MOEXIPRIL HCl. RSP
(20-312)

K.B.
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NDA: 20-312 **Submission Date:** 12-18-92, 4-30-93, 5-17-93 and 7-7-93
Moexipril HCl Tablet, 7.5 and 15 mg.
Brand Name: Moex™.
Sponsor: Besselaar **Reviewer:** Rajendra S. Pradhan
Type of Submission: Original NME Priority: 1S

Synopsis: The sponsor has adequately studied the pharmacokinetics (single and multiple dose), metabolism and excretion of prodrug moexipril and its active metabolite moexiprilat. Pharmacokinetics was studied over the dose range proposed in the package insert. Acceptable studies have also been performed in renally impaired patients and cirrhotic patients. Drug interaction between moexipril or moexiprilat and hydrochlorothiazide, digoxin, warfarin and nifedipine were studied. The sponsor has attempted to correlate plasma drug concentration to ACE-inhibition (a pharmacodynamic marker). An acceptable dissolution data has been provided on different strengths but not on broken tablets.

Recommendation: The sponsor's NDA 20-312 appears to be acceptable for meeting the biopharmaceutics requirements, provided that the comments are addressed satisfactorily by the sponsor.

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Appendix II
Individual Subject Data on Studies Listed Under Appendix I
Annotated Package Insert

Background: Moexipril hydrochloride is ethylester of moexiprilat, a long acting, non-sulfhydryl, nonpeptide angiotensin-converting enzyme (ACE) inhibitor. Moexipril hydrochloride is white to off-white powder. At room temperature it is about 10% W/V soluble in distilled water. Moexipril is a prodrug; following oral administration, it is bioactivated by hydrolysis of ethylester to moexiprilat. The sponsor is proposing to market coated tablets containing 7.5 mg and 15 mg of moexipril hydrochloride for oral administration. The sponsor has submitted 25 studies in support of the NDA. The first 13 studies listed under Appendix I are considered as important studies while others as supportive information. The recommended dosing is 7.5 to 60 mg/day administered in a single daily dose one hour prior to meals. It is recommended that dosage should be adjusted to blood pressure response.

Summary of Bioavailability/Pharmacokinetics/Pharmacodynamics:
I. Bioavailability and Bioequivalence:
Absolute bioavailability for moexiprilat was not determined.

The to be marketed tablet formulation (15 mg), was bioequivalent to capsule formulation (15 mg), used in clinical studies except without a 5% overage. (Note: The clinical trial capsule and the capsule used in the bioequivalence study were made from the same blend. The bio study capsule batch was filled 5% less in weight than the clinical trial capsule). Considering the allowable tolerance limits for content uniformity for moexipril in the tablet (5% acceptable/Dr. Piechocki HFD 110) and based on all the available pharmacodynamic data it was concluded that 15.75 mg dose strength was not pharmacodynamically different from 15 mg dose of moexipril. The to be marketed tablet formulation (7.5 mg), is compositionally proportional to 15 mg tablet. Both tablets are scored.

II. Pharmacokinetics:
Absorption: The absorption of moexipril from the tablet and capsule formulations was rapid. For fasting conditions, the mean Tmax occurred between 0.6 and 1.5 hr. The absolute bioavailability of moexiprilat was not determined but for moexipril it was 22%. Both the rate and the extent of absorption were decreased when moexipril was administered (single dose) after a standard high fat breakfast. The AUC and Cmax for moexiprilat were reduced by 55% and 80% respectively after administration of moexipril postprandially.

Metabolism: The metabolite profiles in plasma and urine were determined by administering C^{14}-moexipril orally and by iv. After oral dosing, the metabolite profile for plasma showed moexipril to be the major radiolabelled component at 1 hr after dosing. The other metabolites present in the plasma were diketopiperazine moexiprilat, moexiprilat, diketopiperazine moexipril

and an unknown metabolite P4. All these metabolites were also seen in urine indicating that they are also at least partially eliminated renally (about 15% of total radioactivity). About 74% of total radioactivity was excreted in feces which included moexipril, moexiprilat, diketopiperazine moexiprilat in addition to unknown metabolites F1, F2, F3, F4, F5 and F6. On multiple oral dosing, the plasma radioactivity, moexipril or moexiprilat concentration time profile did not change. The urinary and fecal metabolite profile also remained the same on day one and day six of multiple dose administration (15 mg QD).

After intravenous administration of C^{14}-moexipril, plasma metabolic profile (10 min after administration) consisted of moexipril, moexiprilat and diketopiperazine moexiprilat. No P4 was observed after iv dosing. The urinary profile after iv dosing showed significant amounts of moexipril and moexiprilat but small amounts of diketopiperazine moexiprilat (about 65% of total radioactive dose). Moexiprilat, to lesser amount diketopiperazine moexiprilat and unknown metabolite F3 contributed to most of the radioactivity in faeces (about 26% of total radioactive dose). Up to five other minor metabolites were seen in faeces in addition to traces of moexipril.

Total recovery of radioactivity over 96 hours, both for oral and iv routes was about 90%. The radioactivity half life ranged from 1 to 4 hr.

Distribution: Both moexipril and moexiprilat bind mainly to plasma albumin. The binding can be considered as moderate (over concentration range 0.3 to 10 μg/ml). In young healthy subjects (under 45 yr) protein binding for moexipril was 88.2% (SD 1.8) and for moexiprilat 60.3 (SD 6.2). In elderly healthy subjects (over 65 yr) protein binding decreases ($\sim$ 48%). The volume of distribution (V_d), was determined to be 64 liters and the clearance from plasma (CL_p), was 419 ml/min for moexipril (after administration of the 5 mg iv dose to healthy young males).

Elimination: Unchanged moexipril is eliminated mainly in the urine, and moexiprilat is eliminated in both the urine and feces. The mean values for elimination half-life for moexipril ranged from 0.6 hr to 1.7 hr for all the studies of normal subjects. The $t_{1/2}$ of moexipril did not depend on dose. The mean values for elimination half-life for moexiprilat ranged from 0.8 hr to 53 hr for all the studies of normal subjects. The intersubject variation seen in $t_{1/2}$ of moexiprilat could be due to variation in binding of moexiprilat with ACE. The mean elimination $t_{1/2}$ for moexiprilat calculated using urine data was 4.3 hr in elderly subjects and 3.2 hr in younger subjects.

Multiple-Dose Kinetics: Comparison of single dose and multiple dose pharmacokinetics was studied in two different studies. Moexiprilat showed moderate accumulation (Accumulation ratio of about 1.3) on multiple (15 mg) QD dosing for five days, in both normal younger subjects and normal elderly subjects. There appeared a trend for an increase in the ratio of moexipril to moexiprilat on day 5. In the second study, which had a small number of subjects per group (4) and a parallel design, twice daily administration (BID) of 120 mg of moexipril for 15 days, did not show any moexiprilat accumulation, however, BID administration of 60 mg showed 100% accumulation (note: the latter is not a recommended dose in the labelling).

III. Dose and Dosage Form Proportionality:
In a study where 3.75, 7.5, 15 and 30 mg moexipril doses were administered to healthy subjects in a crossover design, lower doses showed higher bioavailability than higher doses (15 and 30

mg). This probably is due to dose independent contribution of the terminal phase of moexiprilat to AUC. It has been shown that the terminal phase due to the residual binding of drug to ACE has half life greater than 30 hr. This phase can certainly contribute more to AUC of small doses than AUC of large doses. There was an increasing trend in dose normalized Cmax with dose.

IV. Special Populations:

Renal Impairment: It was shown that $t_{1/2}$ values for moexipril and moexiprilat increased with decreasing renal function. Upon administration of single 15 mg dose the $t_{1/2}$ value for moexipril increased from 1.1 (SD 0.2) hr for subjects with creatinine clearance (CrCl) > 90 ml/min to 2.2 (SD 0.7) hr for subjects with CrCl from 10 to 40 ml/min. The AUC for moexipril increased from 60 to 70 ng hr/ml. The $t_{1/2}$ value for moexiprilat increased from 1.5 (0.5) hr for subjects with creatinine clearance (CrCl) > 90 ml/min to 5.3 (SD 3.6) hr for subjects with CrCl from 10 to 40 ml/min. The AUC for moexiprilat increased from 150 to 268 ng hr/ml. Accumulation of moexipril and moexiprilat is not expected for the recommended doses in patients with mild to moderate renal impairment (CrCl >40 ml/min). With CrCl $\leq$ 40 ml/min, dosage reduction should be considered.

Hepatic Impairment: In a cross study comparison it was seen that, for moexipril (single 15 mg dose), dose normalized Cmax was about 1.5 times higher and dose normalized AUC was about 1.5 to 2 times nigher for cirrhotic subjects than for the normal subjects. For moexiprilat, dose normalized Cmax was lower (= by 25%) for the cirrhotic subjects, but dose normalized AUC was about 2 to 2.5 times higher. The $t_{1/2}$ was longer for moexipril and moexiprilat for the cirrhotic subjects. Thus, pharmacokinetics of moexipril and moexiprilat were significantly altered in cirrhotic subjects compared with normal subjects, but plasma concentrations in cirrhotic subjects returned to levels similar to those in normal volunteer between 12 and 24 hr postdosing. Accumulation of moexipril and moexiprilat is not expected at this dose in cirrhotic subjects. However, since the pharmacokinetics across the recommended dose range has not been established in these patients, caution should be exercised at higher doses in these patients. / ok

Elderly: The mean elimination $t_{1/2}$ for moexiprilat calculated using urine data was 4.3 hr in elderly subjects and 3.2 hr in younger subjects. In elderly healthy subjects (over 65 yr) protein binding was lower ($\sim$ 48%). Following 15 mg QD moexipril administration, the mean Cmax and $AUC_{0\text{-}24}$ for both moexipril and moexiprilat were approximately 30 % higher in the elderly group than in the younger group on day one and on day five. The total body clearance for moexipril and moexiprilat were lower in the elderly group than in the younger group. ok

V. Drug Interactions:

The results of moexipril interaction studies (hydrochlorothiazide HCTZ, digoxin, cimetidine and nifedipine retard) are summarized below.

Study No.	Dosage Form	Dose (mg)	Moexipril C_{max} (ng/mL)	Moexipril T_{max} (hr)	Moexipril AUC (ng·hr/mL)	Moexipril $t_{1/2}$ (hr)	Moexiprilat C_{max} (ng/mL)	Moexiprilat T_{max} (hr)	Moexiprilat AUC (ng·hr/mL)	Moexiprilat $t_{1/2}$ (hr)
GHBA 625R	Capsule	30	248	1.2	437	-	71	1.6	203	-
		30 + HCTZ	241	0.8	416	-	69	1.6	215	-
GHBA 626	Capsule	30	190	0.9	296	-	52	1.6	169	-
		30 + digoxin	182	1.0	299	-	57	1.8	177	-
GHBA 627	Capsule	30	254	0.9	406	0.6	68	1.5	226	0.9
		30 + cimetidine	206	1.0	378	0.6	82	1.6	255	0.8
GHBA 693	Capsule	15	100	1.0	150	0.8	18	1.7	89	0.9
		15 + nifedipine	122	1.0	193	0.7	25	1.5	71	0.9

Neither HCTZ, digoxin, cimetidine nor nifedipine (given as CR) had any significant effect on the pharmacokinetics of either moexipril or moexiprilat. Administration of moexipril did not affect mean total urinary excretion of HCTZ; mean Cmax, AUC or Tmax for digoxin and mean Cmax, AUC or $t_{1/2}$ for nifedipine. Mean Tmax for nifedipine administered together with moexipril occurred earlier 1.3 (SD 0.7) than nifedipine administered alone 2.4 (SD 2.1).

The following table shows that coadministration of moexipril with warfarin had no demonstrable effects on plasma warfarin concentrations.

Parameters	50 mg Warfarin	15 mg Moexipril + 50 mg Warfarin
Warfarin (S)		
Cmax (μg/ml)	2.85 ± 0.35	2.79 ± 0.37
Tmax (hr)	1.8 ± 0.9	2.5 ± 3.4
$AUC_{(0-t)}$ (μg hr/ml)	94.8 ± 15.7	95.3 ± 18.4
Warfarin (R)		
Cmax (μg/ml)	2.80 ± 0.42	2.81 ± 0.34
Tmax (hr)	2.1 ± 1.1	2.5 ± 3.4
$AUC_{(0-t)}$ (μg hr/ml)	124 ± 21	125 ± 28

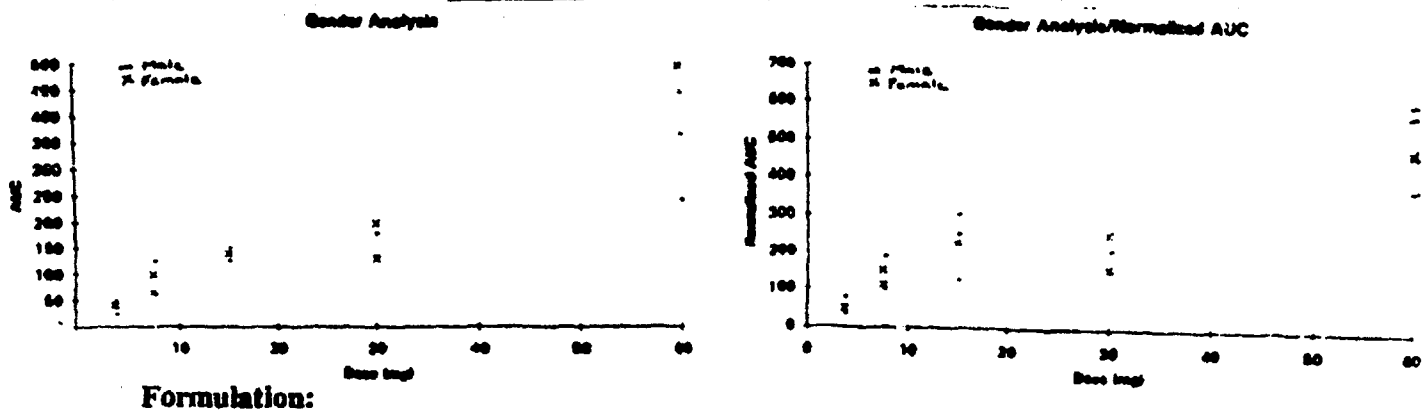
There was no effect on the anticoagulant effects of warfarin for 5 days, as measured by elongation of the prothrombin time. Medical officer should note the increased number of adverse effects (headache and dizziness) associated with concomitant administration of moexipril and warfarin.

VI. Pharmacokinetic/Pharmacodynamic Relationship:

The sponsor has used ACE inhibition as a marker for drug activity and compared it with moexiprilat concentration using simple Emax model. The EC50 was calculated to be 0.4 ng/ml for moexiprilat. However it was seen that ACE inhibition was still more than 50% when blood pressure had returned to predose value, implying that in addition to plasma ACE inhibition, other factors may contribute to the lowering of blood pressure.

VII. Gender Analysis:

The firm did not submit any gender analysis. Based on the study which had sufficient female subjects (about 50% of male subjects), it was concluded by this reviewer, that there is no gender difference in moexiprilat pharmacokinetics over a dose range of 3.75 to 30 mg. The figures below show that at 60 mg dose, the female subject had the highest exposure. When corrected for weight, however, the AUC for this subject was lower. (In the following fig on the right AUC was normalized to a reference body weight of 60 kg). This comparison was non-statistical due to limited subjects per dose group.



Formulation:

The tablet formulation 7.5 mg is compositionally proportional to 15.0 mg tablet.

Dissolution:

The sponsor has proposed dissolution method of USP XXII apparatus II at 50 rpm, in 900 ml water at 37°C, with sampling time at 15 min and a specification of at least dissolved in 15 min according to USP <711> dissolution acceptance table.

This specification is not acceptable and after reviewing the in vitro dissolution data, Division of Biopharmaceutics recommends a Q of not less than in 15 min.

General Comments (Need not be sent to the firm):

The sponsor has not studied the pharmacokinetics in patients with CHF.

The drug interaction study with nifedipine utilizes a controlled release formulation of nifedipine. Upon coadministration of 20 mg nifedipine with 15 mg moexipril, there was a marginal increase (16% for mean AUC and 15% for mean Cmax) in moexipril plasma levels. Higher doses of moexipril with immediate release nifedipine may have potential for interaction.

Comments to the Pharmacologist: Under Carcinogenesis, Mutagenesis, Impairment of Fertility section of labeling, the firm claims that mice and rats were exposed to doses 150 times higher than human dose. Based on a comparison between rats and humans and using area under radioactivity versus time curve as an exposure parameter and considering 60 mg as highest human dose, 75 mg/kg/day produces only about 2 fold higher exposure to animals. This statement is based on linear extrapolation of exposure from 15 mg to 60 mg dose in humans. Although the animal doses were several fold higher than humans, due to different disposition the exposure scale in animals translated to only about two times that of the humans.

Comments to be Sent to the Firm:
The dissolution specification proposed by the firm is not acceptable. The Division of Biopharmaceutics recommends a Q of not less than in 15 min.

The firm is requested to submit in vitro dissolution data in deionized water on half Moex™ tablet (7.5 and 15 mg/broken at the score) using the same dissolution method conditions used for the full tablet. The data should be provided to Division of Biopharmaceutics in a format where comparison can be made between in vitro dissolution of full and half Moex™ tablet.

The firm should attempt an in vitro characterization of enzymes involved in moexipril metabolism.

Labeling Comments:

1. The statement 'The extent of absorption may be reduced when MOEX™ tablets are administered with high fat breakfast' should be replaced by following statement.
'Upon single dose administration of 15 mg MOEX™ with a high fat breakfast to normal volunteers, the area under the plasma concentration versus time curve (AUC) and peak plasma concentration (Cmax) of moexiprilat is reduced by up to 50% and 80% respectively'.

2. The statement 'The serum protein binding of moexipril is about 90% and that of moexiprilat about 75%, as measured by equilibrium dialysis at 25°C; on the basis of in vitro studies, the degree of protein binding should be unaffected by age, hepatic dysfunction, renal dysfunction or concentration (over concentration range of 0.3 - 10 μg/ml)' should be replaced by following statement.
'The serum protein binding of moexipril is about 90% and that of moexiprilat about 65%, as measured by equilibrium dialysis at 25°C. On the basis of in vitro studies, the degree of protein binding was unaffected by hepatic dysfunction or concentration (over concentration range of 0.3 - 10 μg/ml). In healthy elderly subjects over 65 years of age, moexiprilat protein binding was 48%'.

3. The statement ' In elderly male subjects (65-80 year old) with clinically normal renal and hepatic function, there appear to be no difference in pharmacokinetic parameters compared to those of younger subjects (19-42 years old)' should be replaced by following statement.
'In elderly male subjects (65-80 year old) the AUC and Cmax of moexiprilat tends to be about 30% higner than in younger subjects (19-42 years old)'.

4. The statement 'The kinetics of moexipril have been shown to be dose-proportional within the range of 3.75 mg to 30 mg' should be replaced by following statement:
'In the dose range of 3.75 to 30 mg, the pharmacokinetics of moexipril may be considered dose proportional. Highest dose, however, was not evaluated'.

5. The firm should state 'Moexiprilat showed moderate accumulation upon multiple dosing of moexipril'.

6. The firm should replace the paragraph, under 'Pharmacokinetics and Metabolism', on effective half life by the following:
'Based on multiple dose administration of 15 mg QD for 5 days to healthy young and elderly subjects, the mean effective half life was estimated to be about 12 hr'.

7. The firm should replace the statement in the 'Precaution' section under Impaired Liver Function with 'In patients with hepatic dysfunction due to cirrhosis, a single 15 mg dose study showed moderate increases in AUC values of moexipril and moexiprilat. Caution should be exercised in dosing these patients'.

8. Under 'Pharmacokinetics and Metabolism' section regarding hepatic cirrhosis patients, state: 'Patients with hepatic cirrhosis showed moderate increases in AUCs as compared to normal subjects when a single 15mg dose was administered'.

9. In the 'Drug Interaction' section, the firm should specify that nifedipine was administered as a controlled release formulation.

10. The ingredients for the tablet coat should be listed in the labelling.

11. Under 'Dosage Adjustment in Renal Impairment', 'Pharmacokinetics and Metabolism' sections the cut off point for creatinine clearance should be change from $\leq$30 ml/min to $\leq$40 ml/min. Also in 'Precaution' section the statement 'In patients with glomerular filtration rate $\leq$ 30 ml/min, peak moexipril level and half life increase, and time to steady state may be delayed' should be replaced by following statement:
'In patients with creatinine clearance $\leq$ 40 ml/min, moexiprilat half life increase, and time to steady state may be delayed'.

12. In 'Pharmacokinetic and Metabolism' section, the statement regarding the site of absorption should be deleted since a conclusive study has not been conducted.

9/30/93

Rajendra S. Pradhan, Ph.D.
Division of Biopharmaceutics

RD Initialed by Ameeta Parekh, Ph.D. Ameeta Parekh 9/30/93

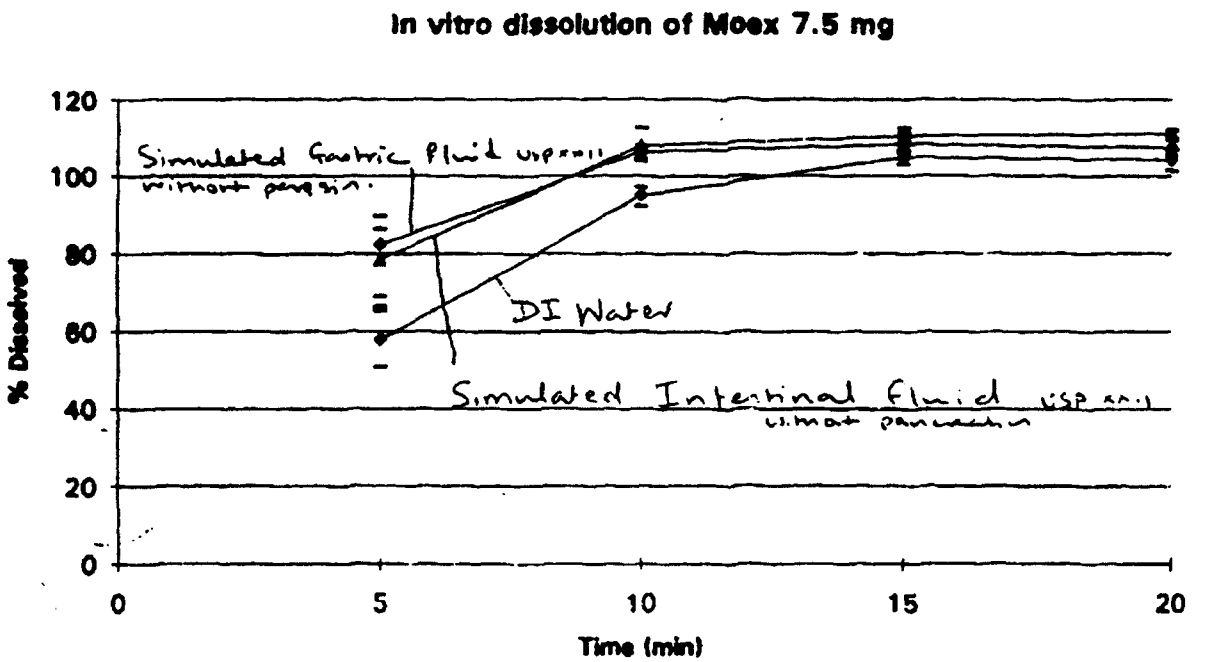
Biopharm Day: Collins, Fleischer, Hepp, Ludden, Parekh, Pradhan.

cc NDA 20-312, HFD 110, HFD 426 (Fleischer/Pradhan) Reviewer, Chron, Drug, FOI
(HFD-19), HFD 340 (Viswanathan), Food, Metabolism.

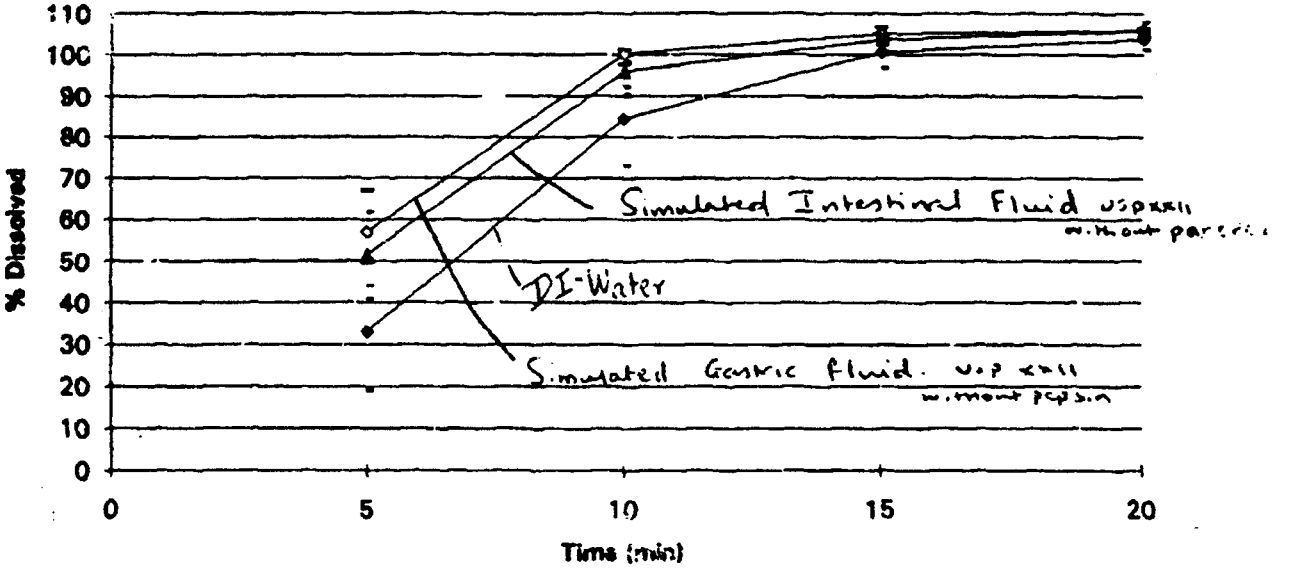
In vitro Dissolution of Moex™ Tablet

Apparatus:	USPXXII, <711>, apparatus II (paddle).
Dissolution Medium:	Deionized and degased water of 37°C and 900 ml.
Paddle speed:	50 rpm
No. of units:	6

The dissolution apparatus was combined with a UV spectrometer with flow through cuvettes. The dissolution medium from the 6 vessels was pumped through the cuvettes in a 5 minutes interval. After recording the absorption at 280 nm, the medium was repumped into the vessels. Thus, the absorption of the samples was recorded over a time period of 5 to 30 min. Similar procedure was also followed for dissolution in simulated gastric and intestinal fluids. These simulated mediums were prepared according to USP XXII specifications, except the enzymes.


In vitro dissolution of Moex 7.5 mg
120
100
80
60
40
20
0
% Dissolved
0
5
10
15
20
Time (min)
DI Water

In vitro dissolution of Moex 15 mg



. REGULATORY SPECIFICATIONS / ANALYTICAL METHODS:
The firm has made the following (highlighted) changes in it's specifications (15.8).

A. DRUG SUBSTANCE SPECIFICATIONS & TESTS (1.1, 000115; 1.2, 000009)

Test	Specifications (1.2, 000009-10)	Method	Volpage ref.
Appearance	Fine white to off white powder	PH20585.ABV.010	1.2, (000013)
Odor	Odorless	PH20585.ABV.020	1.2, (000014)
Particle Size (microscopy)	50% 50 µ or less 90% 100 µ or less	PH20585.ABV.025	1.2, (000015-6)
Identification	IR Spectra	PH20585.ABV.030	1.2,(000017-9)
Purity			
Water Content (Karl Fischer)(15.8, 16)	NMT 1.0%	PH20585.ABV.040	1.2, (00021-2)
Specific Rotation	$[\alpha]^{25}$ = — ° - — ° calc on the anhydrous basis (c = w/v in absolute —)	PH20585.ABV.050	1.2, (000022-3)
Foreign Related Substances (HPLC) (15.8, 17)	NMT % Total NMT % NMT % any other known impurity NMT % any individual unknown impurity	PH20585.ABV.060	1.2, (000024-9)
Heavy Metals (Pb)	NMT 10 ppm	PH20585.ABV.080	1.2, (000037-40)
Residual Solvents (15.8, 17)	NMT 0.1 % Any individual solvent NMT 0.3% Sum of all residual solvents	PH20585.ABV.070	1.2, (000030-6)
Residue on Ignition (Sulfated Ash)	NMT 0.1 %	PH20585.ABV.09	1.2, (000041-2)
Assay: (As Moexipril HCl)	(On anhydrous and solvent free basis)		
Potentiometric (15.8, 17) HPLC	— % — %	PH20585.ABV.120 PH20585.ABV.110	1.2, (000043-7) 1.2, (000048-52

6. REGULATORY SPECIFICATIONS AND METHODS FOR DRUG PRODUCT:

B. REGULATORY SPECIFICATIONS AND METHODS (1.3, 000006)

Finished Product:

Test		Method	Specifications
Appearance	7.5 mg 15 mg	PH0638.ABV.010	Round pink coated tablet with white core, both sides convex arched, scored and engraved with "M" and "7.5" on one side and "SP" on the other side. Round red coated tablet with white core, both sides convex arched, scored and engraved with "M" and "15" on one side and "SP" on the other side.
Diameter	7.5 mg 15 mg	PH0638.ABV.030	6.0 - 6.2 mm 8.0 - 8.2 mm
Thickness	7.5 mg 15 mg	PH0638.ABV.030	3.1 - 3.5 mm 3.6 - 4.0 mm
Tablet Weight	7.5 mg 15 mg		90-98 mg 180 -194 mg
Disintegration		3707.SPC.04	NMT 10 minutes
Odor		PH0638.ABV.020	Odorless to faint characteristic odor
Identification HPLC UV Ferric Oxide Titanium Dioxide		 3707.ANA.420 3707.ANA.220 PH0638.ABV.130 PH0638.ABV.130	 Retention time complies with that of standard Spectra are similar
Total Related Substances (15.8,2-7)		3707.ANA.320	NMT % Total NMT % NMT % Moexiprilate NMT % No individual unknown substance
Water (Coulometric) (15.8, 3)		A11g.ABV.010	NMT than 7.5%

Dissolution	3707.ANA.430	Each unit NLT — % (Q) in 15 minutes S1 6 Each unit NLT — % S2 6 Ave. 12 units () ≥ —%, NMT 2 units < — % S3 12 Ave. 24 units (S1+S2+S3) ≥ — %, NMT 2 units < — %
Content Uniformity	3707.ANA.410 (USP XXII <905>	10 of 10 within 85-115% of LC with a CV of 6% 29 of 30 " " " " " NMT 1 outside 75-125% LC range and CV NGT 7.8%
Assay: (As Moexipril HCl) HPLC	3707.ANA.420	100 ± 5% of LC

1. 7.5 mg tablets reference 1.3A, 000115-8
2. 15.0 mg tablets reference 1.3A, 000121-6

APPEARS THIS WAY
ON ORIGINAL