# CENTER FOR DRUG EVALUATION AND RESEARCH

## Approval Package for:

*APPLICATION NUMBER:*

**ANDA 76-894**

**Name:** Torsemide Tablets, 5 mg, 10 mg, 20 mg, and 100 mg

**Sponsor:** Apotex Corp.

**Approval Date:** May 31, 2005

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# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

**ANDA 76-894**

# APPROVAL LETTER

ANDA 76-894

MAY 31 2005

Apotex Corp.
Attention: Marcy Macdonald
U.S. Agent for: Apotex Inc.
616 Heathrow Drive
Lincolnshire, IL 60069

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated November 6, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Torsemide Tablets, 5 mg, 10 mg, 20 mg, and 100 mg.

Reference is also made to your amendments dated June 30, August 9, August 16, and November 12, 2004; and January 4, March 24, May 6, and May 11, 2005.

We have completed the review of this abbreviated application, and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Torsemide Tablets 5 mg, 10 mg, 20 mg, and 100 mg to be bioequivalent and therefore, therapeutically equivalent to the listed drug, (Demadex® Tablets, 5 mg, 10 mg, 20 mg, and 100 mg, respectively, of Hoffmann La Roche, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

The listed drug product (RLD) referenced in your application, Demadex® Tablets, 5 mg, 10 mg, 20 mg, and 100 mg of Hoffmann La Roche, Inc. (Roche) is subject to a period of patent protection. As noted in the agency's publication entitled Approved Drug Products with Therapeutic Equivalence Evaluations, the "Orange Book", U.S. Patent No. RE34,672 (the '672 patent) is scheduled to expire on August 11, 2006. Your application contains a paragraph IV patent certification under section 505(j)(2)(A)(vii)(IV) of the Act stating that the '672 patent is invalid and will not be infringed by your manufacture, use, or sale of Torsemide Tablets 5 mg, 10 mg, 20 mg, and 100 mg under

this ANDA. Section 505(j)(5)(B)(iii) of the act provides that approval of an ANDA shall be made effective immediately, unless an action is brought against Apotex Inc. (Apotex) for infringement of the '672 patent that was the subject of the paragraph IV certification. This action must have been brought against Apotex prior to the expiration of 45 days from the date the notice you provided under paragraph (2)(B)(i) was received by the NDA/patent holder. You have notified the agency that Apotex complied with the requirements of Section 505(j)(2)(B) of the Act, and that no action for infringement of the '672 patent was brought against Apotex within the statutory 45-day period, which action would have resulted in a 30-month stay under section 505(j)(5)(B)(iii).[1]

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

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

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert(s) directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising, and Communications (HFD-42)
5600 Fishers Lane
Rockville, MD 20857

[1] Because information on the '672 patent was submitted to FDA before August 18, 2003, this reference to section 505(j)(5)(B)(iii) is to that section of the Act as in effect prior to December 8, 2003, when the Medicare Prescription Drug, Improvement and Modernization Act (MMA)(Public Law 108-173) was enacted. See MMA § 1101(c)(3).

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Division of Drug Marketing, Advertising, and Communications (HFD-42) with a completed Form FDA 2253 at the time of their initial use.

Sincerely yours,

Gary Buehler 5/31/05
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 76-894

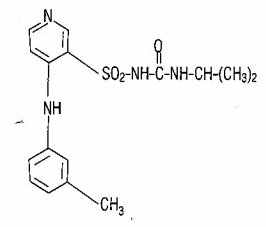
# LABELING

# TORSEMIDE TABLETS
## 5 mg, 10 mg, 20 mg and 100 mg

**℞ Only**

## DESCRIPTION

Torsemide is a diuretic of the pyridine-sulfonylurea class. Its chemical name is 1-isopropyl-3-[(4-*m*-toluidino-3-pyridyl) sulfonyl]urea and its structural formula is:




Its molecular formula is $C_{16}H_{20}N_4O_3S$, its $pK_a$ is 7.1, and its molecular weight is 348.43.

Torsemide is a white to off-white crystalline powder. Each tablet, for oral administration, contains 5 mg, 10 mg, 20 mg or 100 mg of torsemide. In addition, each tablet contains the following inactive ingredients: colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, and microcrystalline cellulose.

## CLINICAL PHARMACOLOGY

### Mechanism of Action

Micropuncture studies in animals have shown that torsemide acts from within the lumen of the thick ascending portion of the loop of Henle, where it inhibits the $Na^+/K^+/2Cl^-$-carrier system. Clinical pharmacology studies have confirmed this site of action in humans, and effects in other segments of the nephron have not been demonstrated. Diuretic activity thus correlates better with the rate of drug excretion in the urine than with the concentration in the blood.

Torsemide increases the urinary excretion of sodium, chloride, and water, but it does not significantly alter glomerular filtration rate, renal plasma flow, or acid-base balance.

### Pharmacokinetics and Metabolism

The bioavailability of torsemide tablets is approximately 80%, with little intersubject variation; the 90% confidence interval is 75% to 89%. The drug is absorbed with little first-pass metabolism, and the serum concentration reaches its peak ($C_{max}$) within 1 hour after oral administration. $C_{max}$ and area under the serum concentration-time curve (AUC) after oral administration are proportional to dose over the range of 2.5 mg to 200 mg. Simultaneous food intake delays the time to $C_{max}$ by about 30 minutes, but overall bioavailability (AUC) and diuretic activity are unchanged. Absorption is essentially unaffected by renal or hepatic dysfunction.

The volume of distribution of torsemide is 12 liters to 15 liters in normal adults or in patients with mild to moderate renal failure or congestive heart failure. In patients with hepatic cirrhosis, the volume of distribution is approximately doubled.

In normal subjects the elimination half-life of torsemide is approximately 3.5 hours. Torsemide is cleared from the circulation by both hepatic metabolism (approximately 80% of total clearance) and excretion into the urine (approximately 20% of total clearance in patients with normal renal function). The major metabolite in humans is the carboxylic acid derivative, which is biologically inactive. Two of the lesser metabolites possess some diuretic activity, but for practical purposes metabolism terminates the action of the drug.

Because torsemide is extensively bound to plasma protein (>99%), very little enters tubular urine via glomerular filtration. Most renal clearance of torsemide occurs via active secretion of the drug by the proximal tubules into tubular urine.

In patients with decompensated congestive heart failure, hepatic and renal clearance are both reduced, probably because of hepatic congestion and decreased renal plasma flow, respectively. The total clearance of torsemide is approximately 50% of that seen in healthy volunteers, and the plasma half-life and AUC are correspondingly increased. Because of reduced renal clearance, a smaller fraction of any given dose is delivered to the intraluminal site of action, so at any given dose there is less natriuresis in patients with congestive heart failure than in normal subjects.

In patients with renal failure, renal clearance of torsemide is markedly decreased but total plasma clearance is not significantly altered. A smaller fraction of the administered dose is delivered to the intraluminal site of action, and the natriuretic action of any given dose of diuretic is reduced. A diuretic response in renal failure may still be achieved if patients are given higher doses. The total plasma clearance and elimination half-life of torsemide remain normal under the conditions of impaired renal function because metabolic elimination by the liver remains intact.

In patients with hepatic cirrhosis, the volume of distribution, plasma half-life, and renal clearance are all increased, but total clearance is unchanged.

The pharmacokinetic profile of torsemide in healthy elderly subjects is similar to that in young subjects except for a decrease in renal clearance related to the decline in renal function that commonly occurs with aging. However, total plasma clearance and elimination half-life remain unchanged.

### Clinical Effects

With oral dosing, the onset of diuresis occurs within 1 hour and the peak effect occurs during the first or second hour. Independent of the route of administration, diuresis lasts about 6 to 8 hours. In healthy subjects given single doses, the dose-response relationship for sodium excretion is linear over the dose range of 2.5 mg to 20 mg. The increase in potassium excretion is negligible after a single dose of up to 10 mg and only slight (5 mEq to 15 mEq) after a single dose of 20 mg.

***Congestive Heart Failure:*** Torsemide has been studied in controlled trials in patients with New York Heart Association Class II to Class IV congestive heart failure. Patients who received 10 mg to 20 mg of daily torsemide in these studies achieved significantly greater reductions in weight and edema than did patients who received placebo.

***Nonanuric Renal Failure:*** In single-dose studies in patients with nonanuric renal failure, high doses of torsemide (20 mg to 200 mg) caused marked increases in water and sodium excretion. In patients with nonanuric renal failure, severe enough to require hemodialysis, chronic treatment with up to 200 mg of daily torsemide has not been shown to change steady-state fluid retention. When patients in a study of acute renal failure received total daily doses of 520 mg to 1200 mg of torsemide, 19% experienced seizures. Ninety-six patients were treated in this study; 6/32 treated with torsemide experienced seizures, 6/32 treated with comparably high doses of furosemide experienced seizures, and 1/32 treated with placebo experienced a seizure.

***Hepatic Cirrhosis:*** When given with aldosterone antagonists, torsemide also caused increases in sodium and fluid excretion in patients with edema or ascites due to hepatic cirrhosis. Urinary sodium excretion rate relative to the urinary excretion rate of torsemide is less in cirrhotic patients than in healthy subjects (possibly because of the hyperaldosteronism and resultant sodium retention that are characteristic of portal hypertension and ascites). However, because of the increased renal clearance of torsemide in patients with hepatic cirrhosis, these factors tend to balance each other, and the result is an overall natriuretic response that is similar to that seen in healthy subjects. Chronic use of any diuretic in hepatic disease has not been studied in adequate and well-controlled trials.

***Essential Hypertension:*** In patients with essential hypertension, torsemide has been shown in controlled studies to lower blood pressure when administered once a day at doses of 5 mg to 10 mg. The antihypertensive effect is near maximal after 4 to 6 weeks of treatment, but it may continue to increase for up to 12 weeks. Systolic and diastolic supine and standing blood pressures are all reduced. There is no significant orthostatic effect, and there is only a minimal peak-trough difference in blood pressure reduction.

The antihypertensive effects of torsemide are, like those of other diuretics, on the average greater in black patients (a low-renin population) than in nonblack patients.

When torsemide is first administered, daily urinary sodium excretion increases for at least a week. With chronic administration, however, daily sodium loss comes into balance with dietary sodium intake. If the administration of torsemide is suddenly stopped, blood pressure returns to pretreatment levels over several days, without overshoot.

Torsemide has been administered together with β-adrenergic blocking agents, ACE inhibitors, and

When torsemide is first administered, daily urinary sodium excretion increases for at least a week. With chronic administration, however, daily sodium loss comes into balance with dietary sodium intake. If the administration of torsemide is suddenly stopped, blood pressure returns to pretreatment levels over several days, without overshoot.

Torsemide has been administered together with β-adrenergic blocking agents, ACE inhibitors, and calcium-channel blockers. Adverse drug interactions have not been observed, and special dosage adjustment has not been necessary.

## INDICATIONS AND USAGE

Torsemide tablets are indicated for the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease. Use of torsemide has been found to be effective for the treatment of edema associated with chronic renal failure. Chronic use of any diuretic in hepatic disease has not been studied in adequate and well-controlled trials.

Torsemide tablets are indicated for the treatment of hypertension alone or in combination with other antihypertensive agents.

## CONTRAINDICATIONS

Torsemide tablets are contraindicated in patients with known hypersensitivity to torsemide or to sulfonylureas.

Torsemide tablets are contraindicated in patients who are anuric.

## WARNINGS

### Hepatic Disease With Cirrhosis and Ascites

Torsemide should be used with caution in patients with hepatic disease with cirrhosis and ascites, since sudden alterations of fluid and electrolyte balance may precipitate hepatic coma. In these patients, diuresis with torsemide (or any other diuretic) is best initiated in the hospital. To prevent hypokalemia and metabolic alkalosis, an aldosterone antagonist or potassium-sparing drug should be used concomitantly with torsemide.

### Ototoxicity

Tinnitus and hearing loss (usually reversible) have been observed after rapid intravenous injection of other loop diuretics and have also been observed after oral torsemide. It is not certain that these events were attributable to torsemide. Ototoxicity has also been seen in animal studies when very high plasma levels of torsemide were induced.

### Volume and Electrolyte Depletion

Patients receiving diuretics should be observed for clinical evidence of electrolyte imbalance, hypovolemia, or prerenal azotemia. Symptoms of these disturbances may include one or more of the following: dryness of the mouth, thirst, weakness, lethargy, drowsiness, restlessness, muscle pains or cramps, muscular fatigue, hypotension, oliguria, tachycardia, nausea, and vomiting. Excessive diuresis may cause dehydration, blood-volume reduction, and possibly thrombosis and embolism, especially in elderly patients. In patients who develop fluid and electrolyte imbalances, hypovolemia, or prerenal azotemia, the observed laboratory changes may include hyper- or hyponatremia, hyper- or hypochloremia, hyper- or hypokalemia, acid-base abnormalities, and increased blood urea nitrogen (BUN). If any of these occur, torsemide should be discontinued until the situation is corrected; torsemide may be restarted at a lower dose.

In controlled studies in the United States, torsemide was administered to hypertensive patients at doses of 5 mg or 10 mg daily. After 6 weeks at these doses, the mean decrease in serum potassium was approximately 0.1 mEq/L. The percentage of patients who had a serum potassium level below 3.5 mEq/L at any time during the studies was essentially the same in patients who received torsemide (1.5%) as in those who received placebo (3%). In patients followed for 1 year, there was no further change in mean serum potassium levels. In patients with congestive heart failure, hepatic cirrhosis, or renal disease treated with torsemide at doses higher than those studied in United States antihypertensive trials, hypokalemia was observed with greater frequency, in a dose-related manner.

In patients with cardiovascular disease, especially those receiving digitalis glycosides, diuretic-induced hypokalemia may be a risk factor for the development of arrhythmias. The risk of hypokalemia is greatest in patients with cirrhosis of the liver, in patients experiencing a brisk diuresis, in patients who are receiving inadequate oral intake of electrolytes, and in patients receiving concomitant therapy with corticosteroids or ACTH.

Periodic monitoring of serum potassium and other electrolytes is advised in patients treated with torsemide.

## PRECAUTIONS

### Laboratory Values

***Potassium:*** See **WARNINGS.**

***Calcium:*** Single doses of torsemide increased the urinary excretion of calcium by normal subjects, but serum calcium levels were slightly increased in 4- to 6-week hypertension trials. In a long-term study of patients with congestive heart failure, the average 1-year change in serum calcium was a decrease of 0.10 mg/dL (0.02 mmol/L). Among 426 patients treated with torsemide for an average of 11 months, hypocalcemia was not reported as an adverse event.

***Magnesium:*** Single doses of torsemide caused healthy volunteers to increase their urinary excretion of magnesium, but serum magnesium levels were slightly increased in 4- to 6-week hypertension trials. In long-term hypertension studies, the average 1-year change in serum magnesium was an increase of 0.03 mg/dL (0.01 mmol/L). Among 426 patients treated with torsemide for an average of 11 months, one case of hypomagnesemia (1.3 mg/dL [0.53 mmol/L]) was reported as an adverse event.

In a long-term clinical study of torsemide in patients with congestive heart failure, the estimated annual change in serum magnesium was an increase of 0.2 mg/dL (0.08 mmol/L), but these data are confounded by the fact that many of these patients received magnesium supplements. In a 4-week study in which magnesium supplementation was not given, the rate of occurrence of serum magnesium levels below 1.7 mg/dL (0.70 mmol/L) was 6% and 9% in the groups receiving 5 mg and 10 mg of torsemide, respectively.

***Blood Urea Nitrogen (BUN), Creatinine and Uric Acid:*** Torsemide produces small dose-related increases in each of these laboratory values. In hypertensive patients who received 10 mg of torsemide daily for 6 weeks, the mean increase in blood urea nitrogen was 1.8 mg/dL (0.6 mmol/L), the mean increase in serum creatinine was 0.05 mg/dL (4 mmol/L), and the mean increase in serum uric acid was 1.2 mg/dL (70 mmol/L). Little further change occurred with long-term treatment, and all changes reversed when treatment was discontinued.

Symptomatic gout has been reported in patients receiving torsemide, but its incidence has been similar to that seen in patients receiving placebo.

***Glucose:*** Hypertensive patients who received 10 mg of daily torsemide experienced a mean increase in serum glucose concentration of 5.5 mg/dL (0.3 mmol/L) after 6 weeks of therapy, with a further increase of 1.8 mg/dL (0.1 mmol/L) during the subsequent year. In long-term studies in diabetics, mean fasting glucose values were not significantly changed from baseline. Cases of hyperglycemia have been reported but are uncommon.

***Serum Lipids:*** In the controlled short-term hypertension studies in the United States, daily doses of 5 mg, 10 mg, and 20 mg of torsemide were associated with increases in total plasma cholesterol of 4, 4, and 8 mg/dL (0.10 to 0.20 mmol/L), respectively. The changes subsided during chronic therapy.

In the same short-term hypertension studies, daily doses of 5 mg, 10 mg and 20 mg of torsemide were associated with mean increases in plasma triglycerides of 16, 13 and 71 mg/dL (0.15 to 0.80 mmol/L), respectively.

In long-term studies of 5 mg to 20 mg of torsemide daily, no clinically significant differences from baseline lipid values were observed after 1 year of therapy.

***Other:*** In long-term studies in hypertensive patients, torsemide has been associated with small mean decreases in hemoglobin, hematocrit, and erythrocyte count and small mean increases in white blood cell count, platelet count, and serum alkaline phosphatase. Although statistically significant, all of these changes were medically inconsequential. No

significant trends have been observed in any liver enzyme tests other than alkaline phosphatase.

**Drug Interactions**

In patients with essential hypertension, torsemide has been administered together with beta-blockers, ACE inhibitors, and calcium-channel blockers. In patients with congestive heart failure, torsemide has been administered together with digitalis glycosides, ACE inhibitors, and organic nitrates. None of these combined uses was associated with new or unexpected adverse events.

Torsemide does not affect the protein binding of glyburide or of warfarin, the anticoagulant effect of phenprocoumon (a related coumarin derivative), or the pharmacokinetics of digoxin or carvedilol (a vasodilator/beta-blocker). In healthy subjects, coadministration of torsemide was associated with significant reduction in the renal clearance of spironolactone, with corresponding increases in the AUC. However, clinical experience indicates that dosage adjustment of either agent is not required.

Because torsemide and salicylates compete for secretion by renal tubules, patients receiving high doses of salicylates may experience salicylate toxicity when torsemide is concomitantly administered. Also, although possible interactions between torsemide and nonsteroidal anti-inflammatory agents (including aspirin) have not been studied, coadministration of these agents with another loop diuretic (furosemide) has occasionally been associated with renal dysfunction.

The natriuretic effect of torsemide (like that of many other diuretics) is partially inhibited by the concomitant administration of indomethacin. This effect has been demonstrated for torsemide under conditions of dietary sodium restriction (50 mEq/day) but not in the presence of normal sodium intake (150 mEq/day).

The pharmacokinetic profile and diuretic activity of torsemide are not altered by cimetidine or spironolactone. Coadministration of digoxin is reported to increase the area under the curve for torsemide by 50%, but dose adjustment of torsemide is not necessary.

Concomitant use of torsemide and cholestyramine has not been studied in humans but, in a study in animals, coadministration of cholestyramine decreased the absorption of orally administered torsemide. If torsemide and cholestyramine are used concomitantly, simultaneous administration is not recommended.

Coadministration of probenecid reduces secretion of torsemide into the proximal tubule and thereby decreases the diuretic activity of torsemide.

Other diuretics are known to reduce the renal clearance of lithium, inducing a high risk of lithium toxicity, so coadministration of lithium and diuretics should be undertaken with great caution, if at all. Coadministration of lithium and torsemide has not been studied.

Other diuretics have been reported to increase the ototoxic potential of aminoglycoside antibiotics and of ethacrynic acid, especially in the presence of impaired renal function. These potential interactions with torsemide have not been studied.

**Carcinogenesis, Mutagenesis and Impairment of Fertility**

No overall increase in tumor incidence was found when torsemide was given to rats and mice throughout their lives at doses up to 9 mg/kg/day (rats) and 32 mg/kg/day (mice). On a body-weight basis, these doses are 27 to 96 times a human dose of 20 mg; on a body-surface-area basis, they are 5 to 8 times this dose. In the rat study, the high-dose female group demonstrated renal tubular injury, interstitial inflammation, and a statistically significant increase in renal adenomas and carcinomas. The tumor incidence in this group was, however, not much higher than the incidence sometimes seen in historical controls. Similar signs of chronic non-neoplastic renal injury have been reported in high-dose animal studies of other diuretics such as furosemide and hydrochlorothiazide.

No mutagenic activity was detected in any of a variety of *in vivo* and *in vitro* tests of torsemide and its major human metabolite. The tests included the Ames test in bacteria (with and without metabolic activation), tests for chromosome aberrations and sister-chromatid exchanges in human lymphocytes, tests for various nuclear anomalies in cells found in hamster and murine bone marrow, tests for unscheduled DNA synthesis in mice and rats, and others.

In doses up to 25 mg/kg/day (75 times a human dose of 20 mg on a body-weight basis; 13 times this dose on a body-surface-area basis), torsemide had no adverse effect on the reproductive performance of male or female rats.

**Pregnancy**

***Pregnancy Category B:*** There was no fetotoxicity or teratogenicity in rats treated with up to 5 mg/kg/day of torsemide (on a mg/kg basis, this is 15 times a human dose of 20 mg/day; on a mg/m$^2$ basis, the animal dose is 10 times the human dose), or in rabbits, treated with 1.6 mg/kg/day (on a mg/kg basis, 5 times the human dose of 20 mg/kg/day; on a mg/m$^2$ basis, 1.7 times this dose). Fetal and maternal toxicity (decrease in average body weight, increase in fetal resorption and delayed fetal ossification) occurred in rabbits and rats given doses 4 (rabbits) and 5 (rats) times larger. Adequate and well-controlled studies have not been carried out in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

**Labor and Delivery**

The effect of torsemide on labor and delivery is unknown.

**Nursing Mothers**

It is not known whether torsemide is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when torsemide is administered to a nursing woman.

**Pediatric Use**

Safety and effectiveness in pediatric patients have not been established.

Administration of another loop diuretic to severely premature infants with edema due to patent ductus arteriosus and hyaline membrane disease has occasionally been associated with renal calcifications, sometimes barely visible on X-ray but sometimes in staghorn form, filling the renal pelves. Some of these calculi have been dissolved, and hypercalciuria has been reported to have decreased, when chlorothiazide has been coadministered along with the loop diuretic. In other premature neonates with hyaline membrane disease, another loop diuretic has been reported to increase the risk of persistent patent ductus arteriosus, possibly through a prostaglandin-E-mediated process. The use of torsemide in such patients has not been studied.

**Geriatric Use**

Of the total number of patients who received torsemide in United States clinical studies, 24% were 65 or older while about 4% were 75 or older. No specific age-related differences in effectiveness or safety were observed between younger patients and elderly patients.

## ADVERSE REACTIONS

At the time of approval, torsemide had been evaluated for safety in approximately 4000 subjects: over 800 of these subjects received torsemide for at least 6 months, and over 380 were treated for more than 1 year. Among these subjects were 564 who received torsemide during United States-based trials in which 274 other subjects received placebo.

The reported side effects of torsemide were generally transient, and there was no relationship between side effects and age, sex, race, or duration of therapy. Discontinuation of therapy due to side effects occurred in 3.5% of United States patients treated with torsemide and in 4.4% of patients treated with placebo. In studies conducted in the United States and Europe, discontinuation rates due to side effects were 3.0% (38/1250) with torsemide and 3.4% (13/380) with furosemide in patients with congestive heart failure, 2.0% (8/409) with torsemide and 4.8% (11/230) with furosemide in patients with renal insufficiency, and 7.6% (13/170) with torsemide and 0% (0/33) with furosemide in patients with cirrhosis.

The most common reasons for discontinuation of therapy with torsemide were (in descending order of frequency) dizziness, headache, nausea, weakness, vomiting, hyperglycemia, excessive urination, hyperuricemia, hypokalemia, excessive thirst, hypovolemia, impotence, esophageal hemorrhage, and dyspepsia. Dropout rates for these adverse events ranged from 0.1% to 0.5%.

The side effects considered possibly or probably related to study drug that occurred in United States placebo-controlled trials in more than 1% of patients treated with torsemide are shown in Table 1.

**Table 1: Reactions Possibly or Probably Drug-Related United States Placebo-Controlled Studies Incidence (Percentages of Patients)**

| | Torsemide (N=564) | Placebo (N=274) |
|---|---|---|
| Headache | 7.3 | 9.1 |
| Excessive Urination | 6.7 | 2.2 |
| Dizziness | 3.2 | 4.0 |
| Rhinitis | 2.8 | 2.2 |
| Asthenia | 2.0 | 1.5 |
| Diarrhea | 2.0 | 1.1 |
| ECG Abnormality | 2.0 | 0.4 |
| Cough Increase | 2.0 | 1.5 |
| Constipation | 1.8 | 0.7 |
| Nausea | 1.8 | 0.4 |
| Arthralgia | 1.8 | 0.7 |
| Dyspepsia | 1.6 | 0.7 |
| Sore Throat | 1.6 | 0.7 |
| Myalgia | 1.6 | 1.5 |
| Chest Pain | 1.2 | 0.4 |
| Insomnia | 1.2 | 1.8 |
| Edema | 1.1 | 1.1 |
| Nervousness | 1.1 | 0.4 |

The daily doses of torsemide used in these trials ranged from 1.25 mg to 20 mg, with most patients receiving 5 mg to 10 mg; the duration of treatment ranged from 1 to 52 days, with a median of 41 days. Of the side effects listed in the table, only "excessive urination" occurred significantly more frequently in patients treated with torsemide than in patients treated with placebo. In the placebo-controlled hypertension studies whose design allowed side-effect rates to be attributed to dose, excessive urination was reported by 1% of patients receiving placebo, 4% of those treated with 5 mg of daily torsemide, and 15% of those treated with 10 mg. The complaint of excessive urination was generally not reported as an adverse event among patients who received torsemide for cardiac, renal, or hepatic failure.

Serious adverse events reported in the clinical studies for which a drug relationship could not be excluded were atrial fibrillation, chest pain, diarrhea, digitalis intoxication, gastrointestinal hemorrhage, hyperglycemia, hyperuricemia, hypokalemia, hypotension, hypovolemia, shunt thrombosis, rash, rectal bleeding, syncope, and ventricular tachycardia.

Angioedema has been reported in a patient exposed to torsemide who was later found to be allergic to sulfa drugs.

Of the adverse reactions during placebo-controlled trials listed without taking into account assessment of relatedness to drug therapy, arthritis and various other nonspecific musculoskeletal problems were more frequently reported in association with torsemide than with placebo, even though gout was somewhat more frequently associated with placebo. These reactions did not increase in frequency or severity with the dose of torsemide. One patient in the group treated with torsemide withdrew due to myalgia, and one in the placebo group withdrew due to gout.

***Hypokalemia:*** See **WARNINGS.**

## OVERDOSAGE

There is no human experience with overdoses of torsemide, but the signs and symptoms of overdosage can be anticipated to be those of excessive pharmacologic effect: dehydration, hypovolemia, hypotension, hyponatremia, hypokalemia, hypochloremic alkalosis, and hemoconcentration. Treatment of overdosage should consist of fluid and electrolyte replacement.

Laboratory determinations of serum levels of torsemide and its metabolites are not widely available.

No data are available to suggest physiological maneuvers (e.g., maneuvers to change the pH of the urine) that might accelerate elimination of torsemide and its metabolites. Torsemide is not dialyzable, so hemodialysis will not accelerate elimination.

## DOSAGE AND ADMINISTRATION

### General

Torsemide tablets may be given at any time in relation to a meal, as convenient. Special dosage adjustment in elderly patients is not necessary.

Because of the high bioavailability of torsemide, oral and intravenous doses are therapeutically equivalent, so patients may be switched to and from the intravenous form with no change in dose.

***Congestive Heart Failure:*** The usual initial dose is 10 mg or 20 mg of once-daily oral torsemide. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 200 mg have not been adequately studied.

***Chronic Renal Failure:*** The usual initial dose of torsemide is 20 mg of once-daily oral torsemide. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 200 mg have not been adequately studied.

***Hepatic Cirrhosis:*** The usual initial dose is 5 mg or 10 mg of once-daily oral torsemide, administered together with an aldosterone antagonist or a potassium-sparing diuretic. If the diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained. Single doses higher than 40 mg have not been adequately studied.

Chronic use of any diuretic in hepatic disease has not been studied in adequate and well-controlled trials.

***Hypertension:*** The usual initial dose is 5 mg once daily. If the 5 mg dose does not provide adequate reduction in blood pressure within 4 to 6 weeks, the dose may be increased to 10 mg once daily. If the response to 10 mg is insufficient, an additional antihypertensive agent should be added to the treatment regimen.

## HOW SUPPLIED

Torsemide Tablets 5 mg are available for oral administration as white to off-white, capsule shaped, scored tablets, imprinted "APO" on one side and "T" bisect "5" on the other side. They are supplied as follows:
Bottles of 100 (NDC 60505-0232-1)
Bottles of 1000 (NDC 60505-0232-2).

Torsemide Tablets 10 mg are available for oral administration as white to off-white, capsule shaped, scored tablets, imprinted "APO" on one side and "TO" bisect "10" on the other side. They are supplied as follows:
Bottles of 100 (NDC 60505-0233-1)
Bottles of 1000 (NDC 60505-0233-2).

Torsemide Tablets 20 mg are available for oral administration as white to off-white, capsule shaped, scored tablets, imprinted "APO" on one side and "TO" bisect "20" on the other side. They are supplied as follows:
Bottles of 100 (NDC 60505-0234-1)
Bottles of 1000 (NDC 60505-0234-2).

Torsemide Tablets 100 mg are available for oral administration as white to off-white, capsule shaped, scored tablets, imprinted "APO" on one side and "TOR" bisect "100" on the other side. They are supplied as follows:
Bottles of 100 (NDC 60505-0235-1)
Bottles of 1000 (NDC 60505-0235-2).

### Storage

Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].

Dispense in a tight, light-resistant container [see USP].

**TORPHARM INC.**
**TORSEMIDE TABLETS**
**5 mg, 10 mg, 20 mg and 100 mg**

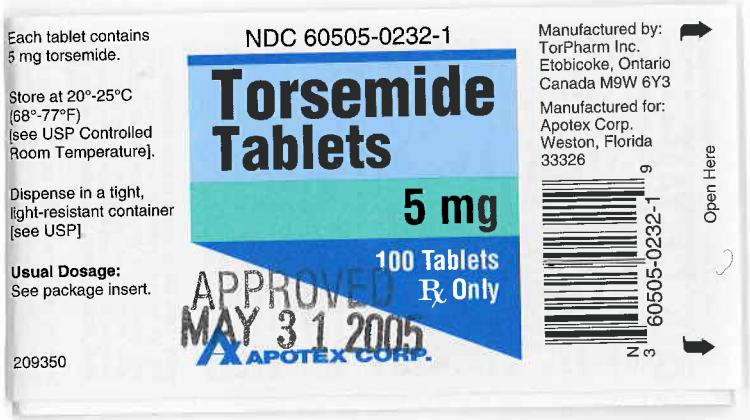
| Manufactured by: | Manufactured for: |
|---|---|
| TorPharm Inc. | Apotex Corp. |
| Etobicoke, Ontario | Weston, Florida |
| Canada M9W 6Y3 | 33326 |

*(TORSEMIDE-TAB-R01-51X100-LFLT-012004)*

Revised: January 2004

209350

Rev. 1


Each tablet contains
5 mg torsemide.
Store at 20°-25°C
(68°-77°F)
[see USP Controlled
Room Temperature].
Dispense in a tight,
light-resistant container
[see USP].
Usual Dosage:
See package insert.
209350
NDC 60505-0232-1
Torsemide
Tablets
5 mg
100 Tablets
℞ Only
APPROVED
MAY 3 1 2005
APOTEX CORP.
Manufactured by:
TorPharm Inc.
Etobicoke, Ontario
Canada M9W 6Y3
Manufactured for:
Apotex Corp.
Weston, Florida
33326
N 3 60505-0232-1 9
Open Here

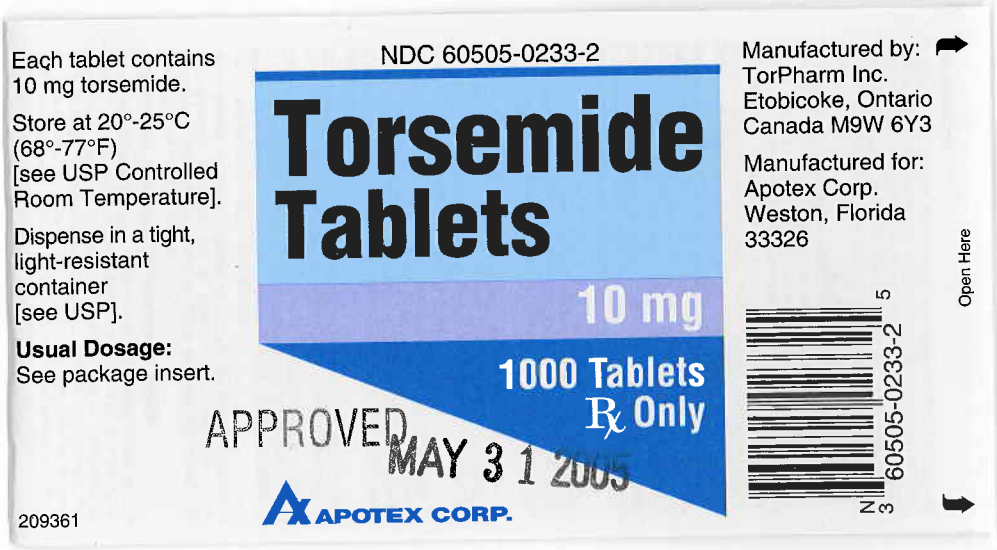
49


Each tablet contains
5 mg torsemide.
Store at 20°-25°C
(68°-77°F)
[see USP Controlled
Room Temperature].
Dispense in a tight,
light-resistant container
[see USP].
Usual Dosage:
See package insert.
209357
NDC 60505-0232-2
Torsemide
Tablets
5 mg
1000 Tablets
℞ Only
APPROVED
MAY 3 1 2005
APOTEX CORP.
Manufactured by:
TorPharm Inc.
Etobicoke, Ontario
Canada M9W 6Y3
Manufactured for:
Apotex Corp.
Weston, Florida
33326
N 3 60505-0232-2 6
Open Here

62


Each tablet contains 10 mg torsemide.
Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container [see USP].
Usual Dosage: See package insert.
209359
NDC 60505-0233-1
Torsemide Tablets
10 mg
100 Tablets
Rx Only
APPROVED MAY 31 2005
APOTEX CORP.
Manufactured by: TorPharm Inc. Etobicoke, Ontario Canada M9W 6Y3
Manufactured for: Apotex Corp. Weston, Florida 33326
N 3 60505-0233-1 8
Open Here

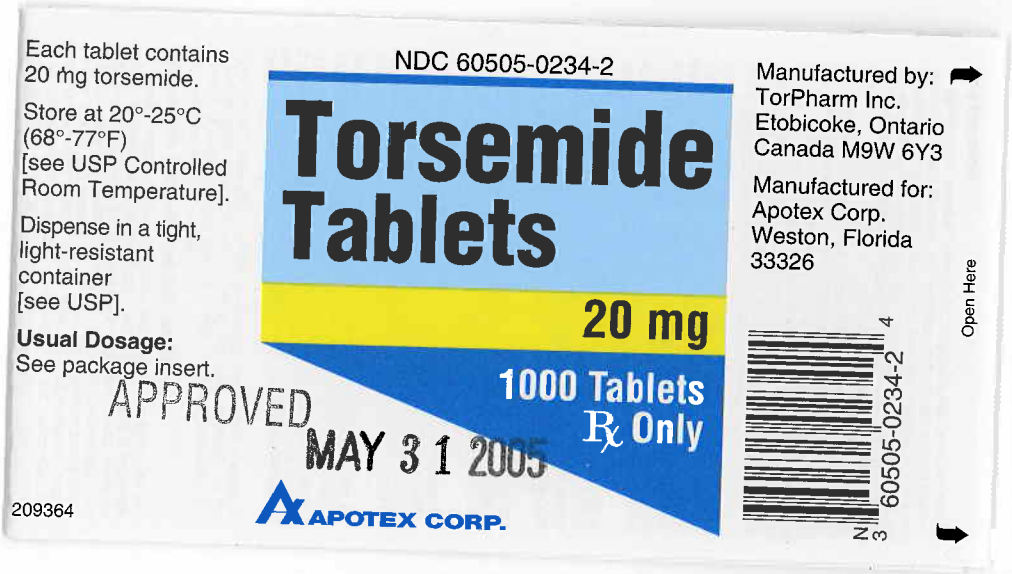
7 5


Each tablet contains 10 mg torsemide.
Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container [see USP].
Usual Dosage: See package insert.
209361
NDC 60505-0233-2
Torsemide Tablets
10 mg
1000 Tablets
Rx Only
APPROVED MAY 31 2005
APOTEX CORP.
Manufactured by: TorPharm Inc. Etobicoke, Ontario Canada M9W 6Y3
Manufactured for: Apotex Corp. Weston, Florida 33326
N 3 60505-0233-2 5
Open Here

8 8


Each tablet contains 20 mg torsemide.
Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container [see USP].
Usual Dosage: See package insert.
209362
NDC 60505-0234-1
Torsemide Tablets
20 mg
100 Tablets
Rx Only
APOTEX CORP.
Manufactured by: TorPharm Inc. Etobicoke, Ontario Canada M9W 6Y3
Manufactured for: Apotex Corp. Weston, Florida 33326
Open Here
60505-0234-1

101


Each tablet contains 20 mg torsemide.
Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container [see USP].
Usual Dosage: See package insert.
APPROVED MAY 31 2005
209364
NDC 60505-0234-2
Torsemide Tablets
20 mg
1000 Tablets
Rx Only
APOTEX CORP.
Manufactured by: TorPharm Inc. Etobicoke, Ontario Canada M9W 6Y3
Manufactured for: Apotex Corp. Weston, Florida 33326
Open Here
60505-0234-2

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Each tablet contains 100 mg torsemide.
Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container [see USP].
Usual Dosage: See package insert.
APPROVED
MAY 31 2005
209368
NDC 60505-0235-2
Torsemide Tablets
100 mg
1000 Tablets
℞ Only
APOTEX CORP.
Manufactured by:
TorPharm Inc.
Etobicoke, Ontario
Canada M9W 6Y3
Manufactured for:
Apotex Corp.
Weston, Florida
33326
Open Here
3 60505-0235-2 3




Each tablet contains 100 mg torsemide.
Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].
Dispense in a tight, light-resistant container [see USP].
Usual Dosage: See package insert.
APPROVED
MAY 31 2005
209367
NDC 60505-0235-1
Torsemide Tablets
100 mg
100 Tablets
℞ Only
APOTEX CORP.
Manufactured by:
TorPharm Inc.
Etobicoke, Ontario
Canada M9W 6Y3
Manufactured for:
Apotex Corp.
Weston, Florida
33326
Open Here
3 60505-0235-1 6

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 76-894

# LABELING REVIEWS

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

| | |
|---|---|
| ANDA Number: | 76-894 |
| Date of Submission: | November 6, 2003 |
| Applicant's Name: | TorPharm Inc. |
| Established Name: | Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg |

Labeling Deficiencies

1. CONTAINER [Bottles of 100s and 1000s]
   Satisfactory in draft.

2. INSERT
   a. CLINICAL PHARMACOLOGY, Clinical Effects, first paragraph: Delete the first sentence.
   b. CONTRAINDICATIONS, second sentence: "Torsemide tablets are contraindicated..."
   c. DOSAGE AND ADMINISTRATION, General: add as the second sentence "Because of the high bioavailability of torsemide, oral and intravenous doses are therapeutically equivalent, so patients may be switched to and from the intravenous form with no change in dose."

Please revise your labels and labeling, as instructed above, and submit 12 copies of final printed labels and labeling.

Prior to approval, it may be necessary to revise your labeling subsequent to approved changes for the reference listed drug. In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address -

http://www.fda.gov/cder/cdernew/listserv.html

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submission with all differences annotated and explained.

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

## REVIEW OF PROFESSIONAL LABELING CHECK LIST

| Established Name | Yes | No | N.A. |
|---|---|---|---|
| Different name than on acceptance to file letter? | | X | |
| Is this product a USP item? If so, USP supplement in which verification was assured. USP 27 | | X | |
| Is this name different than that used in the Orange Book? | | X | |
| If not USP, has the product name been proposed in the PF? | | | X |
| Error Prevention Analysis | | | |
| Has the firm proposed a proprietary name? If yes, complete this subsection. | | X | |
| Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? | | | X |
| Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? | | | X |
| Packaging | | | |
| Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. | | X | |
| Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. | | X | |
| Does the package proposed have any safety and/or regulatory concerns? | | X | |
| If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection? | | | X |
| Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration? | | | X |
| Is the strength and/or concentration of the product unsupported by the insert labeling? | | X | |
| Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect? | | | X |
| Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? | | X | |
| Are there any other safety concerns? | | X | |
| Labeling | | | |
| Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). | | X | |
| Has applicant failed to clearly differentiate multiple product strengths? | | X | |
| Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines) | | X | |
| Labeling(continued) | | | |
| Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA) | | X | |
| Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed? | | X | |
| Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED? | | X | |
| Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. | | X | |
| Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR | | | |
| Is the scoring configuration different than the RLD? | | X | |
| Has the firm failed to describe the scoring in the HOW SUPPLIED section? | | X | |
| Inactive Ingredients: (FTR: List page # in application where inactives are listed) | | | |

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

## NOTES/QUESTIONS TO THE CHEMIST:

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## FOR THE RECORD:

1. MODEL LABELING

   Review was based on the labeling of the most recently approved labeling for the reference listed drug; Demadex®; Approved February 13, 1998, 20-136/S-011; revised December, 1997. This is a combined insert of the Tablets and Injection. Therefore, information pertaining to the Injection formulation should be carved out except for one sentence in the D&A section.

   Drug substance: USP; Drug product: non-USP

2. PATENTS/EXCLUSIVITIES

   **Patent Data**

   [redacted]

   020136 001 RE34672 AUG 11,2006

   Torpharm provided a PIV certification to this patent.

   **Exclusivity Data**

   There is no unexpired exclusivity for this product.

   [Vol. B1.1, pg. 9 & 11]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
   TorPharm Inc.
   50 Steinway Boulevard
   Stobicoke, Ontario

M9W 6Y3
Canada
[Vol.B.1.2, pg. 4988]

4. CONTAINER/CLOSURE
Bottle: HDPE
Caps: Screw Caps
[Vol. B1.4, pg. 5485]

5. INACTIVE INGREDIENTS
The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. B1.2, pg. 4823] Torsemide, colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose

6. PACKAGING CONFIGURATIONS
RLD: The innovator markets their product as 5mg, 10mg, 20mg and 100mg strength in bottles containing 100 and tablets and unit dose packages of 100
ANDA: The applicant proposes to market the 5mg, 10mg, 20mg and 100mg strengths bottles of 100s and 1000s
[Vol. B1.4, pg. 5485]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
USP: Preserve in well-closed containers. (note: drug substance is USP, not the drug product)
RLD: Container: Store at 15 - 30°C (59 – 86°F)
Insert: Store all dosage forms at controlled room temperature, 15 - 30°C (59 – 86°F). Do not Freeze.
ANDA: Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].
Stability: 25°/60%RH [Vol. 1.5, pg. 6043]

8. DISPENSING STATEMENTS COMPARISON
USP: Not applicable
RLD: Container only: Dispense in tight containers as defined in USP/NF.
ANDA: Dispense in a tight, light-resistant container [see USP].

9. TABLET IMPRINT & SCORING

RLD-tablets are scored

ANDA: [vol. A1.4]
- 5 mg: White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "T" bisect "5" on the other side. [pg. 5659]
- 10 mg: White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "TO" bisect "10" on the other side. [pg. 5666]
- 20 mg: White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "TO" bisect "20" on the other side. [pg. 5673]
- 100 mg: White to off white capsule shaped, scored tablets with "APO" on one side and "TOR" bisect "100" on the other side. [pg. 5679

10. BIOAVAILABILITY/BIOEQUIVALENCE:

Pending as of 12/29/2003

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Date of Review: January 7, 2004 Date of Submission: November 6, 2003

Primary Reviewer: Ruby Wu RWu Date: 1/7/04

Team Leader: John Grace John Grace 1/9/2004

cc:
ANDA: 76-894
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSNZ\TORPHARM\LTRS&REV\76894.na1.L.doc
Review

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

ANDA Number: 76-894
Date of Submission: February 16, 2004
Applicant's Name: TorPharm Inc.
Established Name: Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg

**APPROVAL SUMMARY**

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

2. CONTAINER [Bottles of 100s and 1000s]
Satisfactory in final print as of the February 16, 2004 amendment. [Vol. A2.1]

3. EXTENDED OUTSERT:
Satisfactory in final print as of the February 16, 2004 amendment. [Vol. A2.1, Revised Jan 2004]

4. Revisions needed post-approval: No.

5. Patent Data – NDA 20-136

| Patent No. | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| RE34672 | August 11, 2006 | None | | Paragraph IV | None |

Exclusivity Data– NDA 20-136

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

**BASIS OF APPROVAL:**
Was this approval based upon a petition? No
What is the RLD on the 356(h) form: Demadex®
NDA Number: N 20-136/S-011
NDA Drug Name: Demadex®
NDA Firm: Boehringer Mannheim Corporation
Date of Approval of NDA Insert and supplement: NDA 20-136/S-011; Revised December 1997; Approved February 13, 1998;
Has this been verified by the MIS system for the NDA? Yes
Was this approval based upon an OGD labeling guidance? No
Basis of Approval for the Container Labels: Most recently approved labeling of the reference listed drug

# REVIEW OF PROFESSIONAL LABELING CHECK LIST

| Established Name | Yes | No | N.A. |
|---|---|---|---|
| Different name than on acceptance to file letter? | | X | |
| Is this product a USP item? If so, USP supplement in which verification was assured. USP 27 | | X | |
| Is this name different than that used in the Orange Book? | | X | |
| If not USP, has the product name been proposed in the PF? | | | X |
| Error Prevention Analysis | | | |
| Has the firm proposed a proprietary name? If yes, complete this subsection. | | X | |
| Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present? | | | X |
| Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified? | | | X |
| Packaging | | | |
| Is this a new packaging configuration, never been approved by an ANDA or NDA? If yes, describe in FTR. | | X | |
| Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. | | X | |
| Does the package proposed have any safety and/or regulatory concerns? | | X | |
| If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection? | | | X |
| Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration? | | | X |
| Is the strength and/or concentration of the product unsupported by the insert labeling? | | X | |
| Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect? | | | X |
| Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product? | | X | |
| Are there any other safety concerns? | | X | |
| Labeling | | | |
| Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label). | | x | |
| Has applicant failed to clearly differentiate multiple product strengths? | | X | |
| Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines) | | X | |
| Labeling(continued) | | | |
| Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA) | | X | |
| Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed? | | X | |
| Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED? | | X | |
| Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported. | | X | |
| Scoring: Describe scoring configuration of RLD and applicant (page #) in the FTR | | | |
| Is the scoring configuration different than the RLD? | | x | |
| Has the firm failed to describe the scoring in the HOW SUPPLIED section? | | X | |
| Inactive Ingredients: (FTR: List page # in application where inactives are listed) | | | |

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

**NOTES/QUESTIONS TO THE CHEMIST:**

---

**FOR THE RECORD:**

1. MODEL LABELING

Review was based on the labeling of the most recently approved labeling for the reference listed drug; Demadex®; Approved February 13, 1998, 20-136/S-011; revised December, 1997. This is a combined insert of the Tablets and Injection. Therefore, information pertaining to the Injection formulation should be carved out except for one sentence in the D&A section.

Drug substance: USP; Drug product: non-USP

2. PATENTS/EXCLUSIVITIES NDA 20-136

| Patent No. | Patent Expiration | Use Code | Description | How Filed | Labeling Impact |
|---|---|---|---|---|---|
| RE34672 | August 11, 2006 | None | | Paragraph IV | None |

Exclusivity Data

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

Torpharm provided a PIV certification to this patent.
[Vol. B1.1, pg. 9 & 11]

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
TorPharm Inc.
50 Steinway Boulevard
Stobicoke, Ontario

M9W 6Y3
Canada
[Vol.B.1.2, pg. 4988]

4. CONTAINER/CLOSURE
Bottle: HDPE
Caps: Screw Caps
[Vol. B1.4, pg. 5485]

5. INACTIVE INGREDIENTS
The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. B1.2, pg. 4823] Torsemide, colloidal silicon dioxide, crospovidone, lactose monohydrate, magnesium stearate, microcrystalline cellulose

6. PACKAGING CONFIGURATIONS
RLD: The innovator markets their product as 5mg, 10mg, 20mg and 100mg strength in bottles containing 100 and tablets and unit dose packages of 100
ANDA: The applicant proposes to market the 5mg, 10mg, 20mg and 100mg strengths bottles of 100s and 1000s
[Vol. B1.4, pg. 5485]

7. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
USP: Preserve in well-closed containers. (note: drug substance is USP, not the drug product)
RLD: Container: Store at 15 - 30°C (59 – 86°F)
Insert: Store all dosage forms at controlled room temperature, 15 - 30°C (59 – 86°F). Do not Freeze.
ANDA: Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature].
Stability: 25°/60%RH [Vol. 1.5, pg. 6043]

8. DISPENSING STATEMENTS COMPARISON
USP: Not applicable
RLD: Container only: Dispense in tight containers as defined in USP/NF.
ANDA: Dispense in a tight, light-resistant container [see USP].

9. TABLET IMPRINT & SCORING

RLD-tablets are scored

ANDA: [vol. A1.4]

- 5 mg: White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "T" bisect "5" on the other side. [pg. 5659]
- 10 mg: White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "TO" bisect "10" on the other side. [pg. 5666]
- 20 mg: White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "TO" bisect "20" on the other side. [pg. 5673]
- 100 mg: White to off white capsule shaped, scored tablets with "APO" on one side and "TOR" bisect "100" on the other side. [pg. 5679

10. BIOAVAILABILITY/BIOEQUIVALENCE:

Pending as of 03/08/04

---

Date of Review: March 8, 2004 Date of Submission: February 16, 2004

Primary Reviewer: Ruby Wu RWu Date: 3/8/04

Team Leader: John Grace Date: 3/10/04

cc:
ANDA: 76-894
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSNZ\TORPHARM\LTRS&REV\76894.ap.L.doc
Review

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 76-894

# CHEMISTRY REVIEWS

# ANDA 76-894

## Torsemide Tablets 5 mg, 10 mg, 20 mg, and 100 mg

## TorPharm Inc.

**Kathy P. Woodland**
**Chemistry Division I**

# Table of Contents

# Chemistry Review Data Sheet

1. ANDA 76-894

2. REVIEW #: 1

3. REVIEW DATE: April 20, 2004

4. REVIEWER: Kathy P. Woodland

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| N/A | |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| **Firm:** | |
| Original Submission | November 6, 2003 |
| New Correspondence | December 9, 2003 |
| Labeling Amendment | February 16, 2004 |
| Patent Amendment | February 25, 2004 |
| **Agency:** | |
| Agency Acknowledgement Letter (Acceptable for filing: November 7, 2003) | December 15, 2003 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | TorPharm Inc. |
| Address: | 50 Steinway Boulevard<br>Etobicoke, Ontario M9W 6Y3 Canada |
| Agent: | Apotex Corp.<br>616 Heathrow Drive, Lincolnshire, IL 60069 |
| Representative: | Marcy Macdonald |
| Telephone: | 847-821-8005 |
| Fax: | 847-353-2982 |

## 8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Torsemide Tablets

## 9. LEGAL BASIS FOR SUBMISSION:

a. The basis for TorPharm's proposed ANDA for Torsemide Tablets 5 mg, 10 mg, 20 mg, and 100 mg is the approved, listed drug, DEMADEX Tablets 5 mg, 10 mg, 20 mg, and 100 mg, the subject of NDA#020136, held by Roche Laboratories Inc. and Boehringer Mannheim Corporation Therapeutics Division.

b. TorPharm certified that in their opinion and to the best of their knowledge, US Patent RE34,672, expiring August 11, 2006, will not be infringed upon by the manufacture, use or sale by TorPharm of Torsemide Tablets 5 mg, 10 mg, 20 mg, and 100 mg for which the application is submitted.

c. According to information published in the Approved Drug Products Therapeutic Equivalence Evaluations, there are no exclusivities listed for DEMADEX Tablets 5 mg, 10 mg, 20 mg, and 100 mg.

## 10. PHARMACOL. CATEGORY:

Treatment of edema associated with congestive heart failure, renal disease, or hepatic disease. Treatment of hypertension alone or in combination with other antihypertensive agents.

## 11. DOSAGE FORM: Tablets

## 12. STRENGTH/POTENCY: 5 mg, 10 mg, 20 mg, and 100 mg

## 13. ROUTE OF ADMINISTRATION: Oral

## 14. Rx/OTC DISPENSED: _x__Rx ___OTC

## 15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

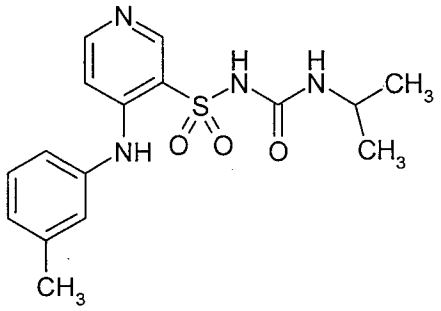
_____SPOTS product – Form Completed

___x___Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Chemistry Review Data Sheet

Generic Name: Torsemide
Chemical Name: 1-Isopropyl-3-(4-*m*-toluidino-3-pyridyl)sulfonyl urea
Formula: $C_{16}H_{20}N_4O_3S$, Molecular weight: 348.42, CAS registry number(s): 56211-40-6



## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE | STATUS | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | | 1 | Inadequate | 4/15/04 | Reviewed by K. Woodland |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | IV | | | 4 | | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| ANDA for Torsemide Tablets | ANDA 76-110 (by Teva Pharms) | Approved by OGD on 05/14/02 |
| ANDA for Torsemide Tablets | ANDA 76-226 (by Par Pharm) | Approved by OGD on 05/27/03 |
| ANDA for Torsemide Tablets | ANDA 76-346 (by Pliva Pharm ) | Approved by OGD on 05/30/03 |

## 18. STATUS:

| **CONSULTS/ CMC RELATED REVIEWS** | **RECOMMENDATION** | **DATE** | **REVIEWER** |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Pending | | |
| Methods Validation | N/A | | |
| Labeling | Acceptable | 3/10/04 | Ruby Wu |
| Bioequivalence | Pending | | |
| EA | N/A | | |
| Radiopharmaceutical | N/A | | |

## 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. __x__ Yes _____ No If no, explain reason(s) below:

APPEARS THIS WAY
ON ORIGINAL

# The Chemistry Review for ANDA 76-894

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

Not Approvable

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Torsemide is a white to off white odorless crystalline powder. It is slightly soluble in sodium hydroxide, hydrochloric acid, ethanol and methanol, slightly soluble in acetone and chloroform, practically insoluble in distilled water and ethyl ether. Torsemide is known to exist in different polymorphic forms. Its formula is $C_{16}H_{20}N_4O_3S$, and it's molecular weight is 348.42.

Drug Product: Torsemide Tablets are available for oral administration as 5 mg, 10 mg, 20 mg, and 100 mg Tablets. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, crospovidone, magnesium stearate, and colloidal silicon dioxide. The tablets have the following description:

| | |
|---|---|
| 5 mg: | White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "T" bisect "5" on the other side. |
| 10 mg: | White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "TO" bisect "10" on the other side. |
| 20 mg: | White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "TO" bisect "20" on the other side |
| 100 mg: | White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "TOR" bisect "100" on the other side |

### B. Description of How the Drug Product is Intended to be Used

Torsemide is a diuretic of the pyridine-sulfonylurea class. Torsemide tablets are indicated for the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease. Torsemide tablets are indicated for the treatment of

hypertension alone or in combination with other antihypertensive agents. Single doses fall in the following ranges:

| | |
|---|---|
| Congestive Heart Failure: | 10 mg or 20 mg once daily* |
| Chronic Renal Failure: | 20 mg once daily* |
| Hepatic Cirrhosis | 5 mg or 10 mg once daily* |

*If the desired diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained.

Tablets are to be stored at $20^0$ -$25^0$C ($68^0$-$77^0$F). Dispense in a tight, light-resistant container. The expiration of the product is 2 years.

**C. Basis for Approvability or Not-Approval Recommendation**

There are Chemistry deficiencies in the areas of components/composition, synthesis, raw material controls, container, laboratory controls, and stability. EES and Bioequivalence are pending.

## III. Administrative

**A. Reviewer's Signature** Kathy P. Woodland

**B. Endorsement Block**

HFD-620/Kathy Woodland/review chemist/ Kathy Woodland 4/23/04
HFD-620/Shing Liu, Ph.D./team leader/ S.H.Liu 4/23/04
HFD-617/Wanda Pamphile, Pharm.D./project manager/ ~~WP~~ 4/23/04

V:\FIRMSNZ\TORPHARM\LTRS7REV\76894.CR1.DOC

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of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

4.

5.

6.

7.

8.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The USP methods for Torsemide USP are the regulatory methods. In the event of a dispute, the USP method will prevail.

2. All facilities referenced in the ANDA should have a satisfactory compliance evaluation at the time of approval. We have requested an evaluation from the Office of Compliance.

3. The bioequivalence portion of your submission is under review. Deficiencies, if any, will be communicated to you separately. If the Division of

Bioequivalence recommends that you revise your dissolution method and/or specifications, please update your ANDA as follows:

a. Provide revised specification sheets for the drug product release and stability to reflect the revised dissolution method and specifications.

b. Conduct the dissolution test by using the recommended dissolution test method and specifications on the 3rd month accelerated stability samples for all packaging configurations, and submit your test results. You may use samples which have already been taken out from the accelerated stability study chamber and placed under ambient conditions.

c. If the aforementioned accelerated stability samples are no longer available, please pull samples from the control room temperature stability chamber and conduct the dissolution test using the recommended dissolution test method and specifications. Please submit test results as soon as possible, and do not wait for the next stability testing time point.

   Please be advised that the age of the samples at the time of testing may be the expiration dating period that the Agency will grant to the drug product. For example, if the samples have been kept in the control room temperature stability chamber for 14 months, the expiration dating period for the ANDA may be 14 months, provided that the recommended dissolution specifications and all other stability test specifications are met.

d. If you do not have full term stability data to show that the samples meet the recommended dissolution specifications at the 24 month test station, please provide a revised stability protocol to reflect the reduced expiration dating period.

4. Please submit any updated stability data.

Sincerely yours,

for 4/23/04

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

SEP 1 0 2004

# ANDA 76-894

## Torsemide Tablets 5 mg, 10 mg, 20 mg, and 100 mg

## Apotex, Inc.

**Kathy P. Woodland**
**Chemistry Division I**

# Table of Contents

# Chemistry Review Data Sheet

1. ANDA 76-894

2. REVIEW #: 2

3. REVIEW DATE: July 30, 2004
   September 9, 2004 (revised)

4. REVIEWER: Kathy P. Woodland

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| **Firm:** | |
| Original Submission | November 6, 2003 |
| New Correspondence | December 9, 2003 |
| Labeling Amendment | February 16, 2004 |
| Patent Amendment | February 25, 2004 |
| **Agency:** | |
| Agency Acknowledgement Letter (Acceptable for filing: November 7, 2003) | December 15, 2003 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Amendment (CMC) | June 30, 2004 |
| New Correspondence (name change) | June 30, 2004 |
| Patent Amendment | July 26, 2004 |
| Bio Amendment | August 9, 2004 |
| Bio Amendment | August 16, 2004 |

7. NAME & ADDRESS OF APPLICANT:

| | |
|---|---|
| Name: | Apotex Inc.-(formerly TorPharm, Inc.) |
| Address: | 50 Steinway Boulevard |

Chemistry Review Data Sheet

Etobicoke, Ontario M9W 6Y3 Canada

| | |
|---|---|
| Agent: | Apotex Corp.<br>616 Heathrow Drive, Lincolnshire, IL 60069 |
| Representative: | Marcy Macdonald |
| Telephone: | 847-821-8005 |
| Fax: | 847-353-2982 |

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Torsemide Tablets

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for TorPharm's proposed ANDA for Torsemide Tablets 5 mg, 10 mg, 20 mg, and 100 mg is the approved, listed drug, DEMADEX Tablets 5 mg, 10 mg, 20 mg, and 100 mg, the subject of NDA#020136, held by Roche Laboratories Inc. and Boehringer Mannheim Corporation Therapeutics Division.

b. TorPharm certified that in their opinion and to the best of their knowledge, US Patent RE34,672, expiring August 11, 2006, will not be infringed upon by the manufacture, use or sale by TorPharm of Torsemide Tablets 5 mg, 10 mg, 20 mg, and 100 mg for which the application is submitted.

c. According to information published in the Approved Drug Products Therapeutic Equivalence Evaluations, there are no exclusivities listed for DEMADEX Tablets 5 mg, 10 mg, 20 mg, and 100 mg.

10. PHARMACOL. CATEGORY:

Treatment of edema associated with congestive heart failure, renal disease, or hepatic disease. Treatment of hypertension alone or in combination with other antihypertensive agents.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 5 mg, 10 mg, 20 mg, and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

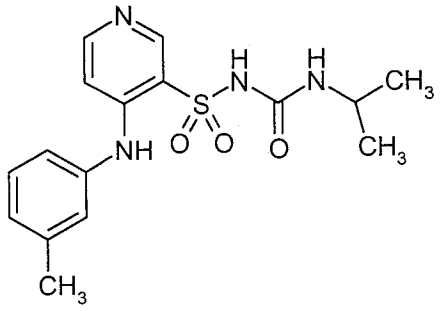
Chemistry Review Data Sheet

_____SPOTS product – Form Completed

___x___Not a SPOTS product

## 16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Generic Name: Torsemide
Chemical Name: 1-Isopropyl-3-(4-*m*-toluidino-3-pyridyl)sulfonyl urea
Formula: $C_{16}H_{20}N_4O_3S$, Molecular weight: 348.42, CAS registry number(s): 56211-40-6



## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE | STATUS | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | | 1 | Inadequate | 7/31/04 | Reviewed by K. Woodland |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | IV | | | 4 | | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| ANDA for Torsemide Tablets | ANDA 76-110 (by Teva Pharms) | Approved by OGD on 05/14/02 |
| ANDA for Torsemide Tablets | ANDA 76-226 (by Par Pharm) | Approved by OGD on 05/27/03 |
| ANDA for Torsemide Tablets | ANDA 76-346 (by Pliva Pharm ) | Approved by OGD on 05/30/03 |

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Acceptable | 7/22/04 | S. Adams |
| Methods Validation | N/A | | |
| Labeling | Acceptable | 3/10/04 | R. Wu |
| Bioequivalence | Deficient | 8/31/04 | H. Nguyen |
| EA | N/A | | |
| Radiopharmaceutical | N/A | | |

## 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __x__ No If no, explain reason(s) below:

**Minor Amendment**

# The Chemistry Review for ANDA 76-894

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

Not Approvable

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Torsemide is a white to off white odorless crystalline powder. It is slightly soluble in sodium hydroxide, hydrochloric acid, ethanol and methanol, slightly soluble in acetone and chloroform, practically insoluble in distilled water and ethyl ether. Torsemide is known to exist in different polymorphic forms. Its formula is $C_{16}H_{20}N_4O_3S$, and it's molecular weight is 348.42.

Drug Product: Torsemide Tablets are available for oral administration as 5 mg, 10 mg, 20 mg, and 100 mg Tablets. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, crospovidone, magnesium stearate, and colloidal silicon dioxide. The tablets have the following description:

| | |
|---|---|
| 5 mg: | White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "T" bisect "5" on the other side. |
| 10 mg: | White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "TO" bisect "10" on the other side. |
| 20 mg: | White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "TO" bisect "20" on the other side |
| 100 mg: | White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "TOR" bisect "100" on the other side |

### B. Description of How the Drug Product is Intended to be Used

Torsemide is a diuretic of the pyridine-sulfonylurea class. Torsemide tablets are indicated for the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease. The MDD is 100 mg. Torsemide tablets are indicated for the

treatment of hypertension alone or in combination with other antihypertensive agents. Single doses fall in the following ranges:

| | |
|---|---|
| Congestive Heart Failure: | 10 mg or 20 mg once daily* |
| Chronic Renal Failure: | 20 mg once daily* |
| Hepatic Cirrhosis | 5 mg or 10 mg once daily* |

*If the desired diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained.

Tablets are to be stored at $20^0$ -$25^0$C ($68^0$-$77^0$F). Dispense in a tight, light-resistant container. The expiration of the product is 2 years.

**C. Basis for Approvability or Not-Approval Recommendation**

There are Chemistry deficiencies in the areas of synthesis and laboratory controls. Bioequivalence is deficient.

## III. Administrative

**A. Reviewer's Signature** Kathy P. Woodland

**B. Endorsement Block**

HFD-620/Kathy Woodland/review chemist/9/8/04 K Woodland 9/10/04
HFD-620/Shing Liu, Ph.D./team leader/9/8/04 S.H. Liu 9/10/04
HFD-617/Wanda Pamphile, Pharm.D./project manager/ ~~WP~~ 9/9/04

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F/T by: wp 9/9/04

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confidential commercial

information from

CHEMISTRY REVIEW #2

## 36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-894 APPLICANT: Apotex, Inc.

DRUG PRODUCT: Torsemide Tablets, 5 mg, 10 mg, 20 mg, and 100 mg

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File (DMF) No. [redacted], was found deficient. The DMF holder has been notified. Please do not respond to this letter until you have been informed by the DMF holder that all deficiencies have been addressed.

2. Please submit [redacted] test for the drug product.

3. Please refer to the revised COA sent by your drug substance manufacturer and revise the [redacted] limit accordingly. Please submit a revised COA with complete testing.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

Please respond to the bioequivalence deficiencies communicated to you via facsimile on September 7, 2004.

Sincerely yours,

for 9/10/04

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

# ANDA 76-894

## Torsemide Tablets 5 mg, 10 mg, 20 mg, and 100 mg

## Apotex Inc. (Formerly TorPharm Inc.)

**Kathy P. Woodland**
**Chemistry Division I**

# Table of Contents

# Chemistry Review Data Sheet

1. ANDA 76-894

2. REVIEW #: 3

3. REVIEW DATE: February 16, 2005
   (Revised) March 30, 2005

4. REVIEWER: Kathy P. Woodland

5. PREVIOUS DOCUMENTS:

| Previous Documents | Document Date |
|---|---|
| **Firm:** | |
| Original Submission | November 6, 2003 |
| New Correspondence | December 9, 2003 |
| Labeling Amendment | February 16, 2004 |
| Patent Amendment | February 25, 2004 |
| Amendment | June 30, 2004 |
| **Agency:** | |
| Agency Acknowledgement Letter (Acceptable for filing: November 7, 2003) | December 15, 2003 |

6. SUBMISSION(S) BEING REVIEWED:

| Submission(s) Reviewed | Document Date |
|---|---|
| Amendment | November 12, 2004 |
| Telephone Amendment | March 24, 2005 |

**7. NAME & ADDRESS OF APPLICANT:**

| | |
|---|---|
| Name: | Apotex Inc.- Etobicoke Site (formerly TorPharm Inc.) |
| Address: | 50 Steinway Boulevard<br>Etobicoke, Ontario M9W 6Y3 Canada |
| Agent: | Apotex Corp.<br>616 Heathrow Drive, Lincolnshire, IL 60069 |

Chemistry Review Data Sheet

Representative: Marcy Macdonald
Telephone: 847-821-8005
Fax: 847-353-2982

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: None
b) Non-Proprietary Name (USAN): Torsemide Tablets

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Apotex's (TorPharm's) proposed ANDA for Torsemide Tablets 5 mg, 10 mg, 20 mg, and 100 mg is the approved, listed drug, DEMADEX Tablets 5 mg, 10 mg, 20 mg, and 100 mg, the subject of NDA#020136, held by Roche Laboratories Inc. and Boehringer Mannheim Corporation Therapeutics Division.

b. Apotex (TorPharm) certified that in their opinion and to the best of their knowledge, US Patent RE34,672, expiring August 11, 2006, will not be infringed upon by the manufacture, use or sale by Apotex (TorPharm) of Torsemide Tablets 5 mg, 10 mg, 20 mg, and 100 mg for which the application is submitted.

c. According to information published in the Approved Drug Products Therapeutic Equivalence Evaluations, there are no exclusivities listed for DEMADEX Tablets 5 mg, 10 mg, 20 mg, and 100 mg.

10. PHARMACOL. CATEGORY:

Treatment of edema associated with congestive heart failure, renal disease, or hepatic disease. Treatment of hypertension alone or in combination with other antihypertensive agents.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 5 mg, 10 mg, 20 mg, and 100 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _x__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

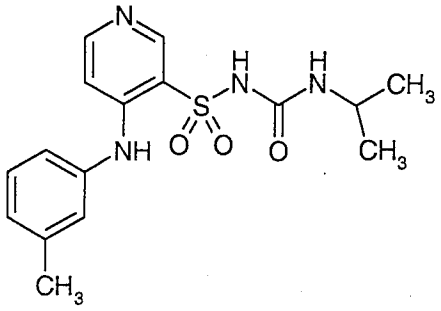
_____SPOTS product – Form Completed

___x___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

APPEARS THIS WAY
ON ORIGINAL

Generic Name: Torsemide
Chemical Name: 1-Isopropyl-3-(4-*m*-toluidino-3-pyridyl)sulfonyl urea
Formula: $C_{16}H_{20}N_4O_3S$, Molecular weight: 348.42, CAS registry number(s): 56211-40-6



## 17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs:**

| DMF # | TYPE | HOLDER | ITEM REFERENCED | CODE | STATUS | DATE REVIEW COMPLETED | COMMENTS |
|---|---|---|---|---|---|---|---|
| | II | | | 1 | Adequate | 2/16/05 | Reviewed by K. Woodland |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | III | | | 4 | | | |
| | IV | | | 4 | | | |

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")
[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

**B. Other Documents:**

| DOCUMENT | APPLICATION NUMBER | DESCRIPTION |
|---|---|---|
| ANDA for Torsemide Tablets | ANDA 76-110 (by Teva Pharms) | Approved by OGD on 05/14/02 |
| ANDA for Torsemide Tablets | ANDA 76-226 (by Par Pharm) | Approved by OGD on 05/27/03 |
| ANDA for Torsemide Tablets | ANDA 76-346 (by Pliva Pharm ) | Approved by OGD on 05/30/03 |

## 18. STATUS:

| CONSULTS/ CMC RELATED REVIEWS | RECOMMENDATION | DATE | REVIEWER |
|---|---|---|---|
| Microbiology | N/A | | |
| EES | Acceptable | 7/22/04 | S. Adams |
| Methods Validation | N/A | | |
| Labeling | Acceptable | 3/10/04 | Ruby Wu |
| Bioequivalence | Acceptable | 5/19/05 | H. Nguyen |
| EA | N/A | | |
| Radiopharmaceutical | N/A | | |

## 19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __x__ No If no, explain reason(s) below:

**Minor Amendment**

**APPEARS THIS WAY ON ORIGINAL**

# The Chemistry Review for ANDA 76-894

## *The Executive Summary*

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

Approvable

### B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

## II. Summary of Chemistry Assessments

### A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance: Torsemide is a white to off white odorless crystalline powder. It is slightly soluble in sodium hydroxide, hydrochloric acid, ethanol and methanol, slightly soluble in acetone and chloroform, practically insoluble in distilled water and ethyl ether. Torsemide is known to exist in different polymorphic forms. Its formula is $C_{16}H_{20}N_4O_3S$, and it's molecular weight is 348.42.

Drug Product: Torsemide Tablets are available for oral administration as 5 mg, 10 mg, 20 mg, and 100 mg Tablets. Inactive ingredients include lactose monohydrate, microcrystalline cellulose, crospovidone, magnesium stearate, and colloidal silicon dioxide. The tablets have the following description:

| | |
|---|---|
| 5 mg: | White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "T" bisect "5" on the other side. |
| 10 mg: | White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "TO" bisect "10" on the other side. |
| 20 mg: | White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "TO" bisect "20" on the other side |
| 100 mg: | White to off white, capsule shaped, scored tablets with "APO" imprinted on one side and "TOR" bisect "100" on the other side |

### B. Description of How the Drug Product is Intended to be Used

Torsemide is a diuretic of the pyridine-sulfonylurea class. Torsemide tablets are indicated for the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease. The MDD is 100 mg. Torsemide tablets are indicated for the

treatment of hypertension alone or in combination with other antihypertensive agents. Single doses fall in the following ranges:

| | |
|---|---|
| Congestive Heart Failure: | 10 mg or 20 mg once daily* |
| Chronic Renal Failure: | 20 mg once daily* |
| Hepatic Cirrhosis | 5 mg or 10 mg once daily* |

*If the desired diuretic response is inadequate, the dose should be titrated upward by approximately doubling until the desired diuretic response is obtained.

Tablets are to be stored at $20^0$ -$25^0$C ($68^0$-$77^0$F). Dispense in a tight, light-resistant container. The expiration of the product is 2 years.

**C. Basis for Approvability or Not-Approval Recommendation**

Approvable

## III. Administrative

**A. Reviewer's Signature**

Kathy P. Woodland

**B. Endorsement Block**

HFD-620/K. Woodland/review chemist/ K Woodland 5/25/05
HFD-620/A. Mueller, Ph.D./team leader/ for 5/25/05
HFD-617/B. Danso, Pharm.D./project manager/5-25-05 5/26/05

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F/T by:

Redacted 8 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

The drug substance is listed in the USP. The drug product is not compendial. Method validation will not be issued for this ANDA based on the current criteria, which are listed in the following table:

| Criterion | Justification/Risk |
|---|---|
| New emerging analytical technologies | Not Applicable |
| Analytical methods for novel/complex drug delivery systems (e.g. TDS, MDI, nasal spray) | Not Applicable |
| Chromatographic methods for resolving multiple drug components with concomitant impurities/degradants | Not Applicable |
| chromatographic methods for quantitation of low dose drugs | Not Applicable |
| Others | Not Applicable |

**32. LABELING** Acceptable on 3/10/04 by Ruby Wu

**33. ESTABLISHMENT INSPECTION** Acceptable on 7/22/04 by S.Adams

**34. BIOEQUIVALENCE** Acceptable on 5/19/05 by H. Nguyen

**35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION: Satisfactory Rv #1**

cc: ANDA 76-894
ANDA DUP 76-894
DIV FILE
Field Copy

Endorsements:

HFD-620/Kathy Woodland/Review Chemist/ Kwoodland 5/25/05
HFD-620/A.Mueller, Ph.D./Team Leader/ for 5/26/05
HFD-617/B.Danso, Pharm.D./Project Manager/5-25-05 5/26/05
F/T by:
V:\FIRMSAM\Apotex\LTRS&REV\76894.cr3.doc
**TYPE OF LETTER:** APPROVABLE

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 76-894

# BIOEQUIVALENCE REVIEWS

# DIVISION OF BIOEQUIVALENCE REVIEW

| | |
|---|---|
| **ANDA No.** | 76-894 |
| **Drug Product Name** | Torsemide Tablets |
| **Strength** | 5 mg, 10 mg, 20 mg & 100 mg |
| **Applicant Name** | Torpharm Inc. |
| **Address** | Etobicoke, Ontario, Canada |
| **Submission Date(s)** | November 6, 2003 |
| **Amendment Date(s)** | August 9, 2004 & August 16, 2004 |
| **Reviewer** | **Hoainhon Nguyen** |
| **First Generic** | **No** |
| **File Location** | **V:\firmsnz\torpharm\ltrs&rev\76894n1103.doc** |

## I. Executive Summary

The firm has submitted a single-dose, 2-way crossover fasting bioequivalence study and a single-dose, 2-way crossover nonfasting bioequivalence study comparing the test product, Torsemide Tablets, 20 mg, with the RLD product, Roche's Demadex® (torsemide) Tablets, 20 mg. The fasting study was performed in 30 normal males at a dose of 1x20 mg and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE in the fasted state (AUCt 0.99, 97.0-101.7; AUCinf 0.99, 97.1-101.7; Cmax 0.99, 91.1-107.8). The nonfasting study was performed in 30 normal males at a dose of 1x20 mg and resulted in acceptable data (point-estimate, 90% CI) that demonstrate BE in the fed state (AUCt 1.00, 97.8-102.5; AUCinf 1.00, 97.8-102.3; Cmax 1.09, 99.5-118.9).

The firm has also submitted a waiver request for the lower strengths, 5 mg and 10 mg, and the higher strength, 100 mg, of the test product, based on the formulation proportionality and dissolution profile comparability between these strengths and the 20 mg strength. The dissolution testing for all strengths of the test and reference products, using the FDA-recommended method, is acceptable. The lower strengths were found proportionally similar to the 20 mg strength. The waiver request for the 5 mg and 10 mg strengths was granted per 21 CFR 320.22 (d)(2). The formulation of the 100 mg strength is not considered proportionally similar to that of the 20 mg strength. The waiver request for the 100 mg strength of the test product is therefore denied at this time. The DBE request the firm to provide additional data as evidence that the proposed 100 mg tablet is bioequivalent to Roche Laboratories' Demadex® tablet, 100 mg. The additional evidence may be in the form of direct *in vivo* comparisons that have already been conducted, or any other methods that would support a decision to grant a waiver of *in vivo* testing for the proposed product. Examples may include pilot studies and/or additional *in vitro* studies conducted with multiple media of varying pHs (i.e. additional comparative dissolution data on 20 mg and 100 mg tablets in water, acetate buffer pH 4.5, phosphate buffer pH 6.5 and phosphate buffer pH 7.5).

This application is **incomplete** pending firm's response to the deficiency.

## II. Table of Contents



## III. Submission Summary

### A. Drug Product Information

| | |
|---|---|
| **Test Product** | Torsemide Tablets |
| **Reference Product** | Demadex® Tablets, 5 mg, 10 mg, 20 mg & 100 mg. The 20 mg strength is the designated RLD strength due to safety concern with administration of 100 mg dose to normal volunteers. |
| **RLD Manufacturer** | Roche |
| **NDA No.** | 20-136 |
| **RLD Approval Date** | 08/23/93 |
| **Indication** | A diuretic indicated for the treatment of edema associated with congestive heart failure, renal disease or hepatic disease. |

## B. PK/PD Information (Ref: PDR 2004 & csi.micromedex.com)

| | |
|---|---|
| **Bioavailability** | 80% |
| **Food Effect** | Simultaneous food intake delays the time to Cmax by about 30 minutes, but overall bioavailability (AUC) and diuretic activity are unchanged. |
| **Tmax** | 1 hour |
| **Metabolism** | The drug is cleared from the circulation by both hepatic metabolism and excretion into the urine. The major metabolite in humans is the carboxylic acid derivative, which is biologically inactive. |
| **Excretion** | Excreted unchanged in urine. |
| **Half-life** | 3.5 hours |
| **Relevant OGD or DBE History** | The following ANDA's were submitted and found acceptable: #76-346 (Pliva; 12/03/01), 76-226 (Par; 08/24/01), 76-110(Teva; 02/01/01). For these ANDA's, a single-dose fasting bioequivalence study and a single-dose nonfasting bioequivalence study were submitted for the 20 mg strength and a waiver request was granted for the 5 mg, 10 mg and 100 mg strengths based on the formulation proportionality and dissolution profile comparability. The 20 mg strength was used in the studies due to safety concern with administration of 100 mg dose. Torsemide was measured for the studies. Moreover, Pliva's 100 mg tablet formulation was not proportionally similar to its 20 mg tablet formulation as per the definitions in the General BA/BE guidance. The DBE however granted waiver of BE study for Pliva's 100 mg Tablet based on i) the firm's rationale/explanation, ii) the additional comparative dissolution data and iii) the excellent results of BE studies and dissolution testing (review on V:\firmsnz\pliva\ltrs&rev\76346S0704.doc). Control Documents # 01-502 [redacted] and 00-266[redacted] and Protocol No. 02-032 conveyed the same bioequivalence requirements followed by the above ANDA's.<br><br>The dissolution testing method and specification used for the above ANDA's and currently recommended for the drug product are as follows:<br>USP Apparatus II(paddle) @ 50 rpm<br>900 mL of 0.1 N HCl @ 37°C<br>NLT —%(Q) dissolved in 15 minutes |

## C. Contents of Submission

| Study Types | Yes/No? | How many? |
|---|---|---|
| Single-dose fasting | Yes | 1 |
| Single-dose fed | Yes | 1 |
| Steady-state | No | |
| In vitro dissolution | Yes | 4 |
| Waiver requests | Yes | 3 |
| BCS Waivers | No | |
| Vasoconstrictor Studies | No | |
| Clinical Endpoints | No | |
| Failed Studies | No | |
| Amendments | Yes | 2 |

## D. Pre-Study Bioanalytical Method Validation

| | |
|---|---|
| **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 |

## E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

| Study Summary, Fasting Bioequivalence Study | |
|---|---|
| **Study No.** | AA03121 |
| **Study Design** | Two-way crossover |
| **No. of subjects enrolled** | 32 |
| **No. of subjects completing** | 30 |
| **No. of subjects analyzed** | 30 |
| **Subjects (Healthy or Patients?)** | Healthy |
| **Sex(es) included (how many?)** | Male: 30 Female: 0 |
| **Test product** | Torpharm's Torsemide Tablets |
| **Reference product** | Roche's Demadex® Tablets |
| **Strength tested** | 20 mg |
| **Dose** | 1x 20 mg |

| Summary of Statistical Analysis, Fasting Bioequivalence Study (N=30) | | |
|---|---|---|
| **Parameter** | **Point Estimate** | **90% Confidence Interval** |
| **$AUC_{0-t}$** | 0.99 | 97.0-101.7 |
| **$AUC_{\infty}$** | 0.99 | 97.1-101.7 |
| **$C_{max}$** | 0.99 | 91.1-107.8 |

| Reanalysis of Study Samples, Fasting Bioequivalence Study<br>Additional information in Appendix, Table 6 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **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** |
| **There was no PK repeat sample.** | | | | | | | | |

Did use of recalculated plasma concentration data change study outcome? N/A

2. Single-dose Fed Bioequivalence Study

| Study Summary, Fed Bioequivalence Study | |
|---|---|
| **Study No.** | AA03122 |
| **Study Design** | Two-way crossover |
| **No. of subjects enrolled** | 32 |
| **No. of subjects completing** | 30 |
| **No. of subjects analyzed** | 30 |
| **Subjects (Healthy or Patients?)** | Healthy |
| **Sex(es) included (how many?)** | Male 30 Female 0 |
| **Test product** | TorPharm's Torsemide Tablets |
| **Reference product** | Roche's Demadex® Tablets |
| **Strength tested** | 20 mg |
| **Dose** | 1x20 mg |

| Summary of Statistical Analysis, Fed Bioequivalence Study (N=30) | | |
|---|---|---|
| **Parameter** | **Point Estimate** | **90% Confidence Interval** |
| **$AUC_{0-t}$** | 1.00 | 97.8-102.5 |
| **$AUC_{\infty}$** | 1.00 | 97.8-102.3 |
| **$C_{max}$** | 1.09 | 99.5-118.9 |

| Reanalysis of Study Samples, Fed Bioequivalence Study<br>Additional information in Appendix, Table 17 | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 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 |
| There was no PK repeat sample. | | | | | | | | |

F. Formulation

| | |
|---|---|
| **Location in appendix** | SectionIV.B, Page 25 |
| **Are inactive ingredients within IIG limits?** | **Yes** |
| **If no, list ingredients outside of limits** | |
| **If a tablet, is the product scored?** | **No** |
| **If yes, which strengths are scored?** | |
| **Is scoring of RLD the same as test?** | **No** |
| **Is the formulation acceptable?** | **See Deficiency Comments** |
| **If not acceptable, why?** | |

G. In Vitro Dissolution

| | |
|---|---|
| **Source of Method (USP, FDA or Firm)** | 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*** | —%(Q) in 15 minutes |
| **F2 metric calculated?** | No. |
| **If no, reason why F2 not calculated** | The RLD product is fast dissolving and CV% is high for the first time point for the test product. |
| **Is method acceptable?** | Yes |
| **If not then why?** | |

***NOTE:** 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 dissolution data summarized in the review Appendix). The specification as proposed by the firm above has been found acceptable for the test product. See Dr. Tran's email in the review Appendix.

## H. Waiver Request(s)

| | |
|---|---|
| Strengths for which waivers are requested | 5 mg, 10 mg and 100 mg |
| Regulation cited | 21 CFR 320.22(d)(2) |
| Proportional to strength tested in vivo? | Yes |
| Is dissolution acceptable? | Yes |
| Waivers granted? | Yes to 5 mg and 10 mg |
| If not then why? | No to 100 mg (see deficiency) |

## I. Deficiency Comments

The formulation of the 100 mg strength is not considered proportionally similar to that of the 20 mg strength which underwent acceptable *in vivo* bioequivalence testing. The waiver request for the 100 mg strength is denied. The firm is recommended to submit additional comparative dissolution data on 20 mg and 100 mg tablets in water, acetate buffer pH 4.5, phosphate buffer pH 6.5 and phosphate buffer pH 7.5.

## J. Recommendations

1. The single-dose, fasting bioequivalence and the single-dose, nonfasting bioequivalence study conducted by 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, have been found **acceptable** by the Division of Bioequivalence. The test product, TorPharm'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 TorPharm 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 —% (Q) of the labeled amounts of the drug in the dosage form is dissolved in 30 minutes.

3. The dissolution testing conducted by TorPharm 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, TorPharm's Torsemide Tablets, 5 mg and 10 mg, is deemed bioequivalent to the reference product, Roche's Demadex® (torsemide) Tablets, 5 mg, 10 mg ~~and 100 mg~~, respectively.

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4. The formulation of the 100 mg strength of the test product is NOT proportionally similar to that of the 20 mg strength which underwent acceptable *in vivo* bioequivalence testing. The waiver request for the 100 mg strength is therefore **denied at this time**. The firm is recommended to provide additional data as evidence that the proposed 100 mg tablet is bioequivalent to Roche Laboratories' Demadex® tablet, 100 mg. The additional evidence may be in the form of direct *in vivo* comparisons that have already been conducted, or any other methods that would support a decision to grant a waiver of *in vivo* testing for the proposed product. Examples may include pilot studies and/or additional *in vitro* studies conducted with multiple media of varying pHs.(i.e. additional comparative dissolution data on 20 mg and 100 mg tablets in water, acetate buffer pH 4.5, phosphate buffer pH 6.5 and phosphate buffer pH 7.5).

The application is **incomplete** pending the firm's response to the deficiency.

8/31/04

Hoainhon Nguyen, Team I, Date Signed

8/31/2004

Shriniwas Nerurkar, Team I, Date Signed

for 8/31/04

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

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# IV. Appendix

## A. Individual Study Reviews

### 1. Single-dose Fasting Bioequivalence Study

a) Study Design

| Study Information | |
|---|---|
| **Study Number** | AA03121 |
| **Study Title** | Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of TorPharm and Roche Pharmaceuticals (Demadex®) 20 mg Torsemide Tablets in Healthy Adult Male Volunteers Under Fasting Conditions |
| **Clinical Site** | [redacted] |
| **Principal Investigator** | [redacted], M.D. |
| **Study/Dosing Dates** | 03/13/03 - 03/22/03 |
| **Analytical Site** | [redacted] |
| **Analytical Director** | [redacted] |
| **Analysis Dates** | 03/27/03 - 04/04/03 |
| **Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)** | 22 days |

| Treatment ID | Test | Reference |
|---|---|---|
| **Product Name** | Torsemide | Demadex® Tablets |
| **Manufacturer** | TorPharm | Roche |
| **Batch/Lot No.** | FD2133A | 0201 |
| **Manufacture Date** | 10/02 | |
| **Expiration Date** | 10/04 | 01/05 |
| **Strength** | 20 mg | 20 mg |
| **Dosage Form** | Tablets | Tablets |
| **Batch Size** | [redacted] | |
| **Production Batch Size** | | |
| **Potency** | 100.2% | 97.2% |
| **Content Uniformity (mean, %CV)** | 100.2%(RSD=1.1%) | 100.4%(RSD=1.7%) |
| **Formulation** | See Appendix Section B | |
| **Dose Administered** | 1x20 mg* | 1x20 mg* |
| **Route of Administration** | Oral | |

**NOTE:** Subjects were required to drink 240 mL of Gatorade® 10 hours before dosing and again 1 hour before dosing for prevention of electrolyte depletion as the result of diuretic administration. Water was restricted from 1 hour predose to 1 hour postdose.

| | |
|---|---|
| **No. of Sequences** | 2 |
| **No. of Periods** | 2 |
| **No. of Treatments** | 2 |
| **No. of Groups** | 1 |
| **Washout Period** | 7 days |
| **Randomization Scheme** | Yes |
| **Blood Sampling Times** | Predose, 0.167, 0.25, 0.5, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.50, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours postdose |
| **Blood Volume Collected/Sample** | 3 mL/sample |
| **Blood Sample Processing/Storage** | Blood samples were collected in Vacutainers® collection tubes containing EDTA, centrifuged and harvested for plasma which was stored at -20°c until analysis. |
| **IRB Approval** | Yes |
| **Informed Consent** | Yes |
| **Subjects Demographics** | See Table 1 |
| **Length of Fasting** | Approximately 10 hours prior to dosing until 4 hours postdose |
| **Length of Confinement** | Approximately 10 hours prior to dosing until 24 hours postdose |
| **Safety Monitoring** | Vital signs (seated blood pressure and heart rate) were taken at 1, 2, 4, 8, 12 and 24 hours postdose. The vital signs readings were performed within approximately 10 minutes of the scheduled blood draws where applicable. Subjects were monitored for adverse effects during the study periods. |

**Comments on Study Design: Acceptable**

b) Clinical Results

**Table 1 Demographics of Study Subjects**

| Age | | Weight (kg) | | Age Groups | | Gender | | Race | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Range | % | Sex | % | Category | % |
| | | | | <18 | 0.0 | | | Caucasian | 90.0 |
| Mean | 31.07 | Mean | 75.57 | 18-40 | 86.7 | Male | 100.0 | Afr. Amer. | 3.3 |
| SD | 8.12 | SD | 7.44 | 41-64 | 13.3 | Female | 0.0 | Hispanic | 3.3 |
| Range | 19 | Range | 61.6 | 65-75 | 0.0 | | | Asian | 3.3 |
| | 44 | | 88 | >75 | 0.0 | | | Others | 0.0 |

**Table 2 Dropout Information**

| Subject No | Reason | Period | Replaced? |
|---|---|---|---|
| **6** | Tested positive for cannabinoids | II | Yes, with Subject #31 |
| **16** | Personal reasons | II | Yes, with Subject #32 |

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**Table 3 Study Adverse Events**

| Adverse Event Description | # in Test Group | # in Ref. Group |
|---|---|---|
| Feels hyper | | 1 |
| Tension behind right ear | | 1 |
| Headache | 4 | 5 |
| Back pain | | 1 |
| Abdominal pain | 1 | 1 |
| Gastric reflux | | 1 |
| Feels hot | 2 | 3 |
| Nausea | 3 | 2 |
| Dizziness | 2 | 4 |
| Vomited | | 2 |
| Burning sensation when urinating | 2 | |
| Constipated | 1 | |
| Bruise at venipuncture site left arm | 1 | |
| Lower abdominal pain | 2 | |
| Feels weak | 1 | |
| Pressure in the eyes | | 1 |
| Numbness in left arm | | 1 |
| Burping | 1 | |
| Loss of appetite | | 1 |
| Upset stomach | 1 | |
| Total: | 21 | 24 |

**Table 4 Protocol Deviations**

There was no significant protocol deviation that might have compromised the integrity of the study. Deviations in blood sampling were corrected by using the actual sampling times.

**Comments on Dropouts/Adverse Events/Protocol Deviations:** None

c) Bioanalytical Results

**Table 5 Assay Quality Control – Within Study**

| | Torsemide | | |
|---|---|---|---|
| **QC Conc. (ng/mL)** | 60.0(n=42) | 2000 (n=42) | 4000 (n=42) |
| **Inter day Precision (%CV)** | 3.9 | 3.8 | 3.0 |
| **Inter day Accuracy (%)** | 110.2 | 99.0 | 98.3 |
| **Cal. Standards Conc. (ng/mL)** | 20.0, 40.0, 250, 750, 2500, 3800, 4500, 5040 | | |
| **Inter day Precision (%CV)** | 1.6 - 6.8 | | |
| **Inter day Accuracy (%)** | 96.5 - 108.5 | | |
| **Linearity Range (range of $R^2$ values)** | 0.9988-0.9999 | | |

**Comments on Study Assay Quality Control:** Acceptable

| | |
|---|---|
| **Any interfering peaks in chromatograms?** | No |
| **Were 20% of chromatograms included?** | Yes |
| **Were chromatograms serially or randomly selected?** | Randomly selected. |

**Comments on Chromatograms:** Acceptable

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

None submitted

**Table 7 Additional Comments on Repeat Assays**

| | |
|---|---|
| Were all SOPs followed? | N/A |
| Did recalculation of plasma concentrations change the study outcome? | N/A. There was no recalculation of plasma concentrations. |
| Does the reviewer agree with the outcome of the repeat assays? | N/A |
| If no, reason for disagreement | |

**Summary/Conclusions, Study Assays:** The analytical method validation is acceptable.

d) Pharmacokinetic Results

**Table 8 Arithmetic Mean Pharmacokinetic Parameters (N=30)**

Mean plasma concentrations are presented in Table 11and Figure 1

| Parameter | Units | Test | | Reference | | T/R |
|---|---|---|---|---|---|---|
| | | Mean | %CV | Mean | % CV | |
| **AUC0-t** | Ng.hr/Ml | 6311 | 36 | 6394 | 40 | 0.99 |
| **AUC∞** | Ng.hr/mL | 6516 | 37 | 6603 | 43 | 0.99 |
| **Cmax** | Ng/mL | 2814 | 24 | 2866 | 27 | 0.98 |
| **Tmax** | Hrs | 1.02 | 39 | 1.00 | 44 | 1.02 |
| **T1/2** | Hrs | 3.60 | 25 | 3.55 | 26 | 1.01 |
| **Kel** | $Hr^{-1}$ | 0.202 | 22 | 0.206 | 24 | 0.98 |

**Table 9 Geometric Means and 90% Confidence Intervals (N=30)**

| Parameter | Test | Reference | T/R | 90% CI |
|---|---|---|---|---|
| | Mean | Mean | | |
| **AUC0-t** | 6042 | 6084 | 0.99 | 97.0-101.7 |
| **AUC∞** | 6224 | 6262 | 0.99 | 97.1-101.7 |
| **Cmax** | 2733 | 2758 | 0.99 | 91.1-107.8 |

**Table 10 Additional Study Information**

| | |
|---|---|
| Root mean square error, AUC0-t | 0.053585 |
| Root mean square error, AUC∞ | 0.052119 |
| Root mean square error, Cmax | 0.191441 |
| Kel and AUC∞ determined for how many subjects? | All |
| Do you agree or disagree with firm's decision? | Yes |
| Indicate the number of subjects with the following: | |
| -measurable drug concentrations at 0 hr | 0 |
| -first measurable drug concentration as Cmax | 0 |
| Were the subjects dosed as more than one group? | No |

**Comments on Pharmacokinetic and Statistical Analysis:** None

**Summary and Conclusions, Single-Dose Fasting Bioequivalence Study:** The fasting study is acceptable. The 90% confidence intervals for lnCmax, lnAUCt and lnAUCinfinity were within the acceptable limits of [80.0-125.0].

## Table 11 Torsemide Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (ng/mL)

### Test Treatment

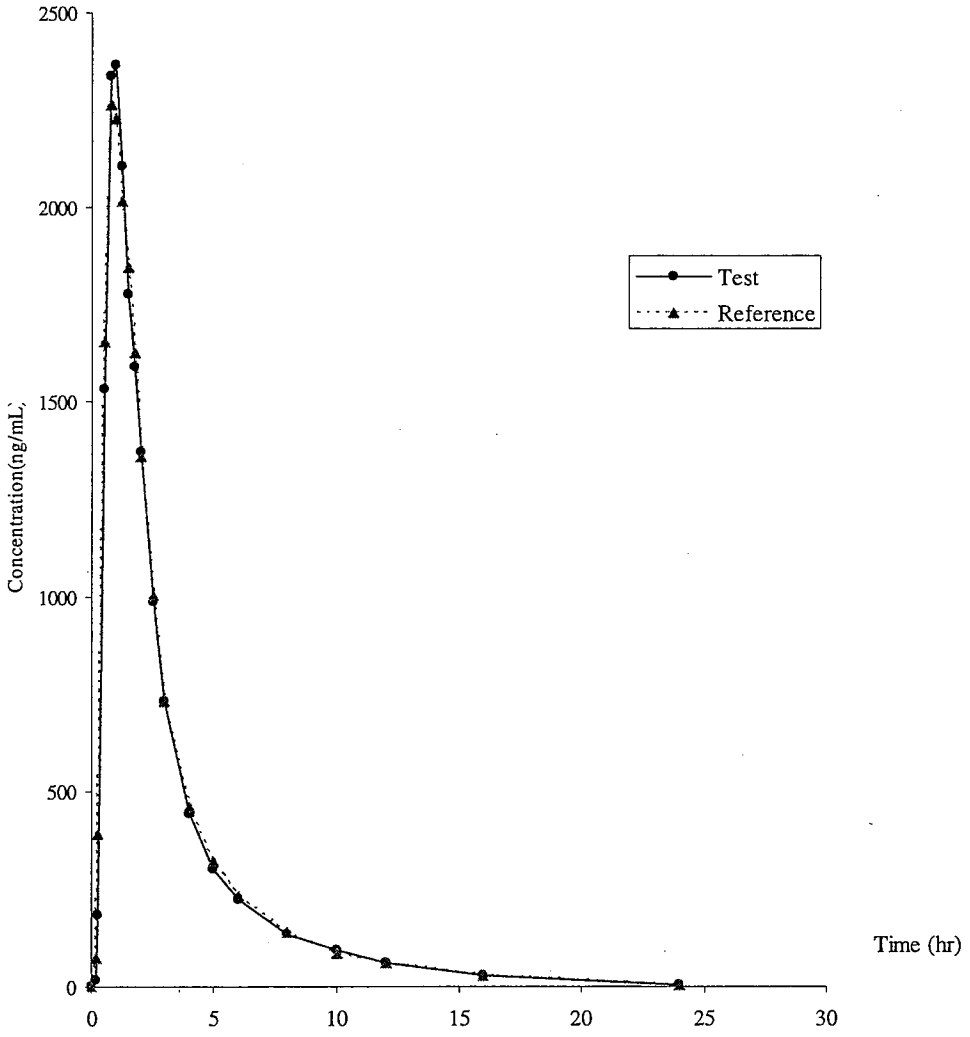
| Time | N | Mean | Std Dev | Minimum | Maximum |
|---|---|---|---|---|---|
| Hour0 | 30 | 0.000 | 0.000 | 0.000 | 0.000 |
| Hour0.167 | 30 | 18.137 | 39.682 | 0.000 | 204.000 |
| Hour0.25 | 30 | 184.087 | 253.252 | 0.000 | 1060.000 |
| Hour0.50 | 30 | 1532.327 | 1141.707 | 29.500 | 4530.000 |
| Hour0.75 | 30 | 2338.500 | 1078.969 | 125.000 | 4010.000 |
| Hour1 | 30 | 2365.933 | 853.628 | 279.000 | 3430.000 |
| Hour1.25 | 30 | 2106.967 | 648.039 | 468.000 | 3260.000 |
| Hour1.50 | 30 | 1775.967 | 428.381 | 939.000 | 2530.000 |
| Hour1.75 | 30 | 1591.867 | 413.586 | 629.000 | 2440.000 |
| Hour2 | 30 | 1371.933 | 413.669 | 524.000 | 2270.000 |
| Hour2.50 | 30 | 986.700 | 304.234 | 320.000 | 1640.000 |
| Hour3 | 30 | 730.533 | 252.947 | 221.000 | 1570.000 |
| Hour4 | 30 | 441.767 | 188.020 | 145.000 | 1210.000 |
| Hour5 | 30 | 301.583 | 149.792 | 88.500 | 935.000 |
| Hour6 | 30 | 224.840 | 125.109 | 67.200 | 792.000 |
| Hour8 | 30 | 133.730 | 77.199 | 32.700 | 465.000 |
| Hour10 | 30 | 94.703 | 100.495 | 22.100 | 604.000 |
| Hour12 | 30 | 59.853 | 60.519 | 0.000 | 356.000 |
| Hour16 | 30 | 27.893 | 42.327 | 0.000 | 229.000 |
| Hour24 | 30 | 3.733 | 20.448 | 0.000 | 112.000 |

### Reference Treatment

| Time | N | Mean | Std Dev | Minimum | Maximum |
|---|---|---|---|---|---|
| Hour0 | 30 | 0.000 | 0.000 | 0.000 | 0.000 |
| Hour0.167 | 30 | 72.660 | 108.325 | 0.000 | 438.000 |
| Hour0.25 | 30 | 388.077 | 480.727 | 0.000 | 1910.000 |
| Hour0.50 | 30 | 1657.140 | 1331.632 | 37.300 | 4300.000 |
| Hour0.75 | 30 | 2266.010 | 1214.950 | 66.300 | 4070.000 |
| Hour1 | 30 | 2227.257 | 934.232 | 80.700 | 3630.000 |
| Hour1.25 | 30 | 2018.193 | 705.700 | 92.800 | 3130.000 |
| Hour1.50 | 30 | 1845.067 | 527.303 | 212.000 | 3150.000 |
| Hour1.75 | 30 | 1627.400 | 591.334 | 632.000 | 3800.000 |
| Hour2 | 30 | 1361.600 | 511.460 | 813.000 | 3150.000 |
| Hour2.50 | 30 | 1003.633 | 427.803 | 530.000 | 2290.000 |
| Hour3 | 30 | 732.167 | 333.323 | 381.000 | 1700.000 |
| Hour4 | 30 | 459.000 | 239.011 | 220.000 | 1360.000 |
| Hour5 | 30 | 319.400 | 188.744 | 133.000 | 1100.000 |
| Hour6 | 30 | 231.930 | 148.794 | 84.900 | 902.000 |
| Hour8 | 30 | 139.070 | 103.367 | 55.500 | 629.000 |
| Hour10 | 30 | 85.940 | 91.334 | 0.000 | 543.000 |
| Hour12 | 30 | 60.880 | 70.637 | 0.000 | 413.000 |
| Hour16 | 30 | 28.720 | 50.671 | 0.000 | 280.000 |
| Hour24 | 30 | 4.633 | 25.378 | 0.000 | 139.000 |

## Figure 1

**Torsemide Mean Plasma Concentrations**
**Single Dose Fasting Study**



2. Single-dose Fed Bioequivalence Study

a) Study Design

| **Study Information** | |
|---|---|
| **Study Number** | AA03122 |
| **Study Title** | Comparative, Randomized, Single-Dose, 2-Way Crossover Bioavailability Study of TorPharm and Roche Pharmaceuticals (Demadex®) 20 mg Torsemide Tablets in Healthy Adult Male Volunteers Under Fed Conditions |
| **Clinical Site** | [redacted] |
| **Principal Investigator** | [redacted] M.D. |
| **Study/Dosing Dates** | 04/28/03 - 05/07/03 |
| **Analytical Site** | [redacted] |
| **Analytical Director** | [redacted] |
| **Analysis Dates** | 05/20/03 - 06/02/03 |
| **Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)** | 35 days |

| **Treatment ID** | **Test Product** | **Reference Product** |
|---|---|---|
| **Product Name** | Torsemide | Demadex® Tablets |
| **Manufacturer** | TorPharm | Roche |
| **Batch/Lot No.** | FD2133A | 0201 |
| **Manufacture Date** | 10/02 | |
| **Expiration Date** | 10/04 | 01/05 |
| **Strength** | 20 mg | 20 mg |
| **Dosage Form** | Tablets | Tablets |
| **Batch Size** | [redacted] | |
| **Production Batch Size** | | |
| **Potency** | 100.2% | 97.2% |
| **Content Uniformity** | 100.2%(RSD=1.1%) | 100.4%(RSD=1.7%) |
| **Formulation** | See Appendix Section B | |
| **Dose Administered** | 1x20 mg* | 1x20 mg* |
| **Route of Administration** | Oral | |

**NOTE:** Subjects were required to drink 240 mL of Gatorade® 10 hours before dosing and again 2 hours before dosing for prevention of electrolyte depletion as the result of diuretic administration. Water was restricted from 1 hour predose to 1 hour postdose.

| | |
|---|---|
| **No. of Sequences** | 2 |
| **No. of Periods** | 2 |
| **No. of Treatments** | 2 |
| **No. of Groups** | 1 |
| **Washout Period** | 7 days |
| **Randomization Scheme** | Yes |
| **Blood Sampling Times** | Predose, 0.25, 0.5, 0.75, 1, 1.25, 1.50, 1.75, 2, 2.33, 2.67, 3, 4, 5, 6, 8, 10, 12, 16 and 24 hours postdose |
| **Blood Volume Collected/Sample** | 3 mL/sample |
| **Blood Sample Processing/Storage** | Blood samples were collected in Vacutainers® collection tubes containing EDTA, centrifuged and harvested for plasma which was stored at -20°c until analysis. |
| **IRB Approval** | Yes |
| **Informed Consent** | Yes |
| **Subjects Demographics** | See **Table 12** |
| **Length of Fasting before Meal** | A standard breakfast was given 30 minutes following an approximately 10 hours overnight fast. The subjects fasted for a period of 4 hours postdose. |
| **Length of Confinement** | Approximately 10 hours predose until 24 hours postdose. |
| **Safety Monitoring** | Vital signs (seated blood pressure and heart rate) were taken at 1, 2, 4, 8, 12 and 24 hours postdose. The vital signs readings were performed within approximately 10 minutes of the scheduled blood draws where applicable. Subjects were monitored for adverse effects during the study periods. |
| **Standard FDA Meal Used?** | 2 buttered slices of toast, 2 fried eggs, 2 strips of bacon, 1 serving of hash brown potatoes, and 240 mL of whole milk. |
| **If no, then meal is listed in table below** | |

| **Composition of Meal Used in Fed Bioequivalence Study** | | |
|---|---|---|
| **Composition** | **Percent** | **Kcal** |
| Fat | Not provided | Not provided |
| Carbohydrate | Not provided | Not provided |
| Protein | Not provided | Not provided |
| Total | | |

**Comments on Study Design:** None

b) Clinical Results

**Table 12 Demographics of Study Subjects**

| Age | | Weight (kg) | | Age Groups | | Gender | | Race | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Range | % | Sex | % | Category | % |
| | | | | <18 | 0.0 | | | Caucasian | 76.7 |
| Mean | 31.97 | Mean | 74.57 | 18-40 | 93.3 | Male | 100.0 | Afr. Amer. | 13.3 |
| SD | 6.71 | SD | 7.58 | 41-64 | 6.7 | Female | 0.0 | Hispanic | 10.0 |
| Range | 20 | Range | 60.2 | 65-75 | 0.0 | | | Asian | 0.0 |
| | 43 | | 88 | >75 | 0.0 | | | Others | 0.0 |

**Table 13 Dropout Information**

| Subject No | Reason | Period | Replaced? |
|---|---|---|---|
| 12 | Personal reasons | II | Yes, with Subject #31 |

**Table 14 Study Adverse Events**

| Adverse Event Description | # in Test Group | # in Ref. Group |
|---|---|---|
| Decreased appetite | 1 | |
| Dizziness | 3 | 1 |
| Headache | 3 | 2 |
| Numbness at both legs | 1 | |
| Hematoma left arm | 1 | |
| Nausea | 1 | |
| Feels hot | 1 | |
| Perpiring | | 1 |
| Pain in lower back | | 1 |
| Pain in pubic area | | 1 |
| Lower abdominal pain on right side | 1 | |
| Flatulence | | 1 |
| Sleepiness | | 1 |
| Redness on left eye | 1 | 1 |
| Redness on right eye | 1 | 1 |
| Coughing | | 1 |
| Runny nose | 1 | |
| Total: | 15 | 11 |

**Table 15 Protocol Deviations**

There was no significant protocol deviation that might have compromised the integrity of the study. Blood sampling deviations were corrected by using the actual sampling times.

**Comments on Adverse Events/Protocol Deviations:** None

c) Bioanalytical Results

**Table 16 Assay Quality Control – Within Study**

| | Torsemide | | |
|---|---|---|---|
| **QC Conc. (ng/mL)** | 60.0(n=42) | 2000 (n=42) | 4000 (n=42) |
| **Inter day Precision (%CV)** | 10.3 | 3.9 | 2.2 |
| **Inter day Accuracy (%)** | 107.2 | 98.5 | 98.3 |
| **Cal. Standards Conc. (ng/mL)** | 20.0, 40.0, 250, 750, 2500, 3800, 4500, 5040 | | |
| **Inter day Precision (%CV)** | 1.3-4.4 | | |
| **Inter day Accuracy (%)** | 97.2-106.5 | | |
| **Linearity Range (range of $R^2$ values)** | 0.9994-0.9998 | | |

**Comments on Study Assay Quality Control:** Acceptable.

| | |
|---|---|
| **Any interfering peaks in chromatograms?** | No |
| **Were 20% of chromatograms included?** | Yes |
| **Were chromatograms serially or randomly selected?** | Randomly selected. |

**Comments on Chromatograms:** The chromatograms were acceptable.

**Table 17 SOP's dealing with analytical repeats**

None submitted.

**Table 18 Additional Comments on Repeat Assays**

| | |
|---|---|
| Were all SOPs followed? | Yes |
| Did recalculation of plasma concentrations change the study outcome? | N/A. There was no recalculation of plasma concentrations by the reviewer. |
| Does the reviewer agree with the outcome of the repeat assays? | N/A |
| If no, reason for disagreement | |

**Summary/Conclusions, Study Assays:** The analytical method validation is acceptable.

d) Pharmacokinetic Results

**Table 19 Arithmetic Mean Pharmacokinetic Parameters (N=30)**

Mean plasma concentrations are presented in Table 22and Figure 2

| Parameter | Units | Test | | Reference | | T/R |
|---|---|---|---|---|---|---|
| | | Mean | %CV | Mean | % CV | |
| AUC0-t | Ng.hr/mL | 6814 | 33 | 6823 | 34 | 1.00 |
| AUC∞ | Ng.hr/mL | 7007 | 34 | 7023 | 35 | 1.00 |
| Cmax | Ng/mL | 2185 | 21 | 2028 | 27 | 1.08 |
| Tmax | Hrs | 1.87 | 54 | 1.67 | 57 | 1.12 |
| T1/2 | Hrs | 3.34 | 23 | 3.34 | 23 | 1.00 |
| Kel | $Hr^{-1}$ | 0.217 | 20 | 0.216 | 18 | 1.00 |

**Table 20 Geometric Means and 90% Confidence Intervals (N=30)**

| Parameter | Test | Reference | T/R | 90% CI |
|---|---|---|---|---|
| | Mean | Mean | | |
| AUC0-t | 6532 | 6526 | 1.00 | 97.8-102.5 |
| AUC∞ | 6711 | 6709 | 1.00 | 97.8-102.3 |
| Cmax | 2135 | 1963 | 1.09 | 99.5-118.9 |

**Table 21 Additional Study Information**

| | |
|---|---|
| Root mean square error, AUC0-t | 0.053533 |
| Root mean square error, AUC∞ | 0.050688 |
| Root mean square error, Cmax | 0.203009 |
| Kel and AUC∞ determined for how many subjects? | All |
| Do you agree or disagree with firm's decision? | Yes |
| Indicate the number of subjects with the following: | |
| -measurable drug concentrations at 0 hr | 0 |
| -first measurable drug concentration as Cmax | 0 |
| Were the subjects dosed as more than one group? | No |

**Comments on Pharmacokinetic and Statistical Analysis:** None

**Summary/Conclusions, Single-Dose Fed Bioequivalence Study:** The nonfasting study is acceptable. The 90% confidence intervals for lnCmax, lnAUCt and lnAUCinfinity were within the acceptable limits of [80.0-125.0].

## Table 22 Torsemide Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

### Test Treatment

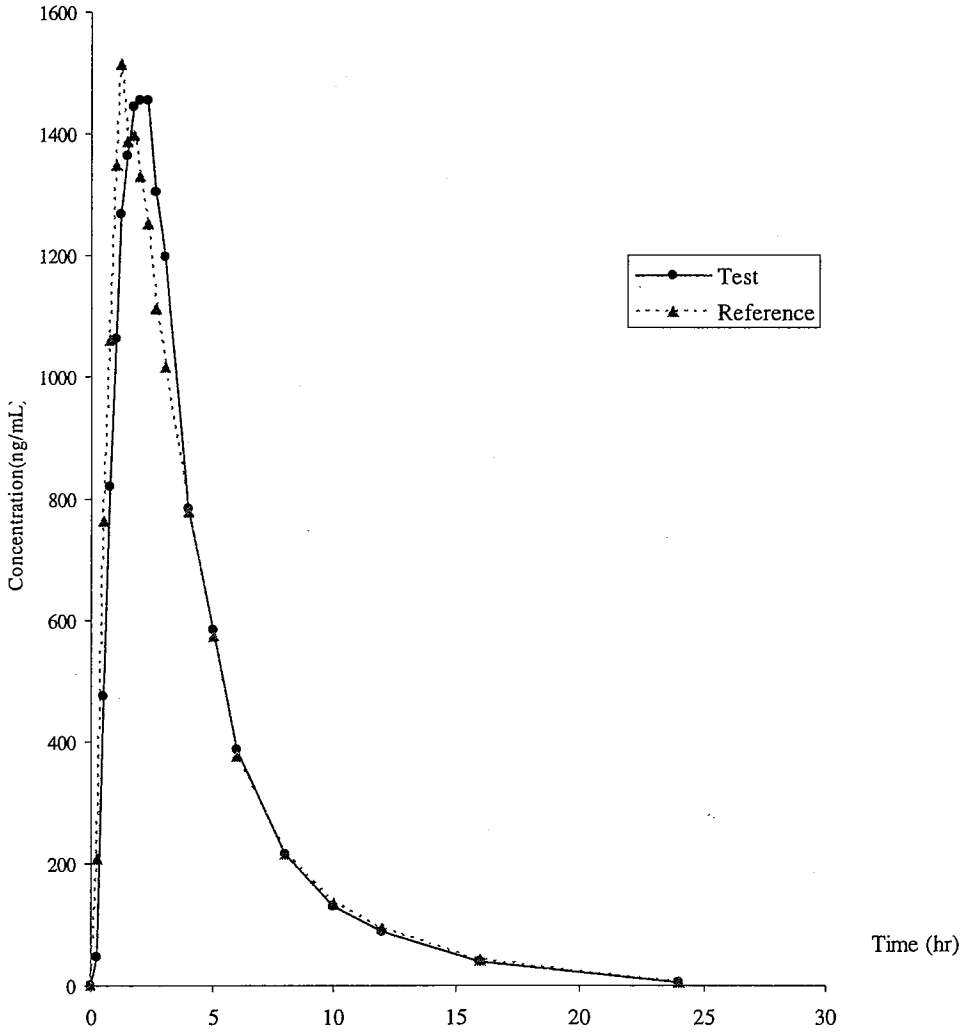
| Time | N | Mean | Std Dev | Minimum | Maximum |
|---|---|---|---|---|---|
| Hour0 | 30 | 0.000 | 0.000 | 0.000 | 0.000 |
| Hour0.25 | 30 | 46.633 | 120.812 | 0.000 | 622.000 |
| Hour0.50 | 30 | 474.327 | 785.039 | 0.000 | 3060.000 |
| Hour0.75 | 30 | 820.333 | 960.933 | 0.000 | 3030.000 |
| Hour1 | 30 | 1063.677 | 966.764 | 0.000 | 2850.000 |
| Hour1.25 | 30 | 1267.780 | 903.226 | 22.400 | 2790.000 |
| Hour1.50 | 30 | 1364.630 | 743.230 | 0.000 | 2700.000 |
| Hour1.75 | 30 | 1444.467 | 569.064 | 208.000 | 2380.000 |
| Hour2 | 30 | 1455.533 | 533.655 | 408.000 | 2620.000 |
| Hour2.33 | 30 | 1454.900 | 471.118 | 635.000 | 2560.000 |
| Hour2.67 | 30 | 1305.433 | 491.023 | 534.000 | 2380.000 |
| Hour3 | 30 | 1198.033 | 540.309 | 404.000 | 2430.000 |
| Hour4 | 30 | 783.433 | 391.662 | 241.000 | 1540.000 |
| Hour5 | 30 | 582.700 | 340.769 | 170.000 | 1460.000 |
| Hour6 | 30 | 386.233 | 235.099 | 126.000 | 1090.000 |
| Hour8 | 30 | 215.850 | 146.108 | 62.200 | 800.000 |
| Hour10 | 30 | 129.377 | 92.978 | 34.600 | 501.000 |
| Hour12 | 30 | 87.200 | 75.281 | 0.000 | 415.000 |
| Hour16 | 30 | 39.893 | 46.521 | 0.000 | 240.000 |
| Hour24 | 30 | 5.967 | 19.126 | 0.000 | 96.900 |

### Reference Treatment

| Time | N | Mean | Std Dev | Minimum | Maximum |
|---|---|---|---|---|---|
| Hour0 | 30 | 0.000 | 0.000 | 0.000 | 0.000 |
| Hour0.25 | 30 | 207.813 | 335.121 | 0.000 | 1260.000 |
| Hour0.50 | 30 | 763.217 | 922.773 | 0.000 | 3120.000 |
| Hour0.75 | 30 | 1061.330 | 929.217 | 0.000 | 3040.000 |
| Hour1 | 30 | 1348.583 | 868.365 | 32.800 | 3070.000 |
| Hour1.25 | 30 | 1514.850 | 778.907 | 54.500 | 3280.000 |
| Hour1.50 | 30 | 1387.200 | 646.517 | 0.000 | 2440.000 |
| Hour1.75 | 30 | 1398.967 | 549.667 | 220.000 | 2630.000 |
| Hour2 | 30 | 1330.167 | 482.229 | 288.000 | 2240.000 |
| Hour2.33 | 30 | 1251.233 | 436.469 | 516.000 | 2140.000 |
| Hour2.67 | 30 | 1112.533 | 398.119 | 450.000 | 1930.000 |
| Hour3 | 30 | 1016.500 | 390.238 | 358.000 | 1910.000 |
| Hour4 | 30 | 778.700 | 424.685 | 218.000 | 1880.000 |
| Hour5 | 30 | 572.833 | 342.257 | 147.000 | 1610.000 |
| Hour6 | 30 | 376.000 | 247.049 | 108.000 | 1380.000 |
| Hour8 | 30 | 215.337 | 155.955 | 64.300 | 913.000 |
| Hour10 | 30 | 134.487 | 102.482 | 36.600 | 591.000 |
| Hour12 | 30 | 92.620 | 82.534 | 23.000 | 446.000 |
| Hour16 | 30 | 40.633 | 50.504 | 0.000 | 269.000 |
| Hour24 | 30 | 6.450 | 21.460 | 0.000 | 111.000 |

## Figure 2

**Torsemide Mean Plasma Concentrations**
**Single Dose Nonfasting Study**



**B. Formulation Data**

| 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** | | | | |
| **Crospovidone NF** | | | | |
| **Magnesium Stearate NF** | | | | |
| **Collodial Silicon Dioxide NF** | | | | |
| **Total** | 50 mg | 100 mg | 200 mg | 280 mg |

**Comments:** The formulations of the 5 mg and 10 mg are proportionally similar. The inactive ingredients of all strengths are within the approved IIG ranges. The formulation of the 100 mg strength, however, is NOT considered as proportionally similar to the 20 mg strength, per the current BA/BE guidance. **The waiver request for the 100 mg is therefore denied at this time.**

## C. Dissolution Data

**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 specifications** | —%(Q) in 30 minutes** |
| **Current FDA-recommended specification** | —%(Q) in 15 minutes* |

***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 dissolution data summarized in the review Appendix). The specification as proposed by the firm above has been found acceptable for the test product. See Dr. Tran's email in the review Appendix.

**Table 23**

| 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 | |

**Table 24**

| 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 | |

**Table 25**

| 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 26**

| 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 | |

APPEARS THIS WAY
ON ORIGINAL

## D. SAS Output

### 1. Fasting Study:

76894FAST.txt

### 2. Nonfasting Study:

76894FED.txt

## E. An e-mail from Dr. Tran

**From:** Tran, Nhan L
**Sent:** Monday, August 02, 2004 8:17 AM
**To:** Nguyen, Hoainhon T
**Cc:** Nerurkar, Shriniwas G
**Subject:** RE: Dissolution Spec for ANDA 76-894 (TorPham's Torsemide Tablets) - CORRECTION

**Follow Up Flag:** Follow up
**Flag Status:** Flagged

Hi Hoai:

In reviewing the data, I agree with you that this generic may not meet the FDA's spec at S1 level for lower strengths. Your proposed spec is OK but I believe the firm's proposed spec makes more sense, if you look at the overall data across strengths. Please keep in mind that the proposed spec is set based on freshly made batches and the dissolution may become slower after a long storage. If we set the spec too tight, there will be lots (batches) failure in the future, not because they are not good batches but because the spec is too strict (over discriminating). On the other hand, we do not want the spec to be too liberal to be indiscriminating.
Hence I think the firm's spec is appropriate and should be accepted as proposed (NLT — %/30 min).

Thanks again for asking,

-----Original Message-----
**From:** Nguyen, Hoainhon T
**Sent:** Wednesday, July 28, 2004 4:19 PM
**To:** Tran, Nhan L
**Cc:** Nerurkar, Shriniwas G; Nguyen, Hoainhon T
**Subject:** FW: Dissolution Spec for ANDA 76-894 (TorPham's Torsemide Tablets) - CORRECTION

Hi Tran,
The attachment below is the correct version of the dissolution data. Please disregard the previously sent file. Thanks, Hoai

-----Original Message-----
**From:** Nguyen, Hoainhon T
**Sent:** Wednesday, July 28, 2004 9:55 AM
**To:** Tran, Nhan L
**Cc:** Nerurkar, Shriniwas G; Nguyen, Hoainhon T

**Subject:** Dissolution Spec for ANDA 76-894 (TorPham's Torsemide Tablets)

Hi Tran,
Please see attached for the dissolution data. Please give your input for the following scenario: Our current spec for the drug product is NLT —%(Q) in 15 minutes. The ANDA dissolution data did not include 15-minute time point. However, for the lowest strength, 5 mg, at 20 minutes, the range was —— %. That means this strength would not pass Stage 1 testing using our current spec. I am proposing to set the spec at NLT —% in 20 minutes. I am not sure we should request the firm to repeat the dissolution testing with 15-minute time point included just to set a different spec anyway. Thanks in advance for your assistance.
Hoai
<< File: 76894dissolutiondata.doc >>

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-894 APPLICANT: TorPharm Inc.

DRUG PRODUCT: Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg

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

The formulation of the 100 mg strength is not considered proportionally similar to that of the 20 mg strength which underwent acceptable *in vivo* bioequivalence testing. The waiver request for the 100 mg strength is therefore denied at this time. Please provide additional data as evidence that your proposed 100 mg tablet is bioequivalent to Roche Laboratories' Demadex® tablet, 100 mg. The additional evidence may be in the form of direct *in vivo* comparisons that have already been conducted, or any other methods that would support a decision to grant a waiver of *in vivo* testing for the proposed product. Examples may include pilot studies and/or additional *in vitro* studies conducted with multiple media of varying pHs. (i.e. additional comparative dissolution data on 20 mg and 100 mg tablets in water, acetate buffer pH 4.5, phosphate buffer pH 6.5 and phosphate buffer pH 7.5).

Sincerely yours,

Barbara M Davit

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

CC:ANDA 76-894
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ SNerurkar

8/31/04

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ SNerurkar
HFD-617/ A. Sigler
HFD-650/ D. Conner 8/31/04

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BIOEQUIVALENCY - ACCEPTABLE Submission date: 11-06-03, 08-09-04,08-16-04

1. FASTING STUDY (STF)
   Clinical: [redacted]
   Analytical: [redacted]
   Strength: 20 mg
   ✓ **Outcome: AC**

2. NONFASTING STUDY (STP)
   Clinical: [redacted]
   Analytical: [redacted]
   Strength: 20 mg
   ✓ **Outcome: AC**

3. DISSOLUTION WAIVERS (DIW)
   Strength: 5 mg
   ✓ **Outcome: AC**

4. DISSOLUTION WAIVERS (DIW)
   Strength: 10 mg
   ✓ **Outcome: AC**

5. DISSOLUTION WAIVERS (DIW)
   Strength: 100 mg
   ✓ **Outcome: UN**

4. STUDY AMENDMENTS (STA) Telephone Amendments provided potency assay and content uniformity data. NOTE: The first Telephone Amendment dated August 9, 2004 provided incorrect information.
   Strength: 20 mg
   X **Outcome: NC**

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
**AC** - Acceptable **NC** - No credit

3.1 (FO)

# DIVISION OF BIOEQUIVALENCE REVIEW

| | |
|---|---|
| **ANDA No.** | 76-894 |
| **Drug Product Name** | Torsemide Tablets |
| **Strength** | 5 mg, 10 mg, 20 mg & 100 mg |
| **Applicant Name** | Apotex Inc. (formerly Torpharm Inc.) |
| **Address** | Etobicoke, Ontario, Canada |
| **Submission Date(s)** | January 4, 2005 |
| **Amendment Date(s)** | |
| **Reviewer** | **Hoainhon Nguyen** |
| **First Generic** | **No** |
| **File Location** | **V:\firmsnz\torpharm\ltrs&rev\76894a0105.doc & v:\firmsam\apotex\ltrs&rev\76894a0105.doc** |

## I. Executive Summary

The firm has submitted the current amendment in response to the DBE's deficiency comments in the letter dated September 1, 2004. The DBE has found that the formulation of the 100 mg strength is not considered proportionally similar to that of the 20 mg strength which underwent acceptable *in vivo* bioequivalence testing. The waiver request for the 100 mg strength of the test product was denied. The DBE requested that the firm provide additional data as evidence that the proposed 100 mg tablet is bioequivalent to Roche Laboratories' Demadex® tablet, 100 mg.

In the current amendment, the firm has submitted additional *in vitro* dissolution data, from testing in different pH media, comparing between the two strengths, 20 mg and 100 mg, of the test and RLD products. The firm has also provided rationale to support the waiver request for the 100 mg strength. The additional information as submitted is considered adequate and acceptable. The waiver request for the 100 mg strength is granted.
The fasting and nonfasting studies and dissolution testing for the 20 mg strength of the test product are acceptable, and the dissolution waivers were granted for the 5 mg and 10 mg strengths. The DBE also agreed with the firm's proposed dissolution specification. (See the review of the original submission, v:\firmsnz\torpharm\ltrs&rev\76894n1103.doc).

The application is **complete** with no further deficiencies.

## II. Table of Contents

## III. Submission Summary

### A. Drug Product Information

| | |
|---|---|
| **Test Product** | Torsemide Tablets |
| **Reference Product** | Demadex® Tablets, 5 mg, 10 mg, 20 mg & 100 mg. The 20 mg strength is the designated RLD strength due to safety concern with administration of 100 mg dose to normal volunteers. |
| **RLD Manufacturer** | Roche |
| **NDA No.** | 20-136 |
| **RLD Approval Date** | 08/23/93 |
| **Indication** | A diuretic indicated for the treatment of edema associated with congestive heart failure, renal disease or hepatic disease. |

### B. PK/PD Information

See the review of the original submission, v:\firmsnz\torpharm\ltrs&rev\76894n1103.doc

### C. Contents of Submission

| Study Types | Yes/No? | How many? |
|---|---|---|
| **Single-dose fasting** | No | |
| **Single-dose fed** | No | |
| **Steady-state** | No | |
| **In vitro dissolution** | Yes | 1 |
| **Waiver requests** | Yes | 3 |
| **BCS Waivers** | No | |
| **Vasoconstrictor Studies** | No | |
| **Clinical Endpoints** | No | |
| **Failed Studies** | No | |
| **Amendments** | Yes | 1 |

## D. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

See the complete review of the studies in v:\firmsnz\torpharm\ltrs&rev\76894n1103.doc

| Study Summary, Fasting Bioequivalence Study | |
|---|---|
| **Study No.** | AA03121 |
| **Study Design** | Two-way crossover |
| **No. of subjects enrolled** | 32 |
| **No. of subjects completing** | 30 |
| **No. of subjects analyzed** | 30 |
| **Subjects (Healthy or Patients?)** | Healthy |
| **Sex(es) included (how many?)** | Male: 30 Female: 0 |
| **Test product** | Apotex's Torsemide Tablets |
| **Reference product** | Roche's Demadex® Tablets |
| **Strength tested** | 20 mg |
| **Dose** | 1x 20 mg |

| Summary of Statistical Analysis, Fasting Bioequivalence Study (N=30) | | |
|---|---|---|
| **Parameter** | **Point Estimate** | **90% Confidence Interval** |
| **$AUC_{0-t}$** | 0.99 | 97.0-101.7 |
| **$AUC_{\infty}$** | 0.99 | 97.1-101.7 |
| **$C_{max}$** | 0.99 | 91.1-107.8 |

| Reanalysis of Study Samples, Fasting Bioequivalence Study | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **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** |
| **There was no PK repeat sample.** | | | | | | | | |

Did use of recalculated plasma concentration data change study outcome? N/A

2. Single-dose Fed Bioequivalence Study

| Study Summary, Fed Bioequivalence Study | |
|---|---|
| **Study No.** | AA03122 |
| **Study Design** | Two-way crossover |
| **No. of subjects enrolled** | 32 |
| **No. of subjects completing** | 30 |
| **No. of subjects analyzed** | 30 |
| **Subjects (Healthy or Patients?)** | Healthy |
| **Sex(es) included (how many?)** | Male 30 Female 0 |
| **Test product** | Apotex's Torsemide Tablets |
| **Reference product** | Roche's Demadex® Tablets |
| **Strength tested** | 20 mg |
| **Dose** | 1x20 mg |

| Summary of Statistical Analysis, Fed Bioequivalence Study (N=30) | | |
|---|---|---|
| **Parameter** | **Point Estimate** | **90% Confidence Interval** |
| **$AUC_{0-t}$** | 1.00 | 97.8-102.5 |
| **$AUC_{\infty}$** | 1.00 | 97.8-102.3 |
| **$C_{max}$** | 1.09 | 99.5-118.9 |

| Reanalysis of Study Samples, Fed Bioequivalence Study | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **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** |
| **There was no PK repeat sample.** | | | | | | | | |

**E. Formulation**

See the review of the original submission, v:\firsmnz\torpharm\ltrs&rev\76894n1103.doc

| | |
|---|---|
| **Location in appendix** | SectionIV.A, Page 8 |
| **Are inactive ingredients within IIG limits?** | **Yes** |
| **If a tablet, is the product scored?** | **No** |
| **Is scoring of RLD the same as test?** | **No** |
| **Is the formulation acceptable?** | **The formulation of the 100 mg strength of the test product was found not proportionally similar to that of the 20 mg strength which underwent acceptable *in vivo* bioequivalence testing.** |

### F. In Vitro Dissolution

| | |
|---|---|
| **Source of Method (USP, FDA or Firm)** | 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*** | —%(Q) in 15 minutes |
| **F2 metric calculated?** | No. |
| **If no, reason why F2 not calculated** | The RLD product is fast dissolving and CV% is high for the first time point for the test product. |
| **Is method acceptable?** | Yes |
| **If not then why?** | |

***NOTE:** 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 dissolution data summarized in the review Appendix). The specification as proposed by the firm above has been found acceptable for the test product. See Dr. Tran's email in the review Appendix.

### G. Waiver Request(s)

| | |
|---|---|
| Strengths for which waivers are requested | 5 mg, 10 mg and 100 mg |
| Regulation cited | 21 CFR 320.22(d)(2) |
| Proportional to strength tested in vivo? | Yes |
| Is dissolution acceptable? | Yes |
| Waivers granted? | Yes |

### H. Comments

1. The firm has provided additional information to support its waiver request for its 100 mg strength. The information includes additional dissolution data from testing conducted in water, pH 7.5, 6.8 and 4.5 in addition to dissolution data from testing in 0.1 N HCl submitted previously. Comparison between the 20 mg and 100 mg strengths of the test product showed that Similarity Factor F2 was greater than 50 for water and pH 7.5 media, less than 50 for pH 6.8 and pH 4.5 media, and not calculatable for 0.1 N HCl medium (due to fast dissolving). Comparison between the test and reference products of the same strength as well as between the 20 mg and 100 mg strengths of the RLD product was not possible because both 20 mg and 100 mg strengths of the RLD product were fast dissolving.

2. For ANDA 76-346 (Torsemide Tablets; Pliva; 07/08/03), the formulation of the 100 mg strength was also not proportionally similar to the 20 mg strength which underwent acceptable *in vivo* bioequivalence testing. Dissolution testing in 0.1 N HCl, water, pH 6.5 and pH 7.5 (using USP apparatus II(paddle) at 50 rpm and 900 mL of media) showed

fast dissolving profiles for both the 20 mg and 100 mg of both the test and RLD products. Dissolution data for pH 4.5 media were not available. The formulation of the 100 mg strength of Pliva'sTorsemide Tablets was found acceptable based on the submitted dissolution data, the linearity PK of torsemide over the dose range of 2.5 to 200 mg, and the fact that formulation proportionality between the 20 mg and 100 mg strengths does not exist in any of the currently marketed torsemide tablet products, including the RLD and approved generic formulations (See Appendix).

3. According to the OCPB review of NDA 20-136 (submissions dated 02/28/91 through 04/16/92), when dissolution testing was conducted in water, using UPS apparatus II(paddle) at 50 rpm, the dissolution data for the 5 mg, 10 mg and 20 mg were found to be much faster than the 100 mg strength.

4. The firm presented the following supportive information based on the RLD product's labeling:

- Cmax and AUC after oral administration of torsemide tablets are proportional to dose over the range of 2.5 mg to 200 mg
- Simultaneous food intake delays the time to Cmax by about 30 minutes, but overall bioavailability (AUC) and diuretic activity are unchanged
- Because of the high bioavailability of torsemide (absolute bioavailability of approximately ~ %), oral and intravenous doses are therapeutically equivalent, so patients may be switched to and from the intravenous form with no change in dose.

*"The information obtained from the labeling indicates that despite the differences in dissolution of torsemide among different strengths (2.5 mg and 200 mg), the delay of absorption of torsemide due to food, and the difference in drug delivery between the oral and intravenous forms of the drug, no clinically significant differences in the drug's bioavailability and/or its therapeutically effects are resulted."*

5. Based on the information discussed in Comments 1 through 4 above, the formulation of the 100 mg strength of the current test product is considered acceptable even though it is not proportionally similar to the formulation of the 20 mg strength by the current general BA/BE guidance. The request for waiver of *in vivo* bioequivalence studies for the 100 mg strength is granted based on acceptable bioequivalence studies of the 20 mg strength and acceptable dissolution data of the 100 mg strength obtained using the FDA-recommended method (See the review of the original submission, v:\firmsnz\torpharm\ ltrs&rev\76894n1103.doc).

## I. Recommendations

From the review of the original submission, v:\firmsnz\torpharm\ltrs&rev\ 76894n1103.doc:

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—% (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 current review:

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.

3/1/05

Hoainhon Nguyen, Team I, Date Signed

3/1/2005

Shriniwas Nerurkar, Team I, Date Signed

3/1/05

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

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## IV. Appendix

### A. Formulation Data

**NOT TO BE RELEASED UNDER FOI**

| 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 | | | | |
| Crospovidone NF | | | | |
| Magnesium Stearate NF | | | | |
| Collodial Silicon Dioxide NF | | | | |
| Total | 50 mg | 100 mg | 200 mg | 280 mg |

**Comments:** The formulations of the 5 mg and 10 mg are proportionally similar to that of the 20 mg strength. The inactive ingredients of all strengths are within the approved IIG ranges. The formulation of the 100 mg strength, however, is NOT considered as proportionally similar to the 20 mg strength, per the current BA/BE guidance. Following are other approved generic formulations and the RLD formulation (From the review v:\firmsnz\pliva\ltrs&rev\76346s0703):

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confidential commercial

information from

BIOEQUIVALENCE REVIEW

## B. Dissolution Data

**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** | — %(Q) in 15 minutes* |

***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 1**

| 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 2**

| 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 3**

| 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 4**

| 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 5**

| 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 6**

| 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 7**

| 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 8**

| 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 9**

| 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 10**

| 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.

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-894

APPLICANT: Apotex Inc.(formerly TorPharm Inc.)

DRUG PRODUCT: Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg

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

We agree with your proposed dissolution method and specification as follows:

> 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 specifications:
>
> Not less than —% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner

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

# DIVISION OF BIOEQUIVALENCE REVIEW ADDENDUM

| | |
|---|---|
| **ANDA No.** | 76-894 |
| **Drug Product Name** | Torsemide Tablets |
| **Strength** | 5 mg, 10 mg, 20 mg & 100 mg |
| **Applicant Name** | Apotex Inc. (formerly Torpharm Inc.) |
| **Address** | Etobicoke, Ontario, Canada |
| **Submission Date(s)** | January 4, 2005 |
| **Amendment Date(s)** | |
| **Reviewer** | **Hoainhon Nguyen** |
| **First Generic** | **No** |
| **File Location** | **V:\firmsnz\torpharm\ltrs&rev\76894addendum0105.doc & v:\firmsam\apotex\ltrs&rev\76894addendum0105.doc** |

This is an addendum to the review of the submission dated January 4, 2005, v:\firmsnz\torpharm\ltrs&rev\76894a0105 (also, v:\firmsam\apotex\ltrs&rev\ 76894a0105). The original review has been revised to request the firm to clarify its dissolution data and its proposed dissolution method and specification **for the 5 mg strength** of the test product. It came to the DBE's attention after the review was completed that the dissolution method stated in the dissolution testing report and the dissolution method proposed for the lowest strength in the Testing Procedure (reviewed by the Division of Chemistry) were different. The DBE had recommended the same dissolution method for all strengths of the test product based on the data submitted in the dissolution testing report. The recommended dissolution method and specification are as follows: in 900 mL of 0.1N HCl using the USP apparatus II(paddle) @ 50rpm; NLT —% dissolved in 15 minutes. Although the same method was stated for the 5 mg strength in the dissolution testing report (Vol. C1.12, page 4772), the firm proposed the following method only for the 5 mg strength in the Testing Procedure (Vol. C1.12, page 4817) : in — **mL** of 0.1N HCl using the USP apparatus II(paddle) @ 50 rpm, with no justification given for the difference in volume of medium used.

The firm is requested to confirm the method actually used to generate the dissolution data for the 5 mg strength as submitted in the submission dated November 6, 2003. If the proposed method was actually used to obtain the submitted dissolution data for the 5 mg strength, the firm is asked to provide justification for using different medium volume for this strength. Otherwise, the firm is asked to provide its acknowledgement of the following FDA method and specification: in 900 mL of 0.1N HCl using the USP apparatus II(paddle) @ 50rpm; NLT —% dissolved in 15 minutes. The firm should revise the Testing Procedure to comply with the Agency's recommendations

The application is **incomplete** pending the firm's response. (All other previous recommendations by the DBE for the ANDA remain unchanged (as stated in the original review, v:\firmsam\apotex\ltrs&rev\76894a0105.doc) including the dissolution method and specification for the other strengths of the test product.)

4/26/05

Hoainhon Nguyen, Team I, Date Signed

4/26/2005

Shriniwas Nerurkar, Team I, Date Signed

4/26/05

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

HNguyen\03-22-05/firmsam/apotex/ltrs&rev/76894addendum0105.doc

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-894

APPLICANT: Apotex Inc.(formerly TorPharm Inc.)

DRUG PRODUCT: Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg

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

The dissolution testing is considered **incomplete**. On Vol. C1.12, page 4772, of the submission dated November 6, 2003, you have described the dissolution method used for the dissolution data of the 5 mg strength as follows:

| | |
|---|---|
| Medium | 0.1N HCl |
| Volume (mL) | 900 mL |
| USP Apparatus Type | II (paddle) |
| Rotation (rpm) | 50 rpm |

This was the same method that was described for the dissolution data of other strengths of the test product as well. However, in the Testing Procedure in Vol. C1.12, page 4817, of the submission dated November 6, 2003, you have proposed a different dissolution method for the 5 mg strength alone as follows:

| | |
|---|---|
| Medium | 0.1N HCl |
| Volume (mL) | [redacted] **mL** |
| USP Apparatus Type | II (paddle) |
| Rotation (rpm) | 50 rpm |

1. Please confirm which dissolution method was used to generate the dissolution data for the 5 mg strength as provided in the November 6, 2003 submission.

2. If the proposed method was actually used to obtain the submitted dissolution data for the 5 mg strength, please provide justification for using a different medium volume for this strength.

3. Otherwise, please provide your acknowledgement of the FDA's method and specification as recommended below for all strengths:

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

Not less than — ₃(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please also revise the Testing Procedure accordingly to comply with the Agency's recommendations.

Sincerely yours,

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

APPEARS THIS WAY
ON ORIGINAL

4.1 (FO)

# DIVISION OF BIOEQUIVALENCE REVIEW

| | |
|---|---|
| **ANDA No.** | 76-894 |
| **Drug Product Name** | Torsemide Tablets |
| **Strength** | 5 mg, 10 mg, 20 mg & 100 mg |
| **Applicant Name** | Apotex Inc. (formerly Torpharm Inc.) |
| **Address** | Etobicoke, Ontario, Canada |
| **Submission Date(s)** | May 6, 2005 & May 11, 2005 |
| **Amendment Date(s)** | |
| **Reviewer** | **Hoainhon Nguyen** |
| **First Generic** | **No** |
| **File Location** | **V:\firmsnz\torpharm\ltrs&rev\76894a0505.doc & v:\firmsam\apotex\ltrs&rev\76894a0505.doc** |

## I. Executive Summary

The firm has submitted the current amendments in response to the DBE's deficiency comments in the letter dated May 3, 2005 (See the review addendum, v:\firmsam\apotex\ltrs&rev\76894addendum0105.doc). The DBE had found discrepancy in the dissolution report for the 5 mg strength, in which the volume of dissolution medium (900 mL) was not the same as that proposed in Testing Procedure document (— mL) submitted to the Division of Chemistry). The firm was requested to clarify the actual dissolution volume used for the testing of the lowest strength. In the amendment dated May 6, 2005, the firm confirmed the volume used was — mL (only for the 5 mg strength) but also accepted the DBE's recommended method harmonizing the use of 900 mL volume for all strengths, as well as the recommended specification for all strengths. The Telephone Amendment dated May 11, 2005 provided the dissolution data for the 5 mg strength tested using the 900 mL volume. The data met the DBE's previously recommended specification of NLT — %(Q) in 30 minutes.

The current amendments are acceptable. The DBE's previous recommendation granting the waiver request for the 5 mg strength (as stated in the review, v:\firmsnz\torpharm\ltrs&rev\76894n1103.doc) remains the same. All other previous recommendations by the DBE for the ANDA also remain unchanged, concerning the fasting and nonfasting studies and dissolution testing for the 20 mg strength of the test product (as stated in the review, v:\firmsnz\torpharm\ltrs&rev\76894n1103.doc), and the dissolution method/specification as well as waiver request for the other strengths of the test product (as stated in the reviews, v:\firmsam\apotex\ltrs&rev\76894a0105.doc).

The application is **complete** with no further deficiencies.

## II. Table of Contents

## III. Submission Summary

### A. Drug Product Information

| | |
|---|---|
| **Test Product** | Torsemide Tablets |
| **Reference Product** | Demadex® Tablets, 5 mg, 10 mg, 20 mg & 100 mg. The 20 mg strength is the designated RLD strength due to safety concern with administration of 100 mg dose to normal volunteers. |
| **RLD Manufacturer** | Roche |
| **NDA No.** | 20-136 |
| **RLD Approval Date** | 08/23/93 |
| **Indication** | A diuretic indicated for the treatment of edema associated with congestive heart failure, renal disease or hepatic disease. |

### B. PK/PD Information

See the review of the original submission, v:\firmsnz\torpharm\ltrs&rev\76894n1103.doc

### C. Contents of Submission

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

## D. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

See the complete review of the studies in v:\firmsnz\torpharm\ltrs&rev\76894n1103.doc

| Study Summary, Fasting Bioequivalence Study | |
|---|---|
| **Study No.** | AA03121 |
| **Study Design** | Two-way crossover |
| **No. of subjects enrolled** | 32 |
| **No. of subjects completing** | 30 |
| **No. of subjects analyzed** | 30 |
| **Subjects (Healthy or Patients?)** | Healthy |
| **Sex(es) included (how many?)** | Male: 30 Female: 0 |
| **Test product** | Apotex's Torsemide Tablets |
| **Reference product** | Roche's Demadex® Tablets |
| **Strength tested** | 20 mg |
| **Dose** | 1x 20 mg |

| Summary of Statistical Analysis, Fasting Bioequivalence Study (N=30) | | |
|---|---|---|
| **Parameter** | **Point Estimate** | **90% Confidence Interval** |
| **$AUC_{0-t}$** | 0.99 | 97.0-101.7 |
| **$AUC_{\infty}$** | 0.99 | 97.1-101.7 |
| **$C_{max}$** | 0.99 | 91.1-107.8 |

| Reanalysis of Study Samples, Fasting Bioequivalence Study | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **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** | |
| **There was no PK repeat sample.** | | | | | | | | | |

Did use of recalculated plasma concentration data change study outcome? N/A

2. Single-dose Fed Bioequivalence Study

| Study Summary, Fed Bioequivalence Study | |
|---|---|
| **Study No.** | AA03122 |
| **Study Design** | Two-way crossover |
| **No. of subjects enrolled** | 32 |
| **No. of subjects completing** | 30 |
| **No. of subjects analyzed** | 30 |
| **Subjects (Healthy or Patients?)** | Healthy |
| **Sex(es) included (how many?)** | Male 30 Female 0 |
| **Test product** | Apotex's Torsemide Tablets |
| **Reference product** | Roche's Demadex® Tablets |
| **Strength tested** | 20 mg |
| **Dose** | 1x20 mg |

| Summary of Statistical Analysis, Fed Bioequivalence Study (N=30) | | |
|---|---|---|
| **Parameter** | **Point Estimate** | **90% Confidence Interval** |
| **$AUC_{0-t}$** | 1.00 | 97.8-102.5 |
| **$AUC_{\infty}$** | 1.00 | 97.8-102.3 |
| **$C_{max}$** | 1.09 | 99.5-118.9 |

| Reanalysis of Study Samples, Fed Bioequivalence Study | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| **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** |
| **There was no PK repeat sample.** | | | | | | | | |

**E. Formulation**

See the review, v:\firsmnz\torpharm\ltrs&rev\76894a0105.doc

**Location in appendix** SectionIV.A, Page 8
**Are inactive ingredients within IIG limits?** **Yes**
**If a tablet, is the product scored?** **No**
**Is scoring of RLD the same as test?** **Yes (no scoring)**
**Is the formulation acceptable?** **Yes**

### F. In Vitro Dissolution

| | |
|---|---|
| **Source of Method (USP, FDA or Firm)** | 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 |
| **FDA-recommended specification based on the test product's data*** | — %(Q) in 30 minutes |
| **F2 metric calculated?** | No. |
| **If no, reason why F2 not calculated** | The RLD product is fast dissolving and CV% is high for the first time point for the test product. |
| **Is method acceptable?** | Yes |
| **If not then why?** | |

***NOTE:** See the discussion of the specification in the review, v:\firmsam\apotex\ ltrs&rev\76894a0105.doc.

### G. Waiver Request(s)

See the reviews, v:\firsmnz\torpharm\ltrs&rev\76894a0105.doc and v:\firmsam\apotex\ ltrs&rev\76894n1103.

| | |
|---|---|
| Strengths for which waivers are requested | 5 mg, 10 mg and 100 mg |
| Regulation cited | 21 CFR 320.22(d)(2) |
| Proportional to strength tested in vivo? | Yes |
| Is dissolution acceptable? | Yes |
| Waivers granted? | Yes |

### H. Comments

1. The firm confirmed in the amendment dated May 6, 2005 that the dissolution volume used for the testing of the 5 mg strength was — mL, not 900 mL as stated in the original dissolution report.

2. Although the firm originally proposed to use — mL dissolution volume for the 5 mg strength, and 900 mL for all other strengths, the firm agreed to harmonize the dissolution medium for all strengths (in response to the deficiency received during the teleconference held on March 23, 2005 with Benjamin Danso (Project Manager), Dr. Albert Mueller (Chemist) and Kathy Woodland Outlaw (Chemist) from the OGD.

3. In addition, the firm provided its acknowledgement of the FDA's method and specification as recommended in the DBE's letter dated May 3, 2005, as follows:

*"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 specifications:*

*Not less than —%(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes."*

The firm indicated that *"the above specification limit has always been incorporated in Apotex Inc.'s Drug Product Release and Stability Testing Specifications for Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg."*

4. Since the firm had not submitted the dissolution data for the 5 mg strength using the FDA-recommended method (with 900 mL dissolution volume), the firm was asked to conduct additional dissolution testing for the lowest strength. The data were submitted in the Telephone Amendment dated May 11, 2005 and summarized in the current review Appendix. The data met the FDA-recommended specification of NLT —%(Q) in 30 minutes acknowledged by the firm previously.

The firm's responses in the current amendments are considered adequate and acceptable. The DBE's previous recommendation granting the waiver request for the 5 mg strength (as stated in the review, v:\firmsnz\torpharm\ ltrs&rev\76894n1103.doc) remains the same. All other previous recommendations by the DBE for the ANDA also remain unchanged, concerning the fasting and nonfasting studies and dissolution testing for the 20 mg strength of the test product (as stated in the review, v:\firmsnz\torpharm\ ltrs&rev\76894n1103.doc), and the dissolution method/specification as well as waiver request for the other strengths of the test product (as stated in the reviews, v:\firmsam\apotex\ltrs&rev\76894a0105.doc).

The application is **complete** with no further deficiencies.

## I. Recommendations

From the review of the original submission, v:\firmsnz\torpharm\ltrs&rev\ 76894n1103.doc:

> 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 —% (Q) of the labeled amounts of the drug in the dosage form is dissolved in 30 minutes.

From the reviews, v:\firmsnz\torpharm\ltrs&rev\ 76894n1103.doc, v:\firmsam\apotex\ ltrs&rev\76894a0105.doc and the current review:

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\ 76894a0105.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.

The application is **complete** with no further bioequivalence deficiency at this time.

5/19/05

Hoainhon Nguyen, Team I, Date Signed

5/19/2005

Shriniwas Nerurkar, Team I, Date Signed

5/20/05

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

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## IV. Appendix

### A. Formulation Data

NOT TO BE RELEASED UNDER FOI

| 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 | | | | |
| Crospovidone NF | | | | |
| Magnesium Stearate NF | | | | |
| Collodial Silicon Dioxide NF | | | | |
| Total | 50 mg | 100 mg | 200 mg | 280 mg |

### B. Dissolution Data

Testing Conditions:

APPEARS THIS WAY
ON ORIGINAL

| | |
|---|---|
| **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 1**

| 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 | |

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-894

APPLICANT: Apotex Inc.(formerly TorPharm Inc.)

DRUG PRODUCT: Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg

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

We acknowledge that you conduct dissolution testing for the all strengths of the test product using the following dissolution method and specification:

> The dissolution testing is 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 specifications:
>
> Not less than —%(Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalence 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 bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

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

CC:ANDA 76-894
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-652/ Bio Secretary - Bio Drug File
HFD-652/ HNguyen
HFD-652/ SNerurkar

Endorsements: (Final with Dates)
HFD-652/ HNguyen
HFD-652/ SNerurkar 5/19/05
HFD-617/ A. Sigler
HFD-650/ D. Conner 5/20/05

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Printed in final on / /

BIOEQUIVALENCY - ACCEPTABLE Submission date: 05/06/05 & 05/11/05

1. STUDY AMENDMENTS (STA) Strength: All strengths
**Outcome: AC**

OUTCOME DECISIONS: **IC** - Incomplete **UN** - Unacceptable (fatal flaw)
**AC** - Acceptable **NC** - No credit

5

MAY 20 2005

**OFFICE OF GENERIC DRUGS**
**DIVISION OF BIOEQUIVALENCE**

**ANDA #:** 76-894 **SPONSOR:** Apotex Inc. (formerly Torpharm. Inc.)

**DRUG & DOSAGE FORM:** Torsemide Tablets

**STRENGTH(S):** 5 mg, 10 mg, 20 mg & 100 mg

**TYPES OF STUDIES:** Fasting and Nonfasting (20 mg)

**CLINICAL STUDY SITE(S):** ———

**ANALYTICAL SITE(S):** ———

**STUDY SUMMARY:** Acceptable

**DISSOLUTION:** Acceptable

**DSI INSPECTION STATUS**

| | | | |
|---|---|---|---|
| Inspection needed: | NO | **Inspection status:** | **Inspection results:** |
| First Generic | NO | | |
| New facility | | | |
| For cause | | | |
| Other | | | |

Proposed Dissolution Method and Specifications from Original Submission Acceptable?

Yes _____ No _____ (If no, project Manager should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Specifications acknowledged by firm? Yes X No ___

**AMENDMENT DATE:** _____

**PROJECT MANAGER:** _____ **DATE:** _____

**PRIMARY REVIEWER:** Hoainhon Nguyen **BRANCH:** I
INITIAL: _____ DATE: 5/19/05

**TEAM LEADER:** Shriniwas Nerurkar, Ph.D. **BRANCH:** I
INITIAL: _____ DATE: 5/19/2005

**DIRECTOR, DIVISION OF BIOEQUIVALENCE:** Dale P. Conner, Pharm.D.
INITIAL: _____ DATE: 5/20/05

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 76-894

# ADMINISTRATIVE DOCUMENTS

# RECORD OF TELEPHONE CONVERSATION

| | |
|---|---|
| **ANDA #:** | 76-894 |
| **DATE:** | December 8, 2003 |
| **TIME:** | 11:00 am |
| **DRUG:** | Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg |
| **FIRM:** | Ms. Marcy Macdonald for Apotex Corp. |
| **FDA PARTICIPANTS:** | Emily Thomas |
| **PHONE NUMBER:** | 847-279-7740 |
| **TOPIC:** | Missing info |

I asked Ms. Macdonald for a couple of items. I need the accelerated stability data for lot FD2134a for the 100 count bottle of 100 mg strength. I also need a revised 356h form with the correct approved holder name, ROCHE.

## Danso, Benjamin

**From:** Grace, John F
**Sent:** Thursday, April 28, 2005 1:12 PM
**To:** Wu, Ruby (Chi-Ann); Danso, Benjamin
**Subject:** RE: FPL Review status for 76-894 (Apotex Torsemide)

I concur

-----Original Message-----
**From:** Wu, Ruby (Chi-Ann)
**Sent:** Thursday, April 28, 2005 12:30 PM
**To:** Grace, John F; Danso, Benjamin
**Subject:** FW: FPL Review status for 76-894 (Apotex Torsemide)

John,

Drug substance is USP. Drug product not subject to a USP 28 Monograph.

Checked DSS, DFS and OB. The labeling AP summary sign-off on 3/10/04 remains acceptable.

Ruby

-----Original Message-----
**From:** Danso, Benjamin
**Sent:** Thursday, April 28, 2005 12:15 PM
**To:** Wu, Ruby (Chi-Ann); Grace, John F
**Subject:** FPL Review status for 76-894 (Apotex Torsemide)

Hi Ruby/ John

Attached is a scanned copy of the final approval letter and the fpl sign off sheet. Please confirm if Apotex labeling is still in good standing, and that approval is ok to move forward. Your response to this mail will be attached to the final approval letter, and will represent your signatures.
Thanks

<< File: 76894.ApFPL.pdf >>

*LT Benjamin Danso, Pharm.D.*
7500 Standish Pl
OGD/HFD-617/MPN2
Rockville, MD 20855
DansoB@CDER.FDA.GOV

76-894

## OGD APPROVAL ROUTING SUMMARY

**ANDA #** 76-894 **Applicant** Apotex Corp.
**Drug** Torsemide Tablets **Strength(s)** 5 mg, 10 mg, 20 mg, and 100 mg
**APPROVAL** ☒ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **OTHER** ☐

| **REVIEWER:** | **DRAFT Package** | **FINAL Package** |
|---|---|---|
| 1. Martin Shimer<br>Chief, Reg. Support Branch | Date 27APR05<br>Initials MS | Date 5/31/05 Rec'd for<br>Initials |

Contains GDEA certification: Yes ☑ No ☐ (required if sub after 6/1/92)
Determ. of Involvement? Yes ☐ No ☐
Pediatric Exclusivity System
RLD = NDA# 20-136
Patent/Exclusivity Certification: Yes ☑ No ☐
Date Checked N/A
If Para. IV Certification- did applicant
Notify patent holder/NDA holder Yes ☑ No ☐
Nothing Submitted ☐
Was applicant sued w/in 45 days: Yes ☐ No ☑
Written request issued ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Study Submitted ☐
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑
Date of latest Labeling Review/Approval Summary
Any filing status changes requiring addition Labeling Review Yes ☐ No ☑
Type of Letter: PIV to PE 672 patent → not sued w/in 45 days. 180 exclusivity
Comments: the subject drug product was expired NDA 76-110 TEVA Eligible for FULL APPROVAL

| | | |
|---|---|---|
| 2. Project Manager, _Ben Danso_ Team_5_<br>Review Support Branch | Date 4/27/05<br>Initials_BD__ | Date_____<br>Initials_____ |

Original Rec'd date_11/6/03 ✓
Date Acceptable for Filing_11/7/03
Patent Certification (type)_P IV
Date Patent/Exclus.expires_8/11/06
Citizens' Petition/Legal Case Yes☐ No ☒
(If YES, attach email from PM to CP coord)
First Generic Yes ☐ No ☒ Date of Sterility Assur. App. _____
Methods Val. Samples Pending Yes ☐ No ☐
MV Commitment Rcd. from Firm Yes ☐ No ☐
Acceptable Bio reviews tabbed Yes ☒ No ☐
Suitability Petition/Pediatric Waiver
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐
Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

EER Status Pending ☐ Acceptable ☒ OAI ☐
Date of EER Status 6/22/04
Date of Office Bio Review _3/01/05
Date of Labeling Approv. Sum _3/10/04
Labeling Acceptable Email Rec'd Yes ☒ No ☐
Labeling Acceptable Email filed Yes ☒ No ☐
Interim Dissol. Specs in AP Ltr: Yes ☐
Modified-release dosage form: Yes ☐ No ☐

| | | |
|---|---|---|
| 3. David Read **(PP IVs Only)** Pre-MMA Language included ☑<br>OGD Regulatory Counsel, Post-MMA Language Included ☐<br>Comments: see revised version. | | Date 4/28/05<br>Initials |

| | | |
|---|---|---|
| 4. Div. Dir./~~Deputy Dir.~~<br>Chemistry Div. I ~~II OR~~ III<br>Comments: The CMC section is satisfactory | | Date 5/27/05<br>Initials RLC |

IEWER: FINAL ACTION

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
NA. Multiple ANDAs have been approved for this drug product.

6. Vacant RLD=Demadex Tablets 5mg, 10mg, 20mg, 100mg Date_____
Deputy Dir., DLPS Initials_____
Hoffmann La Roche, Inc.
NDA 20-136

7. Peter Rickman Date 5/31/05
Director, DLPS Initials Request for
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes ☐ No ☐
Comments: Acceptable EES dated 7/20/04 (Verified 5/31/05) NDAI. Waiver noted- Bioequivalence studies (fasting and non-fasting) on 20mg strengths found acceptable 8/31/04. Waiver granted to 5mg and 10mg strengths under 21CFR 320.22(d)(2). Waiver granted for 100mg strength 3/1/05. Dissolution testing on all 4 strengths found acceptable. Office Level bio endorsed 3/1/05 and 5/20/05. ORA found acceptable 3/10/04 (Laboratory endorsed 4/28/05). CMC found acceptable for approval 5/26/05- Methods validation was not requested for the drug product.

8. Robert L. West Date 5/31/2005
Deputy Director, OGD Initials Robert West
Para.IV Patent Cert: Yes ☒ No ☐; Pending Legal Action: Yes ☐ No ☒; Petition: Yes ☐ No ☐
Comments: Apotex made a paragraph IV certification to the '672 patent (8/11/06). Apotex was not sued for patent infringement within the 45-day period. There is no unexpired exclusivity listed in the current "Orange Book" for this drug product.
This ANDA is recommended for approval.

9. Gary Buehler Date 5/31/05
Director, OGD Initials GB
Comments:
First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

10. Project Manager, Team _Ben Danso__ Date 5/31/05
Review Support Branch Initials BD
NA Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
12:57 Time notified of approval by phone 1:15 Time approval letter faxed
FDA Notification:
5/31/05 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
5/31/05 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.
Marcy is out.
spoke w/ Kalpesh Shroff

File V:/division/dlps/approvrou9.doc

# CENTER FOR DRUG EVALUATION AND RESEARCH

*APPLICATION NUMBER:*

# ANDA 76-894

# CORRESPONDENCE

# Tor Pharm Inc.

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

NEW CORRESP
(NC)

To whom it may concern:

**Re: Telephone Amendment For Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg, ANDA #76-894**

TorPharm Inc., 50 Steinway Boulevard, Etobicoke, Ontario, Canada, M9W 6Y3, is hereby amending ANDA number 76-894 for Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg. This amendment is being filed to as per the FDA Telephone Call dated December 8, 2003 from Emily Thomas, OGD Regulatory Support. This amendment is being submitted to replace the FDA 356h Form and the 100 mg accelerated stability pages of the Original ANDA.

Should you have any questions or concerns regarding the enclosed, please do not hesitate to contact me at (416) 675-8406 or by fax at (416) 675-0340.

Jennifer Docherty
Manager, Regulatory Affairs

December 09, 2003
Date

**TORPHARM INC.**

**Amendment to ANDA # 76-894**
**Torsemide Tablets**
**5 mg, 10 mg, 20 mg and 100 mg**

RECEIVED
DEC 11 2003
OGD/CDER



50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-3388 Fax: (416) 675-0340

ANDA 76-894

DEC 15 2003

Apotex Corp.
U.S. Agent for TorPharm Inc.
Attention: Marcy Macdonald
616 Heathrow Drive
Lincolnshire, IL 60069

Dear Madam:

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

Reference is made to the telephone conversation dated December 8, 2003 and your correspondence dated December 9, 2003.

NAME OF DRUG: Torsemide Tablets, 5 mg, 10 mg, 20 mg and 100 mg

DATE OF APPLICATION: November 6, 2003

DATE (RECEIVED) ACCEPTABLE FOR FILING: November 7, 2003

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

**CONTENTS OF THE NOTICE**

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

**SENDING THE NOTICE**

In accordance with 21 CFR 314.95(a):

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

1) Each owner of the patent or the representative designated by the owner to receive the notice.

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

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

**DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE**

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

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

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

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

**DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME**

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

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

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

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

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

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

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

Should you have questions concerning this application, contact:

Wanda Pamphile
Project Manager
(301) 827-5848

Sincerely yours,

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

# Tor Pharm Inc.

February 16, 2004

ORIG AMENDMENT
N/AF

FPL

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

To Whom It May Concern:

**Re: MINOR AMENDMENT**
**(Includes Final Printed Labeling)**
**Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg**
**ANDA No. 76-894**

TorPharm Inc. is hereby submitting a Minor Amendment for final printed labeling for Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg (ANDA No. 76-894) in response to the FDA Deficiency Letter dated January 12, 2004. The Minor Amendment is being submitted in triplicate (Review, Archival and Desk Copy). Please note that as requested, a desk copy for the labeling reviewer has also been provided.

Should you have any questions or concerns regarding the enclosed, please do not hesitate to contact me at (416) 675-8406, by fax at (416) 675-0340 or by email at jdochert@apotex.com.

Sincerely,

Jennifer Docherty
Manager, Regulatory Affairs

RECEIVED
FEB 19 2004

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

# Tor Pharm Inc.

February 25, 2004.

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

To Whom It May Concern:

Re: **PATENT AMENDMENT**
**Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg**
**ANDA No. 76-894**

TorPharm Inc., is hereby amending ANDA number 76-894 for Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg. This amendment is being filed as a notice of non-litigation for U.S. Patent Number RE34, 672. The 45-day period from the receipt of the notice of certification from the patent holders has expired.

Should you have any questions or concerns regarding the enclosed, please do not hesitate to contact me at (416) 675-8406 or by fax at (416) 675-0340 or by email at jdochert@apotex.com.

Sincerely,

Jennifer Docherty
Manager, Regulatory Affairs

RECEIVED
FEB 26 2004
OGD/CDER

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340

ORIGINAL 3.1

# Tor Pharm Inc.

June 30, 2004

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

ORIG AMENDMENT
N/A M

To Whom It May Concern:

**Re: MINOR AMENDMENT**
**Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg**
**ANDA No. 76-894**

Apotex Inc. is hereby submitting a Minor Amendment for Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg for ANDA No. 76-894. The Amendment is being submitted in response to the FDA Minor Deficiency Letter dated April 26, 2004. This Amendment is submitted in triplicate (Archival, Review, and Field copies), and contains one volume. The required Field Copy Certification can be found in the last section of the Amendment.

Please note that TorPharm Inc. has assumed the name Apotex Inc. to reflect the name of its parent company, effective April 1, 2004. A letter outlining the details of this change has been submitted under separate cover on June 30, 2004.

Should you have any questions or concerns, please do not hesitate to contact me at (416) 675-0338 ext. 4207, by fax at (416) 675-0340 or by e-mail at bsandhu@apotex.com.

Sincerely,

Barinder Sandhu
Project Leader, Regulatory Affairs

RECEIVED
JUL - 1 2004
OGD / CDER

cc: John Hems, Director, U.S. and Canadian Regulatory Affairs, Apotex Inc.
Marcy Macdonald, Director, Regulatory Affairs, Apotex Corp.

*50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3 Phone: (416) 675-0338 Fax: (416) 675-0340*

ORIGINAL 3.1

# Tor Pharm Inc.

June 30, 2004

XA

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

NAI
7/13/04

To Whom It May Concern:

**Re:** **Company Name Change from TorPharm Inc. to Apotex Inc.**
**Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg**
**ANDA No. 76-894**

Please be advised that TorPharm Inc. has assumed the name Apotex Inc. to reflect the name of its parent company, effective April 1, 2004. The FDA Form 356h has been provided.

Please also note that, where necessary, in order to distinguish between the Apotex sites, the company formerly known as TorPharm Inc. will now be referred to as Apotex Inc. – Etobicoke Site and the parent site will be referred to as Apotex Inc. – Signet Campus.

Establishment Registration and Drug Listing forms will be revised and submitted accordingly.

Should you have any questions or concerns regarding the above changes, please do not hesitate to contact me by telephone at (416) 675-0338 ext. 4207, by fax at (416) 675-0340 or by e-mail at bsandhu@apotex.com.

Sincerely,

Barinder Sandhu
Project Leader, Regulatory Affairs
Apotex Inc. – Etobicoke Site
(formerly TorPharm Inc.)

RECEIVED
JUL 0 1 2004
OGD / CDER

APOTEX INC.
ANADA'S PHARMACEUTICAL COMPANY
OCIÉTÉ PHARMACEUTIQUE ENTIÈREMENT CANADIENNE

8/25/04
RE for RE 34,672
and NDA Send within
45 days
S. Middleton

July 26, 2004

XP

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

To Whom It May Concern:

**Re: PATENT AMENDMENT**
**Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg**
**ANDA No. 76-894**

Apotex Inc. is hereby amending ANDA No. 76-894 for Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg. This Amendment is being filed as proof of patent notification to the NDA holder and patent holder for U.S. Patent No. RE34,672.

In addition, this Amendment is being filed as a notice of non-litigation for U.S. Patent No. RE34,672. The 45-day period from the receipt of the notice of certification from the patent holder has expired.

Please note that this information has been previously submitted to FDA in a Patent Amendment dated February 25, 2004, however the supporting documentation for the Registered Mail Receipts was not included. The Registered Mail Receipts are included in this Amendment.

Should you have any questions or concerns regarding the enclosed, please do not hesitate to contact me at (416) 675-0338 ext. 4207, by fax at (416) 675-0340 or by e-mail at bsandhu@apotex.com.

Sincerely,

Barinder Sandhu
Project Leader, Regulatory Affairs

RECEIVED
JUL 26 2004
OGD / CDER

cc: John Hems, Director, U.S. and Canadian Regulatory Affairs, Apotex Inc.
Marcy Macdonald, Director, Regulatory Affairs, Apotex Corp.

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3
Tel. 416.675.0338 Fax. 416.675.0340 www.apotex.com

Proudly Canadian

3.1

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

ORIGINAL

August 9, 2004

ORIG AMENDMENT
N/AB

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

To Whom It May Concern:

**Re: TELEPHONE AMENDMENT**
**Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg**
**ANDA No. 76-894**

Apotex Inc. is hereby submitting a Telephone Amendment for Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg for ANDA No. 76-894. The Amendment is being submitted in response to the telephone deficiency received from Aaron Sigler on August 6, 2004. This Amendment is submitted in triplicate (Archival, Review, and Field copies), and contains one volume. The required Field Copy Certification can be found in the last section of the Amendment.

Should you have any questions or concerns, please do not hesitate to contact me at (416) 675-0338 ext. 4207, by fax at (416) 675-0340 or by e-mail at bsandhu@apotex.com.

Sincerely,

Barinder Sandhu
Project Leader, Regulatory Affairs

cc: John Hems, Director, U.S. and Canadian Regulatory Affairs, Apotex Inc.
Marcy Macdonald, Director, Regulatory Affairs, Apotex Corp.

RECEIVED
AUG 12 2004
OGD / CDER

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3
Tel. 416.675.0338 Fax. 416.675.0340 www.apotex.com

Proudly Canadian

APOTEX INC.

ORIG AMENDMENT

N/AB

August 16, 2004

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

To Whom It May Concern:

**Re: TELEPHONE AMENDMENT**
**Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg**
**ANDA No. 76-894**

Apotex Inc. is hereby submitting a Telephone Amendment for Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg for ANDA No. 76-894. The Amendment is being submitted in response to the telephone deficiency received from Aaron Sigler on August 12, 2004. This Amendment is submitted in triplicate (Archival, Review, and Field copies), and contains one volume. The required Field Copy Certification can be found in the last section of the Amendment.

Should you have any questions or concerns, please do not hesitate to contact me at (416) 675-0338 ext. 4207, by fax at (416) 675-0340 or by e-mail at bsandhu@apotex.com.

Sincerely,

Barinder Sandhu
Project Leader, Regulatory Affairs

cc: John Hems, Director, U.S. and Canadian Regulatory Affairs, Apotex Inc.
Marcy Macdonald, Director, Regulatory Affairs, Apotex Corp.

RECEIVED
AUG 17 2004
OGD/CDER

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3
Tel. 416.675.0338 Fax. 416.675.0340 www.apotex.com

APOTEX INC.

November 12, 2004

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

ORIG AMENDMENT
N/AM

To Whom It May Concern:

Re: **MINOR AMENDMENT**
**Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg**
**ANDA No. 76-894**

Apotex Inc. is hereby submitting a Minor Amendment for Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg for ANDA No. 76-894. This Minor Amendment is being submitted in response to the FDA Deficiency Letter dated September 10, 2004.

This Amendment is submitted in triplicate (Archival, Review, and Field copies), and contains one volume. The required Field Copy Certification can be found in the last section of the Amendment.

Should you have any questions or concerns, please do not hesitate to contact me at (416) 675-0338 ext. 4207, by fax at (416) 675-0340 or by e-mail at bsandhu@apotex.com.

Sincerely,

Barinder Sandhu
Project Leader, Regulatory Affairs

cc: Bernice Tao, Associate Director, U.S. Regulatory Affairs, Apotex Inc.
Michael Lisjak, Manager, Regulatory Affairs, Apotex Corp.

RECEIVED
NOV 15 2004
OGD / CDER

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3
Tel. 416.675.0338 Fax. 416.675.0340 www.apotex.com

3.1

APOTEX INC.

January 4, 2005

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

ORIG AMENDMENT
N/AB

To Whom It May Concern:

**RE: BIOEQUIVALENCY AMENDMENT**
**Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg**
**ANDA No. 76-894**

Apotex Inc. is hereby amending its ANDA No. 76-894 for Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg in response to the FDA Deficiency Letter dated September 1, 2004.

This Bioequivalency Amendment contains one volume, is being submitted in triplicate (Archival, Review and Field copies), and the required Field Copy Certification can be found in the last section of the Amendment.

Dissolution data in multiple media of varying pHs for the 20 mg and 100 mg strengths have been included in this Bioequivalency Amendment.

Should you have any questions or concerns regarding the enclosed, please do not hesitate to contact me by telephone at (416) 675-0338 ext. 4207, by fax at (416) 675-0340 or by e-mail at bsandhu@apotex.com.

Sincerely,

Barinder Sandhu
Project Leader, Regulatory Affairs

cc: Bernice Tao, Associate Director, Regulatory Affairs – Solid Dose US, Apotex Inc.
Marcy Macdonald, Director, Regulatory Affairs, Apotex Corp.

RECEIVED
JAN 05 2005
OGD / CDER

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3
Tel. 416.675.0338 Fax. 416.675.0340 www.apotex.com

APOTEX INC.

ORIG AMENDMENT

March 24, 2005

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

To Whom It May Concern:

**Re: TELEPHONE AMENDMENT**
**Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg**
**ANDA No. 76-894**

Apotex Inc. is hereby submitting a Telephone Amendment for Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg for ANDA No. 76-894. This Telephone Amendment is being submitted in response to the deficiency received during the teleconference held on March 23, 2005 with Benjamin Danso (Project Manager), Dr. Albert Mueller (Chemist) and Kathy Woodland Outlaw (Chemist) from OGD. This Amendment is submitted in triplicate (Archival, Review, and Field copies), and contains one volume. The required Field Copy Certification can be found in the last section of the Amendment.

Should you have any questions or concerns, please do not hesitate to contact me at (416) 675-0338 ext. 4207, by fax at (416) 675-0340 or by e-mail at bsandhu@apotex.com.

Best Regards,

Barinder Sandhu
Project Leader
Regulatory Affairs – Solid Dose (U.S.)

cc: Bernice Tao, Associate Director, Regulatory Affairs – Solid Dose (U.S.), Apotex Inc.
Marcy Macdonald, Director, Regulatory Affairs – Parenterals & U.S. Office, Apotex Corp.

RECEIVED
MAR 30 2005
OGD/CDER

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3
Tel. 416.675.0338 Fax. 416.675.0340 www.apotex.com

APOTEX INC.

ORIG AMENDMENT
N-AB

May 6, 2005

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

To Whom It May Concern:

**Re: BIOEQUIVALENCY AMENDMENT**
**Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg**
**ANDA No. 76-894**

Apotex Inc. is hereby submitting a Bioequivalency Amendment for Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg for ANDA No. 76-894. This Bioequivalency Amendment is being submitted in response to the FDA Deficiency Letter dated May 3, 2005. This Amendment is submitted in triplicate (Archival, Review, and Field copies), and contains one volume. The required Field Copy Certification can be found in the last section of the Amendment.

Furthermore, reference is made in this Amendment to the Telephone Amendment dated March 24, 2005 submitted to FDA in response to the deficiency received during the teleconference held on March 23, 2005 with Benjamin Danso (Project Manager), Dr. Albert Mueller (Chemist) and Kathy Woodland Outlaw (Chemist) from OGD.

Should you have any questions or concerns, please do not hesitate to contact me at (416) 675-0338 ext. 4207, by fax at (416) 675-0340 or by e-mail at bsandhu@apotex.com.

Best Regards,

Barinder Sandhu
Project Leader
Regulatory Affairs – Solid Dose US

cc: Bernice Tao, Associate Director, Regulatory Affairs – Solid Dose US, Apotex Inc.
Marcy Macdonald, Director, Regulatory Affairs – Parenterals & US Office, Apotex Corp.

RECEIVED
MAY 09 2005
OGD/CDER

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3
Tel. 416.675.0338 Fax. 416.675.0340 www.apotex.com

APOTEX INC.

May 11, 2005

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

ORIG AMENDMENT
N/AB

To Whom It May Concern:

**Re: TELEPHONE AMENDMENT**
**Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg**
**ANDA No. 76-894**

Apotex Inc. is hereby submitting a Telephone Amendment for Torsemide Tablets 5 mg, 10 mg, 20 mg and 100 mg for ANDA No. 76-894. The Telephone Amendment is being submitted in response to the bioequivalency deficiency received from Aaron Sigler on May 6, 2005. This Amendment is being submitted in triplicate (Archival, Review, and Field copies), and contains one volume. The required Field Copy Certification can be found in the last section of the Amendment.

Should you have any questions or concerns, please do not hesitate to contact me at (416) 675-0338 ext. 4207, by fax at (416) 675-0340 or by e-mail at bsandhu@apotex.com.

Best Regards,

Barinder Sandhu
Project Leader
Regulatory Affairs – Solid Dose US

cc: Bernice Tao, Associate Director, Regulatory Affairs – Solid Dose US, Apotex Inc.
Marcy Macdonald, Director, Regulatory Affairs – Parenterals & US Office, Apotex Corp.

50 Steinway Blvd., Etobicoke, Ontario, Canada M9W 6Y3
Tel. 416.675.0338 Fax. 416.675.0340 www.apotex.com

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