CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 19532

MEDICAL REVIEW(S)

10/2/87

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

REVIEWER: ROBERT E. KEENAN, MD

NDA: 19-532, Amendment

M.O. REVIEW#: B

Name of Drug: Metolazone (MICROX)

Sponsor: Penwalt Corporation

Date of Correspondence: September 17, 1987

Date Received by Reviewer: September 28, 1987

Date Reviewed Completed: September 28, 1987

Resume:

The sponsor of NDA 19-532, Penwalt Corporation, formally objects to FDA's listing of their new, more bioavailable metolazone formulation (MICROX) "as a diuretic". Their objection is without merit because:

1. Administration of MICROX to human subjects/patients produces a substantial diuresis.

2. Microx, like other diuretics, produces an antihypertensive effect. The approved MICROX labeling states: "The antihypertensive mechanism of action of metolazone is not fully understood but is presumed to be related to its saluretic and diuretic properties."

3. When MICROX, alone, fails to completely control high blood pressure, the package insert suggests that it should be combined with some other antihypertensive drug "with a different mechanism of action" (i.e, add an antihypertensive drug other than a diuretic, because MICROX is a diuretic).

4. The very first sentence in the CLINICAL PHARMACOLOGY section of the approved labeling states: "MICROX is a quinazoline diuretic with properties generally similar to the thiazide diuretics".

in view of these facts (and others), FDA has correctly listed MICROX as a diuretic drug simply because that listing and no other is precise. That MICROX lowers elevated blood pressure, as do all other diuretic agents, is insufficient reason to change its pharmacologic classification.

/S/

Robert Keenan, MD, HFN-110

cc:
Orig. NDA 19-532
HFN-80/DDIR
HFN-110
HFN-110/CSO
HFN-110/RKeenan 9/28/87
klr/9-30/97/09241:ayg/9/30/87

10/19/87

DIVISION OF CARDIO-RENAL DRUG PRODUCTS

MEDICAL OFFICER'S REVIEW

NDA# 19,532 AMMENDMENT REVIEWER: ROBERT E. KEENAN, M.D.

M.O. REVIEW#: C

SPONSOR: Pennwalt Corporation

DRUG: Metolazone (Microx)

DATE OF CORRESPONDENCE: September 3, 1987

DATE RECEIVED BY REVIEWER: September 28, 1987

DATE: REVIEW COMPLETED: October 1, 1987

Resume:

Several problems exist in the "Introductory Promotional Material" which is included in this submission. These issues were discussed with the Division of Drug Advertising, HFN-244, on October 1, 1987. No further action is required.

/S/

Robert E. Keenan, M. D.

cc: Orig/NDA
HFN-110
HFN-110/CSO
HFN-110/REK/10/6/87
ayg/10/6/87/0902e/10/16/87

6/17/87

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
MEDICAL OFFICER'S REVIEW

NDA #: 19-532 REVIEWER: Robert E. Keenan, M.D.

M. O. REVIEW #: A

SPONSOR: Pennwalt Corporation

DRUG: MICROX (metolazone reformulation)

DATE OF CORRESPONDENCE: October 8, 1985

DATE RECEIVED BY REVIEWER: October 21, 1985

DATE REVIEW COMPLETED: March 7, 1986

Resume:

Metolazone, like the several other similar diuretics, possesses beneficial pharmacologic attributes (e.g., antihypertensive) which presumably outweigh its unfavorable pharmacologic actions (e.g., potassium and magnesium loss). If possible, it would appear desirable to determine an optimal metolazone dose (or dosage formulation) that would maximize the beneficial effects while, at the same time, minimize the drug's unfavorable effects. This NDA (#19-532) contains data supporting a new metolazone formulation, allegedly as effective as the old (ZAROXOLYN) tablets in lowering blood pressure while producing less potassium loss.

In addition to the human pharmacokinetics and bioavailability of the new formulation (reviewed separately), NDA 19-532 contains two multi-center clinical studies establishing the drug's safety and efficacy in hypertensive patients. One of these, LDM-101, clearly establishes the antihypertensive equivalence of the new and old metolazone formulations (as well as any difference in potassium loss). The second clinical trial, LDM-102, optimizes a MICROX dosage regimen in a placebo controlled, double-blind, parallel dose-response (0.5 mg/day vs 1.0 mg/day 2.0 mg/day) study in mildly hypertensive patients.

Another difference between the two (antihypertensive) MICROX clinical trials was the severity of hypertension in the respective patient populations enrolled. As shown in Table A, patients included in study LDM-101 were more severely hypertensive ("moderate") than the patients studied in LDM-102 ("mild").

Table A

LDM-101

A Comparison of the Effect of a New Formulation of Metolazone With Marketed Metolazone (Zaroxolyn®) in Patients With Mild to Moderate Hypertension

Principal Investigator	No. of Patients Studied	Status of Study 5/1/85
Schoenberger, James	22	Completed
Schnaper, Harold	45	Completed
Nugent, Charles	72	Completed
Harris, Robert	25	Completed
Moser, Marvin	28	Completed
Miller, Sanford	3	

LDM-102

A Clinical Study of Low-Dose Metolazone: Safety, Efficacy, and Dose Response

Principal Investigator	No. of Patients Studied	Status of Study 5/1/85
Ryan, James	32	Completed
Lasker, Norman	3	
Curry, Harold	33	Completed
Black, Henry	9	
MacKay, James	40	Completed
Boden, Guenther	17	

Of the 12 investigators (6 per study) participating in the 2 multi-center trials, just 7 of the centers produced data sufficiently satisfactory to be included (see Table B) in the respective study analysis. Reasons for not including data from 5 of the multi-center sites generally appear valid. Probably the most controversial of these is exclusion of Dr. Moser (from the LDM-101 data-base). His patient population, at baseline, was comparable to patients enrolled at the other sites. Dr. Moser's patients' response to their assigned therapy was, however, at great variance with

Table B

LDM-101

Investigator	No Pt	Sex M	Sex F	Race C	Race B	Mean Age	Mean Wt	Mean Baseline Diastolic BP
Schoenberger	22	14	8	10	12	48.9	201.0	102.7
Schnaper	45	31	14	13	32	52.9	179.5	98.9
Nugent	72	71	1	59[a]	13	56.8	200.6	102.8
Harris	25	16	9	22[b]	3	48.7	168.8	102.3
Composite	164	132	32	104	60	53.3	192.5	101.6
Moser[c]	28	2	26	0	28	53.4	162.0	107.1
Miller[c]	3	1	2	0	3	--[d]	--[d]	--[d]

LDM-102

Ryan	32	8	24	5	27	57.7	200.3	96.4
Curry	33	16	17	0	33	52.9	178.2	98.5
MacKay	40	20	20	38	2	51.4	183.8	97.9
Composite	105	45	60	43	62	53.8	187.1	97.6

[a]Includes 6 Hispanics.
[b]Includes 1 Hispanic.
[c]Not included in composite; see text.
[d]Number of patients too small to be meaningful.

responses recorded in all other centers, to the extent of producing a statistically significant investigator (Dr. Moser) by treatment interaction. Homogeneity of LDM-101 data, therefore, was only possible by excluding Dr. Moser's study.

I. ANTIHYPERTENSIVE EFFICACY AND SAFETY STUDIES:

A. Study LDM-101: Moderately hypertensive patients, predominantly caucasian, were enrolled in this study. The composite mean diastolic blood pressure of the 164 patients included for analysis was 101.6 mmHg (sitting position). Eligible patients were randomized to one of four study groups after successfully completing a 2-4 week placebo "base-line" period. During a 6-week "active treatment" phase, patients received one of the following four treatments under double-blind conditions:

Microx, 0.5 mg once daily
Microx, 1.0 mg once daily
Microx, 2.0 mg once daily
Zaroxolyn, 2.5 mg once daily

For entry into the placebo phase, the patient's sitting diastolic blood pressure needed to be between 96 and 120 mmHg. For entry into the double-blind treatment phase, sitting diastolic blood pressure had to remain inside the range.

1. Mean changes in sitting blood pressure: Efficacy measurements in LDM-101 compared sitting baseline blood pressures with the two, four and six-week blood pressures. Statistical evaluations were performed only at the four and six-week time points. In addition, an end-point analysis for all patients, regardless of the time of their final visit, was also statistically analyzed.

The mean sitting systolic and diastolic blood pressures are summarized in Table C and Figure 1.

End-point analysis of blood pressure response (sitting) is shown in Table D.

Significant blood pressure decreases occurred at weeks 4 and 6, and also at the final time points (end-point) in all treatment groups. The greatest fall in BP occurred after 2 weeks treatment but the decrease continued for at least 2 more weeks. These results are consistent with those expected of a diuretic "step 1" antihypertensive drug.

2. Categorical (percent responsive patients) blood pressure response: Another way of measuring anti-hypertensive efficacy is to determine the

Table C

Changes in Sitting Blood Pressures ± S.E. (Systolic/Diastolic)
(mm Hg)

	Week 2		Week 4		Week 6		Final Week	
No.of Pts	30		36		34		39	
MICROX 0.5 mg	-10.2 / - 6.2	± 1.9 / 1.3	-13.4 / - 8.7	± 2.3 / 1.5	-12.6 / - 9.6	± 1.9 / 1.3	-11.3 / - 8.3	± 1.9 / 1.4
No.of Pts	41		31		35		43	
MICROX 1.0 mg	-18.0 / -10.5	± 2.3 / 1.4	-22.0 / -12.5	± 3.0 / 1.7	-25.5 / -14.4	± 3.2 / 1.7	-24.0 / -13.3	± 2.8 / 1.5
No.of Pts	37		35		35		38	
MICROX 2.0 mg	-19.6 / - 9.3	± 1.7 / 1.3	-24.0 / -13.0	± 3.1 / 1.5	-24.3 / -14.6	± 2.5 / 1.3	-23.6 / -14.2	± 2.4 / 1.3
No.of Pts	33		34		36		36	
Zaroxolyn 2.5 mg	-13.0 / - 7.3	± 2.0 / 1.2	-16.7 / -10.8	± 1.8 / 1.4	-19.5 / -12.5	± 2.3 / 1.5	-19.0 / -12.2	± 2.3 / 1.4

LDM-101

Mean Change from Baseline, Sitting Blood Pressure
(mm Hg)

Week 6

	MICROX 0.5 mg	MICROX 1.0 mg	MICROX 2.0 mg	Zaroxolyn 2.5 mg
Schoenberger	n=5 -13.7 - 8.4	n=5 -30.7 -19.4	n=4 -22.0 -12.8	n=5 -11.7 -14.1
Schnaper	n=7 - 8.4 -9.2*	n=10 -18.9* -10.6*	n=9 -26.7* -14.1*	n=10 -24.2* -13.3*
Nugent	n=18 -13.9* -10.1*	n=16 -27.7* -14.1*	n=17 -23.3* -14.4*	n=15 -21.0* -12.5*
Harris	n=4 -14.0 - 9.3	n=4 -27.7 -17.6	n=5 -25.3 -17.5[a]	n=6 -14.7* - 9.8*,[a]
Composite	n=34 -12.8*,[b,a] - 9.6*,[c,d]	n=35 -25.5*,[a] -14.4*,[c]	n=35 -24.3*,[b] -14.6*,[d]	n=36 -19.5* -12.5*
Moser**	n=6 - 6.6 -19.6*	n=5 -14.7 -23.8	n=10 -18.0* -23.0*	n=5 -14.4 -28.1

Figure 1

Figure #1

LDM-101

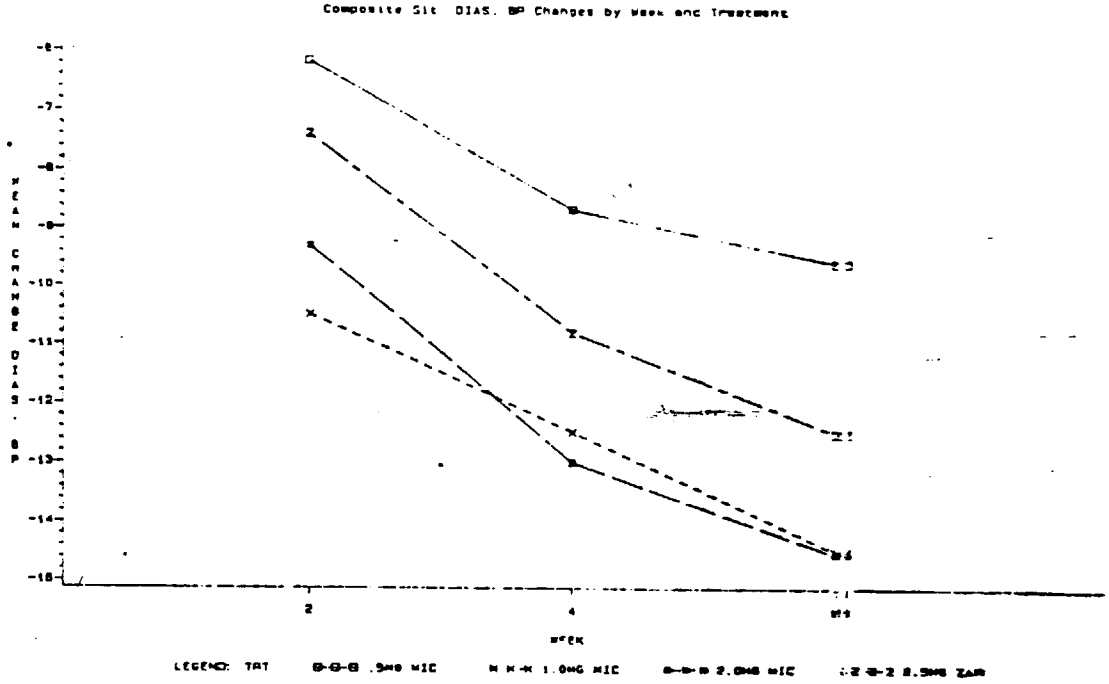


Table D

Final

Schoenberger	n=6 - 9.1 - 6.5	n=6 -32.7 -21.0*	n=5 -22.6 -14.7	n=5 -11.7 -14.1
Schnaper	n=10 - 7.7*,a,b - 5.2[a]	n=12 -18.5* - 9.4*	n=9 -26.7*,a -14.1*	n=10 -24.2*,a -13.3*,a
Nugent	n=18 -13.9* -10.1*	n=18 -25.8* -13.4*	n=17 -23.3* -14.4*	n=17 -19.5* -11.8*
Harris	n=5 -12.1 -10.0	n=17 -21.4* -13.3*	n=7 -20.7 -13.4*	n=6 -14.7* - 9.6*
Composite	n=39 -11.3*,a,b - 8.3*,c,d	n=43 -24.0*,a -13.3*,c	n=38 -23.6*,b -14.2*,d	n=38 -19.0* -12.2*
Moser**	n=7 - 9.9 -18.6*	n=6 -15.6 -23.0*	n=10 -18.0* -23.0*	n=5 -14.4 -26.1

*Statistically significant change from baseline, p <.05, Wilcoxon Signed Ranks Test.

**Not included in composite.

numbers of patients in each therapeutic group that reach a predetermined "goal". The goal is usually a diastolic blood pressure below 90 mmHg and/or a diastolic BP decrease of at least 10 mmHg. Patients attaining either of the two "goals" were determined to have had an adequate response. Results are displayed in Table E.

Table E

LDM-101

Percent Response by Protocol Criteria

	MICROX 0.5 mg	MICROX 1.0 mg	MICROX 2.0 mg	Zaroxolyn 2.5 mg
Schoenberger	n= 5 20	n= 6 50	n= 5 60	n= 5 60
Schnaper	n= 9 44	n=11 55	n= 9 33	n=10 80
Nugent	n=18 33	n=16 50	n=17 76	n=15 47
Harris	n= 4 50	n= 5 60	n= 6 83	n= 6 17
Composite	n=36 36	n=38 53	n=37 65	n=36 53
Moser*	n= 7 86	n= 6 100	n=10 90	n= 5 100

*Not included in composite.

Number of Adequate Responders, Protocol Criteria
(Percent of Treatment Group)

Treatment	Adequate	Not Adequate
MICROX 0.5 mg	13 (36)	23 (64)
MICROX 1.0 mg	20 (53)	18 (47)
MICROX 2.0 mg	24 (65)	13 (35)
Zaroxolyn 2.5 mg	19 (53)	17 (47)

Another method of analyzing categorical response "splits" the non-responders into "good" and "unsatisfactory" categories. End-point analysis using this method is shown in Table F.

Table F

Proportion of Responders at Final Visit

Treatment(mg)	No.	Excellent ≥ 10 mm	Good 5-10 mm	Unsatis-factory No Response
MICROX 0.5	39	17 (44)	9 (23)	13 (33)
MICROX 1.0	43	24 (56)	10 (23)	9 (21)
MICROX 2.0	38	28 (74)	6 (16)	4 (11)
Zaroxolyn 2.5	38	21 (55)	11 (29)	6 (16)

3. Metabolic (potassium) alterations: Serum potassium levels were measured in all patients at baseline and again at the time of week 2, 4, and 6 follow-up visits. At all time points the mean decreases in serum potassium were statistically significant ($p < 0.001$). The extent of the mean decreases in serum potassium appeared to be related to the dose of metolazone administered. Statistically significant differences in serum potassium levels were detected between 0.5 mg Microx and the higher, 1.0 mg and 2.0 mg, Microx doses as well as the 2.5 mg Zaroxolyn dose (see Table G).

Table G

Mean Potassium Changes from Baseline, Week 6
(mEq/L)

LDM-101

	MICROX 0.5 mg	MICROX 1.0 mg	MICROX 2.0 mg	Zaroxolyn 2.5 mg
Schoenberger	n= 5 -0.22[a]	n= 5 -0.34	n= 4 -0.53	n= 5 -0.66
Schnaper	n= 7 -0.47	n=10 -0.44*	n= 9 -0.43*	n=10 -0.72*
Nugent	n=18 -0.53*	n=16 -0.70*	n=17 -0.85*	n=15 -0.80*
Harris	n= 4 -0.33	n= 4 -0.93	n= 5 -0.42	n=35 -0.78*
Composite	n=34 -0.45*[a]	n=35 -0.60*	n=35 -0.65*	n=35 -0.76*,[a]
Moser**	n= 5 -0.82	n= 4 -1.12	n=10 -1.10*	n= 5 -0.98

[a]Significant difference between MICROX and Zaroxolyn
*Significant difference from baseline, Wilcoxon Signed Rank Test.
**Not included in composite

Mean Changes Serum Potassium from Baseline ± S.E.
(mEq/L)

	Week 2	Week 4	Week 6
No.of Pts	30	35	34
MICROX 0.5 mg	-0.44 ± 0.09	-0.47 ± 0.07	-0.45 ± 0.08
No.of Pts	41	30	35
MICROX 1.0 mg	-0.71 ± 0.10	-0.65 ± 0.11	-0.60 ± 0.08
No.of Pts	35	33	35
MICROX 2.0 mg	-0.70 ± 0.09	-0.60 ± 0.09	-0.65 ± 0.11
No.of Pts	33	34	35
Zaroxolyn 2.5 mg	-0.59 ± 0.09	-0.60 ± 0.10	-0.76 ± 0.08

By examining the group means of the lowest serum potassium ever seen during treatment, a dose-related decrease is again easily demonstrated (see Table H).

Table H

Means of Minimum Potassium ± S.D. (mEq/L)

Treatment (mg)	No. of Patients	Baseline	During Treatment	Difference
MICROX 0.5	39	4.41 ± 0.43	3.79 ± 0.41	0.61 ± 0.46
MICROX 1.0	43	4.40 ± 0.38	3.53 ± 0.49	-0.88 ± 0.57
MICROX 2.0	38	4.40 ± 0.43	3.51 ± 0.62	-0.89 ± 0.55
Zaroxolyn 2.5	39	4.26 ± 0.53	3.39 ± 0.39	-0.87 ± 0.45

Hypokalemia was statistically significantly less in the 0.5 mg MICROX treatment group than in the 1.0 mg MICROX group ($p=0.007$) and the 2.0 mg MICROX group ($p < 0.006$).

Still another way of examining the effect of Microx/Zaroxolyn therapy on serum potassium is to distribute patients within each dosage group into categories. Using serum potassium levels above 3.5 as normal, levels between 3.0 and 3.5 as borderline, and those below 3.0 as hypokalemia, drug doses and duration of therapy are distinguishable (see Table U).

Although the study duration was too short to be conclusive, patients on the various Microx doses appeared to show 2 distinct trends: one patient subgroup tended to have a continuing, cumulative decrease for as long as they received the drug; a second subgroup demonstrated an initial decline in serum potassium level but then followed with a partial but continuing recovery. The former exhibited a considerably higher incidence at metolazone doses greater than 1.0 mg/day when compared to lower doses.

4. Weight loss: As expected with diuretic therapy, patients in all treatment groups lost weight (see Table J). Patients in the 2 higher Microx dosage groups appeared to exhibit greater weight loss than patients receiving the low (0.5mg/day) dose. A weight loss dose-response in black patients was numerically present but was not statistically validated. No apparent dose-response occurred in caucasian patients.

Table U

Potassium Range, Number of Patients (Percent)

Week	Range	MICROX 0.5 mg	MICROX 1.0 mg	MICROX 2.0 mg	Zaroxolyn 2.5 mg
		n=40	n=44	n=39	n=40
0	>3.5	40(100)	44(100)	38(97.4)	37(92.5)
	3.0-3.4	0 (0)	0 (0)	1(0.6)	3(7.5)
	<3.0	0 (0)	0 (0)	0 (0)	0 (0)
		n=30	n=41	n=35	n=33
2	>3.5	27(90)	30(73.2)	24(68.6)	22(66.7)
	3.0-3.4	3(10)	7(17.1)	9(25.7)	8(24.2)
	<3.0	0 (0)	4(9.7)	2(5.7)	3(9.1)
		n=35	n=30	n=33	n=34
4	>3.5	32(91.4)	24(80.0)	20(60)	22(64.7)
	3.0-3.4	2(5.7)	4(13.3)	12(36)	11(33.4)
	<3.0	1(2.9)	2(6.7)	1(3)	1(2.9)
		n=34	n=35	n=35	n=35
6	>3.5	28(82.4)	27(77.1)	20(57.1)	19(54.3)
	3.0-3.4	6(17.6)	8(22.9)	14(40.0)	12(34.3)
	<3.0	0 (0)	0 (0)	1(2.9)	4(11.4)
		n=39	n=43	n=37	n=39
Final	>3.5	33(84.7)	30(69.8)	21(56.8)	21(53.8)
	3.0-3.4	6(15.3)	10(23.3)	15(40.5)	13(33.3)
	<3.0	0 (0)	3(6.9)	1(2.7)	5(12.8)

Four patients had serum potassium of less than 3.5 mEq/L at baseline. Three were in the 2.5 mg Zaroxolyn treatment group and one was in the 2.0 mg MICROX treatment group.

Table V

Mean Changes Body Weight, Week 6
(pounds)

	MICROX 1 mg	MICROX 1.0 mg	MICROX 2.0 mg	Zaroxolyn 2.5 mg
Schoenberger	n= 5 -2.5	n= 5 -7.5	n= 4 -3.8	n= 5 -0.8
Schnaper	n= 6 -1.7	n= 9 -2.1	n= 9 -4.9*	n=10 -5.2*
Nugent	n=18 -4.4*	n=16 -5.0*	n=17 -3.8*	n=15 -2.9*
Harris	n= 4 -3.3	n= 5 -5.4	n= 5 -2.7	n= 6 -3.8*
Composite	n=33 -3.5*	n=34 -4.6*	n=35 -3.9*	n=36 -3.4*

*Significant change from baseline, Wilcoxon Signed Rank Test, $p<0.05$.

5. Adverse effects: Overall, the incidence of patient complaints was very low in study LDM-101. ADR incidence and profile is consistent with all of the accumulated clinical experiences with thiazide diuretics Metolazone may possess a somewhat novel dose-response ADR effect, however, which may or may not be of clinical significance (see II. DISCUSSION, below).

B. Study LDM-102: Mildly hypertensive patients (diastolic BP above 90 mmHg), over 50% blacks (62 of 105 patients), were enrolled and qualified to enter this study. The composite mean sitting diastolic blood pressure of the 105 patients included for analysis was 97.6 mmHg (see Table K). Eligible patients were randomized to one of four study groups after successfully (BP stabilized above 90 mmHg diastolic) completing a 4-week placebo run-in baseline. Of 148 patients screened, 105 satisfied eligibility criteria, successfully completed the 4-week placebo baseline, and were randomized into the double-blind, 6-week treatment phase. Patients entering the 6-week double-blind phase were randomized into one of the following four treatment groups:

Placebo, one tablet/day
Microx, 0.5 mg/day
Microx, 1.0 mg/day
Microx, 2.0 mg/day

Table K

Demographics

	Sex		Race		Age Mean	Wt Mean	BP Mean
	M	F	B	C	(yrs)	(lbs)	(mm Hg)
Placebo No. (%)	15 (56)	12 (44)	16 (59)	11 (41)	50.4	194.0	150.9/99.0
MICROX 0.5 mg No. (%)	11 (42)	15 (58)	15 (58)	11 (42)	53.7	181.8	149.0/97.1
MICROX 1.0 mg No. (%)	11 (44)	14 (56)	14 (56)	11 (44)	55.4	176.6	145.7/96.9
MICROX 2.0 mg No. (%)	8 (30)	19 (70)	17 (63)	10 (37)	55.7	195.0	153.8/97.4

1. Mean changes in sitting blood pressure: Efficacy measurement in LDM-102 compared baseline vs treatment blood pressures (sitting) at the 2, 4, and 6-week time points. Statistical evaluations were performed only at the 4 and 6-week time points. In addition, an end-point analysis for all patients, regardless of the time of their final visit, was also statistically performed.

The mean sitting systolic and diastolic group blood pressures are summarized in Table L and Figure 2.

Table L

Mean Changes in Sitting Systolic and Diastolic Blood Pressure ± S.E.
(mm Hg)

	Week 2†	Week 4	Week 6	Final Week
No.of Pts	27	23	23	27
Placebo	- 4.4 ± 2.3 - 2.7 1.0	- 2.9* ± 2.0 - 3.0* 1.2	- 5.9* ± 2.9 - 4.3* 1.5	- 3.2 ± 2.8 - 2.7 1.5
No.of Pts	24	25	24	26
MICROX 0.5 mg	-11.0 ± 2.8 - 5.3 1.3	-10.3* ± 2.9 - 7.3* 1.3	-15.7* ± 2.4 - 8.2* 1.3	-13.6* ± 2.7 - 7.8* 1.3
No.of Pts	25	23	25	25
MICROX 1.0 mg	-12.7 ± 2.9 - 6.8 1.5	-15.3* ± 2.3 - 9.7* 1.2	-12.8* ± 2.7 - 8.0* 1.5	-12.8* ± 2.7 - 8.0* 1.5
No.of Pts	25	24	26	26
MICROX 2.0 mg	-14.4 ± 3.0 - 8.5 1.3	-16.1* ± 2.8 - 7.8* 6.8	-16.2* ± 3.1 - 8.0* 1.3	-16.2* ± 3.1 - 8.0* 1.3

†Week 2 data not analyzed.
*Statistically significant change from baseline, Wilcoxon Signed Ranks Test $p \leq 0.05$.

End-point analysis of mean blood pressure response comparison is shown in Table M.

The changes in sitting diastolic blood pressure in the three Microx treatment groups, when compared to placebo, are statistically significant ($p = 0.02$) at final end-point. At week 6 the differences between both the 0.5 mg/day and 1.0 mg/day Microx groups, compared to placebo are statistically significant but are not different from each other. The difference between the 2.0 mg/day Microx group and the placebo group is borderline ($p = 0.024$). The borderline statistical result (vs placebo) is likely due to an "outlier" clinical center. Dr. Curry's center, for some

Figure 2

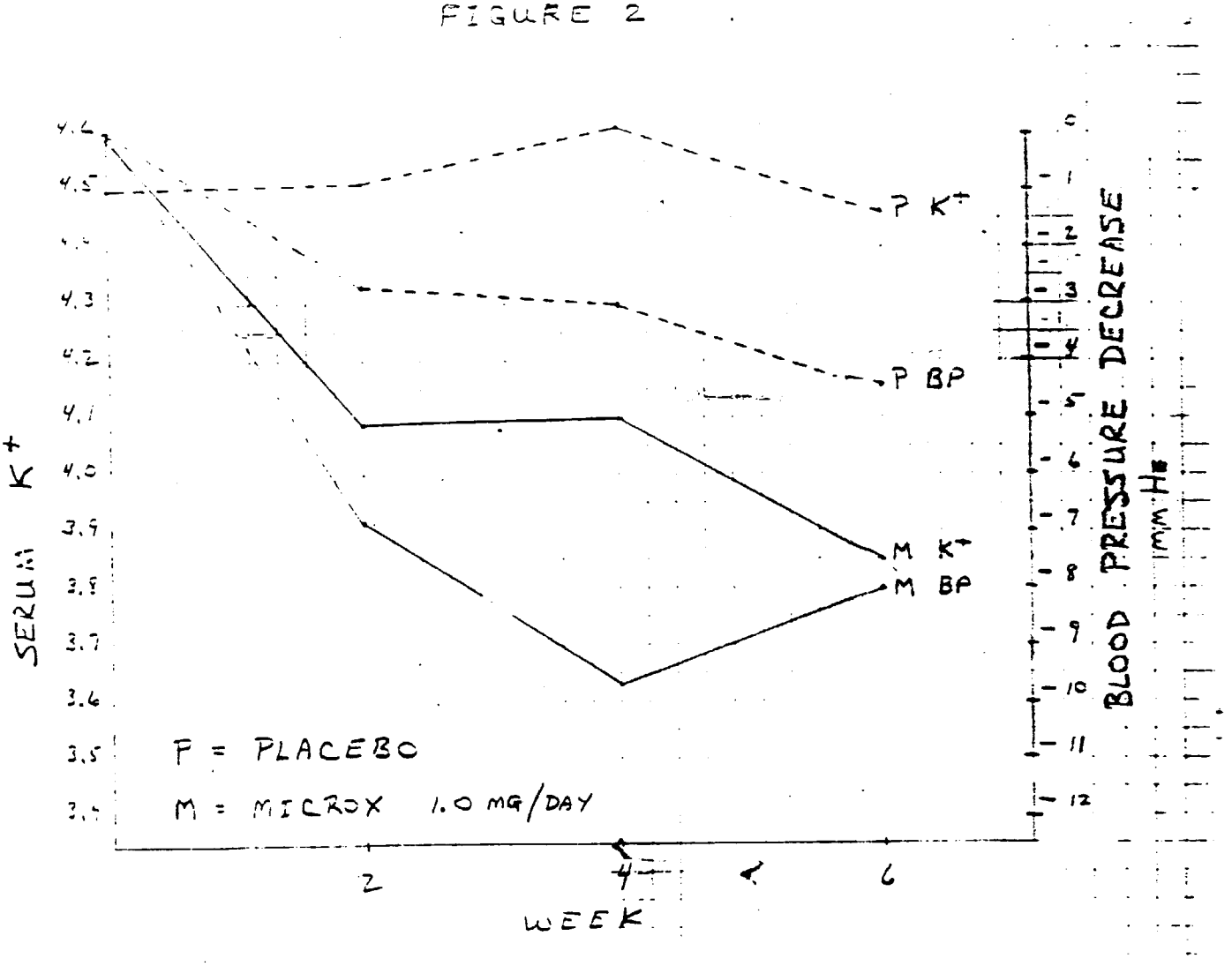


Table M

Mean Blood Pressure Changes, Final Week
(mm Hg)

Treatment	n	Ryan	n	Curry	n	MacKay
Placebo	8	-0.7/-2.4	9	-1.4/-2.8	10	-5.9/-3.0
MICROX 0.5 mg	8	-11.2/-5.0	8	-11.5/-8.7	10	-17.3/-9.3
MICROX 1.0 mg	8	-12.9/-6.9	7	-15.9/-11.7	10	-10.6/-6.4
MICROX 2.0 mg	8	-22.5/-6.8	8	-17.4/-12.1	10	-10.1/-5.7

unexplained reason, included a group of above-average placebo responsive patients. When averaged into the overall, multi-center results, Dr. Curry's placebo group influences the mean blood pressure to a perhaps undue extent.

The changes in sitting diastolic blood pressure in the three Microx treatment groups, when compared to placebo, are statistically significant ($p = 0.02$) at final end-point. At week 6 the differences between both the 0.5 mg/day and 1.0 mg/day Microx groups, compared to placebo are statistically significant but are not different from each other. The difference between the 2.0 mg/day Microx group and the placebo group is borderline ($p = 0.024$). The borderline statistical result (vs placebo) is likely due to an "outlier" clinical center. Dr. Curry's center, for some unexplained reason, included a group of above-average placebo responsive patients. When averaged into the overall, multi-center results, Dr. Curry's placebo group influences the mean blood pressure to a perhaps undue extent.

2. Categorical (percent responsive patients) blood pressure response: The proportion of patients exhibiting a decrease of at least 10 mmHg (adequate response) and the proportion having a diastolic BP decrease of at least 5 mmHg (partial response) are summarized in Table N.

Table N

LDM-102

Percent Response by Protocol Criteria

	Placebo		MICROX 0.5 mg		MICROX 1.0 mg		MICROX 2.0 mg	
	Adq	Part	Adq	Part	Adq	Part	Adq	Part
Ryan	n= 8 0	13	n= 7 14	0	n= 8 25	13	n= 8 13	25
Curry	n= 7 14	14	n= 8 25	38	n= 7 71	14	n= 8 50	25
MacKay	n=10 0	10	n=10 10	40	n=10 20	30	n=10 20	20
Composite	n=25 4	12	n=25 16	28	n=25 36	20	n=26 27	23

As shown in Table N, there were 4% adequate responders in the placebo group vs 16%, 36%, and 27% in the 0.5 mg/day, 1.0 mg/day, and 2.0 mg/day Microx groups, respectively. The differences between each Microx group and placebo were statistically significant. More patients, numerically, in the 1.0 mg/day and 2.0 mg/day Microx groups showed an "adequate" response than in the 0.5 mg/day group, but the difference did not achieve significance.

By defining "responders" in a different way: counting only those patients whose sitting diastolic blood pressure met the predetermined "goal" diastolic BP decrease, there are no apparent differences between the 3 Microx doses tested. All 3 Microx doses, equally, "normalized" significantly greater numbers of patients than did placebo, see Table P.

Table p

Responders Defined as Final DBP <90 or >10 mm Hg from Baseline

Treatment	n	Percent Responders
Placebo	27	19
MICROX 0.5 mg	26	58
MICROX 1.0 mg	25	56
MICROX 2.0 mg	26	58

3. Metabolic (potassium) alterations: Serum potassium levels were measured in all patients at baseline and again at the time of weeks 2, 4, and 6 follow-up visits. At all time points the mean decreases in serum potassium were statistically significantly lower than baseline for all 3 Microx treatment groups. There were no significant changes from baseline in the placebo group (see Table Q).

As in Study LDM-101, the extent of the serum potassium decreases appeared to be directly related to the dose of metolazone administered. Throughout the 6-week treatment phase, the 0.5 mg/day Microx group suffered significantly less potassium loss, on average, than the 2 higher dose groups. Perhaps a better measure of potassium loss with low-dose (0.5 mg/day) Microx may be seen by subtracting the mean fall in the placebo group from the fall in the drug group, 0.38 mEq - .09 mEq = 0.29 mEq.

Categorical distribution of patients within each group according to potassium levels confirms a direct relationship between Microx dose and extent of potassium loss. Whereas more than half (54%) of the patients

Table Q

Mean Changes Serum Potassium ± S.E.
(mEq/L)

	Week 2	Week 4	Week 6
No.of Pts Placebo	26 +0.01 ± 0.07	22 +0.06 ± 0.13	22 -0.09 ± 0.07
No.of Pts MICROX 0.5 mg	24 -0.30 ± 0.14	25 -0.38 ± 0.10	24 -0.38 ± 0.11
No.of Pts MICROX 1.0 mg	25 -0.52 ± 0.10	23 -0.47 ± 0.10	25 -0.74 ± 0.11
No.of Pts MICROX 2.0 mg	25 -0.76 ± 0.09	24 -0.60 ± 0.08	26 -0.77 ± 0.09

There are no significant changes from baseline in serum potassium in the placebo group. The changes from baseline are statistically significant for all three MICROX treatm--- at all time points ($p < 0.05$)[1].

[1]Wilcoxon Signed Ranks Test used for all comparisons from Section IX.

Table R

	Baseline	Week 2	Week 4	Week 6	Final
Placebo	n=27	n=26	n=22	n=22	n=26
≥4.0	26(96.3)	23(88.5)	22(100)	22(100)	25(96.2)
3.5-3.9	1(3.7)	3(11.5)	0	0	1(3.8)
<3.5	0	0	0	0	0
MICROX 0.5 mg	n=26	n=24	n=25	n=24	n=26
≥4.0	22(84.6)	16(66.7)	13(52)	13(54.2)	14(53.9)
3.5-3.9	4(15.4)	5(20.8)	11(44)	7(29.2)	7(26.9)
<3.5	0	3(12.5)	1(4)	4(16.7)	5(19.2)
MICROX 1.0 mg	n=25	n=25	n=23	n=25	n=25
≥4.0	25(100)	13(52)	10(43.5)	12(48)	12(48)
3.5-3.9	0	11(44)	12(52.2)	8(32)	8(32)
<3.5	0	1(4)	1(4.4)	5(20)	5(20)
MICROX 2.0 mg	n=27	n=25	n=24	n=26	n=26
≥4.0	22(81.5)	6(23.1)	11(45.8)	6(23.1)	6(23.1)
3.5-3.9	5(18.5)	11(42.3)	10(41.7)	12(46.2)	12(46.2)
<3.5	0	8(30.8)	3(12.5)	8(30.7)	8(30.8)

All patients had a serum potassium of 3.5 mEq/L or greater at baseline. The majority had serum potassiums greater than or equal to 4.0 mEq/L.

receiving 0.5 mg/day Microx maintained serum potassium above 4.0 mEq/l, just 23% did so while taking the 2.0 mg/day dose. Again, the hint of a response related to duration of Microx therapy appeared (see Table R). There also appears to be a "potassium-loss" dividing line between doses up to and including 1.0 mg/day and doses above 1.0 mg/day (2.0 mg/day and 2.5 mg/day).

4. Weight loss: A Microx-induced diuresis accounted for the statistically significant weight loss observed at week 6. All Microx groups (0.5 mg, 1.0 mg, and 2.0 mg/day) showed significant weight loss when compared to the placebo group. Low dose 0.5 mg/day Microx, however, apparently produced less weight loss than the 2 higher doses (see Table T).

Table T

Mean Changes Body Weight, Week 6
(pounds)

	MICROX ½ mg	MICROX 1.0 mg	MICROX 2.0 mg	Placebo
Ryan	n= 7 -2.4*	n= 8 -3.1	n= 8 -4.4*,†	n= 8 -0.5
Curry	n= 6 -3.7*	n= 7 -2.4*	n= 8 -0.9	n= 5 -0.9
MacKay	n=10 -1.9*	n= 9 -4.1*,†	n=10 -3.7*	n=10 -0.2
Composite	n=23 -2.6*,†	n=24 -3.3*,†	n=25 -3.1*,†	n=26 -0.3

*Significant change from baseline, Wilcoxon Signed Rank Test, $p<0.05$.
†Significantly different than placebo, analysis of covariance, $p\leq 0.027$.

5. Adverse effects: A weight loss dose-response may have been responsible for an observed ADR dose-response. Dizziness, perhaps due to volume depletion occurred at higher incidence rate as the Microx dose increased, 8%, 12%, and 19% for doses 0.5 mg/day, 1.0 mg/day, and 2.0 mg/day. Otherwise, the ADR incidence and profile in Study LDM-102 was consistent with the currently approved metolazone labelling (see Zaroxolyn Package Insert).

II. DISCUSSION:

A. Issues: Like chlorthalidone, metolazone was developed and marketed some 15-20 years ago, before adequate dose-response studies were commonly performed. As a result, useful dose information regarding the drug's pharmacologic actions, primarily its effects on blood pressure and serum potassium, have not been available. Recent reports on various diuretics suggest that appropriate dose-response studies require several weeks of administration at each dose level before the pharmacologic or therapeutic effect of the drug becomes maximal. Furthermore, relevant studies(1) indicate a rather flat dose-response curve in mild hypertensives and a less flat dose-response curve in patients with moderate hypertension. In both instances, however, lower drug doses are equally as effective in lowering blood pressure as are higher doses; at the same time, though, the higher doses produce a greater potassium loss than do the lower doses. Thus, conventional wisdom has established that antihypertensive diuretic drugs should be prescribed at the lowest dose possible for maximal hypotensive effect. Doing this will prevent the excessive losses of potassium observed at the higher diuretic doses, at least in a substantial number of patients.

In an attempt to comply with the conventional wisdom noted above, the sponsor of this NDA reformulated its diuretic drug, metolazone, to alter its bioavailability and plasma kinetics in such a way as to demonstrate the therapeutic efficacy of low doses. Marketed metolazone tablets (Zaroxolyn) are available only in 2.5 mg and 5.0 mg strengths, both (either?) are recommended for the initial treatment of mild/moderate hypertension. The new metolazone formulation (Microx) will be produced in 0.5 mg, 1.0 mg, and 2.0 mg tablet sizes. It is proposed that these dosage forms will encompass the 2.5 mg-5.0 mg Zaroxolyn dose range efficacy at an obviously far lower range (.5 mg-2.0 mg).

While the proposition is attractive, its fulfillment has been just partially met by the sponsor's studies in NDA 19-532. As will be discussed in more detail, the 0.5 mg Microx dose is clearly and substantially more effective than placebo in lowering elevated blood pressure. It is equally clear that the 0.5 mg Microx dose produces far less potassium loss than does 2.5 mg Zaroxolyn. Nevertheless, metolazone at any dose produces substantial potassium loss in virtually all patients to whom it is administered. Severe potassium loss, however, appears in significantly fewer patients on low-dose Microx than on doses above 1.0 mg/day

B. Antihypertensive efficacy: As can be seen in Tables II and III and in Figure X, below, the 0.5 mg Microx (once daily) dosage reduces blood pressure (sitting diastolic) to a significantly greater extent than placebo in mildly hypertensive patients (Study LDM-102). At the same time, however, Microx 0.5 mg/day decreases blood pressure significantly

Table I

Percent. Responders. All Patients, Final

	LDM-101	LDM-102
	n=158	n=154
MICROX 0.5 mg	51.3	57.7
MICROX 1.0 mg	69.9	56.0
MICROX 2.0 mg	61.6	57.7
Zaroxolyn 2.5 mg	65.8	--
Placebo	--	18.5

Table II

LDM-102 Composite

Mean Changes in Sitting Systolic and Diastolic Blood Pressure ± S.E.
(mm Hg)

	Week 2†	Week 4	Week 6	Final Week
No.of Pts	27	23	23	27
Placebo	-4.4 ± 2.3 / -2.7 ± 1.0	-2.9* ± 2.0 / -3.0* ± 1.2	-5.9* ± 2.9 / -4.3* ± 1.5	-3.2 ± 2.6 / -2.7 ± 1.5
No.of Pts	24	25	24	26
MICROX 0.5 mg	-11.0 ± 2.8 / -5.3 ± 1.3	-10.3* ± 2.6 / -7.3* ± 1.1	-15.7* ± 2.4 / -8.2* ± 1.3	-13.6* ± 2.7 / -7.8* ± 1.3
No.of Pts	25	23	25	25
MICROX 1.0 mg	-12.7 ± 2.9 / -6.8 ± 1.5	-15.3* ± 2.3 / -9.7* ± 1.2	-12.8* ± 2.7 / -8.0* ± 1.5	-12.8* ± 2.7 / -8.0* ± 1.5
No.of Pts	25	24	26	25
MICROX 2.0 mg	-14.4 ± 3.0 / -8.5 ± 1.3	-16.1* ± 2.8 / -7.8* ± 6.8	-16.2* ± 3.1 / -8.0* ± 1.3	-16.2* ± 3.1 / -8.0* ± 1.3

†Week 2 data not analyzed.
*Statistically significant change from baseline, Wilcoxon Signed Ranks Test $p \leq 0.05$.

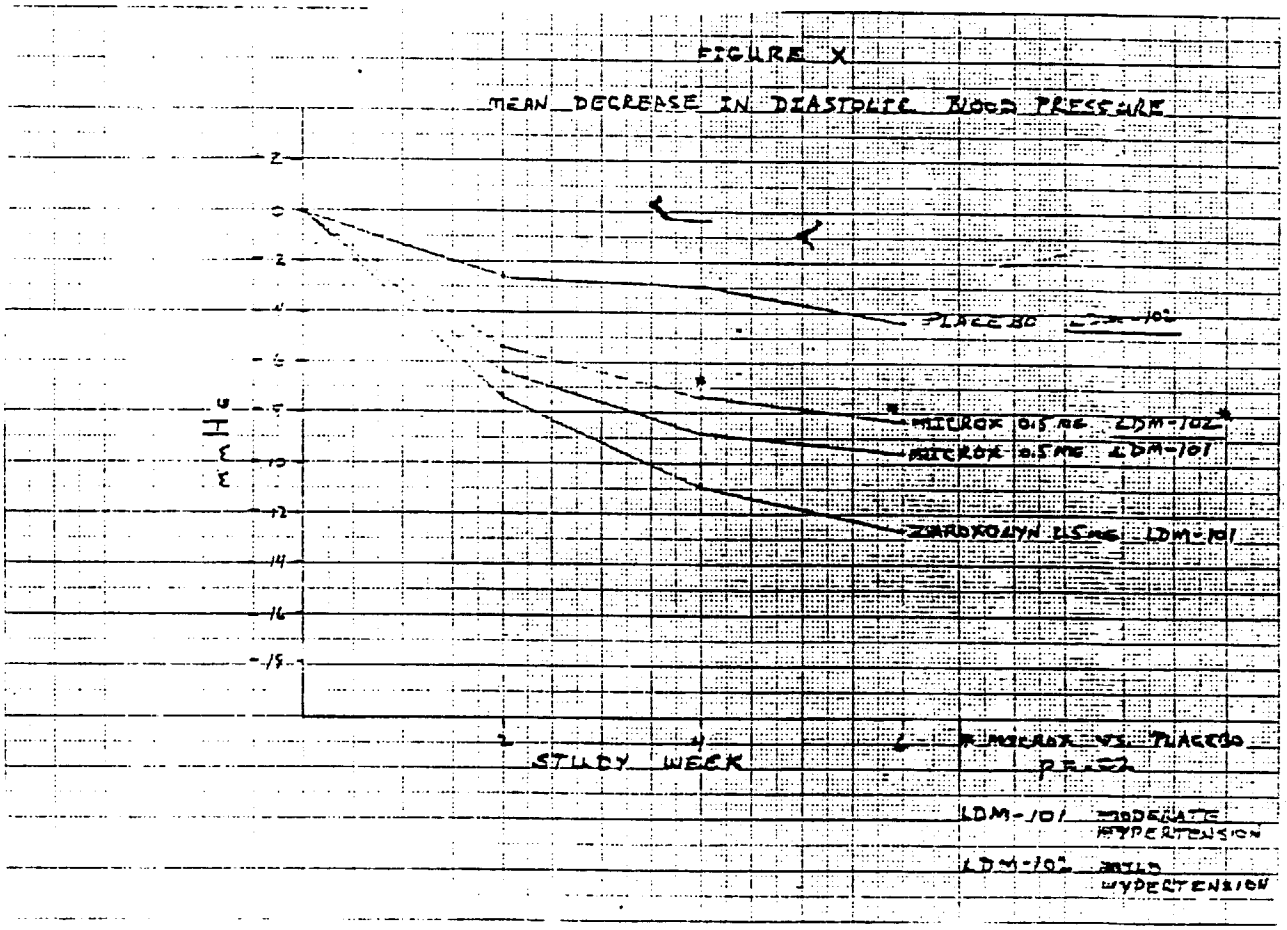
Table III

LDM-101 Composite

Comparison of Mean Change in Sitting and Standing Blood Pressure
(mm Hg)

	Week 2	Week 4	Week 6	Final Week
MICROX 0.5 mg				
Sitting	-10.2/- 6.2	-13.4/- 8.7	-12.6/- 9.6	-11.3/- 8.3
Standing	- 9.7/- 4.5	-13.5/- 6.7	-11.7/- 7.3	-10.1/- 6.5
MICROX 1.0 mg				
Sitting	-18.0/-10.3	-22.0/-12.5	-25.5/-14.4	-24.0/-13.3
Standing	-20.7/-11.2	-23.6/-13.1	-26.5/-14.5	-24.3/-13.3
MICROX 2.0 mg				
Sitting	-19.6/- 9.3	-24.0/-13.0	-24.3/-14.1	-23.6/-14.2
Standing	-18.5/- 9.0	-25.5/-12.6	-26.2/-14.7	-25.2/-14.7
Zaroxolyn 2.5 mg				
Sitting	-13.0/- 7.3	-16.7/-10.6	-19.5/-12.5	-19.0/-12.2
Standing	-13.9/- 5.4	-18.4/- 9.4	-20.4/-11.1	-20.2/-10.8

Figure X



but to a lesser extent than does Zaroxolyn 2.5 mg/day in moderately hypertensive patients (Study LDM-101). Therefore, it appears that Microx 0.5 mg/day represents all the metolazone required while 2.5 mg/day Zaroxolyn represents an overdose in mild hypertension (Table). In moderate hypertension, however, the significant BP decrease produced by Microx 0.5 mg is below an optimal metolazone BP response (i.e., too low a dose, less response than Zaroxolyn 2.5 mg/day). Examination of Tables II and III reveals the lack of difference in the antihypertensive efficacy of the 1.0 mg/day and 2.0 mg/day Microx doses. The extent of BP lowering in moderately hypertensive patients (Study LDM-101, Table III) is greater than the decrease produced by equivalent Microx doses (1.0 mg/day and 2.0 mg/day) in mildly hypertensive patients (Study LDM-102, Table II). End-point analysis (final week) comparison of sitting or standing diastolic BP decrease clearly shows the antihypertensive equivalence of Microx 1.0 mg/day, Microx 2.0 mg/day, and Zaroxolyn 2.5 mg/day. This BP decrease approximates 13 ± 1 mmHg diastolic in moderate hypertension but just 8 mmHg in mild hypertension. Not only are the 1.0 mg/day and 2.0 mg/day Microx doses equivalent in mildly hypertensive patients but neither of these "higher" doses are any better antihypertensives than the "low" Microx 0.5 mg dose (Study LDM-102, Table II).

Regarding the 1.0 mg and 2.0 mg Microx doses, then, it may be concluded that:

a) Microx 2.0 mg/day is no better than 1.0 mg/day in either mild or moderate hypertensive cardiovascular disease.

b) Zaroxolyn 2.5 mg/day, Microx 2.0 mg/day, and Microx 1.0 mg/day are equally as effective as each other in controlling moderately hypertensive patients. The 2.0 mg/day Microx dose is clearly above the maximally effective (1.0 mg/day) Microx dose. Whether the Zaroxolyn 2.5 mg/day dose is equal to or exceeds the (Zaroxolyn) maximally effective dose (in moderate hypertension) is not known.

c) Microx 2.0 mg/day and Microx 1.0 mg/day are both clearly superior to Microx 0.5 mg/day in reducing BP in moderate hypertension.

d) Neither Microx 2.0 mg/day nor Microx 1.0 mg/day (high doses) are any more effective than is Microx 0.5 mg/day in producing an optimal metolazone antihypertensive effect in mildly hypertensive patients.

In summary, the 0.5 mg/day Microx dose is optimal in mild hypertensives and useful in moderate hypertensives. The 1.0 mg/day Microx dose is optimal in moderate hypertensives. No clear antihypertensive utility for the 2.0 mg/day Microx dose has been demonstrated.

C. Effect on potassium: Shown in Tables IV and V and in Figure Y are the observed changes in serum potassium for each of the Microx doses over a period of six weeks. While each group's mean decrease in serum potassium allows a comparison of the average effect of each Microx dose, it yields little information on individual patients. A legitimate question might be: "Of all patients receiving dose x, what was the lowest serum potassium noted in any patient at any time?" The mean of all the lowest values in each group would measure the "worst case" potassium loss which

Table IV

Means of the Minimum Potassium
(mEq/L)

LDM-101

	MICROX ½ mg	MICROX 1.0 mg	MICROX 2.0 mg	Zaroxolyn 2.5 mg
Schoenberger	n= 6 3.95	n= 6 3.68	n= 5 3.42	n= 5 3.34
Schnaper	n=10 3.63	n=12 3.46	n= 9 3.26	n=10 3.33
Nugent	n=18 3.76*	n=18 3.53	n=17 3.42*	n=18 3.31*
Harris	n= 5 3.70	n= 7 3.21	n= 7 3.80	n= 6 3.63
Composite	n=39 3.72*	n=43 3.47*	n=38 3.39	n=38 3.36*

*Statistically significant difference between treatment groups, analysis of covariance.

Table V

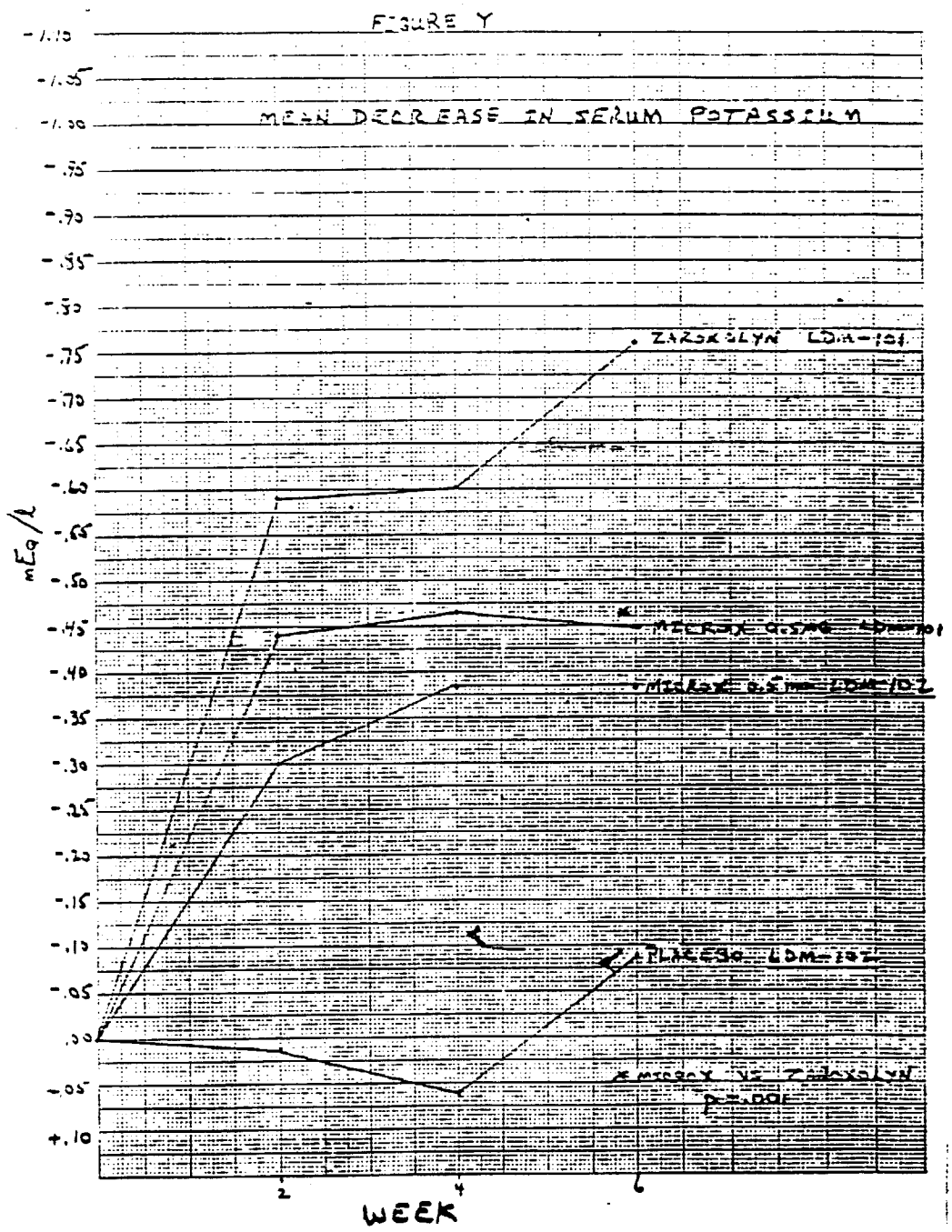
LDM-102

Means of the Minimum Potassium
(mEq/L)

	MICROX ½ mg	MICROX 1.0 mg	MICROX 2.0 mg	Placebo
Ryan	n= 8 3.85	n= 8 3.65[a]	n= 8 3.60[b]	n= 8 4.10[a,b]
Curry	n= 8 3.66[a]	n= 7 3.71[b]	n= 8 3.36[c]	n= 8 4.25[a,b,c]
MacKay	n=10 3.88[a]	n=10 3.70[b]	n=10 3.51[c]	n=10 4.46[a,b,c]
Composite	n=26 3.80[a,d]	n=25 3.69[b]	n=26 3.49[c,d]	n=26 4.28[a,b,c]

[a,b,c,d]Statistically significant difference between groups, analysis of covariance.

Figure Y



each dose would be capable of producing. Means of the lowest, per-patient, serum potassiums ever recorded over the entire 6-week trial are exhibited in Table IV (LDM-101) and Table V (LDM-102).

Examination of the LDM-102 composite average lowest potassium reveals a fairly definite dose-response; Microx 0.5 mg average maximal potassium loss appears to be significantly superior to (i.e., the lowest individual serum potassium levels, when averaged, are higher than) either of the two higher Microx doses. In LDM-101, the Microx 0.5 mg/day dose is again superior to the higher Microx and Zaroxolyn doses when examined in this manner.

While group averages are vital in examining results of clinical trials, they are relatively irrelevant in the one-on-one physician-patient relationship. The practicing physician might rather like to know the odds as to whether each patient will or will not become hypokalemic (defined as a serum potassium below 3.5 mEq/L). By combining all patients from all studies, the overall percent of those becoming hypokalemic can be calculated: None of the patients receiving placebo became hypokalemic (0 of 27 patients = 0%). Fourteen of the 64 patients in the 0.5 mg/day Microx group developed hypokalemia (14 of 64 patients = 22%). Among the 1.0 mg/day Microx patients, 16 of the 64 lost potassium to a hypokalemia (16 of 64 patients = 25%) extent.

Metolazone doses above 1.0 mg/day appear to double the percent of patients becoming hypokalemic. Thirty-one of the 64 patients taking 2.0 mg/day Microx developed serum potassiums below 3.5 mEq/L. The 2.5 mg/day Zaroxolyn dose produced hypokalemia in 16 of the 35 patients receiving the old metolazone formulation. Thus, 48.5% and 46% of patients receiving metolazone doses above 1.0 mg/day, Microx 2.0 mg/day and Zaroxolyn 2.5 mg/day, respectively, became hypokalemic:

COMPOSITE
INCIDENCE OF HYPOKALEMIA*
(PER DOSE-GROUP)

GROUP →	PLACEBO	ZAROXOLYN	MICROX 0.5 mg/day	MICROX 1.0 mg/day	MICROX 2.0 mg/day
NUMBER OF PATIENTS TESTED	27	35	64	64	64
NUMBER OF PATIENTS HYPOKALEMIC	0	16	14	16	31
PERCENTAGE OF PATIENTS HYPOKALEMIC	0%	46%	22%	25%	49%

* HYPOKALEMIA DEFINED AS A SERUM POTASSIUM CONCENTRATION BELOW 3.5 mEq/L

One conclusion that may be reasonably drawn would state that: "Approximately 20-25% of patients receiving 0.5 to 1.0 mg/day metolazone will become hypokalemic; and this incidence nearly doubles to approximately 45-49% when doses above 1.0 mg/day (i.e., 2.0 mg/day Microx and 2.5 mg/day Zaroxolyn) are prescribed." Insofar as metolazone induced potassium loss is concerned, this conclusion may be the most important (after all, the chances of suffering hypokalemia increase from 1 chance in 5 to 1 chance in 2 when doses above 1.0 mg/day are utilized).

Review of the group average serum potassium decrease, per group, fairly well confirms the foregoing discussion, but perhaps not quite as clearly (Tables VI and VII). These were discussed previously (see Tables G and Q).

Table VI

LDM-101 Composite

Mean Changes, Serum Potassium from Baseline ± S.E.
(mEq/L)

	Week 2	Week 4	Week 6
No.of Pts MICROX 0.5 mg	30	35	34
	-0.44 ± 0.09	-0.47 ± 0.07	-0.45 ± 0.08
No.of Pts MICROX 1.0 mg	41	30	35
	-0.71 ± 0.10	-0.65 ± 0.11	-0.60 ± 0.08
No.of Pts MICROX 2.0 mg	35	33	35
	-0.70 ± 0.09	-0.60 ± 0.09	-0.65 ± 0.11
No.of Pts Zaroxolyn 2.5 mg	33	34	35
	-0.59 ± 0.09	-0.60 ± 0.10	-0.76 ± 0.08

LDM-102 Composite

Table VII

Mean Changes Serum Potassium ± S.E.
(mEq/L)

	Week 2	Week 4	Week 6
No.of Pts Placebo	26	22	22
	+0.01 ± 0.07	+0.06 ± 0.13	-0.09 ± 0.07
No.of Pts MICROX 0.5 mg	24	25	24
	-0.30 ± 0.14	-0.38 ± 0.10	-0.38 ± 0.11
No.of Pts MICROX 1.0 mg	25	23	25
	-0.52 ± 0.10	-0.47 ± 0.10	-0.74 ± 0.11
No.of Pts MICROX 2.0 mg	25	24	26
	-0.76 ± 0.09	-0.60 ± 0.08	-0.77 ± 0.09

There are no significant changes from baseline in serum potassium in the placebo group. The changes from baseline are statistically significant for all three MICROX treatment groups at all time points ($p < 0.05$)[1].

[1]Wilcoxon Signed Ranks Test used for all comparisons from baseline in Section IX.

D. Adverse effects: Reformulation of metolazone into lower dosage strengths does not appear to have altered either the incidence or profile of adverse drug reactions. Comparing the ADR profile observed in studies LDM-101 and LDM-102 with the currently approved (Zaroxolyn) labelling reveals a few "new" adverse reactions (not contained in the PDR). Those newly-occurring, in at least 1.0% of the patients studied, include joint pain, sore throat, depression, rash and sexual dysfunction. Draft labelling submitted in the Microx NDA includes all of the "new" adverse drug reactions.

A comparison of the profile and incidence in the 0.5 mg/day Microx groups, from both LDM-101 and LDM-102 combined, with the LDM-102 placebo group is shown in Table VIII, below:

Table VIII

Adverse Experiences, ½ mg Microx and Placebo
LDM-102 by Frequency, No., (%)

	MICROX ½ mg n=74	Placebo LDM-102 n=27
Headache	8 (10.82)	4 (14.8)
Dizziness	6 (8.1)	2 (7.4)
Joint Pain	3 (4.1)	1 (3.7)
Muscle Cramps	2 (2.7)	1 (3.7)
Chest Pain	2 (2.7)	0
Diarrhea	2 (2.7)	0
Fatigue	2 (2.7)	2 (7.4)

Differences in incidence of ADRs between the various Microx doses studied were not significant. Therefore ADRs from all Microx dosage groups, from both studies were combined and compared to the LDM-102 placebo group and the LDM-101 Zaroxolyn group is shown in Table IX.

The metolazone-induced metabolic changes (serum electrolytes, lipids, blood sugar and uric acid) noted in LDM-101 and LDM-102 are consistent with the already well-known and documented alterations.(2)

Table IX

Incidence of Adverse Experiences
Number (Percent)

	MICROX n=226	Placebo (LDM-102) n=27	Zaroxolyn (LDM-101) n=41
Dizziness (lightheadedness)	23 (10.2)	2 (7.4)	2 (4.9)
Headaches	21 (9.3)	4 (14.8)	1 (2.4)
Muscle Cramps	13 (5.8)	1 (3.7)	1 (2.4)
Fatigue (malaise, lethargy, lassitude)	10 (4.4)	2 (7.4)	1 (2.4)
Joint Pain	7 (3.1)	1 (3.7)	2 (4.9)
Chest Pain precordial discomfort)	6 (2.7)	0	2 (4.9)
Constipation	4 (1.8)	1 (3.7)	2 (4.9)
Weakness	4 (1.8)	0	0
Sore Throat	4 (1.8)	0	0
Dry Mouth	3 (1.3)	0	0
Palpitations	3 (1.3)	0	0
Nausea	3 (1.3)	0	0
Abdominal Discomfort (pain, bloating)	3 (1.3)	0	0
Psychologic (nervousness, depression, weird feeling)	3 (1.3)	0	1 (2.4)
Rash	3 (1.3)	0	2 (4.9)
Interim Illness (URI, cold, otitis media)			
Sexual Dysfunction	3 (1.3)	0	1 (2.4)

III. CONCLUSIONS: Taken at face value, the results of metolazone antihypertensive clinical trials LDM-101 and LDM-102 demonstrate the following:

A. Anti-hypertensive efficacy:

1. All of the tested metolazone doses lowered blood pressure to a greater extent than placebo (see Figure X).

2. In mild hypertension, the 0.5 mg/day Microx dose is as effective as any of the higher Microx or Zaroxolyn doses and is therefore optimal (see Table I).

3. In moderate hypertension, the 0.5 mg/day Microx dose is effective in some but the 1.0 mg/day Microx dose "captures" significantly more patients and is therefore optimal (see Table II and Table III).

4. The 2.0 mg/day Microx dose appears to exhibit no increased utility over lower doses in either mild or moderate hypertension (see Table II and Table III).

B. Potassium-loss:

1. Placebo causes no potassium loss.

2. Group average decreases in serum potassium levels show an apparent dose-response, overall significantly more potassium loss with each succeedingly higher dose.

3. The percentage of patients likely to become hypokalemic remains relatively constant at Microx doses of 1.0 mg/day or below. Metolazone doses above 1.0 mg/day, however, significantly increase (double) the percentage of patients suffering drug-induced hypokalemia.

4. Metolazone-induced potassium loss is not insignificant at any dose. The drug, whether the old or new formulation, nearly always causes substantial potassium loss. Logically, then, the lowest dose consistent with meaningful antihypertensive efficacy should be prescribed.

C. Overall: Considering both the blood pressure and potassium issues, together, at the various Microx doses, two dividing lines, respectively, become apparent: severity of hypertension (mild vs moderate) and likelihood of hypokalemia (above and below the 1.0 mg/day Microx dose).

1. The 2.0 mg/day Microx regimen is unacceptable because: (a) it is no more effective than 0.5 mg/day in mild hypertension and no more effective than 1.0 mg/day in moderate hypertension and (b) it produces hypokalemia in nearly twice as many patients as either the 0.5 mg/day or 1.0 mg/day Microx doses.

2. The 0.5 mg/day Microx dose is optimal in mild hypertension because: (a) it lowers mildly elevated blood pressure to the same degree as either of the two higher Microx doses and (b) the average potassium loss, though significant, is less than the higher Microx doses and produces fewer hypokalemic patients than the 2.0 mg/dose.

3. The 1.0 mg/day Microx regimen is optimal in moderate hypertension because: (a) on average, it reduces moderately elevated blood pressure to a significantly greater extent than the 0.5 mg/day Microx dose and (b) it is no worse than the 0.5 mg/day Microx dose in percentage of patients made hypokalemic. However,

4. The 0.5 mg/day Microx dose is as effective as the 1.0 mg/day dose in some moderately hypertensive patients and therefore represents a logical starting dose. Those moderately hypertensive patients not fully responsive to the 0.5 mg/day Microx dose should, obviously, be afforded the 1.0 mg/day dose.

IV. RECOMMENDATIONS:

1. Microx tablets, 0.5 mg and 1.0 mg, are recommended for approval as initial treatment of mild to moderately severe hypertensive patients. Warnings should include a statement regarding significant potassium loss and development of hypokalemia in 20-25% of all patients receiving these doses.

2. Microx tablets, 2.0 mg, offer no efficacy advantage but pose a significantly greater risk of hypokalemia than the 1.0 mg Microx dose. Approval for hypertension is not recommended.

3. No data exists regarding the potential additive effect that Microx may have when combined with an antihypertensive drug. The old formulation, Zaroxolyn, is approved "to enhance the effectiveness of other antihyper- tensive drugs in the more severe forms of hypertension." There is no reason to believe that the new "Microx" formulation would not be equally as effective as Zaroxolyn for this adjunctive use.

4. No data exists regarding the utility of the new Microx formulation in the treatment of edema. The old formulation, Zaroxolyn is approved for treating the edema associated with congestive heart failure and with states of diminished renal function. Given the substantial weight loss observed with Microx, there is little reason to believe that the new formulation would be any less effective than the old. Weight loss dose-response continued beyond the 1.0 mg/day Microx regimen. It may be, therefore, that Microx doses above 1.0 mg/day will be shown to be superior to the lower doses in the treatment of edema.

5. Revision of the labelling Adverse Reactions section is recommended. ADR incidence and profile needs to be updated to include results of the most recent metoxalone studies and literature.

/S/

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cc: Orig. NDA
HFN-110
HFN-110/CSO
HFN-1100/RKeenan
ef/7/29/86;8/8/86/#0574g

References:

(1) Mann, RD and Guarino, RA: CHLORTHALIDONE 25 mg (Symposium Proceedings, White Plains, NY, September 1978), Baltimore 1979, MTB PRESS LTD.

(2) Goodman, LS and Gilman, AG: The Pharmacologic Basis of Therapeutics (7th Edition), New York, 1985, Macmillan.

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Division Director's Review

NDA: 19-532

Sponsor: Pennwalt Corporation

Name of Drug: MICROX

This application presents an interesting dilemma. Pennwalt "reformulated" and in so doing increased the bioavailability of metolazone from that of their marketed metolazone product (Zaroxolyn). Having reformulated and altered bioavailability, Pennwalt performed two adequate and well-controlled trials (LDM-101 and LDM-102) which establish antihypertensive effects of MICROX (their new formulation) at doses of metolazone substantially less than those currently appearing in the Zaroxolyn package insert.

The study identified as LDM-101 lacked a placebo control. However, over dose ranges of 0.5 mg to 2.0 mg of orally administered MICROX, there were dose-related decreases of both blood pressure and serum potassium (see Figures 1 and 2). Although the lack of placebo control makes it impossible to establish firmly the minimally effective dose, and the lack of doses above 2.0 mg makes it impossible to estimate the maximally effective dose, it is clear enough that doses of MICROX between 0.5 mg and 2.0 mg can be expected to lower blood pressure in a dose-related manner. Additionally, dose related potassium loss is well documented.

The study identified as LDM-102 had a parallel placebo control, no obvious dose-related blood pressure change (see Figure 3), but differentiated the hypotensive effects of 0.5, 1 mg and 2 mg of MICROX from placebo. Dose-related potassium loss was clearly documented (see Figure 4).

These findings need to be evaluated in light of the Zaroxolyn labelling which recommends doses between 2.5 mg and 5.0 mg for Zaroxolyn administered once-a-day. Also needing consideration is that we, as well as the majority of the medical community, are eager not to use excessive doses of thiazide diuretics; metolazone is in some respects a thiazide type diuretic.

Based on the submitted bioavailability studies, metolazone in Zaroxolyn is about 55% bioavailable compared to metolazone in MICROX. If this were to be taken to heart, and one assumed the initial dose ranging for Zaroxolyn was appropriate and one assumed the only difference between Zaroxolyn and MICROX was the bioavailability of metolazone, one would predict the dose range of MICROX to be between 1.4 mg and 2.8 mg. In fact, 0.5 mg of MICROX may well be above the ED_{50} for blood pressure effects since LDM-101 and LDM-102 do not establish the minimally effective dose. So prediction does not agree with empirical data and it is not easy to decide which assumption, needed for the prediction, is incorrect.

The pharmacokinetic and bioavailability data are rather poor. Four studies are available to examine LDM-100, the study submitted as part of this NDA; TM-2, a study done when the sponsor was evaluating a metolazone/triamterene formula- tion; DRA 4-78, a study submitted with the original Zaroxolyn NDA.

DRA 4-78 was a ^{14}C-labelled study and for practical purposes is not useful since metolazone was not measured directly. Moreover, insufficient data points were obtained to determine a terminal half-life meaningfully although it is reasonable enough to say it appeared to be 12 hours or longer for ^{14}C metolazone.

Study LDM-100, is the most recent study and measured metolazone (rather than ^{14}C) but in whole blood (not plasma). This study shows metolazone from 2.5 mg Zaroxolyn to peak at 7.7 ± 6.05 hours. A solution of metolazone peaked at 1.25 ± 0.44 hours. For MICROX peak blood levels of metolazone were at 3.2 ± 1.02, 3.7 ± 0.28, 3.75 ± 1.36 and 2.17 ± 0.34 hours for doses of MICROX of 5.0 mg, 2.0 mg, 1.0 mg, and 0.5 mg, respectively.

So, each of the MICROX dosage forms peaked several hours before that of the single estimate available for one dose of Zaroxolyn. This is the first argument that MICROX is a different formulation than Zaroxolyn.

Study TM-2, a study devoted to developing a combination product and using a metolazone formulation similar to MICROX, also found peak blood levels of metolazone at about three hours and confirms LDM-100 with respect to time to peak blood level for MICROX. The ^{14}C study, DRA 4-78 confirms a peak blood level at about six hours for metolazone and/or its metabolites from Zaroxolyn.

Dissolution data are consistent with the above time-to-peak blood level. MICROX is essentially dissolved by two to four hours in vitro at 100 rpm (paddle) in water. Zaroxolyn takes considerably longer to dissolve.

These are reasonable good arguments in support of MICROX being a different formulation of metolazone from Zaroxolyn. They rest heavily on the one Zaroxolyn dose in LDM-100 and also on ^{14}C data. The LDM-100 data for Zaroxolyn are not easy to accept since at face value, the data demand a source of metolazone within the GI tract for well over 25 hours from a single dose. Not a very easy requirement to accept. The ^{14}C data clearly could be from metolazone or any metabolite, so it is not too convincing.

Consequently, one can fairly readily conclude the following:

a) MICROX is a new formulation of an old drug.
b) Metolazone in MICROX is more bioavailable than it is in Zaroxolyn.
c) MICROX and Zaroxolyn are not interchangeable.

However, the data are insufficient to conclude that MICROX is an immediate release formulation (although it trends that way) of metolazone and that Zaroxolyn is a sustained release (although it trends that way) formulation of metolazone.

Since there appear to be differences (although rather poorly defined) in the pharmacokinetics of the two formulations, it is not possible to apply the dose-ranging information for MICROX to Zaroxolyn.

Dose ranging for MICROX has only been done for hypertension. So MICROX cannot simply replace Zaroxolyn on the market since the dose of MICROX for edema is not defined. If MICROX is approved, existing data would require the two incompletely characterized formulations to exist in the market simultaneously; one for hypertension and the other for edema and hypertension. Not an appealing outcome. Particularly not appealing since MICROX and Zaroxolyn are so incompletely compared pharmacokinetically.

On the other hand, even given the increased bioavailability of metolazone in MICROX, a lower and more appropriate dose range has been identified for metolazone. In spite of the inadequacy of characterization of MICROX it seems appropriate to allow a more reasonable dosage form of metolazone to be marketed. Consequently MICROX should be approved.

Pennwalt Corportion has marketing plans which intend to promote MICROX for the treatment of hypertension only. They also have been and intend to continue promoting Zaroxolyn only for edema. The package insert of both products will in several places, and conspicuous, warn against the interchangeability of Zaroxolyn and MICROX. Thus, those that read promotion and read package inserts should be adequately informed.

Generic prescription writing can however lead to confusion since 0.5 mg MICROX (written as metolazone) can be misinterpreted as 5.0 mg Zaroxolyn (written as metolazone. This seems a negligible problem and at approval time is simply being ignored with respect to requiring attention.

There is no safety update with respect to MICROX. Metolazone is a well known and marketed dosage form. No surprises are expected and a safety update is simply busy work and would add nothing to the consideration.

MICROX approval is based upon the two clinical trials (LDM-101 and LDM-102) which were performed by Pennwalt Corporation. Without these two trials the NDA could not have been approved.

The releasable reviews will constitute the Summary Basis of Approval.

cc: Orig. NDA
HFN-70/DHare
HFN-110
HFN-110/CSO
HFN-110/RLipicky
sf:1/7/86:4071c

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