopharmaceutics Review dated September 8, 1999).

   Fifty-two male subjects of Caucasian race (aged 20-48 years) were enrolled in a single-dose, cross-over study. A dose of 30 mg (2x15 mg tablets) was used. The blood samples were collected at 0, 0.25, 0.50, 0.75, 1, 1.5, 2, 2.5, 3, 4, 6, 12, 24, 30 and 36 hours post-dose. A GC/MS method was used for the analysis of moexipril and moexiprilat.

   Both the drug products resulted in mean concentration-time curves that were quite similar for both moexipril and moexiprilat. Since the pre-dose sample in period 2 in several cases (40 out of 51 pre-dose samples) contained a quantifiable concentration of moexiprilat, a baseline correction was applied to data of period 2.
   The following results are reported:

Dose: 2x15 mg tablet

Mean pharmacokinetic parameters of moexipril

	U.S.A. site	Germany site
AUC_{0-t} (h.ng/mL)	325.85	322.94
AUC_{0-36} (hxng/mL)	330.37	326.65
AUC_{0-inf} (hxng/mL)	319.11	324.89
C_{max} (ng/mL)	164.62	170.56
T_{max} (h)	1.09	0.93
K (1/h)	0.5336	0.5386
T_{half} (h)	1.417	1.381

Mean pharmacokinetic parameters of moexiprilat

	U.S.A. site	Germany site
AUC_{0-36} (hxng/mL)	158.56	166.26
C_{max} (ng/mL)	42.20	44.62
T_{max} (h)	1.78	1.66
K (1/h)	0.0029	0.0035
T_{half} (h)	241.0	204.7

Mean pharmacokinetic parameters of moexiprilat, baseline corrected

	U.S.A. site	Germany site
AUC_{0-t} (hxng/mL)	153.71	161.02
AUC_{0-inf} (hxng/mL)	209.04	239.34
C_{max} (ng/mL)	42.06	44.46
T_{max} (h)	1.78	1.66
K (1/h)	0.0269	0.0258
T_{half} (h)	29.02	29.62

Moexipril 90% confidence intervals:

AUC_{0-t}	93-120%
AUC_{0-inf}	92-119%
C_{max}	87-109%

Moexiprilat (baseline corrected) 90% confidence intervals:

AUC_{0-t}	88-108%
AUC_{0-inf}	Not reliable
C_{max}	85-116%

The baseline correction of data in period 2 had only a small impact on the treatment ratios for AUC_{0-t} and C_{max}. The bioequivalence study showed the tablets produced at the new facility are bioequivalent to the tablets produced at the currently approved manufacturing site.

3. Since the reference listed drug manufactured in Germany and in U.S. are bioequivalent, it is not clear why Teva's product is bioequivalent to U.S. reference drug but not to the reference drug manufactured in Germany. The firm did not provide potency of the reference listed drug used in the failed study. The firm should be requested to submit complete failed study data including potency, content uniformity, and dissolution.

Recommendations

1. The bioequivalence study conducted under fasting conditions by Teva on its moexipril 15 mg tablets, lot #1127-005 comparing it to Univasc® 15 mg tablets, lot #0070801 manufactured by Schwarz Pharma has been found incomplete.

2. The bioequivalence study conducted under non-fasting conditions by Teva on its moexipril 15 mg tablets, lot #1127-005 comparing it to Univasc® 15 mg tablets, lot #0070801 manufactured by Schwarz Pharma is acceptable to the Division of Bioequivalence. The study demonstrates that under non-fasting conditions, the bioavailability of moexipril 15 mg tablet manufactured by Teva is similar to the reference product, Univasc® 15 mg tablets manufactured by Schwarz Pharma.
3. The dissolution testing conducted by the firm is not acceptable. The firm should repeat dissolution testing and take samples at 5, 10, 15, 20 and 30 minutes.
4. The waiver of in vivo bioequivalence study requirements for 7.5 mg tablets is denied pending acceptable fasting study and satisfactory dissolution data.

Dhariwal

Kuldeep R. Dhariwal, Ph.D.
Review Branch II
Divisionof Bioequivalence

RD INITIALED S. NERURKAR
FT INITIALED S. NERURKAR _____ Date 10/18/2001

Concur: _____ Date 11/9/2001

for Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

APPEARS THIS WAY
ON ORIGINAL

Table 1

MEAN PLASMA MOEXIPRIL LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS IN FASTING STUDY, N=50

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.03	0.24	0.03	0.23	1.06
0.167	0.20	0.73	0.59	1.04	0.33
0.333	4.87	4.09	8.16	8.26	0.60
0.5	14.82	8.36	17.54	12.58	0.84
0.75	21.95	11.53	19.78	10.21	1.11
1	20.41	12.61	18.05	10.20	1.13
1.25	15.88	9.80	14.72	9.84	1.08
1.5	11.98	7.67	11.84	8.55	1.01
1.75	9.44	6.25	9.15	6.77	1.03
2	7.65	5.58	7.32	5.67	1.05
2.5	4.84	3.77	4.60	4.15	1.05
3	3.04	2.64	2.92	2.68	1.04
4	1.29	1.73	1.19	1.41	1.09
5	0.54	0.83	0.45	0.73	1.20
6	0.34	0.67	0.17	0.47	2.00
7	0.07	0.34	0.04	0.21	1.62
8	0.02	0.15	0.00	0.00	.
10	0.00	0.00	0.00	0.00	.
12	0.00	0.00	0.00	0.00	.
24	0.00	0.00	0.00	0.00	.
48	0.00	0.00	0.00	0.00	.
72	0.00	0.00	0.00	0.00	.
96	0.00	0.00	0.00	0.00	.
144	0.00	0.00	0.00	0.00	.
192	0.00	0.00	0.00	0.00	.

UNIT: PLASMA LEVEL=NG/ML

Table 2

MOEXIPRIL ARITHMETIC MEANS AND RATIOS IN FASTING STUDY, N=50
Test (1), Reference (2)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	34.71	18.31	33.94	17.45	1.02
AUCT	33.01	17.89	31.91	17.07	1.03
CMAX	24.71	11.88	24.67	11.07	1.00
KE	0.90	0.36	0.89	0.32	1.01
LAUCI	30.25	0.54	29.77	0.53	1.02
LAUCT	28.51	0.56	27.72	0.55	1.03
LCMAX	22.13	0.48	22.28	0.47	0.99
THALF	0.94	0.48	0.90	0.41	1.04
TMAX	0.89	0.32	0.88	0.45	1.01

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	35.48	33.95	1.04	94.63	114.36
AUCT	33.29	32.01	1.04	93.82	114.18
CMAX	24.85	24.93	1.00	92.48	106.88
LAUCI	30.80	29.85	1.03	93.57	113.80
LAUCT	28.62	27.83	1.03	93.05	113.65
LCMAX	22.23	22.52	0.99	90.95	107.08

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

Table 3

MEAN PLASMA MOEXIPRILAT LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS IN FASTING STUDY, N=46

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.18	0.21	0.16	0.19	1.08
0.167	0.19	0.22	0.17	0.19	1.14
0.333	0.25	0.27	0.36	0.37	0.70
0.5	0.96	0.94	1.43	1.63	0.67
0.75	4.90	4.66	5.99	6.12	0.82
1	11.33	8.15	12.19	9.09	0.93
1.25	16.55	10.91	16.16	9.75	1.02
1.5	19.17	11.72	18.42	10.36	1.04
1.75	19.63	11.55	18.76	10.32	1.05
2	18.96	10.90	18.34	11.17	1.03
2.5	15.93	8.93	15.29	10.22	1.04
3	12.96	7.51	12.21	8.80	1.06
4	8.32	4.99	7.65	4.89	1.09
5	5.06	2.27	4.87	2.46	1.04
6	4.03	1.40	3.76	1.40	1.07
7	3.44	1.11	3.19	0.95	1.08
8	3.00	0.88	2.79	0.68	1.07
10	2.47	0.64	2.33	0.57	1.06
12	2.22	0.53	2.14	0.52	1.04
24	1.86	0.51	1.84	0.51	1.01
48	1.63	0.48	1.57	0.48	1.04
72	1.42	0.44	1.39	0.41	1.03
96	1.23	0.40	1.21	0.39	1.02
144	1.05	0.38	0.99	0.34	1.06
192	0.88	0.32	0.84	0.30	1.04

UNIT: PLASMA LEVEL=NG/ML

Table 4

MOEXIPRILAT ARITHMETIC MEANS AND RATIOS IN FASTING STUDY, N=46
Test (1), Reference (2)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	505.71	166.75	475.60	157.79	1.06
AUCT	312.19	78.64	299.44	77.05	1.04
CMAX	21.98	11.89	21.37	11.56	1.03
KE	0.01	0.00	0.01	0.00	0.96
LAUCI	479.29	0.34	449.66	0.35	1.07
LAUCT	302.53	0.26	289.26	0.28	1.05
LCMAX	18.67	0.61	18.23	0.60	1.02
THALF	143.49	37.37	137.50	34.43	1.04
TMAX	1.82	0.66	1.64	0.48	1.11

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	501.12	476.20	1.05	100.02	110.45
AUCT	311.06	300.12	1.04	100.16	107.13
CMAX	21.90	21.47	1.02	90.01	114.06
LAUCI	476.08	450.77	1.06	100.70	110.77
LAUCT	301.48	289.99	1.04	100.40	107.65
LCMAX	18.54	18.34	1.01	87.02	117.52

APPEARS THIS WAY
ON ORIGINAL

Table 5

MEAN PLASMA MOEXIPRIL LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS IN NON-FASTING STUDY, N=55

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.167	0.00	0.00	0.09	0.51	0.00
0.333	0.51	1.24	1.11	2.83	0.46
0.5	2.09	2.63	2.70	4.58	0.78
0.75	5.60	4.14	4.94	5.65	1.13
1	7.41	4.21	6.24	5.57	1.19
1.25	8.09	5.37	6.71	5.16	1.21
1.5	6.96	4.22	6.17	3.94	1.13
1.75	6.10	3.72	5.29	3.12	1.15
2	5.23	3.17	4.96	2.70	1.05
2.5	4.13	2.78	4.35	2.72	0.95
3	3.01	2.14	3.37	2.69	0.89
4	1.42	1.48	1.48	1.80	0.96
5	0.25	0.56	0.33	0.66	0.75
6	0.04	0.21	0.02	0.14	2.17
7	0.00	0.00	0.00	0.00	.
8	0.00	0.00	0.00	0.00	.
10	0.00	0.00	0.00	0.00	.
12	0.00	0.00	0.00	0.00	.
24	0.00	0.00	0.00	0.00	.
48	0.00	0.00	0.00	0.00	.
72	0.00	0.00	0.00	0.00	.
96	0.00	0.00	0.00	0.00	.
144	0.00	0.00	0.00	0.00	.
192	0.00	0.00	0.00	0.00	.

UNIT: PLASMA LEVEL=NG/ML

Table 6

MOEXIPRIL ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY, N=55
Test (1), Reference (2)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	18.85	7.69	18.02	7.40	1.05
AUCT	16.30	7.48	15.69	6.99	1.04
CMAX	10.48	4.82	10.16	4.67	1.03
KE	0.84	0.38	0.91	0.39	0.92
LAUCI	17.50	0.38	16.67	0.40	1.05
LAUCT	14.90	0.42	14.41	0.41	1.03
LCMAX	9.61	0.41	9.32	0.41	1.03
THALF	0.98	0.50	0.87	0.33	1.13
TMAX	1.39	0.64	1.54	0.77	0.90

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	18.93	18.03	1.05	99.68	110.23
AUCT	16.32	15.72	1.04	98.76	108.90
CMAX	10.49	10.18	1.03	97.09	109.07
LAUCI	17.60	16.74	1.05	99.03	111.65
LAUCT	14.92	14.44	1.03	97.94	109.05
LCMAX	9.61	9.34	1.03	96.78	109.54

Table 7

MEAN PLASMA MOEXIPRILAT LEVELS FOR TEST (1) AND REFERENCE (2) PRODUCTS IN NON-FASTING STUDY, N=40

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.06	0.12	0.08	0.13	0.82
0.167	0.09	0.14	0.09	0.14	1.00
0.333	0.07	0.12	0.10	0.14	0.76
0.5	0.12	0.17	0.14	0.16	0.86
0.75	0.43	0.59	0.38	0.39	1.13
1	1.14	1.32	0.96	1.10	1.19
1.25	2.05	1.75	1.66	1.80	1.23
1.5	2.98	2.09	2.42	2.22	1.23
1.75	3.65	2.26	3.02	2.59	1.21
2	4.18	2.41	3.65	3.09	1.15
2.5	4.91	2.44	4.56	3.06	1.08
3	5.18	2.37	5.19	2.78	1.00
4	5.00	2.40	5.50	2.96	0.91
5	3.69	1.80	4.22	2.51	0.88
6	2.79	1.04	3.09	1.47	0.90
7	2.47	0.83	2.55	0.93	0.97
8	2.23	0.67	2.26	0.70	0.99
10	2.07	0.61	2.14	0.54	0.96
12	1.92	0.50	1.96	0.52	0.98
24	1.71	0.50	1.72	0.45	1.00
48	1.44	0.39	1.51	0.42	0.95
72	1.34	0.37	1.33	0.38	1.01
96	1.16	0.33	1.20	0.37	0.96
144	0.99	0.31	0.95	0.28	1.04
192	0.81	0.26	0.79	0.23	1.02

UNIT: PLASMA LEVEL=NG/ML

Table 8

MOEXIPRILAT ARITHMETIC MEANS AND RATIOS IN NON-FASTING STUDY, N=40
Test (1), Reference (2)

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	417.63	136.07	414.74	118.99	1.01
AUCT	250.15	65.78	253.65	67.58	0.99
CMAX	6.28	2.72	6.95	3.37	0.90
KE	0.01	0.00	0.01	0.00	0.97
LAUCI	398.55	0.30	398.38	0.29	1.00
LAUCT	241.98	0.26	245.73	0.25	0.98
LCMAX	5.68	0.47	6.14	0.53	0.92
THALF	143.73	28.84	138.73	26.18	1.04
TMAX	2.89	0.96	2.87	0.98	1.01

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR
LOG-TRANSFORMED DATA WERE CONVERTED TO ANTI-LOG IN THE TABLE

LSMEANS AND 90% CONFIDENCE INTERVALS

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
PARAMETER					
AUCI	422.27	412.79	1.02	97.49	107.10
AUCT	250.15	253.65	0.99	95.91	101.33
CMAX	6.28	6.95	0.90	82.00	98.55
LAUCI	402.72	396.75	1.02	97.03	106.19
LAUCT	241.98	245.73	0.98	95.85	101.17
LCMAX	5.68	6.14	0.92	83.58	102.29

FIG 1. PLASMA MOEXIPRIL LEVELS

MOEXIPRIL HCL TABLETS, 15 MG, ANDA #76-204
UNDER FASTING CONDITIONS
DOSE=1 X 15 MG

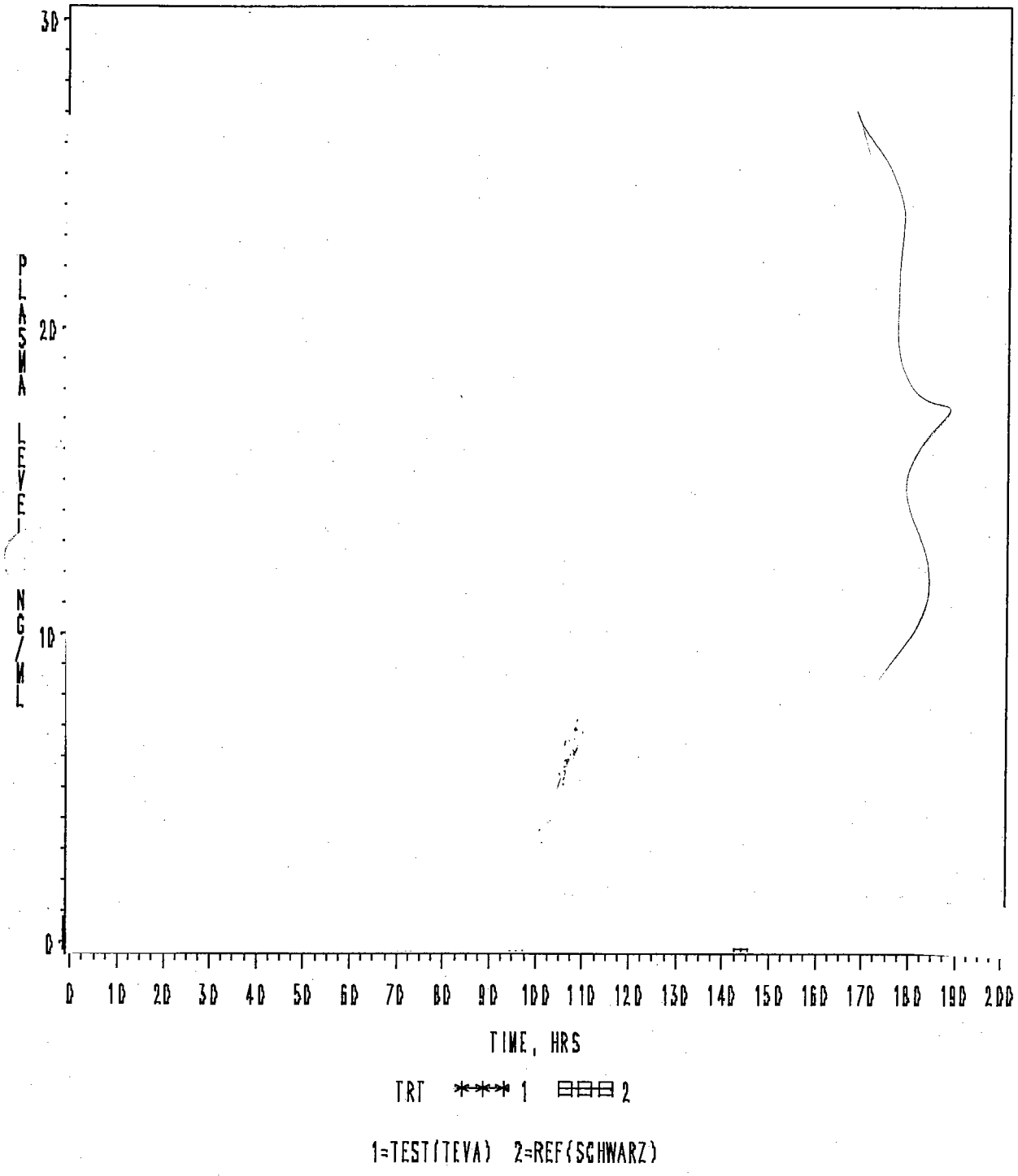


FIG 2. PLASMA MOEXIPRILAT LEVELS

MOEXIPRIL HCL TABLETS, 15 MG, ANDA #76-204
UNDER FASTING CONDITIONS
DOSE=1 X 15 MG

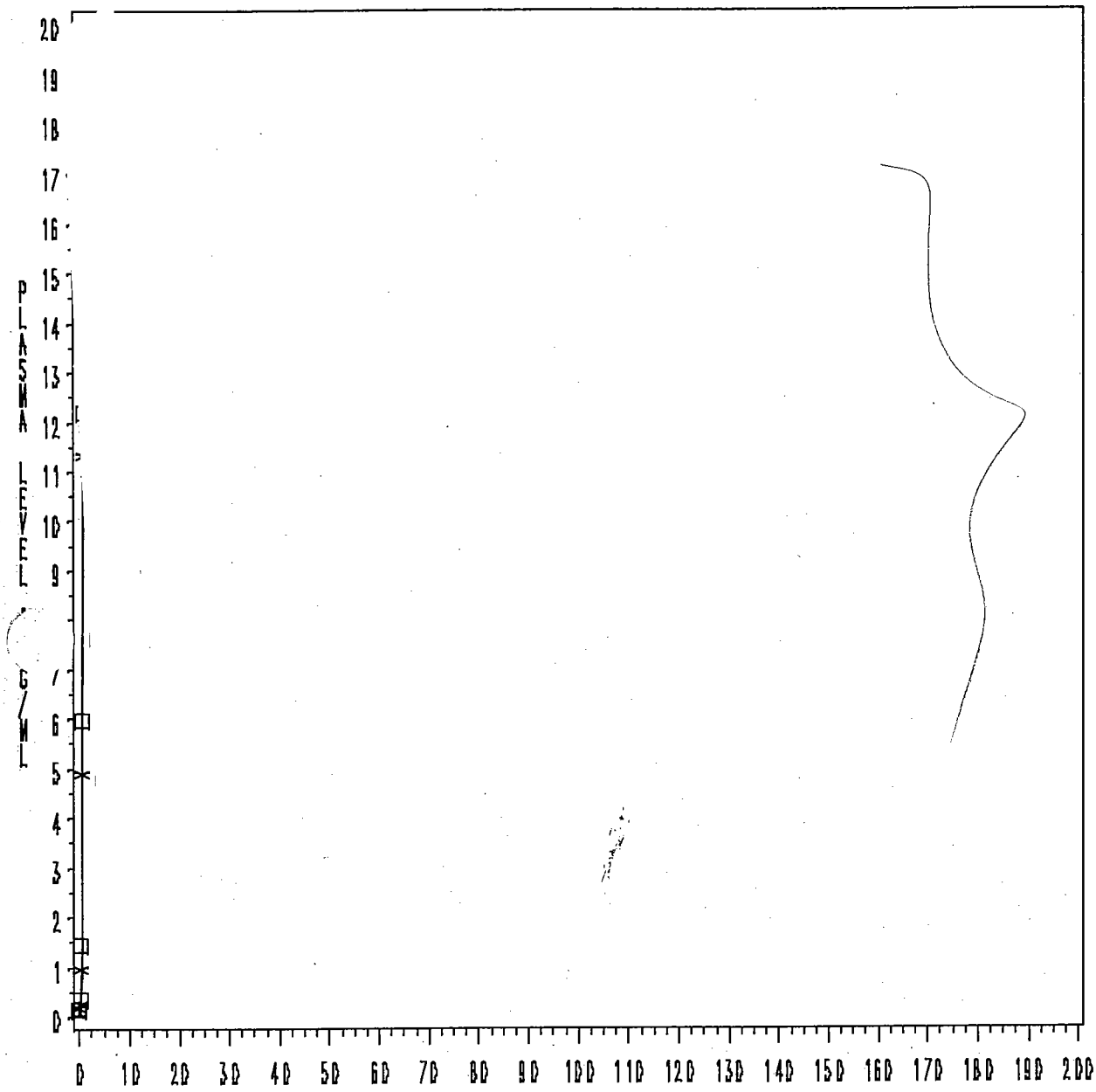


FIG 3. PLASMA MOEXIPRIL LEVELS

MOEXIPRIL HCL TABLETS, 15 MG, ANDA #76-204
UNDER NON-FASTING CONDITIONS
DOSE=1 X 15 MG

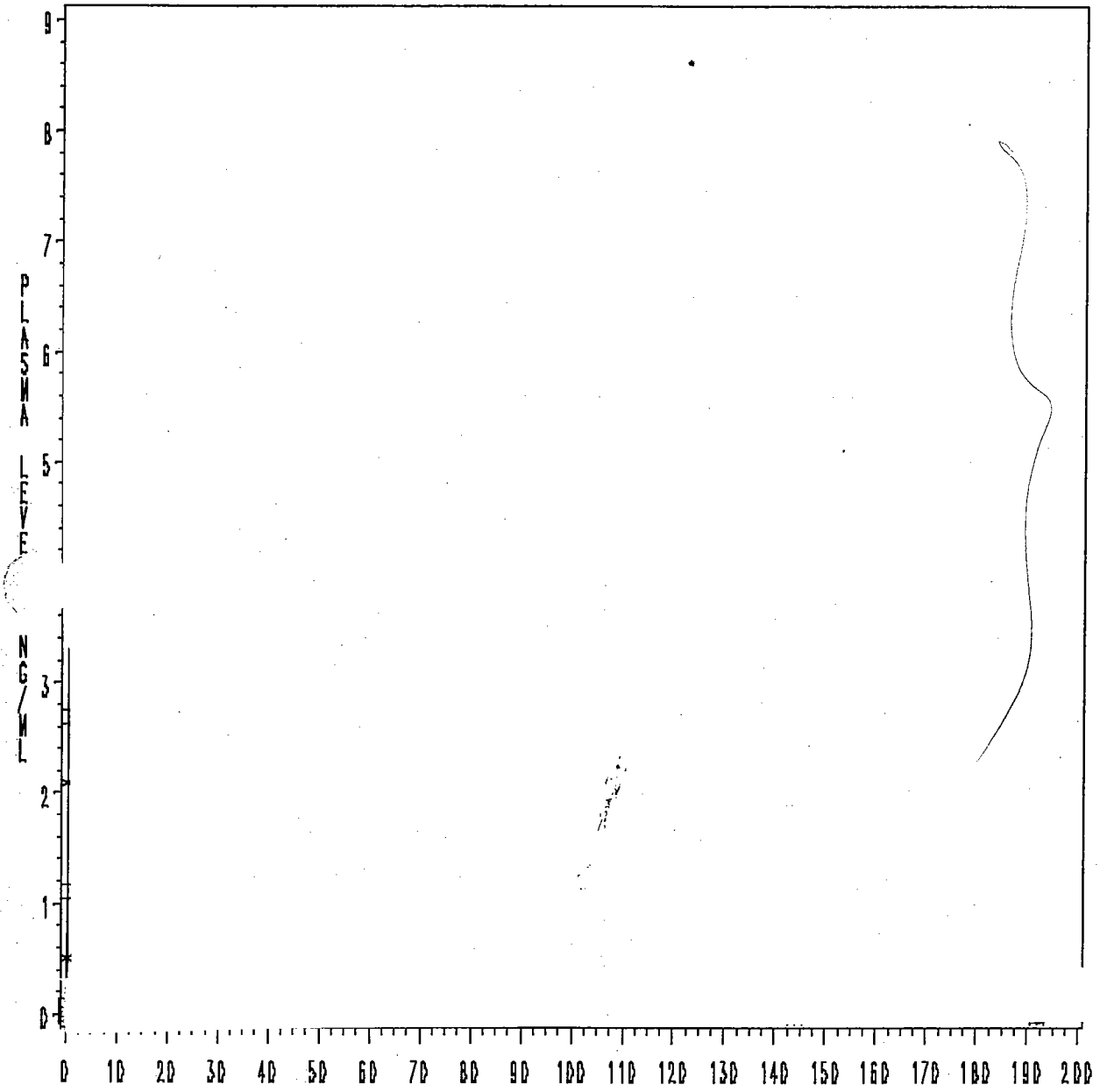
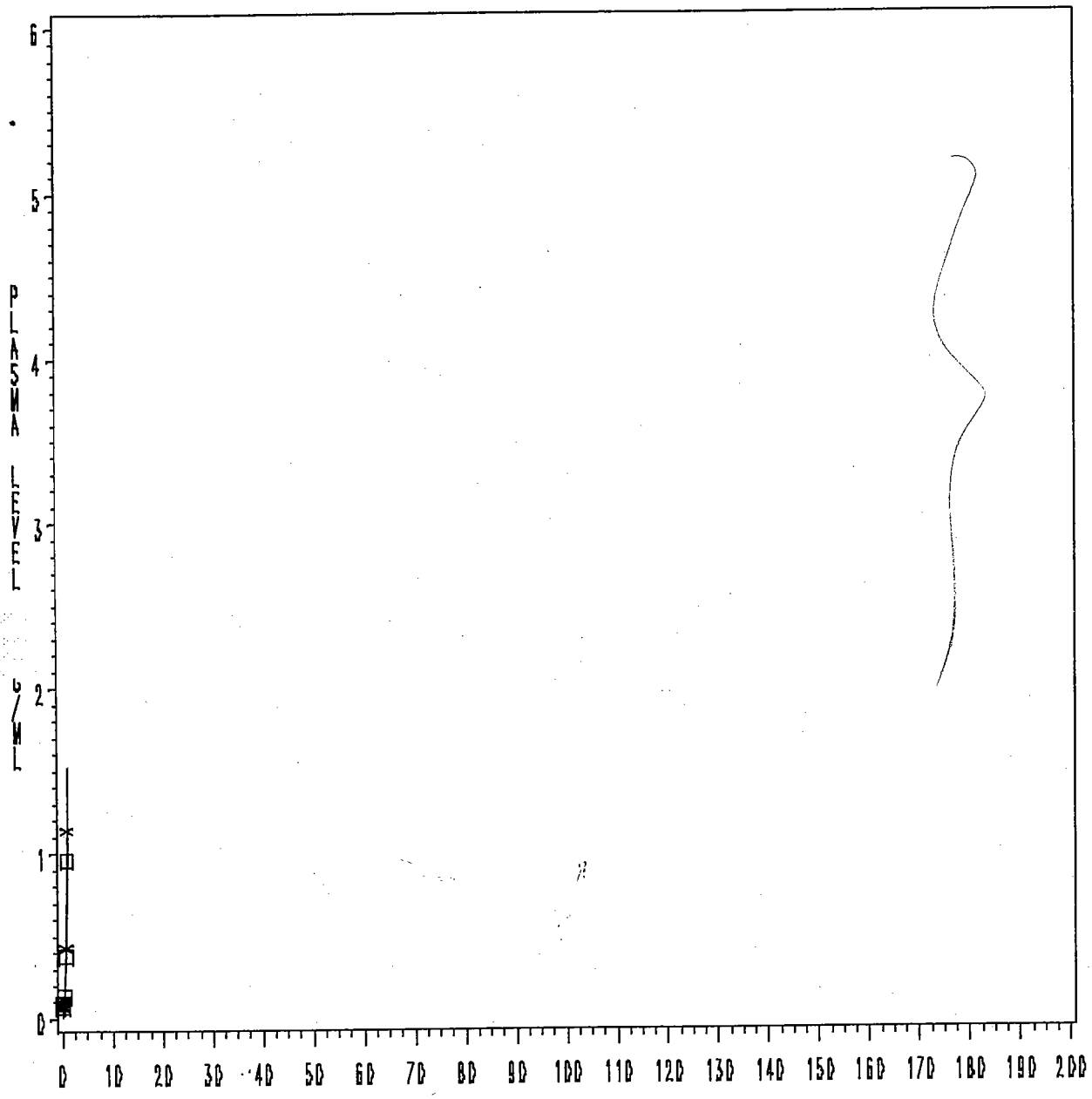


FIG 4. PLASMA MOEXIPRILAT LEVELS

MOEXIPRIL HCL TABLETS, 15 MG, ANDA #76-204
UNDER NON-FASTING CONDITIONS
DOSE=1 X 15 MG



BIOEQUIVALENCY DEFICIENCIES

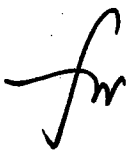
ANDA: 76-204 APPLICANT: Teva Pharmaceuticals

DRUG PRODUCT: Moexipril HCl Tablets, 7.5 mg and 15 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

1. The dissolution testing of the test and reference tablets should be repeated taking samples at early time points (5, 10, 15, 20 and 30 minutes).
2. The data submitted in orange jackets vol. 1.5, 1.6 and 1.7 are repeated in orange jackets 1.8, 1.9 and 1.10 respectively. Please explain.
3. Please submit complete failed fasting bioequivalence study data including potency, content uniformity, and dissolution results.
4. Please note that in future, you should submit the chromatograms from 20% of serially selected subjects. Also, the subjects whose chromatograms are to be submitted should be defined prior to the analysis of the study samples.

Sincerely yours,



Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-204
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Dhariwal DNB 9/24/01
HFD-655/Nerurkar
HFD-617/Nwaba
HFD-650/Dale Conner for Mey 11/9/2001

10/18/01

BIOEQUIVALENCY -DEFICIENCIES Submission Date: 7/16/01

1. **FASTING STUDY** (STF)
Clinical: ~~———~~
Analytical: ~~———~~
Strengths: 15 mg
✓ **Outcome: IC**

2. **FOOD STUDY** (STP)
Clinical: ~~———~~
Analytical: ~~———~~
Strengths: 15 mg
✓ **Outcome: AC**

3. **DISSOLUTION WAIVER** (DIW)
Strengths: 7.5 mg
✓ **Outcome: IC**

Outcome Decisions:

IC - Incomplete

WinBio Comments

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 76-204
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Dhariwal

Printed in final on 12/04/2002

Endorsements: (Final with Dates)
HFD-655/ Dhariwal 12/4/02
HFD-655/ Nerurkar
HFD-650/ D. Conner 12/10/02

BIOEQUIVALENCY - ACCEPTABLE DSI Report Date: 11/27/02

U.S Document

1. **OTHER** (OTH) Strengths: 7.5 mg, 15 mg
DSI report date 11/27/02 **Outcome: AC**

Outcome Decisions: **AC** - Acceptable

APPEARS THIS WAY
ON ORIGINAL

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-204 SPONSOR : Teva

DRUG AND DOSAGE FORM : Moexipril Hydrochloride Tablets

STRENGTH(S) : 7.5 mg and 15 mg

TYPES OF STUDIES : Fasting and Fed

CLINICAL STUDY SITE(S) : ———

ANALYTICAL SITE(S) : ——— (DSI REPORT)

STUDY SUMMARY : The fasting and fed studies are acceptable.

DISSOLUTION : The dissolution testing should be conducted in ——— ——— The test products meet specification of NLT —— (Q) in 20 minutes.

DSI INSPECTION STATUS

Inspection needed: YES	Inspection status:	Inspection results:
First Generic __Yes__	Inspection requested: 1/25/02	Acceptable
New facility _____	Inspection completed: 11/27/02	
For cause _____		
Other _____		

PRIMARY REVIEWER : Kuldeep R. Dhariwal, Ph.D. BRANCH : II

INITIAL : KRD DATE : 12/4/02

TEAM LEADER : S. Nerurkar, Ph. D. BRANCH : II

INITIAL : [signature] DATE : 12/9/2002

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm. D.

INITIAL : DPC DATE : 12/10/02

CC: ANDA 76-204
ANDA DUPLICATE
DIVISION FILE
HFD-651/ Bio Drug File
HFD-655/ Dhariwal

Printed in final on 09/03/2002

Endorsements: (Final with Dates)
HFD-655/ Dhariwal 9/3/02
HFD-655/ Nerurkar
HFD-650/ D. Conner 9/16/02

9/5/02

BIOEQUIVALENCY - ACCEPTABLE

Submission dates: 1/29/02
5/31/02

1. **STUDY AMENDMENT** (STA)
1/29/02

Strengths: 7.5 mg, 15 mg
Outcome: AC

2. **STUDY AMENDMENT** (STA)
5/31/02

Strengths: 7.5 mg, 15 mg
Outcome: AC

Outcome Decisions: **AC** - Acceptable

APPEARS THIS WAY
ON ORIGINAL

CC: ANDA 76-204
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

Endorsements: (Draft and Final with Dates)
HFD-655/Dhariwal 9/26/01
HFD-655/Nerurkar
HFD-617/Nwaba
HFD-650/Dale Conner for 11/9/2001

10/29/01

BIOEQUIVALENCY -DEFICIENCIES Submission Date: 7/16/01

1. **FASTING STUDY** (STF)
Clinical: —
Analytical: —
Strengths: 15 mg
✓ **Outcome: IC**

2. **FOOD STUDY** (STP)
Clinical: —
Analytical: —
✓ Strengths: 15 mg
Outcome: AC

3. **DISSOLUTION WAIVER** (DIW)
Strengths: 7.5 mg
✓ **Outcome: IC**

Outcome Decisions:

IC - Incomplete

WinBio Comments

APPEARS THIS WAY
ON ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-204

ADMINISTRATIVE DOCUMENTS

M E M O R A N D U M

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

DATE : July 25, 2001

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 25-JUL-2001

SUBJECT: Examination of the bioequivalence study, dissolution and request for waiver submitted with an ANDA for Moexipril Hydrochloride Tablets, 7.5 mg and 15 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355 (j)(5)(B)(iv).

Teva Pharmaceutical USA has submitted ANDA 76-204 for Moexipril Hydrochloride Tablets, 7.5 mg and 15 mg. The ANDA contains a certification pursuant to 21 USC 355 (j)(2)(A)(vii)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study, dissolution and request for waiver is complete, and could establish that the product is bioequivalent.

Please evaluate whether the study submitted by Teva on July 16, 2001 for its Moexipril Hydrochloride product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

ANDA 76-204

In determining whether a bio study is "complete" to satisfy statutory requirements, the following items are examined:

1. Study design

   (a) Appropriate number of subjects
   (b) Description of methodology

2. Study results

   (a) Individual and mean data is provided
   (b) Individual demographic data
   (c) Clinical summary

The issue raised in the current situation revolves around whether the study can purport to demonstrate bioequivalence to the listed drug.

We would appreciate a cursory review and your answers to the above questions as soon as possible so we may take action on this application.

DIVISION OF BIOEQUIVALENCE:

✓ Study meets statutory requirements 4+17/27/2001

_____ Study does **NOT** meet statutory requirements

Reason:

APPEARS THIS WAY
ON ORIGINAL

Robert P. Lionne 7/30/01

Director, Division of Bioequivalence Date

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS

ANDA 76-204 DRUG NAME Moexipril HCl FIRM TEVA Pharmaceuticals USA

DOSAGE FORM(s) Tablets, 7.5 & 15 mg

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Protocol	✓				
Assay Methodology	✓				LC
Procedure SOP	✓				
Methods Validation	✓				
Study Results Ln/Lin	✓				
Adverse Events	✓				
IRB Approval	✓				
Dissolution Data	✓				
Pre-screening of patients	✓				
Chromatograms	✓				
Consent forms	✓				
Composition	✓				
Summary of study	✓				
Individual Data & Graphs , Linear & Ln	✓				
PK/PD data disk	✓				
Randomization Schedule	✓				
Protocol Deviations	✓				

	YES	NO	REQUIRED AMOUNT	AMOUNT SENT	COMMENTS
Clinical site	✓				
Analytical site	✓				
Study investigators	✓				
Medical Records	✓				
Clinical Raw Data	✓				
Test Article Inventory	✓				
BIO Batch Size	✓				
Assay of active content drug	✓				
Content uniformity	✓				
Date of manufacture	✓				
Exp. Date RLD	✓				
Biostudy lot numbers	✓				
Statistics	✓				
Summary results provided by the firm indicate studies pass BE criteria	✓				
Waiver requests for other strengths / supporting data	✓				

Additional comments: Drug product is prodrug of moexipril at ACE inhibitor in hypertension treatment.

Acceptable PK summary of data on parent & metabolite - fasting & postprandial conditions.

Studies conducted on 15 mg strength & waiver requested for 7.5 mg based on biostudies, proportionally similar composition & dissolution testing.

Recommendation: (COMPLETE) / INCOMPLETE 7/27/2001

Reviewed by

James Chaney

Date 7/26/2001

Revised 6/7/2000

APPEARS THIS WAY
ON ORIGINAL

Redacted 5

Page(s) of trade secret and /or confidential commercial information

MEMORANDUM

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

21

DATE: 01/25/02

FILE COPY

TO: C.T. Viswanathan, Ph.D.
Associate Director, Division of Scientific Investigations
MPN I, HFD-48

for

THROUGH: Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence, HFD-650

FROM: DBE/GBIB Liaison
Division of Bioequivalence, Office of Generic Drugs, HFD-617, MPN II

SUBJECT: Biopharmaceutics Compliance Program 7348.001

Request for Inspection

References:

ANDA# 76-204
Product Moexipril HCl Tablets 7.5mg, 15mg
Sponsor Teva Pharmaceuticals
(full address, phone, fax, contact) 1090 Horsham Road
North Wales PA 19454
Phillip Erickson 215-591-3141

Submission Date 07/16/01 Nov.

Priority B

A (highest) = ready for approval, outstanding issues
B = Bio review complete, pending chemistry
C (routine) = Bio under review

Due Date 04/25/02.

21

APPEARS THIS WAY
ON ORIGINAL

1. Studies

Study #1
Number: B006539
Title: A relative Bioavailability study of Moexipril HCl 15 mg Tablets under fasting conditions

Clinical Site (full address, phone, fax)

Investigator/Contact

Analytical Site (full address, phone, fax)

Investigator/Contact
Analytical Method

Study #2
Number: B016502
Title: A relative Bioavailability study of Moexipril HCl 15 mg tablets under non-fasting conditi

Clinical Site (full address, phone fax)

Investigator/Contact

Analytical Site (full address, phone, fax)

Investigator/Contact
Analytical Method

Study #3
Number
Title

Clinical Site (full address, phone, fax)

Investigator/Contact

Analytical Site (full address, phone, fax)

Investigator/Contact
Analytical Method

APPEARS THIS WAY
ON ORIGINAL

1. Reason for Inspection Request

_____ Not inspected in the last three years
__✓__ For Cause/Violative history
_____ New Site
_____ Other

only

COMMENTS:

✓1 Only.

2. Bio-study Status

_____ Study under review
__✓__ Study review completed
_____ study incomplete pending additional information from sponsor
_____ study unacceptable with questionable data pending inspection verification
__✓__ study acceptable pending satisfactory inspection results
_____ Other:

CC:

HFD-617 (DBE/GBIB Liaison)
HFD-48 (Viswanathan)
HFD-655 (Bio Reviewer) Kuldeep Dhaniwal.
HFD-655 (PM) Nina Nwaba
HFD-630 (ANDA# 76 204)

APPEARS THIS WAY
ON ORIGINAL

NDA 76-204

MEMORANDUM

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

DATE: November 27, 2002

FROM: Sriram Subramaniam, Ph.D.
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV 11/27/02
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIRs Covering ANDA 76-204,
Moexipril HCl 7.5 mg and 15 mg Tablets,
Sponsored by Teva Pharmaceuticals, Inc.

TO: Dale P. Conner, Pharm. D.
Director
Division of Bioequivalence (HFD-650)

At the request of HFD-650, the Division of Scientific Investigations conducted audits of the following bioequivalence studies:

Protocol #1: **B006539**: A Relative Bioavailability Study of Moexipril HCl 15 mg Tablets Under Fasting Conditions

Protocol #2: **B016502**: A Relative Bioavailability Study of Moexipril HCl 15 mg Tablets Under Non-Fasting Conditions

Protocol #3*: **B006501**: A Relative Bioavailability Study of Moexipril HCl 15 mg Tablets Under Fasting Conditions

The clinical portions of Studies B016502 and B006501 were conducted at [redacted] The clinical portion of Study B006539 was conducted at [redacted] The analytical portions of all the three studies were conducted at [redacted]

* Failed bioequivalence study which was repeated as Study B006539.

Form 483 was not issued at [redacted] (5/28-31/02) and NOVUM (4/9-16/02). The audit reports, dated 8/20/02 and 6/7/02, for the clinical portions of the studies were forwarded earlier to HFD-650 (Attachments).

The analytical portion of the audit at [redacted] focussed on Studies B006539 and B016502. Form 483 was issued to [redacted] at the conclusion of the inspection (10/28-11/1/02). The significant findings and our evaluation of them follows:

Analytical Site: [redacted]

Bioassay analyzed moexipril (MPL) and moexiprilat (MPLT) in human plasma by [redacted]

1. **Failure to assure accuracy of subject moexipril concentrations in Run 7 (Study B006539) and Run 15 (B016502). An interfering peak in the chromatograms of the subject samples affected the quantitation of moexipril in the runs. The chromatograms for the calibration standard and quality control samples in the runs did not exhibit such interference.**

   An unknown merging peak significantly interfered with the integration of MPL peak in many chromatograms for Subject 20 (Run 07) of Study B00659 (Exhibit 1). Similar interference also affected the integration of MPL peak in chromatograms for Subject 32 (Run 15) of Study B016502 (Exhibits 2). Specifically, the chromatograms for subject samples 32,0.5,1 and 32,1.25,2 correspond to Cmax levels for Subject 32 (Exhibit 2). In contrast, the chromatograms for calibration standards and quality controls in Runs 07 and 15 did not exhibit the interference found in the subject sample chromatograms (Exhibit 3).

   In their response, Bioassay stated that manual integration was necessary due to the interference in subject sample chromatograms. According to the firm, the integration was uniform and should not affect study outcome. Contrary to Bioassay's response, the extent of interference precludes accurate integration of MPL peaks and the absence of such interference in standards and QCs prevents accurate quantitation of MPL peaks in subject samples. Therefore, the accuracy of MPL concentrations

for Subject 20 in Study B006539 and Subject 32 in Study B016502 are not reliable.

2. **Integration of chromatographic peaks was not consistent in Run 8 (Study B006539). For example, automatic integration of moexiprilat peak in the "1/0.2" ng/mL calibration standard was different from the manual integration of subject samples "485", "490", "494" and "497".**

   Bioassay automatically integrated MPLT peaks by excluding the shoulder on the peaks in the chromatograms for Standard 1/0.2 and QC 2.5/0.5, (Exhibit 4). In contrast, Bioassay included the shoulder when integrating MPLT peaks in chromatograms for subject samples 12,10,1; 12,12,2; 12,48,1; 12,48,2; and 12,96,1 (Exhibit 5). This finding is not likely to significantly affect the accuracy MPLT concentrations. However, the firm should correct the objectionable practice in future studies.

Conclusions:

The Division of Scientific Investigations concludes that bioequivalence should be reestimated following deletion of moexipril data for:
a. Subject 20 in Study B006539 (Item 1).
b. Subject 32 in Study B016502 (Item 1).

After you have reviewed this transmittal memo, please append it to the original ANDA submission.

Sriram Subramaniam, Ph.D.

Final Classification:
VAI -

Attachment*

* Due to the number of exhibits involved, exhibits will be forwarded only to the HFD-650 director and reviewer.

cc:
HFD-45/RF
HFD-48/Subramaniam(2)/CF
HFD-655/Dhariwal/Nerurkar
HFD-650/Nwaba
HFD-SW1580/Branche
Draft: SS 11/21/02
Edit: MKY MKY 11/27/02
DSI:5415; O:\BE\EIRCOVER\76204TEV.MOE
FACTS ID: 295131

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: AUG 2 0 2002

FROM: Charles A. Snipes, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. Martin K. Yau for CTV
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering ANDA 76-204
Moexipril HCl Tablets 7.5 mg, 15 mg
Sponsored by TEVA Pharmaceuticals USA

TO: Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence (HFD-650)

At the request of HFD-650, the Division of Scientific Investigations conducted an audit of the following bioequivalence studies:

Protocol B006501: A Relative Bioavailability Study of Moexipril HCl 15 mg Tablets Under Fasting Conditions.

Protocol B016502: A Relative Bioavailability Study of Moexipril HCl 15 mg Tablets Under Non-Fasting Conditions.

The clinical portion of these studies was conducted at [redacted] The analytical portion of the studies was performed by [redacted]

Upon the inspection at [redacted] (5/28-31/02), there were no objectionable findings. No Form 483 was issued. Please note that the analytical portions of Protocols B006501 and B016502 have not yet been inspected.

Conclusions:

Following the audits at [redacted] the Division of Scientific Investigations recommends that the clinical portion of Protocols B006501 and B016502 be accepted for review.

After you have reviewed this transmittal memo, please append it to the original ANDA submission.

Charles A. Snipes

Charles A. Snipes, Ph.D.

Final Classification: [redacted] NAI

cc:
HFA-224
HFD-45/rf
HFD-48/Snipes/cf
HFD-650/Sanchez
HFR-SW450/Vega
HFR-SW1580/Branche
HFR-SW1540/Martinez
Draft: CAS 8/20/02
Edit: MKY 8/20/02
File: 5415 O:\BE\76204tev.moe.doc

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

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

DATE: June 7, 2002

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV June 7, 02
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of an EIR Covering:

1. ANDA 76-219 (Mirtazapine Tablets) Sponsored by Eon Laboratories Manufacturing Inc., Laurelton, NY
2. ANDA 76-204 (Moexipril HCl Tablets) Sponsored by Teva Pharmaceuticals, North Wales, PA
3. ANDA 76-257 (Glyburide Tablets) Sponsored by Corepharma LLC, Middlesex, NJ

TO: Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence (HFD-650)

At the request of HFD-650, the Division of Scientific Investigations conducted an audit of the clinical portions of the following three bioequivalence studies.

ANDA 76-219 (Mitrazapine Tablets)

Study #1: Protocol B012001: A Relative Bioavailability Study of Mirtazapine 15 mg Tablets Under Fasting Conditions.

ANDA 76-204 (Moexipril HCl Tablets)

Study #2: Protocol B006539: A Relative Bioavailability Study of Moexipril HCl 15 mg Tablets Under Fasting Conditions.

ANDA 76-257 (Glyburide Tablets)

Study #3: Protocol B011102: A Relative Bioavailability Study of Glyburide 5 mg Tablets Under Non-Fasting Conditions.

The clinical portions of the above studies were all conducted at

Please note that for ANDA 76-204 (Moexipril HCl Tablets), OGD also requested inspection at other study sites

The results and our recommendation of these inspections when completed will be forwarded to OGD in a separate memo.

The Novum inspection was a follow-up to a complaint. The complainant was a volunteer who previously participated in several bioequivalence studies conducted at The complaint contained the following allegations:

1. Records at were manipulated so subjects could pass physical exams to qualify for participating in studies.

2. EKG's were rerun multiple times and failed ones were simply torn up and tossed out.

3. Subjects sneaked in urine samples in order to pass drug screening.

4. In a study that prohibited smoking, some subjects were at times smoking in the bathroom. The nurses brought in cigarettes, and subjects were permitted to keep matches and lighters with them in the clinic.

Following the inspection at (4/9-16/02), no significant problem in the studies audited was found, and no Form FDA-483 was issued. The inspection also found that none of the above allegations could be substantiated (see Attachment 1 for details).

Conclusion:

The allegations in the complaint against [redacted] ere found to be unsubstantiated. We recommend that data in the clinical portions of the following studies be acceptable for review:

Protocol B012001 (ANDA 76-219, Mitrazapine Tablets)
Protocol B006539 (ANDA 76-204, Moexipril HCl Tablets)
Protocol B011102 (ANDA 76-257, Glyburide Tablets)

After you have reviewed this transmittal memo, please append it to the original ANDA submission.

Martin K. Yau 6/7/0

Martin K. Yau, Ph.D.

DSI Final Classification:

NAI - [redacted]

APPEARS THIS WAY
ON ORIGINAL

cc:
HFD-45/RF
HFD-48/Yau/cf
HFD-650/scardina/Sanchez
HFR-CE1515/Mechenbier/Rakestraw
Draft: MKY 6/6/02
Edit: CTV
DSI:5413,5414,5415;O:\BE\EIRCOVER\76219&76257&76204novum.doc

Redacted 22

Page(s) of trade secret and /or confidential commercial information

Sanchez

MEMORANDUM

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

DATE: AUG 2 0 2002

FROM: Charles A. Snipes, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. Martin K. Yau for CTV
Associate Director, Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of EIR Covering ANDA 76-204
Moexipril HCl Tablets 7.5 mg, 15 mg
Sponsored by TEVA Pharmaceuticals USA

TO: Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence (HFD-650)

At the request of HFD-650, the Division of Scientific Investigations conducted an audit of the following bioequivalence studies:

Protocol B006501: A Relative Bioavailability Study of Moexipril HCl 15 mg Tablets Under Fasting Conditions.

Protocol B016502: A Relative Bioavailability Study of Moexipril HCl 15 mg Tablets Under Non-Fasting Conditions.

The clinical portion of these studies was conducted at [redacted] The analytical portion of the studies was performed by [redacted]

Upon the inspection at [redacted] (5/28-31/02), there were no objectionable findings. No Form 483 was issued. Please note that the analytical portions of Protocols B006501 and B016502 have not yet been inspected.

Conclusions:

Following the audits at [redacted] the Division of Scientific Investigations recommends that the clinical portion of Protocols B006501 and B016502 be accepted for review.

After you have reviewed this transmittal memo, please append it to the original ANDA submission.

Charles A. Snipes

Charles A. Snipes, Ph.D.

Final Classification:

[redacted] **NAI**

cc:
HFA-224
HFD-45/rf
HFD-48/Snipes/cf
HFD-650/Sanchez
HFR-SW450/Vega
HFR-SW1580/Branche
HFR-SW1540/Martinez
Draft: CAS 8/20/02
Edit: MKY 8/20/02
File: 5415 O:\BE\76204tev.moe.doc

APPEARS THIS WAY
ON ORIGINAL

APPROVAL SUMMARY PACKAGE

A. ANDA NUMBER: 76-204

B. FIRM: Teva Pharmaceuticals USA
Attention: Philip Erickson
1090 Horsham Road
North Wales, PA 19454
Phone: (215)-591-3000
Fax: (215)-591-8812

C. DOSAGE FORM: Tablets

D. STRENGTH: 7.5 mg and 15 mg

E. DRUG: Moexipril Hydrochloride Tablets

F. cGMP STATEMENT/EIR UPDATE STATUS: Satisfactory (J. D. Ambrogio, 10/28/02)

G. BIOEQUIVALENCY STUDY: Satisfactory (K. Dhariwal, 12/10/02)

H. METHOD VALIDATION – (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): The drug substance and the drug product do not have USP monographs, therefore methods validation is required. E.S. Walker (11/18/02) indicated that "the methods appear to be suitable for regulatory analysis of this product" with three concerns which were subsequently satisfactorily resolved. Therefore, Methods Validation is Acceptable (S. Dhanesar, 04/02/03).

I. STABILITY – ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION? Containers used in the stability studies are identical to those listed in container section.

J. LABELING: Acceptable (J. Barlow, 8/29/02)

K. STERILIZATION VALIDATION (IF APPLICABLE): N/A

L. SIZE OF BIO BATCH – (FIRM'S SOURCE OF NDS O.K.?):
[redacted]) tablets of 7.5 mg strength and [redacted] tablets of 15 mg strength

M. SIZE OF STABILITY BATCHES – (IF DIFFERENT FROM BIO BATCH WERE THEY MANUFACTURED VIA THE SAME PROCESS?): The Bio Batch and the Stability Batches were the same batch.

N. PROPOSED PRODUCTION BATCH – MANUFACTURING PROCESS THE SAME AS BIO/STABILITY? Manufacturing process is the same as for exhibit batch. Proposed batch size:
[redacted] tablets of 7.5 mg strength and [redacted] tablets of 15 mg strength

CHEMIST: SDhanesar, Ph.D. DATE: 03/28/03

SUPERVISOR: AMueller, Ph.D. 4-2-03 DATE: 03/28/03

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MEMORANDUM

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

DATE: June 7, 2002

FILE COPY

FROM: Martin K. Yau, Ph.D.
Pharmacologist
Division of Scientific Investigations (HFD-48)

THROUGH: C.T. Viswanathan, Ph.D. CTV June 7, 02
Associate Director - Bioequivalence
Division of Scientific Investigations (HFD-48)

SUBJECT: Review of an EIR Covering:

1. ANDA 76-219 (Mirtazapine Tablets) Sponsored by Eon Laboratories Manufacturing Inc., Laurelton, NY
2. ANDA 76-204 (Moexipril HCl Tablets) Sponsored by Teva Pharmaceuticals, North Wales, PA
3. ANDA 76-257 (Glyburide Tablets) Sponsored by Corepharma LLC, Middlesex, NJ

TO: Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence (HFD-650)

At the request of HFD-650, the Division of Scientific Investigations conducted an audit of the clinical portions of the following three bioequivalence studies.

ANDA 76-219 (Mitrazapine Tablets)

Study #1: Protocol B012001: A Relative Bioavailability Study of Mirtazapine 15 mg Tablets Under Fasting Conditions.

ANDA 76-204 (Moexipril HCl Tablets)

Study #2: Protocol B006539: A Relative Bioavailability Study of Moexipril HCl 15 mg Tablets Under Fasting Conditions.

ANDA 76-257 (Glyburide Tablets)

Study #3: Protocol B011102: A Relative Bioavailability Study of Glyburide 5 mg Tablets Under Non-Fasting Conditions.

The clinical portions of the above studies were all conducted at

Please note that for ANDA 76-204 (Moexipril HCl Tablets), OGD also requested inspection at other study sites

. The results and our recommendation of these inspections when completed will be forwarded to OGD in a separate memo.

The inspection was a follow-up to a complaint. The complainant was a volunteer who previously participated in several bioequivalence studies conducted at The complaint contained the following allegations:

1. Records at were manipulated so subjects could pass physical exams to qualify for participating in studies.

2. EKG's were rerun multiple times and failed ones were simply torn up and tossed out.

3. Subjects sneaked in urine samples in order to pass drug screening.

4. In a study that prohibited smoking, some subjects were at times smoking in the bathroom. The nurses brought in cigarettes, and subjects were permitted to keep matches and lighters with them in the clinic.

Following the inspection at (4/9-16/02), no significant problem in the studies audited was found, and no Form FDA-483 was issued. The inspection also found that none of the above allegations could be substantiated (see Attachment 1 for details).

Conclusion:

The allegations in the complaint against [redacted] were found to be unsubstantiated. We recommend that data in the clinical portions of the following studies be acceptable for review:

Protocol B012001 (ANDA 76-219, Mitrazapine Tablets)
Protocol B006539 (ANDA 76-204, Moexipril HCl Tablets)
Protocol B011102 (ANDA 76-257, Glyburide Tablets)

After you have reviewed this transmittal memo, please append it to the original ANDA submission.

Martin K. Yau 6/7/0:

Martin K. Yau, Ph.D.

DSI Final Classification:

NAI – [redacted]

APPEARS THIS WAY
ON ORIGINAL

cc:
HFD-45/RF
HFD-48/Yau/cf
HFD-650/scardina/Sanchez
HFR-CE1515/Mechenbier/Rakestraw
Draft: MKY 6/6/02
Edit: CTV
DSI:5413,5414,5415;O:\BE\EIRCOVER\76219&76257&76204novum.doc

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Memorandum

Date Monday, April 22, 2002

From D. J. Mechenbier/INV

Subject F/U to Complaint #7944

To DIB, PHI-DO

During inspection of ——— for both IRB and clinical study coverage, attention was given to the allegations made in complaint #7944 and related memo dated 11-7-01. An attempt was made to identify the study about which the allegations were made. The study that most closely fit the given parameters was a study using Digoxin. The complainant's name did not appear among the listed study subjects. Review of this study and three others around the time of the alleged study deviations found indications that subjects were tested for cotinine when suspected of not being truthful about smoking status and that a subject was dismissed from a study and permanently disqualified from future studies when found to be using an inhaler smuggled into the facility during a study.

Inspection of the clinical intake area found urine sample cups in use that provide indication of sample temperature. This feature is intended to prevent substitution of urine samples during screening for study participation.

A close review of EKG's on file with each of the three studies reviewed for bioequivalence coverage found no indication of substitution or manipulation. However, in the absence of a sequential counter, the alleged practice of running multiple EKG's in order to get an acceptable one would not be detectable.

The company uses a screening database in order to eliminate subjects from intake screening that would not fit study criteria. This database also includes subjects that have been disqualified from future participation. Review of the disqualified list found that the complainant had not participated in a study at ——— since sometime in 1999. Further contact with the complainant by phone on 4-11-02 resulted in a statement that he had been disqualified due to his decision to leave an overcrowded study at the time of check-in. At the time of this phone call he made no further mention of his previous allegations. His interest was focused on what he had to do to requalify for future study participation. I advised him of the existence of an IRB advocate and suggested that he contact the advocate.

Daniel J. Mechenbier/INV

To: C.T.Viswanathan, Ph.D./HFD-48

Attempt to follow-up on allegations of improprieties during clinical studies at ———, found that the complainant has not participated in any recent studies. Findings during the current inspections of the IRB as well as the bioequivalence clinical area found that controls are in place to prevent and detect problems with unauthorized use of tobacco and concomitant medications; substitution of urine samples, etc. Efforts are made prior to recruiting to eliminate unqualified subjects from entering the clinical screening process. None of the allegations could be substantiated. No further follow-up is planned at this time.

Cynthia L. Rakestraw/SI

Dist. O: HFR-MA150, Files
cc: HFD-48, Yau
cc: HFR-MA1515

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

76-204

CORRESPONDENCE

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

March 27, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION – OUTCOME OF LITIGATION AND REQUEST FOR FINAL APPROVAL

NEW CORRESP
NC

ANDA 76-204
MOEXIPRIL HYDROCHLORIDE TABLETS 7.5 mg and 15 mg
PATENT INFORMATION – OUTCOME OF LITIGATION AND REQUEST FOR FINAL APPROVAL

Dear Mr. Buehler:

We submit herewith notification of the outcome of litigation regarding U.S Patent No. 4,743,450: Civil Action Number 01-4995(DRD). The United States District Court, District of New Jersey, has ordered that judgement be entered in favor of TEVA Pharmaceuticals USA and against Schwarz Pharma, Inc. and Schwarz Pharma AG. The date of this order is March 24, 2003. A copy of the order is provided herein. Having received this favorable order, and having addressed all of the Agency's review comments, we hereby respectfully request final approval of ANDA 76-204 as expeditiously as possible. We believe that we are not only eligible for final approval at this time, but also for a period of generic exclusivity for having filed the first substantially complete application for this drug that contained a paragraph IV certification. As the summary judgement order constitutes a triggering event, our exclusivity clock has begun to run. Should you have comments or questions, please feel free to contact me by telephone at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE
Enclosure

RECEIVED
MAR 2 8 2003
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Direct Dial: (215) 591 3141
Direct FAX: (215) 591 8812
philip.erickson@tevausa.com

February 26, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT

ORIG AMENDMENT
N/A-m

ANDA #76-204
MOEXIPRIL HYDROCHLORIDE TABLETS, 7.5 mg and 15 mg
MINOR AMENDMENT – RESPONSE TO FEBRUARY 13, 2003 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced pending ANDA in response to your review letter dated February 13, 2003. Your comments are addressed in the order in which they were presented. A copy of your letter is provided in **Attachment 1**.

A. Chemistry Deficiencies

1. Please note, that the concentration of each component in the resolution solution is [redacted] This solution is used for qualitative evaluation of the chromatography, so small amounts of undissolved impurities will not effect the system suitability results.

   The stock concentration of Moexipril in the Sample Preparation is [redacted] If 1406-HB and 1405 were present at their highest respective release/stability limits, their concentrations in the Sample Preparation would be [redacted] for 1406-HB and [redacted] for 1405. These concentrations are roughly [redacted] less than that of the resolution solution. To verify that these impurities are dissolved at these levels, solutions were prepared at [redacted] for 1406-HB and [redacted] for 1405. These solutions showed no evidence of undissolved material indicating that the Sample Preparation is acceptable.

2. Since Impurity A is not commercially available, the resolution is calculated from a peak in the resolution solution at the corresponding relative retention time. Since the other resolution requirements are more indicative of the chromatographic performance

of the method, we have removed this system suitability requirement. Please find enclosed in **Attachment 2** the updated Finish Product Procedure Manual for Moexipril Hydrochloride Tablets 7.5 mg and 15 mg.

3. The [redacted] (Assay and Related Substances) test method for drug product has been run internally in our Analytical Research and Development department, and Quality Control department; as well as externally in a contract facility and have not experienced this problem. Based upon our method validation robustness testing, provided in **Attachment 3,** there are three parameters that could lead to lower theoretical plate values:

   [redacted] rate above the method specified limit of [redacted]

   Decreased column temperature below the method specified temperature of 45°C.

   Increased initial mobile phase organic component (Solution A) above the method specified amount of [redacted]

   We suggest examining your previous data to ensure that these three criteria were followed. If necessary, we are open to reviewing your chromatograms or conducting a conference call with the Agency to ensure that this issue is resolved.

The information provided herein represents, in our opinion, a complete response to your letter of February 13, 2003 and is submitted towards the continued review of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/ba
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

January 23, 2003

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/am

ANDA # 76-204
MOEXIPRIL HYDROCHLORIDE TABLETS, 7.5 mg and 15 mg
TELEPHONE AMENDMENT – RESPONSE TO A JANUARY 13, 2003 TELEPHONE REQUEST

Dear Mr. Buehler:

We submit herewith a Telephone Amendment to the above-referenced pending ANDA in response to a January 13, 2003 telephone conversation with Craig Kiester of your Office.

Specifcally, dissolution data generated at 20 minutes are being provided herein. Dissolution profile results for multiple strengths and multiple package sizes of Moexipril Hydrochloride Tablets, 15 mg and 7.5 mg are provided in **Attachment 1**. These data were obtained on expired product (30 month retain samples) from our pivotal batches.

From our January 13, 2003 telephone conversation, we understand that the request for the enclosed data is not a request for revision to the existing dissolution parameters currently contained within this pending ANDA. They are for the Agency's informational use only. As such, this information is provided toward the continued review and approval of this application. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosure

RECEIVED
JAN 24 2003
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3141
FAX: (215) 591 8812

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

October 7, 2002

MINOR AMENDMENT

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AM

ANDA # 76-204
MOEXIPRIL HYDROCHLORIDE TABLETS, 7.5 mg and 15 mg
MINOR AMENDMENT – RESPONSE TO AUGUST 26, 2002 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced pending ANDA in response to comments provided in your review letter dated August 26, 2002. Your comments are addressed in the order in which they were presented. A copy of the August 26 letter is provided in **Attachment 1**.

A. Chemistry Deficiencies

1. Responses regarding the active ingredient, Moexipril HCl:

   a. A copy of the cover letter responding to FDA's deficiencies to DMF # ——, is provided in **Attachment 2**.

   b. The proposed release limit for "Total Impurities" has been tightened to NMT —— to correspond to the release specification limit in the drug product (NMT —— Our previous proposal was made in error. Please find the revised Raw Material Procedures Manual indicating this tightened release limit in **Attachment 3**.

   c. Per your request, the drug substance residual solvent limits have been tightened based upon our data. Please find a Certificate of Analysis for an additional drug substance batch (**Attachment 4**) that supports our newly proposed limits. Please note that this Certificate of Analysis supports our proposed limits but the specifications were based on Version 2 of the Raw Material Procedures Manual. Our Raw Material Procedures Manual has been revised accordingly and is contained herein (**Attachment 3**). A method validation addendum for linearity data supporting the proposed limits for our residual solvent method may be found in **Attachment 5**. The following table compares our previously submitted limits with our newly proposed limits.

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	Previously Submitted:	Proposed:
[redacted]	NMT [redacted]	NMT [redacted]
[redacted]	NMT [redacted]	NMT [redacted]
[redacted]	NMT [redacted]	NMT [redacted]
[redacted]	NMT [redacted]	NMT [redacted]

We commit to further evaluate the residual solvent limits as we gain more experience with the material and commit to submit revised limits if appropriate in the first annual report.

2. The proposed stability limit for Impurity A (NMT [redacted]) has been reduced to NMT [redacted] This specification is based on our 24 month room temperature stability data with observed values up to [redacted] Please find a revised Finished Product Procedures Manual in **Attachment 6** that reflects this tightened specification.

3. We note that [redacted] (Impurity 1405) is not a possible degradation product of Moexipril. The stability limit for this impurity has therefore been reduced to NMT [redacted] correspond with the drug substance. Please find the revised Finished Product Procedures Manual in **Attachment 6**.

B. Notes and Acknowledgements:

1. We acknowledge that our internal procedure allowing for conditional release of the active ingredient prior to use in pivotal batches and for subsequent full release testing following pivotal batch production should be discussed with our local FDA District Office. Please note that this issue was discussed at an inspection dated August 7 through August 11, 2000 by Philadelphia District Investigator Debra J. Bennett and Chemist George Pyramides. No negative District observations were received.

2. Updated stability data are provided in **Attachment 7**. Please note that the revised stability impurity and moisture specifications are included in the provided data.

3. We note that our bioequivalence information is under review and any deficiencies will be communicated separately.

4. We also note that our labeling information is under review and any deficiencies will be communicated separately.

Please note that we have revised our [redacted] release specification from [redacted] and revised our moisture stability specification from [redacted] The previously submitted report titled "Moexipril Hydrochloride Tablets, 15 mg and 7.5 mg – Percent [redacted] Determination and Specifications" calculated the maximum amount of [redacted] present in the tablets based upon all ingredients at their upper specification limit for [redacted] content as approximately [redacted]. This calculation does not however include any contributions due to environmental humidity experienced by the product during stability storage. Additionally, the report indicates that we have in fact observed increases of up to [redacted] during stability. The revised Finished Product Procedures Manual (**Attachment 6**) and updated stability summary reports (**Attachment 7**) reflect this revised specification.

The information provided herein represents, in our opinion, a complete response to your letter of August 26, 2002 and is submitted towards the continued review of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosures

APPEARS THIS WAY
ON ORIGINAL

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

Phone: (215) 591 3141
FAX: (215) 591 8812

July 19, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

LABELING AMENDMENT

ORIG AMENDMENT
N/AF

FPL

ANDA #76-204
MOEXIPRIL HYDROCHLORIDE TABLETS, 7.5 mg and 15 mg
LABELING AMENDMENT – RESPONSE TO JUNE 25, 2002 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a labeling amendment in response to a letter dated June 25, 2002 from the Labeling Review Branch. For ease of review, please find a copy of the June 25, 2002 review letter in **Attachment 1**.

Labeling Deficiencies:

1. We note that the container labels for bottles of 100 and 1000 tablets are satisfactory in draft as of the July 16, 2001 submission. Please find 12 final printed copies in **Attachment 2**.

2. The package insert labeling has been revised as requested. Please find 12 copies of final package insert labeling and a comparison to our previous revision in **Attachment 3**.

This information is submitted for your continued review of this pending ANDA. If there are any further questions, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

RECEIVED
JUL 22 2002
OGD / CDER

Sincerely,

PE/jb
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

May 31, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

TELEPHONE AMENDMENT

ORIG AMENDMENT
N/AB

ANDA #76-204
MOEXIPRIL HYDROCHLORIDE TABLETS, 7.5 mg and 15 mg
TELEPHONE AMENDMENT – RESPONSE TO MAY 21, 2002 TELEPHONE REQUEST

Dear Mr. Buehler:

We submit herewith a telephone amendment to the above-referenced pending ANDA in response to a telephone communication on May 21, 2002 between Philip Erickson, Director of Solid Oral Dosage Forms, Regulatory Affairs and Dr. Nina Nwaba of the Division of Bioequivalence. Please find enclosed experimental dissolution profiles generated on Moexipril Hydrochloride Tablets, 15 mg using various media and parameters. This information encompasses early time points for RLD lot numbers 1388800A and 0070801 (**Attachment 1**).

The information provided herein is submitted towards the continued review of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosures

RECEIVED
JUN 0 3 2002
OGD / CDER

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

April 2, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

MINOR AMENDMENT
ORIG AMENDMENT
N/AM

ANDA #76-204
MOEXIPRIL HYDROCHLORIDE TABLETS, 7.5 mg and 15 mg
MINOR AMENDMENT – RESPONSE TO DECEMBER 21, 2001 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a minor amendment to the above-referenced pending ANDA in response to comments provided in your review letter dated December 21, 2001. Your comments are addressed in the order in which they were presented. A copy of this letter is provided in **Attachment 1**.

A. Chemistry Deficiencies

1. Responses regarding the active ingredient, Moexipril HCl:

   a. Please find in **Attachment 2**, the cover letter of the response to the FDA's deficiencies from [redacted] on behalf of the holder of DMF #[redacted]

   b. Our internal procedures allow for the conditional release of a drug substance lot for pivotal lot production based on conducting at least one identification test and review of the manufacturer's certificate of analysis. Full release of the drug substance must be completed before the finished product lot is used for bioequivalence dosing.

      The drug substance lot #1343-012 used in the 7.5 mg strength was conditionally released on 6/6/00 and fully released on 11/20/00. The drug substance lot #1127-167 used in the 15 mg strength was conditionally released on 5/12/00 and fully released on 7/7/00. Bioequivalence dosing started on 8/12/00 for the 15 mg strength. The Certificate of Analysis for lot #1127-167 (V[illegible] dated

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OGD / CDER

Redacted 5

Page(s) of trade secret and /or confidential commercial information

2. It is noted that once the analytical test methods are resolved, a validation will be scheduled with the District Office. Please refer to our validation commitment on page 8766 of the original ANDA submission. We commit to satisfactorily resolve any deficiencies which may be identified and acknowledge that satisfactory methods validation is required for both the drug substance and drug product.

3. Updated stability data is provided in **Attachment 23**.

4. The Division of Bioequivalence has not recommended a change in the dissolution test method or specification. Therefore, no revisions are needed.

C. Labeling Deficiencies:

We acknowledge that the draft product container (100s and 1000s) labeling are satisfactory in draft as of the July 16, 2001 submission. Four copies of draft package insert labeling, which incorporates the revisions recommended from the Labeling Branch's December 21, 2001 review letter, are enclosed in **Attachment 24**. To facilitate review of this submission and in accord with 21 CFR 314.94(a)(8)(iv), we have provided a comparison document of our proposed labeling with that of our last submission in **Attachment 25**. This comparison annotates minor format changes and the revisions recommended in your deficiency comments.

The information provided herein represents, in our opinion, a complete response to your letter of December 21, 2001 and is submitted towards the continued review of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosures

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

January 29, 2002

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCY AMENDMENT

ORIG AMENDMENT
N/AB

ANDA #76-204
MOEXIPRIL HYDROCHLORIDE TABLETS, 7.5 mg and 15 mg
BIOEQUIVALENCY AMENDMENT – RESPONSE TO NOVEMBER 21, 2001 REVIEW LETTER

Dear Mr. Buehler:

We submit herewith a bioequivalency amendment to the above-referenced pending ANDA. The subject of this amendment is our response to comments received from the Division of Bioequivalence in a letter dated November 21, 2001. The response to those bioequivalency comments are provided in the order in which they were presented in the aforementioned review letter. A copy of this letter is enclosed in **Attachment 1**.

Bioequivalency Deficiencies

1. As per your request, dissolution testing of the test and reference tablets was repeated with samples taken at 5, 10, 15, 20 and 30 minutes. Please see **Attachment 2** for the dissolution results.

2. We confirm that the data submitted in orange jackets vol. 1.5, 1.6 and 1.7 are identical to the data submitted in orange jackets vol. 1.8, 1.9 and 1.10. Please disregard this repeated data.

3. The failed fasting bioequivalence study data including potency, content uniformity, and dissolution results are included. Please see **Attachment 3** for the Certificates of Analysis of our product and the reference drug. The failed fasting bioequivalence study is provided in **Attachment 4**.

4. We acknowledge that in future, we should submit the chromatograms from 20% of serially selected subjects and the subjects whose chromatograms are to be submitted should be defined prior to the analysis of the study sample.

The information provided herein represents, in our opinion, a complete response to your letter of November 21, 2001 and is submitted towards the continued review of this pending ANDA. If any additional information or clarification is needed, please do not hesitate to contact me at (215) 591-3141 or via facsimile at (215) 591-8812.

Sincerely,

PE/jb
Enclosures

APPEARS THIS WAY
ON ORIGINAL

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

November 26, 2001

NEW CORRESP
NC

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT INFORMATION

NAT
P.M.P
12/10/01

ANDA # 76-204
MOEXIPRIL HYDROCHLORIDE TABLETS, 7.5 mg and 15 mg
NOTICE OF PATENT CERTIFICATION/ END OF 45 DAY CLOCK/ LEGAL STATUS

Dear Mr. Buehler:

TEVA Pharmaceuticals USA hereby certifies that a Notice of Certification of Non-Infringement of U.S. Patent 4,743,450 (hereafter "the '450 patent") dated September 18, 2001 was provided to Schwarz Pharma, Inc., as the holder of NDA 20-312 for Univasc Tablets, and to Pfizer Pharmaceuticals (formerly Warner-Lambert Company) as owner of the '450 patent, in accord with 21 CFR 314.95(c).

In accord with 21 CFR 314.95(e), TEVA is hereby providing documentation of the receipt of the above-referenced September 18, 2001 notice by Pfizer Pharmaceuticals (on 9/20/01) and Schwarz Pharma, Inc. (on 9/21/01). Copies of the return receipt cards that accompanied the Notices are provided in **Attachment 1**. Please note that the return receipt card from Schwarz was not dated, therefore a copy of the U.S. Postal Service delivery tracking form for this package is also provided. In accord with 21 CFR 314.95(f), the first day of the 45-day period provided for in section 505(j)(4)(B)(iii) of the Act is September 22, 2001. The 45-day period therefore ended on November 5, 2001.

We hereby inform the Agency of a suit filed by Schwarz Pharma and Warner Lambert Company against TEVA concerning U.S. Patent 4,743,450 in the United States District Court of New Jersey. This suit was filed October 26, 2001, which was within the 45-day period. TEVA hereby commits to provide notification of the outcome of this suit in an appropriate submission to this application. A copy of the complaint is provided in **Attachment 2**.

CENTER FOR DRUG
NOV 2 7 2001
EVALUATION AND RESEARCH

This information is submitted for your continued review and evaluation of this ANDA. Should you have any questions regarding the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile (215) 591-8812.

Sincerely,

PE/jbp
Enclosures

APPEARS THIS WAY
ON ORIGINAL

76204

TEVA

Administrative Offices:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

Phone: (215) 591 3000
FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

August 14, 2001

NC for Bio

BIOAVAILABILITY
NEW CORRESP

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

BIOEQUIVALENCE ELECTRONIC SUBMISSION DOCUMENT

ORIGINAL ABBREVIATED NEW DRUG APPLICATION
MOEXIPRIL HYDROCHLORIDE TABLETS, 7.5 mg and 15 mg

Dear Mr. Buehler:

Reference is made to our original abbreviated new drug application dated July 16, 2001 for Moexipril Hydrochloride Tablets, 7.5 mg and 15 mg.

We submit herewith a Bioequivalence Electronic Submission Document (Entry and Validation Application) for the above referenced original abbreviated new drug application. TEVA Pharmaceuticals USA hereby declares that the data contained in the electronic submission is identical to that included in the paper submission. Any differences have been noted in the accompanying companion document.

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

CENTER FOR DRUG EVALUATION AND RESEARCH
AUG 16 2001

PE/jmc
Enclosures

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ANDA 76-204

AUG 22 2001

TEVA Pharmaceuticals USA
Attention: Phillip Erickson
1090 Horsham Road
P.O. Box 1090
North Wales, PA 19454

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated August 2, 2001 and your response dated August 3, 2001.

NAME OF DRUG: Moexipril Hydrochloride Tablets, 7.5 mg and 15 mg

DATE OF APPLICATION: July 16, 2001

DATE (RECEIVED) ACCEPTABLE FOR FILING: July 16, 2001

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

  1) Each owner of the patent or the representative

designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Tim Ames
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Acting Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Corporate Headquarters:
TEVA PHARMACEUTICALS USA
1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

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FAX: (215) 591 8600

Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

76-204

August 3, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESPONDENCE

NC

MOEXIPRIL HYDROCHLORIDE TABLETS, 7.5 mg and 15 mg
NEW CORRESPONDENCE - RESPONSE TO AUGUST 2, 2001 TELEPHONE CONVERSATION

Dear Mr. Buehler:

In response to a telephone communication on August 2, 2001 between Philip Erickson and Beth Fritch of your office, please find enclosed a current cGMP certification for Missouri Analytical Labs. Also, reference is made to the quantitative composition charts in Section 6, page 97 and Section 7, page 7730 of our original application. These charts are identical and do provide the composition of the [redacted] used in our formulations. For your convenience, a copy of this composition chart is provided herein.

This information is submitted for your continued review and evaluation of this ANDA. Should you have any questions regarding the information contained herein, please do not hesitate to contact me at (215) 591-3141 or via facsimile (215) 591-8812.

Sincerely,

PE/jmc
Enclosures

CENTER FOR DRUG
RECD
AUG 14 2001
OGD
EVALUATION AND RESEARCH

76-204

TEVA

Corporate Headquarters:
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1090 Horsham Road, PO Box 1090
North Wales, PA 19454-1090

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Philip Erickson, R.Ph.
Director, Regulatory Affairs
Solid Oral Dosage Forms

76-204

July 20, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ADDENDUM TO ANDA
DATED JULY 6, 2001

NEW CORRESP
NC

MOEXIPRIL HYDROCHLORIDE TABLETS, 7.5 mg and 15 mg
ADDENDUM TO ANDA DATED JULY 6, 2001

Dear Mr. Buehler:

Teva Pharmaceuticals USA herewith submits an addendum to the abbreviated new drug application dated July 6, 2001. Attached are the Investigator Financial Interests and Arrangement Disclosure Forms of three additional investigators used in the *in vivo* bioequivalence study under post-prandial conditions. Also provided herewith is our Certification of Financial Interests and Arrangements of Clinical Investigators Form referencing the aforementioned investigators. For your convenience, duplicate copies have been provided such that they can be easily inserted in the original application as pages 104I, 104J, 104K and 104L.

This information is submitted for your continued review and acceptance of this ANDA. Should you have any further comments or questions, please do not hesitate to call me at (215) 591-3141 or contact me via facsimile at (215) 591-8812.

Sincerely,

Philip Erickson I V.A.

PE/jmc
Enclosures

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Philip Erickson, R.Ph.
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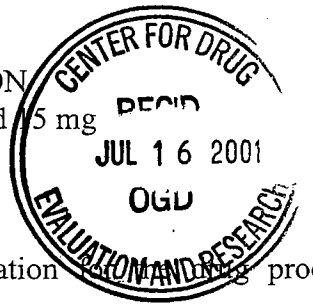
Solid Oral Dosage Forms

505(j)(2)(A) OK
22-AUG-2001
Gregory D. Davis

July 16, 2001

Gary Buehler, Director
Office of Generic Drugs
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Bioequivalence Electronic Submission Document (ESD)



ORIGINAL ABBREVIATED NEW DRUG APPLICATION
MOEXIPRIL HYDROCHLORIDE TABLETS, 7.5 mg and 15 mg

Dear Mr. Buehler:

We submit herewith an abbreviated new drug application for the drug product Moexipril Hydrochloride Tablets, 7.5 mg and 15 mg.

Enclosed are archival and review copies assembled in accord with Office of Generic Drugs February 1999 Guidance for Industry: Organization of an ANDA (OGD #1, Rev. 1). These copies are presented in a total of 38 volumes; 18 for the archival copy and 20 for the review copy.

The application contains a full report of two *in vivo* bioequivalence studies. These studies compared Moexipril Hydrochloride Tablets, 7.5 mg and 15 mg manufactured by TEVA Pharmaceuticals USA to the reference listed drug, Univasc® (moexipril hydrochloride tablets) under both fasting and post-prandial conditions. Submission of the Bio EVA document is to follow under separate cover.

Two separately bound copies of the non-compendial finished product and bulk drug analytical methodology and validation data are included in accord with 21 CFR 314.50(e)(2)(i).

We look forward to your review and comment. Should there be any questions regarding the information contained herein, please do not hesitate to contact me by phone at (215) 591-3141 or by facsimile at (215) 591-8812.

Sincerely,

Philip Erickson/RS

PE/jmc
Enclosures