CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-894/S-002

Name: Torsemide Tablets, 5 mg, 10 mg, 10 mg, and 100 mg

Sponsor: Apotex Corp.

Approval Date: November 7, 2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-894/S-002

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-894/S-002

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA: 76-894 SB-002

Apotex Inc.
Attention: Bernice Toa
150 Signet Drive
Toronto, Canada M9L 1T9

Dear Madam:

This is in reference to your supplemental new drug application dated August 03, 2007, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act, regarding your abbreviated new drug application for Torsemide Tablets, 5 mg, 10 mg, 20 mg, and 100 mg.

The supplemental application, submitted as "Supplement - Response to Letter regarding ———— provides for:

Confirm Validity of Submitted Bioequivalence Studies conducted at ———— .

We have completed the review of the supplemental application and it is approved. We remind you that you must comply with the requirements for an approved abbreviated new drug application described in 21 CFR 314.80-81.

The material submitted is being retained in our files.

Sincerely yours,

{See appended electronic signature page}

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

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Dale Conner
11/7/2007 04:02:59 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-894/S-002

BIOEQUIVALENCE REVIEW

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-894/SB002	
Drug Product Name	Torsemide Tablets	
Strength(s)	5 mg, 10 mg, 20 mg and 100 mg	
Applicant Name	Apotex Inc.	
Address	150 Signet Drive, Toronto, Canada M9L 1T9	
Applicant's Point of Contact	Bernice Tao, Director, Regulatory Affairs US or Kiran Krishan, authorized US Agent for Apotex, Inc.	
Contact's Telephone Number	416-401-7889 or 954-384-3986	
Contact's Fax Number	416-401-3809 or 954-349-4223	
Original Submission Date(s)	November 06, 2003	
Submission Date(s) of Supplement(s) Under Review	August 03, 2007	
Reviewer	April C. Braddy, Ph.D.	
Study Number (s)	AA03121	AA03122
Study Type (s)	Fasting (STF)	Fed (STP)
Strength (s)	20 mg	20 mg
Clinical Site		
Clinical Site Address		
Analytical Site		
Analytical Site Address		

1 EXECUTIVE SUMMARY

This is a review of an independent audit report.

In this supplement, the firm, Apotex, Inc., submitted an independent audit report for its approved ANDA #76-894, Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg. The audit report is in response to the Division of Scientific Investigations Citations issued to ——————. The Agency audited —————— and raised questions about the integrity of the bioanalysis of samples for bioequivalence studies from January 2000 through December 2004. Therefore, based on the Agency's citations for ——, the firm was notified that within six months of the receipt of the letter dated January 10, 2007, they had to either (1) repeat the bioequivalence (BE) studies, (2) re-assay the samples at a different bioanalytical facility, or (3) commission a scientific audit by a qualified independent expert. The firm chose the third option by selecting, the audit firm, ——————, to evaluate the data used to support the acceptability of the firm's fasting BE study No. AA03121 and fed BE AA03122. The evaluation and audit included a detailed review of the BE studies, validation of the analytical method, and standard operating procedures (SOPs). The auditor identified numerous deficiencies and errors that occurred during the BE studies as well as the validation study. The auditor stated that the data "May be Certified" after completion of the required remediation/mitigation by the firm and/or ——. Based on —————— responses to the audit observations, the auditor determined that the BE studies provided by the firm does support its claim that its test product is indeed bioequivalent to the reference product, Demadex® Tablets. The DBE accepts the audit firm's assessment of the validation data and BE studies.

Based on the information provided in the final audit report, the DBE's previous determination that the firm's BE studies, along with acceptable dissolution testing and approved waiver requests for the 5 mg, 10 mg, and 100 mg tables remain unchanged. Apotex's Torsemide Tablets is indeed bioequivalent to Demadex® Tablets by Roche Pharmaceuticals.

At this time, no further communication to the firm is necessary.

The application is considered complete with no deficiencies.

2 TABLE OF CONTENTS

3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Product	Torsemide Tablets, 20 mg
Reference Product	Demadex® Tablets, 20 mg
RLD Manufacturer	Roche
NDA No.	20-136
RLD Approval Date	August 23, 1993
Indication	It is indicated for the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease

3.2 PK/PD Information[1]

Bioavailability	~ 80% with intersubject variability
Food Effect	Delays the time to C_{max} about 30 minutes but no change in overall bioavailability (AUC)
Tmax	1 hr
Metabolism	It undergoes first pass metabolism. It is metabolized by the hepatic cytochrome P_{450} enzyme system. The major metabolite in humans is the carboxylic acid derivative, which is biologically ???
Excretion	Excreted in the urine.
Half-life	3.5 hrs
Drug Specific Issues (if any)	--

3.3 OGD Recommendations for Drug Product

Number of studies recommended:	2, fasting and fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	20 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

[1] 1. Online-Physicians' Desk Reference Electronic Library™. (2007). http://www.thomsonhc.com. Thomson Micromedex: Keyword Search: Demadex. Last accessed: 10/10/2007.
2. Online-Clinical Pharmacology (2007). http://cpip.gsm.com . World-Class Drug Information: Monographs: Torsemide. Last updated: 04/02/2007. Last accessed: 10/10/2007

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	20 mg
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	

Analytes to measure (in plasma/serum/blood):	Torsemide
Bioequivalence based on:	90% CI
Waiver request of in-vivo testing:	5, 10, and 100 mg
Source of most recent recommendations:	\\cdsnas\OGDS6\CONTROLS\2006-docs\06-1233.pdf
Summary of OGD or DBE History (for details, see Appendix 4.4):	According to the Electronic Orange Book (current through August 2007), there are several generic products on the market for Torsemide Tablets:

ANDA	Firm	Strength(s) mg	Approval Date
76-894	Apotex	5, 10, 20, 100	05/31/2005
76-226	Par Pharm	5, 10, 20, 100	05/27/2003
76-346	Pliva	5, 10, 20	05/30/2003
		100	10/19/2004
76-943	Roxane	5, 10, 20, 100	03/01/2005
76-110	Teva	5, 10, 20, 100	03/14/2002

3.4 Contents of Submission

Study Types	Yes/No?	How many?
Amendments	Yes	1

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3.5 Pre-Study Bioanalytical Method Validation[2]

Analyte name	Torsemide
Internal Standard	[redacted]
Method description	LC/MS/MS
QC range	20.0, 60.0, 4000, 8000 ng/mL
Standard curve range	20.0-10,000 ng/mL
Limit of quantitation	20.0 ng/mL
Average recovery of Drug (%)	105.0%
Average Recovery of Int. Std (%)	-
QC Intraday precision range (%)	2.3-12.3%
QC Intraday accuracy range (%)	102.8-105.4%
QC Interday precision range (%)	1.7-4.4%
QC Interday accuracy range (%)	103.0-112.0%
Bench-top stability (hrs)	26 hours
Stock stability (days)	57 days
Processed stability (hrs)	136.5 hours
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	56 days
Dilution integrity	2-fold, 107.0%
Specificity	Acceptable
SOPs submitted	No
Bioanalytical method is acceptable	Yes
20% Validation Chromatograms included (Y/N)	Yes
Random or Serial Selection of Chrom	Random

Comments on the Pre-Study Method Validation:

The original reviewer determined that the pre-study method validation was acceptable.

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[2] Internal file system: ANDA 76-894 Bioequivalence Review
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3.6 In Vivo Studies

Table 1. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Torsemide 1 x 20 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fasting Bioequivalence Study No. AA03121				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng·hr/mL)	6042	6084	0.99	97.0-101.7
AUC0-t (ng·hr/mL)	6224	6262	0.99	97.1-101.7
Cmax (ng/mL)	2733	2758	0.99	91.1-107.8

Torsemide 1 x 20 mg Tablet Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals				
Fed Bioequivalence Study No. AA03122				
Parameter	**Test**	**Reference**	**Ratio**	**90% C.I.**
AUC0-t (ng·hr/mL)	6532	6526	1.00	97.8-102.5
AUC0-t (ng·hr/mL)	6711	6709	1.00	97.8-102.3
Cmax (ng/mL)	2135	1963	1.09	99.5-118.9

Comments from the Reviewer:

1. For both BE studies, the 90% confidence intervals for log-transformed AUC_T, AUC_I, C_{max} are within the acceptable range of 80-125% for torsemide.

2. According to the original review, the firm did not report that any torsemide plasma samples were reassayed for pharmacokinetic (PK) reasons during the BE studies.

3.7 Formulation[2,3]

Location in appendix	Section 4.1, Page 17
If a tablet, is the RLD scored?	**No**
If a tablet, is the test product biobatch scored	**No**
Is the formulation acceptable?	**FORMULATION ACCEPTABLE**
If not acceptable, why?	

[3] Internal file system: ANDA 76-894 Bioequivalence Review V:\FIRMSAM\Apotex\LTRS&REV\76894a0105.doc and V:\FIRMSAM\Apotex\LTRS&REV\76894a0505.doc

3.8 In Vitro Dissolution

Location of DBE Dissolution Review	Internal file system: ANDA 76-894 Bioequivalence Review V:\FIRMSNZ\TORPHARM\LTRS&REV\76894n1103.doc, V:\FIRMSAM\Apotex\LTRS&REV\76894a0105.doc and V:\FIRMSAM\Apotex\LTRS&REV\76894a0505.doc
Source of Method (USP, FDA or Firm)	FDA
Medium	0.1 N HCl
Volume (mL)	900
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
DBE-recommended specifications	— % (Q) in 30 minutes
If a modified-release tablet, was testing done on ½ tablets?	--
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolves and %CV was high for the first time point for the test product
Is method acceptable?	**METHOD ACCEPTABLE**
If not then why?	

3.9 Waiver Request(s)

Strengths for which waivers are requested	5 mg, 10, and 100 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	**WAIVERS GRANTED**
If not then why?	

Redacted 6 page(s)

of trade secret and/or

confidential commercial

information from

BIOEQUIVALENCE REVIEW

5. **Audit Conclusions**: Based on the [redacted] responses to the initial audit observations, the auditor determined that validation data and BE studies results does support the firm's original application for Torsemide Tablets.

3.11 Comments on Audit Findings:

1. The auditor, [redacted] is knowledgeable and employees qualified independent experts capable of conducting an audit of scientific and clinical data to the Agency's standards.

2. The purpose, findings, and conclusion of the audit are acceptable.

3. The fasting BE study No. AA03121 and fed BE study No. AA03122 remains **acceptable** based on the audit report findings.

3.12 Recommendations

Based on the findings from the independent audit report by [redacted], the previous Division of Bioequivalence (DBE) Recommendations as stated below remain unchanged:

From the review of the original submission,
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1. The single-dose, fasting bioequivalence and the single-dose, nonfasting bioequivalence study conducted by Apotex (formerly TorPharm) on the test product, Torsemide Tablets, 20 mg, lot #FD2133, comparing it with the reference product, Roche's Demadex® (torsemide) Tablets, 20 mg, lot # 0201, are **acceptable**. The test product, Apotex's Torsemide Tablets, 20 mg, is bioequivalent to the reference product, Roche's Demadex® (torsemide) Tablets, 20 mg, under fasting and nonfasting conditions.

2. The dissolution testing conducted by Apotex on its Torsemide Tablets, 20 mg, is **acceptable**.

   The dissolution testing should be conducted in 900 mL of 0.1 N HCl at 37°C using USP apparatus II(paddle) at 50 rpm. The test product should meet the following specification:

   Not less than [redacted]% (Q) of the labeled amounts of the drug in the dosage form is dissolved in 30 minutes.

3. The dissolution testing conducted by Apotex on its Torsemide Tablets, 5 mg, 10 mg and 100 mg, is **acceptable**. The formulations of the 5 mg and 10 mg strengths of the test product are proportionally similar to that of the 20 mg strength which underwent acceptable *in vivo* bioequivalence testing. The waiver request for the 5 mg and 10 mg strengths is **granted** per 21 CFR 320.22 (d) (2). The test product, Apotex's Torsemide Tablets, 5 mg and 10 mg, is deemed bioequivalent to the reference product, Roche's Demadex® (torsemide) Tablets, 5 mg, 10 mg, respectively.

From the review, V:\FIRMSAM\Apotex\LTRS&REV\76894a0505.doc: \

4. The waiver request for the 100 mg strength is **granted.** The test product, Apotex's Torsemide Tablets, 100 mg, is deemed bioequivalent to the reference product, Roche's Demadex® (torsemide) Tablets, 100 mg.

3.13 Comments for Other OGD Disciplines

None.

4 APPENDIX

4.1 Formulation Data[2,3]

Ingredient	5 mg	10 mg	20 mg	100 mg
	Per tablet	Per tablet	Per tablet	Per tablet
Torsemide USP	5 mg	10 mg	20 mg	
Lactose Monohydrate NF				
Microcrystalline Cellulose NF				
[redacted]				
Crospovidone NF				
Magnesium Stearate NF				
Collodial Silicon Dioxide NF				
Total	50 mg	100 mg	200 mg	280 mg

Is there an overage of the active pharmaceutical ingredient (API)?	NO
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	None.

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4.2 Dissolution Data

Dissolution Review Path	Internal file system: ANDA 76-894 Bioequivalence Review V:\FIRMSNZ\TORPHARM\LTRS&REV\76894n1103.doc, V:\FIRMSAM\Apotex\LTRS&REV\76894a0105.doc and V:\FIRMSAM\Apotex\LTRS&REV\76894a0505.doc

Table 5. Dissolution Data

Dissolution Conditions	**Apparatus:**	II (Paddle)
	Speed of Rotation:	50 rpm
	Medium:	0.1N HCl
	Volume:	900 mL
	Temperature:	37°C ± 0.5°C
Firm's Proposed Specifications	[redacted]% (Q) in 30 minutes	
Dissolution Testing Site (Name, Address)	Not provided	

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Sampling Time (min)	Test Product, Strength 5 mg Lot No. FD2131			Reference Product, Strength 5 mg Lot No. E2325		
	Mean	%CV	Range	Mean	%CV	Range
5	28	18		50	13	
10	71	8		84	5	
20	91	4		95	2	
30	95	3		96	2	
45	96	2		97	1	
Sampling Time (min)	**Test Product, Strength 10 mg Lot No. FD2132**			**Reference Product, Strength 10 mg Lot No. E1875**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
5	62	23		87	5	
10	90	6		99	1	
20	96	2		100	1	
30	97	1		100	1	
45	97	1		100	1	
Sampling Time (min)	**Test Product, Strength 20 mg Lot No. FD2133**			**Reference Product, Strength 20 mg Lot No. 0201**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
5	18	18		73	4	
10	66	11		95	2	
20	93	4		98	2	
30	97	3		98	2	
45	98	2		98	2	
Sampling Time (min)	**Test Product, Strength 100 mg Lot No. FD2134**			**Reference Product, Strength 100 mg Lot No. E2238**		
	Mean	**%CV**	**Range**	**Mean**	**%CV**	**Range**
5	43	43		74	9	
10	80	11		91	4	
20	93	6		96	2	
30	96	5		96	2	
45	97	4		98	2	

***NOTE 1:** The dissolution data from the original submission (11/06/03) did not contain 15-minute time point.

****NOTE 2:** Although the current FDA-recommended specification for the drug product is NLT — %(Q) dissolved in 15 minutes, this specification is found not appropriate for the test product (See the review of the original submission, v:\firmsnz\torpharm\ltrs&rev\76894n1103.doc). The specification as proposed by the firm above has been found acceptable for the test product.

Table 6

Sampling Time (min)	Test Product, Strength 20 mg Lot No. FD2133A			Reference Product, Strength 20 mg Lot No. 0201		
	Mean	%CV	Range	Mean	%CV	Range
5	84	6		73	4	
10	93	4		95	2	
20	97	3		98	2	
30	98	3		98	2	
45	99	2		98	2	

NOTE: Under the same dissolution testing conditions, the dissolution data for the 20 mg strength of the test are **different** from those given in the previous submission (see below) whereas the dissolution data for the 20 mg strength of the RLD product are the same.

From the original submission dated 11/06/03:

Sampling Time (min)	Test Product, Strength 20 mg Lot No. FD2133			Reference Product, Strength 20 mg Lot No. 0201		
	Mean	%CV	Range	Mean	%CV	Range
5	18	18		73	4	
10	66	11		95	2	
20	93	4		98	2	
30	97	3		98	2	
45	98	2		98	2	

Table 7

Sampling Time (min)	Test Product, Strength 100 mg Lot No. FD2134A			Reference Product, Strength 100 mg Lot No. E2238		
	Mean	%CV	Range	Mean	%CV	Range
5	79	6		74	9	
10	91	8		91	4	
20	93	7		96	2	
30	94	7		96	2	
45	97	5		98	2	

NOTE: Under the same dissolution testing conditions, the dissolution data for the 100 mg strength of the test are **different** from those given in the previous submission (see below) whereas the dissolution data for the 100 mg strength of the RLD product are the same.

From the original submission dated 11/06/03

Sampling Time (min)	Test Product, Strength 100 mg Lot No. FD2134			Reference Product, Strength 100 mg Lot No. E2238		
	Mean	%CV	Range	Mean	%CV	Range
5	43	43		74	9	
10	80	11		91	4	
20	93	6		96	2	
30	96	5		96	2	
45	97	4		98	2	

F2 between the 20 mg and 100 mg strengths of the test product (current submission): No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for both strengths.

F2 between the 20 mg and 100 mg strengths of the test product (original submission): No meaningful F2 can be calculated since the percent dissolved at the third time point was >85% for both strengths and the CV% for the first time point for was >15% for both strengths.

F2 between the 20 mg and 100 mg strengths of the RLD product: No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for both strengths.

F2 between the test and RLD product (current submission): No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for both products.

F2 between the test and RLD product (original submission): No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for both strengths of the RLD products.

Testing Conditions:

Source of Method	Varying pH media
Medium	Water
Volume (mL)	900 mL
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm

Table 8

Sampling Time (min)	Test Product, Strength 20 mg Lot No. FD2133A			Reference Product, Strength 20 mg Lot No. 0201		
	Mean	%CV	Range	Mean	%CV	Range
5	30	9		65	6	
10	51	8		94	4	
15	63	6		99	3	
20	72	4		100	2	
30	82	4		101	2	
45	88	4		101	2	

Table 9

Sampling Time (min)	Test Product, Strength 100 mg Lot No. FD2134A			Reference Product, Strength 100 mg Lot No. E2238		
	Mean	%CV	Range	Mean	%CV	Range
5	25	15		61	9	
10	45	11		84	3	
15	56	8		92	2	
20	64	7		95	2	
30	74	5		98	1	
45	83	4		100	2	

F2 between the 20 mg and 100 mg strengths of the test product: 58.71

F2 between the 20 mg and 100 mg strengths of the RLD product: No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for the 20 mg strength.

F2 between the 100 mg strength of the test and RLD product based on 3 time points: 21.57

F2 between the 20 mg strength of the test and RLD product : No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for the 20 mg strength of the RLD product.

Testing Conditions:

Source of Method	Varying pH media
Medium	pH 7.5 buffer
Volume (mL)	900 mL
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm

Table 10

Sampling Time (min)	Test Product, Strength 20 mg Lot No. FD2133A			Reference Product, Strength 20 mg Lot No. 0201		
	Mean	%CV	Range	Mean	%CV	Range
5	50	33		81	8	
10	74	15		97	3	
15	85	7		98	3	
20	90	5		99	2	
30	94	4		100	2	
45	95	3		100	2	

Table 11

Sampling Time (min)	Test Product, Strength 100 mg Lot No. FD2134A			Reference Product, Strength 100 mg Lot No. E2238		
	Mean	%CV	Range	Mean	%CV	Range
5	43	26		79	8	
10	69	10		93	4	
15	80	7		96	1	
20	85	5		97	1	
30	89	5		97	1	
45	90	5		98	1	

F2 between the 20 mg and 100 mg strengths of the test product based on 3 time points (the 5-minute time point was not used due to high CV%): 64.63

F2 between the 20 mg and 100 mg strengths of the RLD product: No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for both strengths.

F2 between the 100 mg strength of the test and RLD product : No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for the RLD product.

F2 between the 20 mg strength of the test and RLD product : No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for the RLD product.

Testing Conditions:

Source of Method	Varying pH media
Medium	pH 6.5 buffer
Volume (mL)	900 mL
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm

Table 12

Sampling Time (min)	Test Product, Strength 20 mg Lot No. FD2133A			Reference Product, Strength 20 mg Lot No. 0201		
	Mean	%CV	Range	Mean	%CV	Range
5	39	13		81	8	
10	58	11		97	3	
15	69	9		98	3	
20	76	6		99	2	
30	83	5		100	2	
45	88	5		100	2	

Table 13

Sampling Time (min)	Test Product, Strength 100 mg Lot No. FD2134A			Reference Product, Strength 100 mg Lot No. E2238		
	Mean	%CV	Range	Mean	%CV	Range
5	27	9		66	9	
10	45	8		88	3	
15	54	7		94	3	
20	61	7		97	4	
30	70	6		98	4	
45	77	6		99	6	

F2 between the 20 mg and 100 mg strengths of the test product: 43.83

F2 between the 20 mg and 100 mg strengths of the RLD product: No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for both strengths.

F2 between the 100 mg strength of the test and RLD product : No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for the RLD product.

F2 between the 20 mg strength of the test and RLD product : No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for the RLD product.

Testing Conditions:

Source of Method	Varying pH media
Medium	pH 4.5 buffer
Volume (mL)	900 mL
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm

Table 14

Sampling Time (min)	Test Product, Strength 20 mg Lot No. FD2133A			Reference Product, Strength 20 mg Lot No. 0201		
	Mean	%CV	Range	Mean	%CV	Range
5	32	7		64	8	
10	54	5		91	5	
15	65	4		97	4	
20	72	4		99	3	
30	81	3		98	2	
45	88	3		99	2	

Table 15

Sampling Time (min)	Test Product, Strength 100 mg Lot No. FD2134A			Reference Product, Strength 100 mg Lot No. E2238		
	Mean	%CV	Range	Mean	%CV	Range
5	21	11		43	13	
10	38	9		71	5	
15	47	8		82	4	
20	54	8		88	3	
30	63	7		94	2	
45	71	6		98	2	

F2 between the 20 mg and 100 mg strengths of the test product: 39.06

F2 between the 20 mg and 100 mg strengths of the RLD product: No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for the 20 mg strength.

F2 between the 100 mg strength of the test and RLD product based on 4 time points: 25.11

F2 between the 20 mg strength of the test and RLD product : No meaningful F2 can be calculated since the percent dissolved at the second time point was >85% for the RLD product.

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Testing Conditions:

Source of Method	FDA
Medium	0.1 N HCl
Volume (mL)	900 mL
USP Apparatus type	II(paddle)
Rotation (rpm)	50 rpm
Firm's proposed specification	—%(Q) in 30 minutes
Current FDA-recommended specification based on all dissolution data submitted for the test product in the current amendments as well as previous submissions.	—%(Q) in 30 minutes

Table 16

Sampling Time (min)	Test Product, Strength 5 mg Lot No. FD2131B			Reference Product, Strength 5 mg Lot No. E2325		
	Mean	%CV	Range	Mean	%CV	Range
5	77	8		89	5	
10	93	2		98	2	
20	95	2		98	2	
30	95	2		98	2	
45	95	2		98	2	

4.3 Detailed Regulatory History (If Applicable)

None.

4.4 Consult Reviews

None.

4.5 Additional Attachments

None.

4.6 Outcome Page

COMPLETED ASSIGNMENT FOR 76894 ID: 619

Reviewer: Braddy, April **Date Completed:**
Verifier: **Date Verified:**
Division: Division of Bioequivalence
Description: Audit Report

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
619	8/3/2007	Other	Supplement (Audits)	1	1
				Bean Total:	1

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

April Braddy
10/29/2007 06:28:37 AM
BIOPHARMACEUTICS

Moheb H. Makary
10/29/2007 06:39:44 AM
BIOPHARMACEUTICS

Barbara Davit
10/30/2007 03:54:44 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-894/S-002

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

APOTEX INC.
CANADA'S PHARMACEUTICAL COMPANY
SOCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

August 3, 2007

NDA NO. 76-894 REF NO. SB 002
NDA SUPPL. FOR Bio-Rev

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

Dear Mr. Buehler

Re: Torsemide Tablets 5 mg, 10 mg, 20 mg and 100mg
ANDA No. 76-894
Bioequivalence Studies conducted by ————————

Further to our letter dated July 20, 2007 regarding the certification of the bioequivalence studies conducted on Torsemide Tablets 20 mg, and in response to a telephone request by Christina Thompson of the Division of Bioequivalence to myself on July 24, 2007 regarding the requirement for the audit reports from ———— to be submitted, please accept this additional information.

- The process of the audit was carried out in the following manner:

  1) ———— visited the ———————— to conduct an audit of the studies.

  2) ———— reviewed pre-study validation data for accuracy, precision and stability, and confirmed that these parameters were demonstrated with appropriate validation experiments and documentation, and under the conditions of sample processing used for the analysis of samples form study subjects.

  ———— reviewed results of the bioequivalence studies to confirm that, to a reasonable and justifiable extent, anomalous results were investigated and issues related to the contamination were identified and corrected. In addition, where samples were repeated, the auditors made comparison between original and repeat results, assay reproducibility was demonstrated. ———— confirmed that analytical runs were accepted in accordance with established procedures and without bias.

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3) The audit process has been summarised in a Global Audit Report from ——— that is attached. The report provides details of:
    a. An executive summary that lists the bioequivalence studies that were investigated, along with the approach taken as outcomes of the audits. ——— approach and expectations with respect to ——— responses are explained in a separate memo from ——— as attached.
    b. The background with respect to process and the documents actually reviewed.
    c. The audit findings and recommendations/required actions.

As a result of the audit reviews, the data was either accepted for certification as-is or with remediation or the data was rejected for certification.

- The individual audit report for Torsemide Tablets, including the previously submitted certification letter from ——— is provided on the enclosed CD.

We trust that this information is satisfactory. Should you have any further concerns, please do not hesitate to contact me by phone at (416) 401-7889, by fax at (416) 401-3809. Alternatively, please contact Kiran Krishnan , the authorized US agent for Apotex Inc, by telephone at (954) 384-3986, or by fax at (954) 349-4223.

Sincerely,

C. Comelly

for Bernice Tao
Director, Regulatory Affairs US,
Apotex Inc.