CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076466

BIOEQUIVALENCE REVIEWS

MAY 21 2003

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-466
Drug Product Name	Metolazone
Strength	5 & 10 mg
Applicant Name	Eon Labs
Address	Wilson, NC
Submission Date(s)	~~7/26/2002~~ 10/9/2002 Len
Reviewer	Nhan L. Tran
File Location	v:\\firmsam\eon\ltrs&rev\76466N0702

Executive Summary

This application for metolazone tablets includes a fasting BE study and dissolution data. The fasting study is a single-dose two-way crossover study using 36 male and female normal healthy volunteers given a dose of 10 mg. The results (point estimate and 90% CI) of the fasting BE study are LAUCt of 1.02, 94.9-109.6%; LAUCi of 1.01, 94.6-108.1%; and LCmax of 0.99, 86.6-113.2%. The study is acceptable. The dissolution (Apparatus: USP Apparatus 2 (Paddle) at 75 rpm, Medium: 2% SLS in DI water) testing is incomplete since the FDA Recommended Method was not used. In addition, the waiver request for 5 mg tablets is denied because the waiver request does not meet the Agency's criteria. The application is therefore incomplete.

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Submission Summary

A. Drug Product Information

Test Product	Metolazone, Lot # RDW00048
Reference Product	Zaroxolyn, Lot # X-851
Indication	Antihypertensive

B. Contents of Submission

					How many?
Single-dose fasting study	Yes	X	No	☐	1
Single-dose fed study	Yes	☐	No	X	
Steady-state study	Yes	☐	No	X	
In vitro dissolution testing	Yes	Y	No	☐	
Waiver requests	Yes	Y	No	☐	
BCS data	Yes	☐	No	X	
Vasocontrictor studies	Yes	☐	No	X	
Clinical endpoints	Yes	☐	No	X	
Failed studies	Yes	☐	No	X	
Amendments	Yes	☐	No	X	

C. Bioanalytical Method Validation

Number of analytes		1		
Analyte name		metolazone		
Internal Standard		(b) (4)		
Method description		HPLC/MS/MS		
Standard curve range		0.4ng/ml to 100ng/ml		
Limit of quantitation		0.4ng/ml		
Average recovery (%)		93.4%		
Intraday precision range (%)		1.6 to 8.7		
Intraday accuracy range (%)		95.9 to 110		
Interday precision range (%)		4.6 to 8.9		
Interday accuracy range (%)		98.7 to 104		
Bench-top stability (hrs)		24 hrs		
Processed stability (hrs)		47 hrs		
Freeze-thaw stability (cycles)		4 cyles		
Long-term storage stability (days)		51 days		
Dilution integrity	Yes	Y	No	☐
Specificity	Yes	Y	No	☐
SOPs submitted	Yes	Y	No	☐
Bioanalytical method is acceptable	Yes	Y	No	☐

D. In Vivo Studies

Single-dose Fasting Bioequivalence Study

Study No.		B012015		
Study Design	Crossover	X	Parallel	☐
	Two-way	X	Three-way	☐
	Replicate	☐		
No. of subjects enrolled		36		
No. of subjects completing		34		
No. subjects with samples analyzed		34		
Subjects	Healthy	X	Patients	☐
Sex(es) included	Male	X	Female	X
Test product		metolazone		
Reference product		Zaroxolyn		
Strength tested		10 mg		
Dose		1 tablet		

Summary of Statistical Analysis

Parameter	Point Estimate	90% Confidence Interval
AUCt	1.02	94.9 – 109.6
AUCi	1.01	94.6 – 108.1
Cmax	0.99	86.6 – 113.2

The study is acceptable Yes X No ☐

E. Formulation

The test product formulation(s) is/are shown in Formulation Table of the Appendix.
Inactive Ingredients within IIG limits Yes X No ☐
The formulation is acceptable Yes X No ☐

F. In Vitro Dissolution

Methods Submitted	FDA	☐	USP	☐	OTHER	X
Recommended Method based on the data submitted: Pending						
Medium	2%SLS in DI water					
Volume (mL)	900 ml					
USP Apparatus Type	Paddle					
Rotation (rpm)	75 RPM					
Firm's proposed specifications	(b) (4) 60 min					
FDA-recommended specifications	Pending					
In vitro dissolution is acceptable	Yes	☐	No	X		

G. Waiver Request

Yes X No ☐

The applicant requests a waiver of in vivo bioequivalence testing under 21 CFR 320.22 (d)(2) for the following strength(s): 5 mg

The formulation(s) is(are) proportionally similar to that of the strength which underwent acceptable in vivo testing Yes X No ☐

Acceptable dissolution testing, all strengths Yes ☐ No X

H. Deficiency Comments

Yes X No ☐

I. Recommendations

In vitro data is incomplete. More information is needed for review. The waiver request for the 5 mg strength is denied.

IV. Appendix:

REVIEW OF IN-VIVO BE STUDY AND DISSOLUTION DATA

Metolazone Tablets, USP
5, and 10 mg
ANDA 76-466
Reviewer: Nhan L. Tran
v:\new\firmsam\eon\ltrs&rev\76466sdw0702

Eon Labs Inc.
Eon Drive
Wilson, NC
Submission Date:
July 26, 2002

Review of Fasting Bioequivalence Study Dissolution Data and Waiver Requests

Background Information

Indication: Diuretic/Saluretic/Antihypertensive (Quinazoline class). For the treatment of salt and water retention accompanying congestive heart failure and renal diseases as well as for the treatment of hypertension. Most of the drug is excreted in urine unchanged.
Type of Submission: Original ANDA
Contents of Submission:
10 mg Metolazone Tablets, USP: Dissolution data and in vivo bioequivalence study under fasting conditions.
5 mg Metolazone Tablets, USP: Dissolution data and waiver request for in vivo bioequivalence study requirements.
RLD: Zaroxolyn® tablets, 10, and 5 mg manufactured by Medeva Pharmaceuticals Inc.

History

1. Medeva's has approved and listed NDA 17386 for Zaroxolyn (metolazone) 2.5mg, 5mg and 10mg tablets. According to the electronic PDR, the labeling does not mention any food effect studies. The labeling also does not mention whether the firm conducted any studies (viz. 4x2.5mg tablet vs. 1x10mg tablet, 2x5mg tablets vs. 10mg tablet or 2x2.5mg tablets vs. 1x5mg tablet) within the strengths or dose proportionality studies. As per the COMIS database, the three strengths (2.5mg, 5mg, and 10mg tablets) are formulated proportionally same (viz. qualitatively (Q1) same formulation with the total tablet weight of 100mg). **Thus, due to a lack of pharmacokinetic information in NDA, the Division of Bioequivalence relied on the dissolution testing data to decide on waiving of the lower strengths (2.5mg and 5mg tablets).** The comparative dissolution testing data used to make that decision came from the Copley's submission of ANDA 75-543 dated 12/30/1998 (see item #2).

2. Copley's submitted ANDA 75-543, for [redacted] (b) (4) 10mg metoxalone tablets. The submission had i) an acceptable fasting study on the 10mg tablet, ii) formulations for the [redacted] (b) (4) 10mg tablets, and iii) comparative dissolution testing data on [redacted] (b) (4) tablets. Copley requested waivers for the

(b) (4)

[redacted]

3. While reviewing the Copley's ANDA 75-543, Dr. Mamata Gokhale wrote a document entitled (b) (4) [redacted] The document is stored under the address V:\Bio\Mamata2\My document\Metalozone dissolution\Metalozone dissolution.doc.The recommendations from Dr. Gokhale's document are copied below.

Recommendations

1) The DBE should continue to request an *in vivo* bioequivalence study on the (b) (4) [redacted] strength to support bioequivalency of (b) (4) [redacted] strengths to the reference

product. If a generic firm does not plan to market the (b) (4) strength, the DBE should request an *in vivo* bioequivalence study on the (b) (4) strength.

2) The DBE should collect additional in vitro dissolution data to determine whether bio-waivers can be granted to the (b) (4) strengths of a generic product based on comparative dissolution profiles of the corresponding strengths of (b) (4) Tablets.

4. Eon's ANDA 76-466 (the current submission for 5mg and 10mg tablets) was reviewed as a Paragraph 4 submission by Dr. Dhariwal. As per Dr. Dhariwal's recommendations the submission was accepted for a review. Dr. Dhariwal also made a comment for the Regulatory Support Staff to inform Eon that its 5mg tablet is not eligible for a waiver. He made this recommendation based on the dissolution profiles comparison of 5mg and 10mg brand name tablet (f_2 = 48.4).

5. Product labeling for Mykrox® (0.5mg metolazone tablet from Medeva NDA 19-532) from the electronic PDR has the following statement:
"MYKROX TABLETS AND OTHER FORMULATIONS OF METOLAZONE THAT SHARE ITS MORE RAPID AND COMPLETE BIOAVAILABILITY ARE NOT THERAPEUTICALLY EQUIVALENT TO ZAROXOLYN® TABLETS AND OTHER FORMULATIONS OF METOLAZONE THAT SHARE ITS SLOW AND INCOMPLETE BIOAVAILABILITY. FORMULATIONS BIOEQUIVALENT TO MYKROX AND FORMULATIONS BIOEQUIVALENT TO ZAROXOLYN SHOULD NOT BE INTERCHANGED FOR ONE ANOTHER."
Dissolution profile of Mykrox® tablet is different from those of Zaroxolyn tablets (2.5mg,5mg, and 10mg). Therefore the statement cited above provides additional strength to the DBE recommendation of not granting waiver to the generic lower strengths (2.5mg and 5mg) based on the acceptable study on 10mg generic tablet.

6. The OGD received many documents subsequent to Copey's ANDA 75-543. Those are:
   a) Protocol 00-046 from (b) (4) (review by Nouraversani)
   b) CD 02-049 from (b) (4) (review by Lee)
   c) CD 02-194 from (b) (4) (review by Shrivastava)
   d) CD 03-129 from Watson (review by Sanchez)

   The DBE made similar recommendations while responding to these documents. The recommendations were i) conduct a single dose fasting study on the (b) (4) tablet and a single dose fasting study the 10 mg tablet, ii) request a waiver for the (b) (4) tablet, iii) non-fasting study is not necessary, iv) measure the parent drug [no metabolites] in the bioequivalence studies, v) provide formulations of the three strengths to show proportional similarity, and vi) provide comparative dissolution testing data on three strengths.

7. There are other documents that are not helpful for this review (the reason is mentioned).
   a) CD 02-625 from Eon (a telecon with no documentation)
   b) CD 00-305 from Medeva (non bio issue)

c) CD 97-038 from [redacted] (old document)
d) CD 96-105 from [redacted] (old document)
e) CD 95-138 from [redacted] (no record)

8. Recently, the FDA Laboratory conducted dissolution testing on the brand name metolazone tablets (2.5mg, 5mg, and 10mg). The results indicated that the 10mg tablet dissolved quicker than the 2.5mg and 5mg tablets. The f_1 and f_2 values were calculated from the mean dissolution profiles of these tablets. In a comparison of the 2.5mg and 5mg tablets, **f_1 and f_2** values were 6.8 and 65.1 showing similarity of profiles. For the 2.5mg and 10mg tablets the **f_1 and f_2** values were 12.1 and 48.7 showing a similarity by f_1 and a difference by f_2. The 5mg and 10mg tablets had **f_1 and f_2** values of 17.7 and 40.5 showing a difference in the dissolution profiles. These results corroborate the data submitted by [redacted] and Eon (ANDA 76-466).

In conclusion, if a firm submits an ANDA for three strengths (2.5mg, 5mg and 10mg), the DBE will request two single dose bioequivalence studies (5mg and 10mg). If a firm submits an ANDA for two strengths (5mg and 10mg), the DBE will request two single dose studies (5mg and 10mg).

REVIEW OF THE FASTING BIOEQUIVALENCE STUDY

Protocol No.: B012015, Fasting *In-Vivo* Bioequivalence Study

Study Information

Clinical Facility:	Gateway Medical Research.
Medical Director:	David Erasmus, M.D.
Clinical Study Dates:	Period I: March 23, 2002, Period II: April 6, 2002
Analytical Facility:	[redacted]
Analytical Director:	[redacted] M.S.
Analytical Study Dates:	04/025/02 to 05/14/02

Treatment Information		
Treatment ID:	A	B
Test or Reference:	T	R
Product Name:	Metalazone, USP	Zaroxolyn®
Manufacturer:	Eon	Medeva
Expiration Date	-	12/2003
ANDA Batch Size	[redacted]	N/A
Full Batch Size		N/A
Batch/Lot No.:	RDW00048	X-851
Potency	101.8% (101.5% – 102.2%)	101.6% (101.3%-101.9%)
Content Uniformity	99.6% (78%-102.2%)	100.2% (95.8%-101.9%)
Strength:	10 mg	10 mg
Dosage Form:	Tablet	Tablet

Dose Administered:	10 mg	10 mg
Study Condition:	Fasting	Fasting
Length of Fasting:	Overnight	Overnight

Randomization		**Design**	
Randomized:	Y	Design Type:	Crossover
No. of sequences:	2	Replicated Treatment Design:	N
No. of periods:	2	Balanced:	Y
No. of treatments:	2	Washout Period:	14 days

Randomization Scheme:

A B	1	4	6	8	11	16	17	19	20	22	23	25	27	28	29	32	33	36
B A	2	3	5	7	9	10	12	13	14	15	18	21	24	26	30	31	34	35

Subjects characteristics:

Age	**(%)**	Weight		**Race**	**(%)**	Sex	(%)
Mean	**24.7 (19-47)**	Mean	85 kg	**Caucasian**	**32 (94%)**	Male	21 (62%)
18–40	**33 (97.05%)**	Range	66-112kg	**African-Amer**	**2 (6%)**	Female	13 (38%)
41–60	**1 (2.9%)**						

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:	36
Route of administration:	Oral	No. of subjects completing:	34
Dosing interval:	Hr	No. of subjects plasma analyzed:	34
Number of doses:	N/A	No. of dropouts:	2
Loading dose:	mg	Sex(es) included:	Male &Female
Steady state dose time:	N/A	Healthy volunteers only:	Y
Length of infusion:	N/A	No. of adverse reaction events:	16

Blood Sampling (20 samples): Before dosing (time 0) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 8, 12, 16, 24, 30, 36, 48 and 60 hours after dosing. Samples were collected and stored at –20°C until processing.

Study Results

1) Clinical

Adverse Events: 8 subjects (subject #4, 8, 10, 12, 16, 18, 19, and 31) reported 16 adverse events. 8 events from the test and 8 from the reference treatments. None of the adverse events were considered serious.

Protocol Deviations: Subject #20 had 1 dose of a monthly administered injectable contraceptive during the study period. The subject's participation was approved by the PI.
Subject #12 consumed 12 oz of a caffeine containing beverage the day of check-in for period 2. OK to participate per PI.

Dropouts: Subject #4 before period II due to adverse event, subject #35 after period I due to a positive drug screen.

2) Analytical (Not to be released under FOI)

Pre-Study Assay Validation:

Experimental Parameter	Validation	
Analyte	Std.Curve	QC
Detection	LC/MS/MS	LC/MS/MS
Range	0.4 ng/ml – 100 ng/ml	1 ng/ml, 9 ng/ml 75 ng/ml
Minimum Quantifiable Level	0.4 ng/mL	0.4 ng/ml
Intra-day Accuracy (%)	N/A	95.9 – 110
Intra-day Precision (%)	N/A	1.6 – 8.7
Inter-day Accuracy (%CV)	96.5 – 106	98.7 – 104
Inter-day Precision (%CV)	2.4 – 8.1	4.6 – 8.9
% Recovery (Mean)	93.4% for metolazone	56.8% for (b) (4) (Int. Standard)
Stability Freeze/Thaw 24 h at Rm Temp. 47 h (processed) at Rm Temp. Frozen Storage Stability	 Stable for 4 cycles Stable at RT for 24 hrs Stable stable for 51 days @ -20°C	

During Study Assay Validation:

Experimental Parameter	Validation	
Analyte	Std.Curve	QC
Detection	LC/MS/MS	LC/MS/MS
Range	0.4 ng/ml – 100 ng/ml	1 ng/ml, 9 ng/ml 75 ng/ml
Minimum Quantifiable Level	0.4 ng/mL	0.4 ng/ml
Intra-day Accuracy (%)	N/A	95.9 – 110
Intra-day Precision (%)	N/A	1.6 – 8.7
Inter-day Accuracy (%CV)	96.5 – 106	98.7 – 104
Inter-day Precision (%CV)	2.4 – 8.1	4.6 – 8.9
% Recovery (Mean)	93.4% for metolazone	56.8% for (b) (4) (Int. Standard)
Stability Freeze/Thaw 24 h at Rm Temp. 47 h (processed) at Rm Temp. Frozen Storage Stability	 Stable for 4 cycles Stable at RT for 24 hrs Stable stable for 51 days @ -20°C	

Analytical Repeats of the in vivo study samples: Total 105 samples were repeated for various reasons: 64 due to above the limit of quantitation, 21 due to low internal standard, 15 due to processing error, 4 due to high internal standard, 1 due to contamination.

3) Pharmacokinetic:

Mean (%CV) Plasma Concentrations (ng/ml) of metolazone (N=34)

Time(hours)	Test Mean	Test %CV	Ref Mean	Ref %CV	T/R Ratio
0	0.	0.	0.	0.	**
0.5	3.541	198.874	4.609	128.23	0.76
1	22.652	98.984	24.318	73.397	0.931

1.5	44.601	73.439	43.931	64.350	1.01
2	58.828	58.750	62.559	59.367	1.00
2.5	70.368	57.896	71.212	50.004	0.99
3	76.061	57.586	77.124	47.807	0.99
3.5	75.732	50.794	77.168	42.420	0.98
4	75.044	46.446	71.412	39.739	1.05
4.5	69.662	40.509	66.750	35.433	1.04
5	53.954	39.233	51.162	33.113	1.05
6	44.771	37.671	41.441	30.039	1.08
8	33.385	39.413	32.182	34.699	1.04
12	20.535	32.567	19.779	27.833	1.03
16	13.830	36.691	12.854	34.030	1.07
24	10.104	41.051	9.489	38.272	1.06
30	6.593	47.982	6.265	49.231	1.11
36	4.358	63.849	4.244	58.115	1.03
48	2.226	83.570	2.208	72.606	1.01
60	1.259	117.558	1.374	102.108	0.92

Mean Plasma PK Parameters

Parameter	Test Mean	Test %CV	Ref Mean	Ref %CV	T/R Ratio
AUCt	801.173	31.249	779.342	28.248	1.02
AUCi	835.653	32.048	818.772	28.829	1.02
CMAX	90.1	47.89	89.57	42.20	1.00
TMAX	3.353	26.35	3.015	27.233	1.11
KEL	0.096	40.458	0.062	43.806	1.54
T1/2	11.679	39.448	13.381	42.501	0.87

Statistical Analysis: 90% C.I :

	Firm's results		Reviewer's results	
Parameter	Lower 90% CI	Upper 90% CI	Lower 90% CI	Upper 90% CI
LAUCi	94.9	109.6	95	109
LAUCt	94.6	108.1	95	108
LCmax	86.6	113.2	86.6	113

Comment: The reviewer re-calculated all AUCs, re-ran ANOVA and re-estimated 90% C.I.limits. The firm and the reviewer's results are the same.

Conclusion: The fasting study acceptable.

Waiver Request

Applicant is requesting a waiver of in vivo bioequivalence testing for the 5 mg dosage strength. Comparative dissolution profiles were provided for Medeva's Zaroxolyn® tablets, 5 and 10 mg strengths and Eon's Metolazone, USP tablets, 5 and 10 mg strengths. A full list of components in Eon's Metolazone, USP tablets was provided for all the strengths.

Formulation: (Not to be released under FOI)

Ingredient	Amount (mg/tablet)			
	5 mg strength	%	5 mg strength	%
Metolazone, USP	5	5	10	10
Microcrystalline Cellulose, NF, (b) (4) (b) (4)	(b) (4)			(b) (4)
Collodial Silicon Dioxide, NF				
Magnesium Stearate				
FD&C Blue#2 (b) (4) Lake			--	
FD&C Yellow#6 (b) (4) Lake	--			(b) (4)
D&C Yellow#10 (b) (4) Lake	--			
TOTAL TABLET WEIGHT	100	1	100	1

All inactive ingredients are within safety limits approved in FDA Inactive Ingredient Guide.

Tablet characteristics:

Reference Products:
5 mg Tablet: Biconvex, round, blue tablet debossed "ZAROXOLYN" on one side and "5" on the reverse side
10 mg Tablet: Biconvex, round, yellow tablet debossed "ZAROXOLYN" on one side and "10" on the reverse side

Test Products:
5 mg Tablet: Biconvex, oval, blue tablet debossed "E55" on one side and plain on the reverse side
10 mg Tablet: Biconvex, oval, yellow tablet debossed "E56" on one side and plain on the reverse side

IN VITRO DISSOLUTION TESTING

Test Drug: Metolazone, USP Tablets, manufactured by Eon Labs.
Reference Drug: Zaroxolyn® tablets manufactured by Medeva Pharmaceuticals Inc.

I. Conditions for Dissolution

Apparatus: USP Apparatus 2 (Paddle) at 75 rpm, Medium: 2% SLS in DI water
Volume: 900mL, No. Units Tested: 12 Assay Method: HPLC
Firm's proposed tolerance (Q) = (b) (4) in 60 minutes

II. Results of *In Vitro* Dissolution/Release Testing:

Dose Strength: 5 mg

Sampling (min)	Test Product Lot No.: RDW00046			Reference Product Lot No.: X-867		
	Mean %	Range	% CV	Mean %	Range	% CV
15	43.8	(b) (4)	10.2	50.1	(b) (4)	8.1
30	66.5		6.1	69		5.3
45	76.5		4.5	79.1		3.9
60	82.5		3.4	85.2		3.4
75	86.9		2.8	88.9		2.7

Dose Strength: 10 mg

II. Results of *In Vitro* Dissolution/Release Testing:

Sampling (min)	Test Product Lot No.: RDW00048			Reference Product Lot No.: X-851		
	Mean %	Range	% CV	Mean %	Range	% CV
15	57.4	(b) (4)	5.5	66.6	(b) (4)	6.1
30	75		3.6	81		3.5
45	83.2		2.9	87.9		2.4
60	87.9		2.5	92		1.6
75	91.1		2.2	94.5		1.1

F2 factors

PARAMETERS	F2
Test 10 mg vs. Reference 10 mg strengths (Biolots)	61.3
Test 5 mg vs. Reference 5 mg strengths	79.7
Reference 5 mg vs. Reference 10 mg strengths	**48.6**
Test 5 mg vs. Test 10 mg strengths	57.45

Please note that only the reference 5 mg vs. reference 10 mg fails f2 test.

Comments: (on formulation and dissolution testing)

1) The formulations of Metolazone, USP, 5, and 10 mg tablets by Eon Pharmaceuticals Inc., are proportional with respect to active ingredient and similar with respect to inactive ingredients except for (b) (4). The amount of (b) (4) (b) (4) is varied such that the total tablet weight is 100 mg for all the strengths. The test 10mg tablet shows a faster dissolution than the test 5mg tablet. The ratio of (b) (4) is (b) (4) in 5 mg tablet (b) (4) compared to that in 10 mg tablet (b) (4). Such a difference in the ratio may be one of the factors causing a difference in dissolution of these two tablets.

2) The USP26 has a monograph on Metolazone tablet. The monograph does not contain dissolution test. Thus, currently there is no USP dissolution method available for metolazone tablet. There is a dissolution test in the DBE database. The firm used that test. The firm's dissolution testing data passes the specification (NLT (b) (4) in 90 minutes) mentioned in the DBE database. However, the DBE needs more dissolution testing information to determine a single dissolution test with proper specification for this IR product.

3) Three different methods were used for dissolution testing for this IR drug product.

Method 1 (proposed by the Eon) :
900 ml of 2% Sodium Lauryl Sulfate in DI water using USP Paddle apparatus at 75 rpm. The firm used this DBE dissolution test. However, the DBE needs more dissolution testing information to determine a single dissolution test with proper specification for this IR product.

Method 2 (proposed by FDA/OGD/Div. of Bioequivalence): This method was used by Copley's in its ANDA 75-534. The DBE accepted the dissolution testing :
900 ml of 0.05M Sodium Phosphate buffer pH 7.5 with 2% Sodium Lauryl Sulfate using USP Paddle apparatus at 75 rpm. (specification : NLT (b) (4) in 120 minutes)

Method 3 (FDA method for Zaroxolyn®):
900 ml of 0.1N NaOH using USP Basket apparatus at 50 rpm. The use of this method is discouraged since the medium is too drastic and not physiologic. The DBE has concluded that the innovator's method (method 3), is not suitable for the dissolution testing of metolazone tablets.

4) Using the method proposed by the firm, it is noted that dissolution profiles for 5 and 10 mg of the reference products are not comparable. The f2 value is 48.6

Recommendations:

1) The single dose, fasting bioequivalence study, protocol No. B012015, conducted by Eon Pharmaceuticals Inc., on its Metolazone, USP, tablets, 10 mg, Lot # RDW00048 comparing it to Zaroxolyn® 10 mg tablets manufactured by Medeva Pharmaceuticals Inc., Lot # X-851, has been found acceptable by the Division of Bioequivalence. The study demonstrates that Eon's Metolazone, USP, tablet, 10 mg strength, is bioequivalent to Medeva's Zaroxolyn® tablet, 10 mg strength.
2) In vitro dissolution testing conducted by Eon, on its Metolazone, USP tablets, 5, and 10 mg , Lot #RDW00046, and RDW00048 respectively is incomplete. We request that the firm submit complete analytical method validation (HPLC) for dissolution testing, a description of the method used, including mobile phase for HPLC, and the UV detection wavelength.
3) We request that the firm conduct additional comparative dissolution testing in 900 mL 0.05M Sodium Phosphate buffer pH 7.5 with 1% and 2% Sodium Lauryl Sulfate (SLS) at 37^0C using USP Paddle Apparatus at 50 RPM and 75 rpm. Samples should be taken at 15, 30, 45, 60 and 120 minutes.
4) The waiver of in vivo bioequivalence testing requirements for the 5 mg strength is not granted because the 5 mg dosage strength of the innovator does not appear to be proportionally similar in its dissolution behavior to the 10 mg strength. Thus on the basis of *in vitro* dissolution testing data in this submission, the FDA files, and the recent Zaroxolyn® dissolution testing data from FDA labs, the DBE requests an additional fasting bioequivalence study on the 5 mg strength.
5) The firm has two alternatives. As a first alternative the firm may pursue the current ANDA 76-466 for only two strengths (viz. 5mg and 10mg tablets) by submitting an additional fasting study on 5mg tablet. As a second alternative the firm may amend its current ANDA 76-466 for the third strength (viz.. 2.5mg tablet) with an additional fasting study on the 5mg tablet. With this alternative the firm may request a waiver for its 2.5mg tablet.

The firm should be informed of the above recommendations.

Nhan L. Tran, Ph.D.
Review Branch II

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR

Date 5/20/2003

Concur:

Date 5/21/03

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

cc: ANDA# 76466 (original), HFD-655 (Tran, Nerurkar), Drug File, Division File

BIOEQUIVALENCY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA # 76-466 APPLICANT: Eon Labs Inc.

DRUG PRODUCT: Metolazone, USP, 5 and 10 mg Tablets

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

1. Your in vitro dissolution testing on the Metolazone, USP tablets, 5, and 10 mg, Lot #RDW00046, and RDW00048 respectively is incomplete. The Division of Bioequivalence(DBE)requests that you submit a complete analytical method validation (HPLC) for dissolution testing, description of the method used including mobile phase for HPLC, and UV detection wavelength.

2. The DBE requests you to conduct additional comparative dissolution testing in 900 mL 0.05M Sodium Phosphate buffer pH 7.5 with 1% and 2% Sodium Lauryl Sulfate (SLS) at 37^{0}C using USP Paddle Apparatus at 50 RPM and 75 rpm. Samples should be taken at 15, 30, 45, 60 and 120 minutes.

3. The waiver of in vivo bioequivalence testing requirements for the 5 mg strength is not granted because the 5 mg dosage strength of the innovator does not appear to be proportionally similar in its dissolution behavior to the 10 mg strength. Thus on the basis of *in vitro* dissolution testing data in this submission, the FDA files, and the recent Zaroxolyn® dissolution testing data from FDA labs, the DBE requests an additional fasting bioequivalence study on the 5 mg strength.

4. You have two alternatives. As a first alternative you may pursue the current ANDA 76-466 for only two strengths (viz. 5mg and 10mg tablets) by submitting an additional fasting study on 5mg tablet. As a second alternative you may amend your current ANDA 76-466 for the third strength (viz. 2.5mg tablet) with an additional fasting study on the 5mg tablet. With this alternative you may request a waiver for your 2.5mg tablet.

Sincerely yours,

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

Endorsements: (Final with Dates)
HFD-655/ Tran 5/20
HFD-655/ Nerurkar 5/20/03
HFD-650/ D. Conner 5/21/03

Bioequivalency- Incomplete

Submission Date: ~~July 26, 2002~~ October 9, 2002.

1) Fasting Study (STF)
Clinical: Gateway Medical Research
Analytical: (b) (4)

Strength: 10 mg
Outcome: IC

2) Dissolution Waiver (DIW)

Strengths: 5 mg
Outcome: UA

Outcome Decisions: IC- Incomplete

Winbio comments:

DIVISION OF BIOEQUIVALENCE REVIEW
(Revised to delete the 2.5mg strength)

ANDA No.	76-466
Drug Product Name	Metolazone
Strengths	5 & 10 mg
Applicant Name	Eon Labs
Address	Wilson, NC
Submission Date(s)	7/26/2002
Amendment Date(s)	06/27/03
Reviewer	Nhan L. Tran
First Generic	No
File Location	**v:\\firmsam\eon\ltrs&rev\76466A0603**

Executive Summary

Eon is referencing Medeva's Zaroxolyn® 2.5 mg tablet. Eon has submitted the original submission on July 16, 2002 for 10 mg and 5 mg strengths. A biostudy was conducted on the 10 mg strength and a waiver was requested on the 5 mg strength. The DBE has reviewed the submission and has found the study acceptable however; the dissolution testing data was incomplete. Furthermore, the waiver request for the 5 mg strength was denied due to different dissolution behavior between 10 mg and 5 mg strengths. In a letter to the firm, the FDA stated: "*The waiver of in vivo bioequivalence testing requirements for the 5 mg strength is not granted because the 5 mg dosage strength of the innovator does not appear to be proportionally similar in its dissolution behavior to the 10 mg strength. Thus on the basis of in vitro dissolution testing data in this submission, the FDA files, and the recent Zaroxolyn® dissolution testing data from FDA labs, the DBE requests an additional fasting bioequivalence study on the 5 mg strength. The firm has two alternatives. As a first alternative the firm may pursue the current ANDA 76-466 for only two strengths (viz. 5mg and 10mg tablets) by submitting an additional fasting study on 5mg tablet. As a second alternative the firm may amend its current ANDA 76-466 for the third strength (viz.. 2.5mg tablet) with an additional fasting study on the 5mg tablet. With this alternative the firm may request a waiver for its 2.5mg tablet*".

TheThe Division of Bioequivalence concluded that since the firm conducted a BE study on the 2.5 mg strength before the Bio Deficiency letter was issued, the waiver request for the 5 mg strength can be considered based on the result of the study on the 2.5 mg strength, formulation proportionality similar between the 2.5 mg and the 5 mg strength and comparative dissolution data.

The present submission includes a fasting BE study for the 2.5 mg tablet strength and dissolution data. The fasting study is a single-dose two-way crossover study using 34 male and female normal healthy volunteers given a dose of 2x2.5 mg (total = 5mg). The results (point estimate and 90% CI) of the fasting BE study are LAUCt of 1.07, 101-112%; LAUCi of 1.06, 101-111%; and LCmax of 1.08, 97.9-120%. The study is acceptable. Since there is no mention of any food effect in the labeling of the RLD (Zaroxolyn®), the DBE does not request a fed-bioequivalence study for this product. The dissolution (Apparatus: USP Apparatus 2 (Paddle) at 75 rpm, Medium: 900 ml of 2% SLS in 0.05 M NaH_2PO_4 pH 7.5) testing is complete and acceptable.

The application is therefore acceptable.

Note: The three strengths (2.5 mg, 5 mg and 10 mg Tablets) were reviewed in the ANDA 76-466 because Eon had submitted the study on the 2.5 mg strength tablet (cross-referenced) in ANDA 76-466 (5mg and 10mg) for obtaining a waiver for its 5mg strength. However, Eon has recently (April 30, 2003) submitted ANDA 76-732 only for the 2.5 mg strength. Therefore the review for ANDA 76-466 is amended to reflect the necessary changes.

Table of Contents

Submission Summary

A. Drug Product Information

Test Product	Metolazone
Reference Product	Zaroxolin®
RLD Manufacturer	Medeva
NDA No.	17-386
RLD Approval Date	Jan 1, 1982
Indication	Antihypertensive

B. PK/PD Information

Bioavailability	40%
Food Effect	No
Tmax	2-4 hrs
Metabolism	Not metabolized.
Excretion	Unchanged by kidneys
Half-life	14 hrs
Relevant OGD or DBE History	See attachment
Agency Guidance	N/A
Drug Specific Issues (if any)	See attachment

C. Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	No	
Steady-state	No	
In vitro dissolution	Y	2
Waiver requests	Y	1
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	Yes	1

D. Pre-Study Bioanalytical Method Validation

	Parent	Metabolite	Metabolite2
Analyte name	Metolazone		
Internal Standard	(b) (4)		
Method description	HPLC/MS/MS		
QC range	1 ng/ml - 75 ng/ml		
Standard curve range	0.4 ng/ml - 100 ng/ml		
Limit of quantitation	0.4 ng/ml		
Average recovery of Drug (%)	90.7%		
Average Recovery of Int. Std (%)	56.8%		
Intraday precision range (%CV)	1.6% - 8.7%		
Intraday accuracy range (%)	95.9% - 110%		
Interday precision range (%CV)	4.6% - 8.9%		
Interday accuracy range (%)	98.7% - 104%		
Bench-top stability (hrs)	24 hrs		
Stock stability (days)	10 days		
Processed stability (hrs)	47 hrs		
Freeze-thaw stability (cycles)	4 cycles		
Long-term storage stability (days)	51 days		
Dilution integrity	2-fold, 100%		
Specificity	Yes		
SOPs submitted	Yes		
Bioanalytical method is acceptable	Yes		
20% Chromatograms included (Y/N)	Y		
Random Selection of Serial Chromatograms	Y		

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary	
Study No.	B032002
Study Design	2 way crossover
No. of subjects enrolled	36
No. of subjects completing	34
No. of subjects analyzed	34
Subjects (Normal/Patients?)	Normal
Sex(es) included (how many?)	Males: 20 Females: 14
Test product	Metolazone
Reference product	Zaroxolyn
Strength tested	2.5 mg
Dose	2 tablets of 2.5 mg (Total = 5 mg)

Summary of Statistical Analysis Additional Information in Appendix, Table 7 and Table 8		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.07	101% -112%
AUC_{∞}	1.06	101% -111%
C_{max}	1.08	97.9% - 120%

Reanalysis of Study Samples								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Lab accident	4	1	0.29	0.07	4	1	0.29	0.07
Low IS	1	5	0.07	0.37	1	5	0.07	0.37
High IS	1	2	0.07	0.15	1	2	0.07	0.15
Unknown processing error	3	5	0.22	0.37	3	5	0.22	0.37
Total	9	13	0.66	0.96	9	13	0.66	0.96

Did use of recalculated plasma concentration data change study outcome? No

Comments on Fasting Study: Acceptable

2. Single-dose Fed Bioequivalence Study: Not Applicable

Formulation

Location in appendix	Section B, Page 15
Inactive ingredients within IIG Limits (yes or no)	**Y**
If no, list ingredients outside of limits	
If a tablet, is the product scored? (yes or no)	**No**
If yes, which strengths are scored?	
Is scoring of RLD the same as test? (yes or no)	
Formulation is acceptable (yes or no)	**Y**
If not acceptable, why?	**Y**

F. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA
Medium	2% SLS in 0.05M Sodium Phosphate buffer
Volume (mL)	900 ml
USP Apparatus type	2 (Paddle)
Rotation (rpm)	75
Firm's proposed specifications	None
FDA-recommended specifications	NLT (b) (4) 120 minutes
F2 metric calculated (yes or no)	Y
If no, reason why F2 not calculated	
Method is acceptable (yes or no)	Y

F2 metric, other strengths compared to biostudy strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
2.5 mg	10 mg	46.4	55.46
2.5 mg	5 mg	96.9	66.52
5 mg	10 mg	46.5	71.86

F2 metric, test compared to reference	
Strength	F2 metric
2.5 mg	46.1
5 mg	53.6
10 mg	67.8

G. Waiver Request(s)

Strengths for which waivers requested	5 mg
Regulation cited	320.22(d)(2)
Proportional to strength tested in vivo (yes or no)	Y
Dissolution is acceptable (yes or no)	Y
Waiver granted (yes or no)	Y

H. Deficiency Comments: None

I. Recommendations

1. The bioequivalence studies conducted under fasting conditions by Eon Pharmaceuticals on its metolazone tablets, Lot #RDW00048 comparing it to Zaroxolyn® Tablets, lot #X-851 (for the 10 mg strength) and Lot #RDW00047 comparing it to Zaroxolyn® Tablets, lot #20604 (for the 2.5 mg strength) manufactured by Medeva have been found acceptable by the Division of Bioequivalence. The studies demonstrate that Eon Pharmaceutical's metolazone 10 mg tablets and 2.5 mg tablets are bioequivalent to the reference product, Zaroxolyn® 10 mg tablets and 2.5 mg tablets, respectively.

2. The dissolution testing conducted by the firm on its metolazone 2.5 mg and 5 mg tablets is acceptable. The firm has conducted an acceptable *in vivo* bioequivalence study comparing 2.5 mg tablets of the test product with 2.5 mg tablets of the reference product Zaroxolyn® manufactured by Medeva. The formulation for 5 mg strength of the test product is proportionally similar to the 2.5 mg strength of the test product, which underwent bioequivalency testing. The waiver of *in vivo* bioequivalence study requirements for the 5 mg tablets of the test product is granted. The 5 mg tablets of the test product is therefore deemed bioequivalent to the 5 mg tablets of Zaroxolyn® manufactured by Medeva.

3. The dissolution testing should be incorporated into firm's manufacturing controls and stability programs. The dissolution testing should be conducted in 900 mL of 0.05M Sodium phosphate buffer pH 7.5 with 2% sodium lauryl sulfate, using apparatus II (paddles) at 75 rpm. The test product should meet the following specification: NLT (Q) (b) (4) of the labeled content in 120 minutes.

4. From bioequivalence point of view, the firm has met the requirements of *in vivo* bioequivalency and *in vitro* dissolution testing and the application is acceptable.

10/7/03

Reviewer' Name, Branch, Date signed

10/7/2003

Team Leader's Name, Branch, Date signed

for 10/9/03

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

Study Information	
Study Number	1
Study Title	A Relative Bioavailability Study of Metolazone 2.5mg Tablets Under Fasting Conditions
Clinical Site	Gateway Medical Research.
Principal Investigator	Thomas Siler, M.D.
Study/Dosing Dates	Period I: Feb. 15, 2003, Period II: Feb. 22, 2003
Analytical Site	(b) (4)
Analytical Director	(b) (6) M.S.
Analysis Dates	03/05/03 to 03/24/03
Storage Period (no. of days from first sample to final analysis)	18 days

Treatment ID	A	B
Test or Reference	Test	Ref
Product Name	Metolazone	Zaroxolyn
Manufacturer	Eon Lab	Medeva
Batch/Lot No.	RDW00047	20604
Manufacture Date	Feb. 2002	N/A
Expiration Date	N/A	May 2005
Strength	2.5 mg	2.5 mg
Dosage Form	Tablet	Tablet
Batch Size	(b) (4)	N/A
Potency	100.1	98.3
Content Uniformity	100.1 (98.9-101.1)	99.1 (97.3-100.7)
Formulation	See Appendix Section B	
Dose Administered	5 mg (2x2.5 mg)	5 mg (2x2.5 mg)
Route of Administration	PO	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization Scheme	AB:1,4,6,8,11,16,17,19,20,22,23,25,27,28,29,32,33,36 BA:2,3,5,7,9,10,12,13,14,15,18,21,24,26,30,31,34,35
Blood Sampling Times	0,0.5,1,1.5,2,2.5,3,3.5,4,4.5,5,6,8,12,16,24,30,36,48,60
Blood Volume Collected/Sample	10 ml
Blood Sample Processing/Storage	18 days
IRB Approval	Y
Informed Consent	Y
Subjects Demographics	See Table 1
Length of Fasting	Overnight
Length of Confinement	10 hrs predose until 36 hrs post dose
Safety Monitoring	Y

Table 1 Demographics of Study Subjects

Age		Weight		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	33
Mean	31.2	Mean	198.5	18-40	27	Male	21	Afr. Amer.	2
SD	11.3	SD	38.2	41-64	9	Female	15	Hispanic	
Range	19-57	Range	148-272	65-75	0			Asian	
				>75	0			Others (Am. Indian)	1

Study Results

Table 2 Dropout Information

Subject No	27	36
Reason	Due to adverse event	Called to active duty
Period	2	2
Replacement	N	N

Was there a difference in side effects for the test versus the reference? No

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Reference Group
Nose bleed		1
Headache	1	1
Activity induced asthma	1	
Total:	**2**	**2**

Comments: (*on adverse events): Same for the test and reference drug*

Was there a difference in protocol deviations for the test versus the reference? None

Table 4 Protocol Deviations – The firm reported that there were none.

Type	Subject #s (Test)	Subject #s (Reference)

Comments: N/A

Table 5 Assay Validation – Within Study

	Parent								
QC Conc. (ng/mL)	1	9	75						
Inter day Precision (%CV)	9.5	9.3	6.3						
Inter day Accuracy (%)	97.4	96.8	99.1						
Cal. Standards Conc. (ng/mL)	0.4	0.8	2	4	10	20	40	80	100
Inter day Precision (%CV)	1.8	3.5	6.1	3.7	2.5	2	2.9	2.7	5.3
Inter day Accuracy (%)	99.3	99.8	105	101	100	102	100	99.1	95.3
Linearity Range (range of R^2 values)	0.9980 – 0.9996								

Chromatograms: Any interfering peaks? None

Table 6 SOP's dealing with analytical repeats of study samples

SOP No.	Date of SOP	SOP Title
L200.107	June 20, 2001	Sample Analysis (Chromatographic)
		(Volume 2.3, page 2297)

- **Comments on repeat assays.** Identify which SOP's were not followed, as well as which subjects, treatment, and sampling times were involved. None
- Did recalculation of plasma concentrations change the study outcome? No
- Does the reviewer agree with the outcome of the repeat assays? Yes.
- Provide any other comments about repeat assays. None

Comments on Within-Study Validation:

Conclusion: Analytical method is acceptable.

Table 7 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in

Table 10 and Figure 1

Parameter	Units	Test		Reference		T/R
		Mean	%CV	Mean	% CV	
AUC0-t	ng*hr/ml	389.59	26.85	372.21	23.05	1.05
AUC∞	ng/*hr/ml	425.91	29.25	401.03	27.21	1.06
Cmax	ng/ml	41.97	30.12	38.41	26.62	1.09
Tmax	hr	3.17	30.73	3.28	23.09	0.97
T1/2	hr	15.51	55.37	15.97	45.49	0.97
kel	1/hr	0.056	41.78	0.053	49.88	1.05

Table 8 Least Square Geometric Means and 90% Confidence Intervals

Parameter	Test	Reference	T/R	90% CI
AUC0-t	387.68	363.68	1.06	101 – 112
AUC∞	413.11	389.27	1.06	101 – 111
Cmax	40.09	37.05	1.08	97.9 – 120

Table 9 Additional Study Information

Root mean square error, LnAUC0-t	0.1214	
Root mean square error, LnAUC∞	0.1189	
Root mean square error, LnCmax	0.2436	
mean ratio AUC0-t/AUC∞	T =0.94	R =0.93
Range of values, ratio AUC0-t/AUC∞	T =0.81-0.98	R =0.77-0.98

Comments: (on pharmacokinetic analysis)

- kel and AUC∞ were determined for all subjects.
- Indicate the number of subjects with the following:
  a. measurable drug concentrations at 0 hr: None
  b. first scheduled post-dose sampling time as Tmax: None
  c. first measurable drug concentration as Cmax.: None
- Did pharmacokinetic parameters and 90% confidence intervals calculated by the reviewer agree with firm's calculations? Yes
- Were there statistically significant sequence or period effects? No.
- Are the 90% confidence intervals for AUC0-t, AUC∞, Cmax within the acceptable limits of 80-125%: Yes
- If the subjects were dosed as more than one group, comment on the statistical analysis for group effect: N/A

Conclusion: The single-dose fasting bioequivalence study is acceptable.

Table 10 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

Time, hr	Test (n=34)		Reference (n=34)		T/R
	Mean Conc.	%CV	Mean Conc.	%CV	
0	0		0		0
0.5	1.55	115.67	2.19	132.73	0.71
1	11.53	84.70	12.05	68.12	0.96
1.5	22.01	64.43	19.49	55.47	1.123
2	29.03	56.63	26.04	46.29	1.11
2.5	32.53	47.89	30.15	35.78	1.08
3	34.49	41.81	32.84	32.33	1.05
3.5	35.34	37.97	33.15	31.23	1.07
4	35.04	36.45	33.28	30.45	1.05
4.5	33.95	29.45	30.56	30.40	1.11
5	27.76	26.74	25.33	26.36	1.09
6	22.19	24.42	19.70	25.14	1.23
8	16.63	21.52	15.03	23.63	1.10
12	10.18	31.04	8.93	23.86	1.13
16	6.85	32.94	6.13	29.30	1.11
24	4.95	46.28	4.79	37.18	1.03
30	3.13	48.03	3.11	41.63	1.00
36	2.38	60.24	2.45	59.72	0.97
48	1.46	99.44	1.57	84.68	0.93
60	0.76	117.69	0.82	95.96	0.92

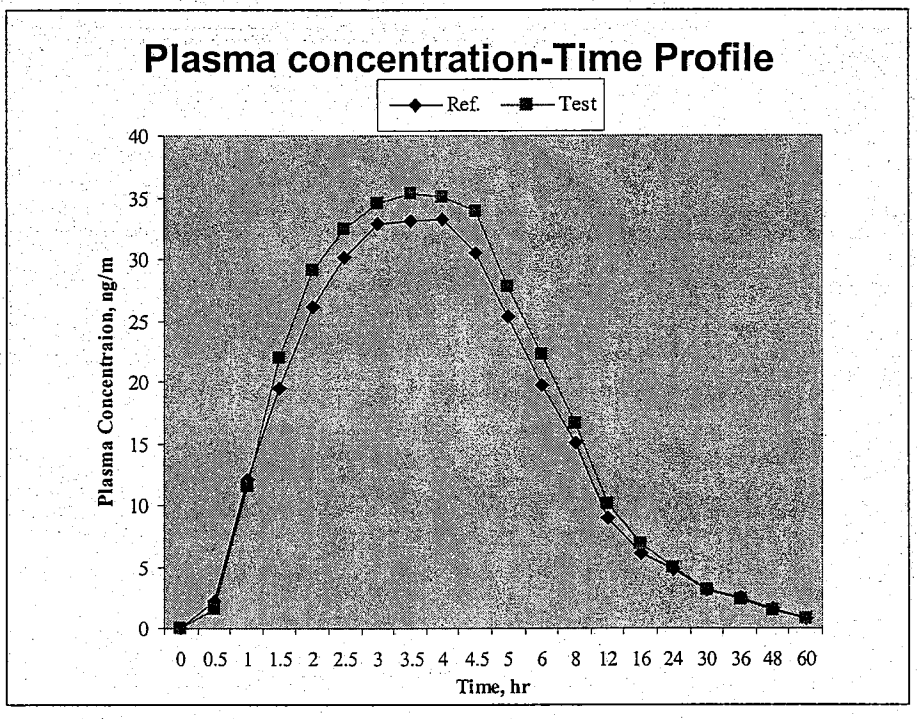


Figure 1 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study:

Single-dose Fed Bioequivalence Study: None - Since there is no mention of any food effect in the labeling of the RLD (Zaroxolyn®), the DBE does not request a fed-bioequivalence study for this product.

Waiver Request

Applicant is requesting a waiver of in vivo bioequivalence testing for the 5 mg dosage strength. Comparative dissolution profiles were provided for Medeva's Zaroxolyn® tablets, 2.5, 5 and 10 mg strengths and Eon's Metolazone, USP tablets, 2.5, 5 and 10 mg strengths. A full list of components in Eon's Metolazone, USP tablets was provided for all the strengths.

B. Formulation Data

Formulation: **(Not to be released under FOI)**

Ingredient	Amount per tablet, mg					
	2.5mg	%w/w	5mg	%w/w	10mg	%w/w
Metolazone, USP	2.5	2.5	5	5	10	10
Microcrystalline Cellulose, NF, (b) (4) (b) (4)						(b) (4)
Collodial Silicon Dioxide, NF						
Magnesium Stearate						
FD&C Blue#2 (b) (4) Lake					(b) (4) ------	------
FD&C Yellow#6 (b) (4) Lake	-----	----	-----	------		(b) (4)
FD&C Red#30 Lake		(b) (4)	------	------	-----	------
D&C Yellow#10 (b) (4) Lake	------	------	------	------		(b) (4)
TOTAL TABLET WEIGHT	100	1	100	1	100	1

All inactive ingredients are within safety limits approved in FDA Inactive Ingredient Guide.

Tablet characteristics:

Reference Products:

2.5 mg Tablet: Biconvex, round, pink tablet debossed "ZAROXOLYN" on one side and "21/2" on the reverse side
5 mg Tablet: Biconvex, round, blue tablet debossed "ZAROXOLYN" on one side and "5" on the reverse side
10 mg Tablet: Biconvex, round, yellow tablet debossed "ZAROXOLYN" on one side and "10" on the reverse side

Test Products:

2.5 mg Tablet: Biconvex, oval, pink tablet debossed "E50" on one side and plain on the reverse side
5 mg Tablet: Biconvex, oval, blue tablet debossed "E55" on one side and plain on the reverse side
10 mg Tablet: Biconvex, oval, yellow tablet debossed "E56" on one side and plain on the reverse side

C. Dissolution Data

Dissolution testing was conducted using the DBE recommended method: 900 ml of 0.05M Sodium Phosphate buffer pH 7.5 with 2% Sodium Lauryl Sulfate (SLS), Paddle Apparatus at 75 rpm.

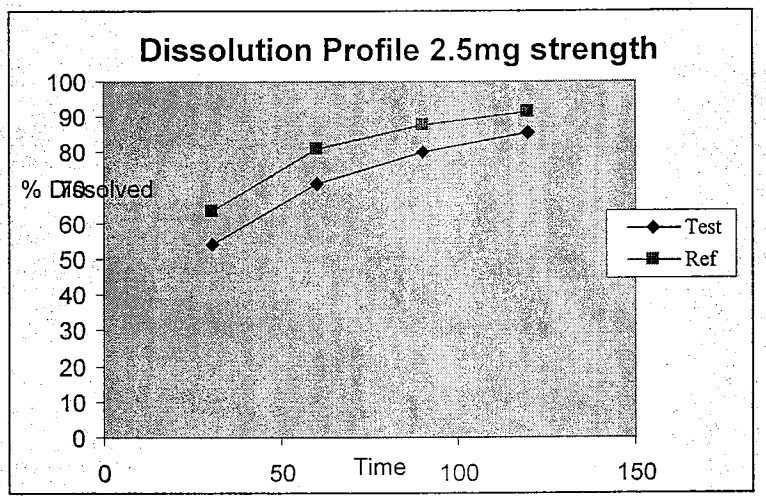
Table 1

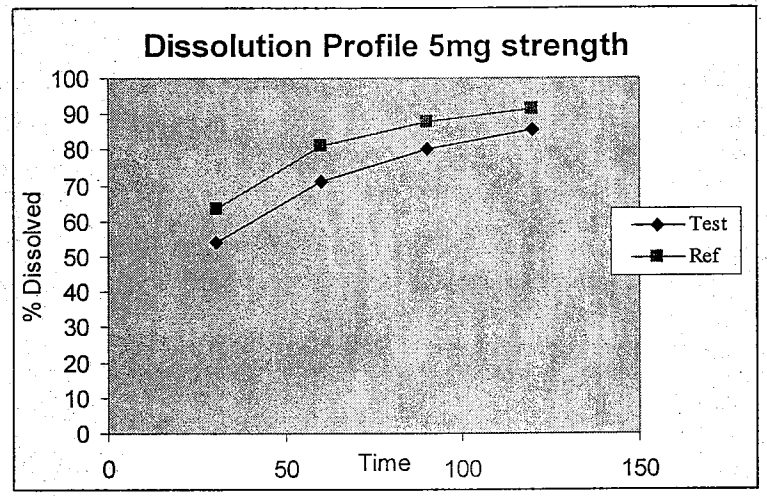
Sampling Time, (minutes)	Test Product, Strength: 2.5 mg Lot No. RDW00047			Reference Product, 2.5 mg Strength Lot No. 20604		
	Mean	%CV	Range	Mean	%CV	Range
30	53	8.9	(b) (4)	67.5	7	(b) (4)
60	70.8	6		84.9	2.8	
90	81.1	4.7		91.4	1.4	
120	86.3	4.4		94.2	1.1	
f2	46.1					
Sampling Time	**Test Product, Strength: 5 mg Lot No. RDW00046**			**Reference Product, 5 mg Strength Lot No. X-867**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
30	53.9	10.9	(b) (4)	63.6	5	(b) (4)
60	71.1	7.2		81	2.9	
90	80.4	5.5		87.9	2.3	
120	85.7	4.7		91.6	1.9	
F2	53.6					
Sampling Time	**Test Product, Strength: 10 mg Lot No. RDW00048**			**Reference Product, 10 mg Strength Lot No. X-851**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
30	69	8.6	(b) (4)	75.9	4.3	(b) (4)
60	84.1	4.8		88	2	
90	90.1	3.2		92.8	1.3	
120	93.4	2.4		95.3	0.9	
F2	67.8					

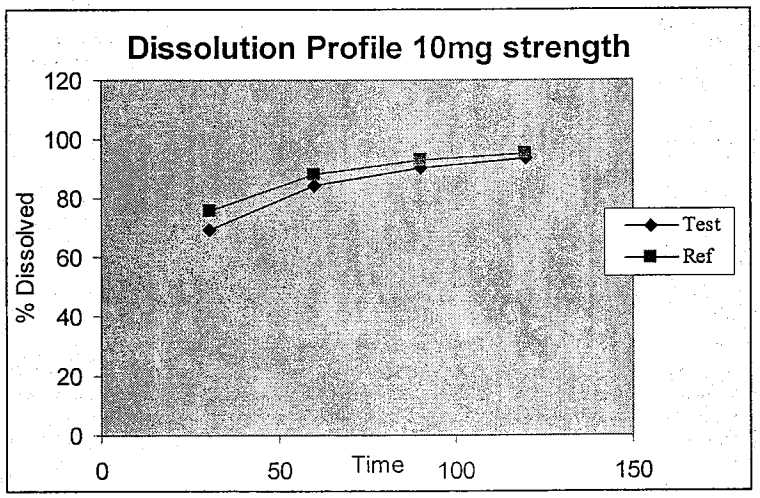
F2 factors

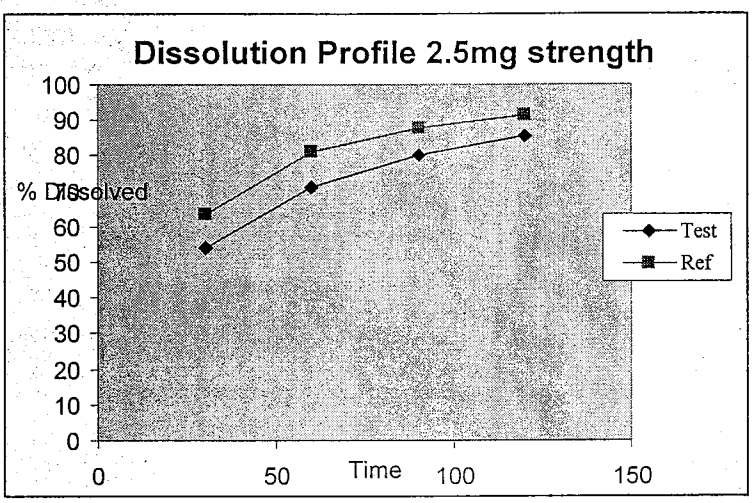
PARAMETERS	F2
Test 10 mg vs. Reference 10 mg strength	**67.8**
Test 5 mg vs. Reference 5 mg strength	**53.6**
Test 2.5 mg vs. Reference 2.5 mg strength	**46.1**
Test 10 mg vs. Test 5 mg strength	**46.5**
Test 10mg vs. Test 2.5 mg strength	**46.4**
Test 5 mg vs. Test 2.5 mg strength	**96.9**

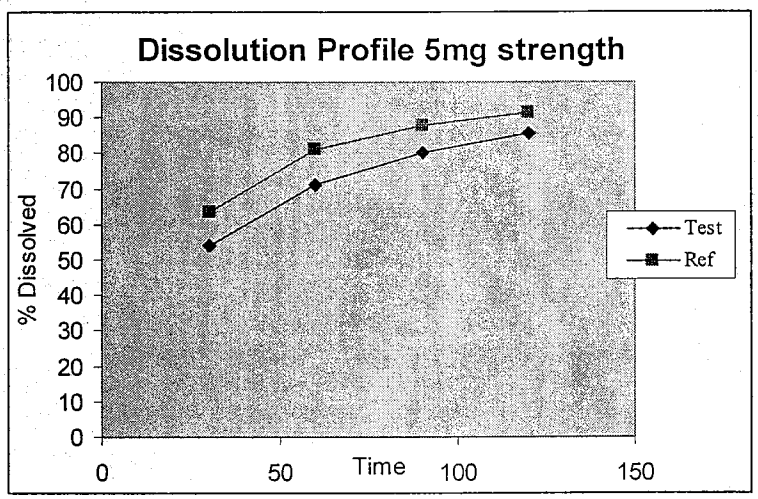
Figure 2 Dissolution Profiles (*optional*)

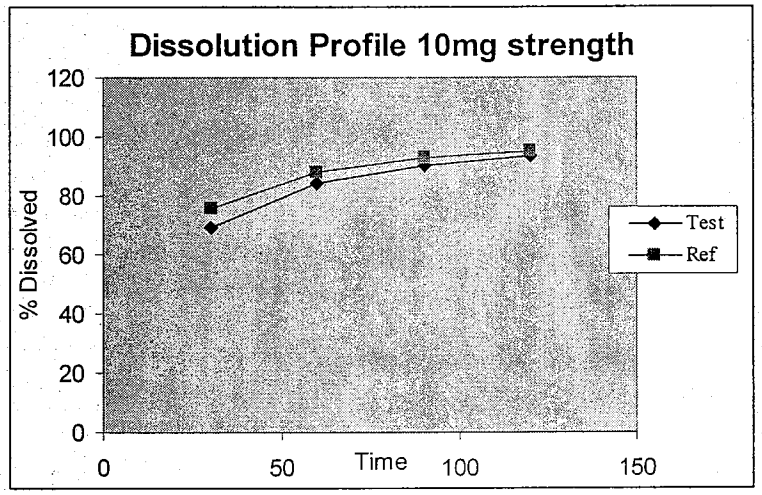


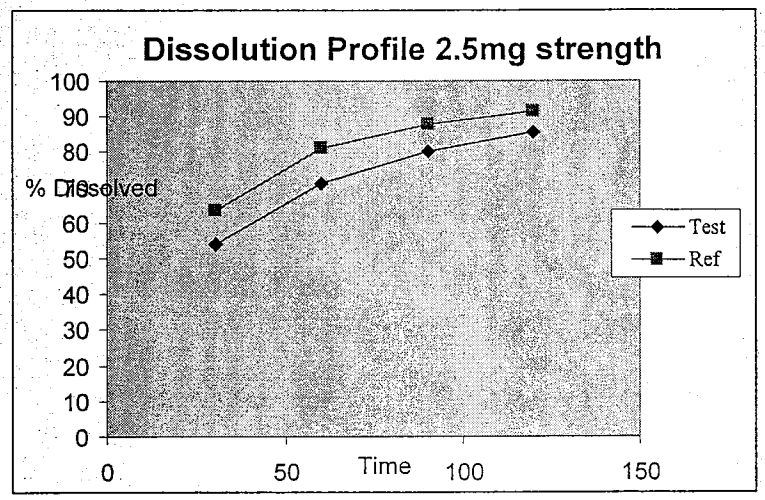


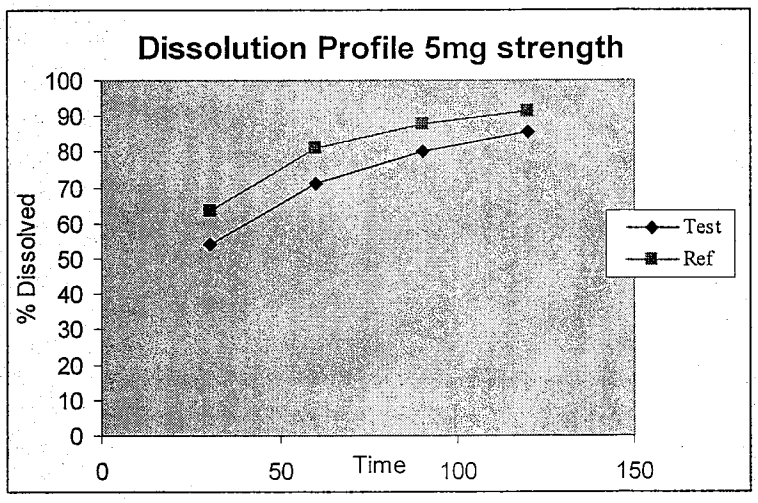


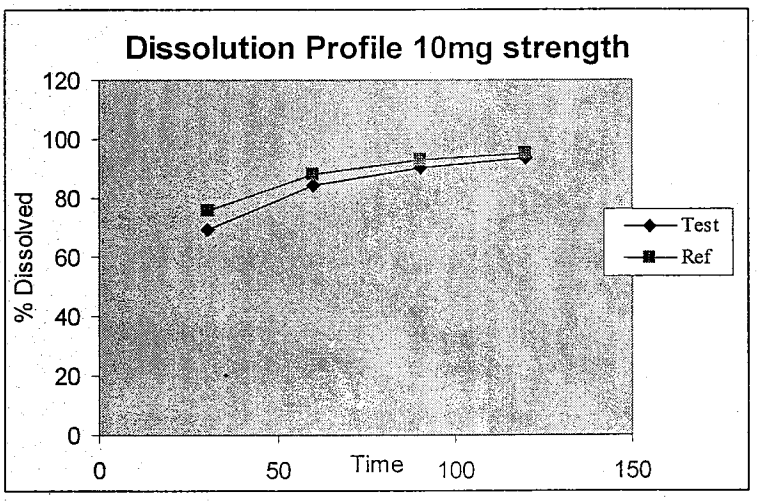

Dissolution Profile 2.5mg strength
% Dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
Time
100
150
Test
Ref


Dissolution Profile 5mg strength
% Dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
Time
100
150
Test
Ref


Dissolution Profile 10mg strength
% Dissolved
120
100
80
60
40
20
0
0
50
Time
100
150
Test
Ref


Dissolution Profile 2.5mg strength
% Dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
Time
100
150
Test
Ref


Dissolution Profile 5mg strength
% Dissolved
100
90
80
70
60
50
40
30
20
10
0
0
50
Time
100
150
Test
Ref


Dissolution Profile 10mg strength
% Dissolved
120
100
80
60
40
20
0
0
50
Time
100
150
Test
Ref

BIOEQUIVALENCY COMMENTS

ANDA: 76-466 APPLICANT: Eon Pharmaceuticals

DRUG PRODUCT: Metolazone, 5 mg and 10 mg Tablets

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

We acknowledge that the following dissolution testing specifications have been incorporated into your stability and quality control programs:

The dissolution testing should be conducted in 900 mL of 2% SLS in 0.05 M NaH_2PO_4 pH 7.5, USP Apparatus II (paddles) at 75 rpm. The test product should meet the following specifications: NLT (Q) (b)(4) in 120 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,

Barbara M Davit

for

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

CC: ANDA
ANDA DUPLICATE
DIVISION FILE
HFD-650/ Bio Secretary - Bio Drug File
HFD-655/ Tran

Endorsements: (Final with Dates)
HFD-655/ Tran 10/7
HFD-655/ Nerurkar 10/7/03
for HFD-650/ D. Conner 10/9/03

BIOEQUIVALENCY - ACCEPTABLE Submission Date: 06/27/2003

1. **FASTING STUDY** (STF)
Clinical: **Gateway Medical Research**
Analytical: (b) (4)

Strengths: 2.5 mg
✓ **Outcome:** **AC**

2. **DISSOLUTION WAIVER** (DIW)

Strengths: 5 mg
✓ **Outcome:** **AC**

Outcome Decisions:
AC - Acceptable

WINBIO COMMENTS: Studies acceptable. Waiver granted.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA #:	**76-466**	**SPONSOR: Eon Pharmaceuticals**
DRUG:	**Metolazone**	
DOSAGE FORM:	**Tablets**	
STRENGTHS/(s):	5 mg, and 10 mg	
TYPE OF STUDIES:	Fasting	
STUDY SITE:	Gateway	

STUDIES SUMMARY: The 90% confidence intervals for $LAUC_{0-t}$, $LAUC_{0-inf}$, and LC_{max} for the fasting studies (10 mg and 2.5 mg) are within acceptable limits.

DISSOLUTION TESTING: Acceptable.

WAIVER REQUEST: The 5 mg tablet strength is proportionally similar in the active and inactive ingredients to 2.5 mg tablets, and the dissolution data is acceptable. The waiver is granted.

DSI INSPECTION STATUS

Inspection needed: YES / X NO	Inspection status:	Inspection results:
First Generic __No___ New facility _No___ For cause __No___ Other ____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER : Nhan L. Tran, Ph.D. BRANCH: II
INITIAL : _____ DATE : 10/07/03

TEAM LEADER : Shriniwas Nerurkar, Ph.D. BRANCH: II
INITIAL : _____ DATE : 10/7/2003

for DIRECTOR, DIVISION OF BIOEQUIVALENCE : Dale P. Conner, Pharm. D.
INITIAL : _____ DATE : 10/9/03

Appears this way on original. Reviewer omitted pages 23-30 in review.

F. Additional Attachments

History

1. Medeva's has approved and listed NDA 17386 for Zaroxolyn (metolazone) 2.5mg, 5mg and 10mg tablets. According to the electronic PDR, the labeling does not mention any food effect studies. The labeling also does not mention whether the firm conducted any studies (viz. 4x2.5mg tablet vs. 1x10mg tablet, 2x5mg tablets vs. 10mg tablet or 2x2.5mg tablets vs. 1x5mg tablet) within the strengths or dose proportionality studies. As per the COMIS database, the three strengths (2.5mg, 5mg, and 10mg tablets) are formulated proportionally same (viz. qualitatively (Q1) same formulation with the total tablet weight of 100mg). **Thus, due to a lack of pharmacokinetic information in NDA, the Division of Bioequivalence relied on the dissolution testing data to decide on waiving of the lower strengths (2.5mg and 5mg tablets).** The comparative dissolution testing data used to make that decision came from the Copley's submission of ANDA 75-543 dated 12/30/1998 (see item #2).

2. Copley's submitted ANDA 75-543, for 2.5mg, 5mg, and 10mg metolazone tablets. The submission had i) an acceptable fasting study on the 10mg tablet, ii) formulations for the 2.5mg, 5mg, and 10mg tablets, and iii) comparative dissolution testing data on all three tablets. Copley requested waivers for the 2.5mg and 5mg tablets. The DBE informed Copley that the 2.5mg and 5mg tablet could not be waived because dissolution profiles of the brand name products 10 mg, 5 mg and 2.5 mg tablets were not similar (f_2 values of the brand name drug products were less than 50). The firm was also informed that to accept 2.5mg and 5mg tablets, it is requested to conduct a single dose fasting study on 2.5mg tablet. The f_2 calculations obtained from the comparative dissolution data are shown below. The f_2 calculations (from two different methods) show that the dissolution profiles of the 2.5mg vs. 5mg brand name tablets are similar while that of 5 mg vs. 10mg and 2.5 mg vs. 10 mg brand name tablets are different. **Copley elected to withdraw the 2.5mg and 5mg tablets from the ANDA 75-543, instead of submitting a study on 2.5mg tablet.**

METHOD 1: 900 ml 0.05M Sodium Phosphate buffer pH 7.5 with 2% Sodium Lauryl Sulfate using USP Paddle Apparatus at 75 rpm.

PRODUCT	STRENGTH	COMPARISON	f_2
Test	2.5 mg	2.5mg vs. 5mg	74
	5 mg	5mg vs. 10mg	61
	10 mg	2.5mg vs. 10mg	71
Reference	2.5 mg	2.5mg vs. 5mg	75
	5 mg	5mg vs. 10mg	**27**
	10 mg	2.5mg vs. 10mg	**24**

METHOD 2: 900 ml 0.05M Sodium Phosphate buffer pH 7.5 with 1% Sodium Lauryl Sulfate using USP Paddle Apparatus at 50 rpm.

PRODUCT	STRENGTH	COMPARISON	f_2
Test	2.5 mg	2.5mg vs. 5mg	63
	5 mg	5mg vs. 10mg	**44**
	10 mg	2.5mg vs. 10mg	**38**

Reference	2.5 mg	2.5mg vs. 5mg	83
	5 mg	5mg vs. 10mg	**23**
	10 mg	2.5mg vs. 10mg	**25**

3. While reviewing the Copley's ANDA 75-543, Dr. Mamata Gokhale wrote a document entitled " **Evaluation of In Vitro Dissolution of Zaroxolyn® (metolazone) Tablets, 2.5, 5, and 10 mg. Review of Data generated by using DBE method by Copley Pharmaceutical Inc., Eon Labs, and Roxane Laboratories Inc**." The document is stored under the address V:\Bio\Mamata2\My document\Metolazone dissolution\Metolazone dissolution.doc.The recommendations from Dr. Gokhale's document are copied below.
Recommendations

1) The DBE should continue to request an *in vivo* bioequivalence study on the 2.5 mg strength to support bioequivalency of 2.5 and 5 mg strengths to the reference product. If a generic firm does not plan to market the 2.5 mg strength, the DBE should request an *in vivo* bioequivalence study on the 5 mg strength.

2) The DBE should collect additional in vitro dissolution data to determine whether bio-waivers can be granted to the 2.5 and 5 mg strengths of a generic product based on comparative dissolution profiles of the corresponding strengths of Zaroxolyn® Tablets.

4. Eon's ANDA 76-466 (the current submission for 5mg and 10mg tablets) was reviewed as a Paragraph 4 submission by Dr. Dhariwal. As per Dr. Dhariwal's recommendations the submission was accepted for a review. Dr. Dhariwal also made a comment for the Regulatory Support Staff to inform Eon that its 5mg tablet is not eligible for a waiver. He made this recommendation based on the dissolution profiles comparison of 5mg and 10mg brand name tablet (f_2 = 48.4).

5. Product labeling for Mykrox® (0.5mg metolazone tablet from Medeva NDA 19-532) from the electronic PDR has the following statement:
"MYKROX TABLETS AND OTHER FORMULATIONS OF METOLAZONE THAT SHARE ITS MORE RAPID AND COMPLETE BIOAVAILABILITY ARE NOT THERAPEUTICALLY EQUIVALENT TO ZAROXOLYN® TABLETS AND OTHER FORMULATIONS OF METOLAZONE THAT SHARE ITS SLOW AND INCOMPLETE BIOAVAILABILITY. FORMULATIONS BIOEQUIVALENT TO MYKROX AND FORMULATIONS BIOEQUIVALENT TO ZAROXOLYN SHOULD NOT BE INTERCHANGED FOR ONE ANOTHER."
Dissolution profile of Mykrox® tablet is different from those of Zaroxolyn tablets (2.5mg,5mg, and 10mg). Therefore the statement cited above provides additional strength to the DBE recommendation of not granting waiver to the generic lower strengths (2.5mg and 5mg) based on the acceptable study on 10mg generic tablet.

6. The OGD received many documents subsequent to Copey's ANDA 75-543. Those are:
   a. Protocol 00-046 from (b) (4) (review by Nouraversani)
   b. CD 02-049 from (b) (4) (review by Lee)
   c. CD 02-194 from (b) (4) (review by Shrivastava)
   d. CD 03-129 from Watson (review by Sanchez)

The DBE made similar recommendations while responding to these documents. The recommendations were i) conduct a single dose fasting study on the 2.5mg tablet and a single dose fasting study the 10 mg tablet, ii) request a waiver for the 5mg tablet, iii) non-fasting study is not necessary, iv) measure the parent drug [no metabolites] in the bioequivalence studies, v) provide formulations of the three strengths to show proportional similarity, and vi) provide comparative dissolution testing data on three strengths.

7. There are other documents that are not helpful for this review (the reason is mentioned).
   a) CD 02-625 from Eon (a telecon with no documentation)
   b) CD 00-305 from Medeva (non bio issue)
   c) CD 97-038 from (b) (4) (old document)
   d) CD 96-105 from (b) (4) (old document)
   e) CD 95-138 from (b) (4) (no record)

8. Recently, the FDA Laboratory conducted dissolution testing on the brand name metolazone tablets (2.5mg, 5mg, and 10mg). The results indicated that the 10mg tablet dissolved quicker than the 2.5mg and 5mg tablets. The f_1 and f_2 values were calculated from the mean dissolution profiles of these tablets. In a comparison of the 2.5mg and 5mg tablets, f_1 and f_2 values were 6.8 and 65.1 showing similarity of profiles. For the 2.5mg and 10mg tablets the f_1 and f_2 values were 12.1 and 48.7 showing a similarity by f_1 and a difference by f_2. The 5mg and 10mg tablets had f_1 and f_2 values of 17.7 and 40.5 showing a difference in the dissolution profiles. These results corroborate the data submitted by Copley (ANDA 75-543) and Eon (ANDA 76-466).

In conclusion, if a firm submits an ANDA for three strengths (2.5mg, 5mg and 10mg), the DBE will request two single dose bioequivalence studies (5mg and 10mg). If a firm submits an ANDA for two strengths (5mg and 10mg), the DBE will request two single dose studies (5mg and 10mg).