CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 76-943

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

Sponsor: Roxane Laboratories, Inc.

Approval Date: March 1, 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-943

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-943

APPROVAL LETTER

ANDA 76-943

MAR 1 2005

Roxane Laboratories, Inc.
Attention: Elizabeth Ernst
1809 Wilson Road
Columbus, OH 43228

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) dated December 12, 2003, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Torsemide Tablets, 5 mg, 10 mg, and 20 mg.

Reference is also made to your amendments dated September 17, and October 27, 2004, and January 19, 2005.

The listed drug product (RLD) referenced in your application, Demadex® Tablets 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 to the '672 patent under Section 505(j)(2)(A)(vii)(IV) of the Act stating that the '672 patent will not be infringed by your manufacture, use, or sale of Torsemide Tablets, 5 mg, 10 mg, and 20 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 was brought against Roxane Laboratories, Inc. (Roxane) for infringement of the '672 patent which was the subject of the paragraph IV certification. This action must have been brought against Roxane prior to the expiration of forty-five 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 Roxane complied with the requirements of Section 505(j)(2)(B) of the Act, and that no legal action for infringement of the '672 patent was brought against Roxane within the statutory forty-five day period.

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, and 20 mg, to be bioequivalent and therefore, therapeutically equivalent to the listed drug, (Demadex Tablets®, 5 mg, 10 mg, and 20 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.

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.

Postmarketing 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

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 3/1/05
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-943
Division File
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APPROVAL

CMC satisfactory
2/23/05

3/1/05

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-943

LABELING

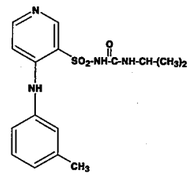
Roxane Laboratories, Inc.
Columbus, Ohio 43216

TORSEMIDE
Tablets

R_x 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 pKa is 7.1, and its molecular weight is 348.43.

Torsemide is a white to off-white crystalline powder. The tablets for oral administration also contain crospovidone, lactose (anhydrous), magnesium stearate, microcrystalline cellulose, and povidone.

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 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 0.1 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 (0.7 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 (0.1 to 0.2 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 0.8mmol/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% (38/1250) with torsemide and 3.4% (13/380) with furosemide in patients with congestive heart failure, 2% (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 Tablets (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 (eg, 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 the elderly 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 are supplied as white to off-white, round tablets. The 5 mg tablets are scored on one side and debossed with the product identification "54 015" on the other side. The 10 mg tablets are scored on one side and debossed with the product identification '54 016" on the other side. The 20 mg tablets are scored on one side and debossed with the product identification "54 017" on the other side.

0054-0075-25	5 mg white to off-white tablet, bottle of 100
0054-0076-25	10 mg white to off-white tablet, bottle of 100
0054-0076-20	10 mg white to off-white tablet, 10x10 unit dose
0054-0077-25	20 mg white to off white tablet, bottle of 100
0054-0077-29	20 mg white to off-white tablet, bottle of 500
0054-0077-20	20 mg white to off-white tablet, 10x10 unit dose

Storage

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

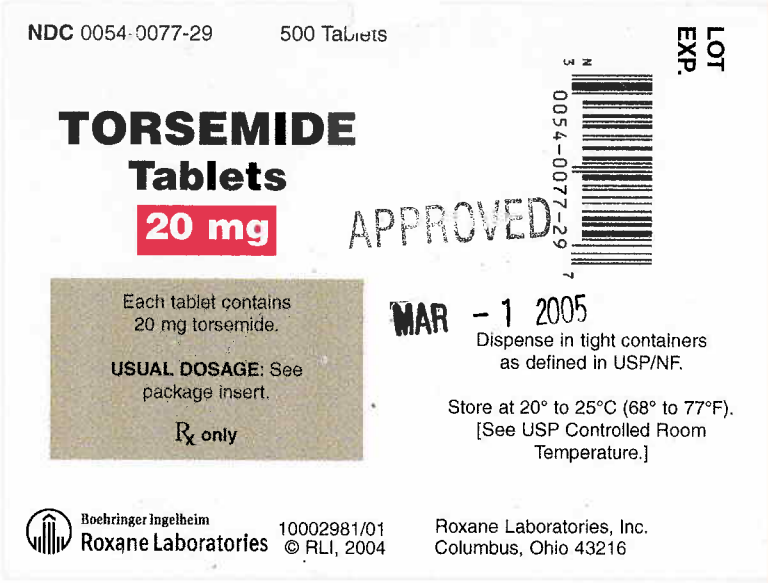
10002994/01 Revised March 2004

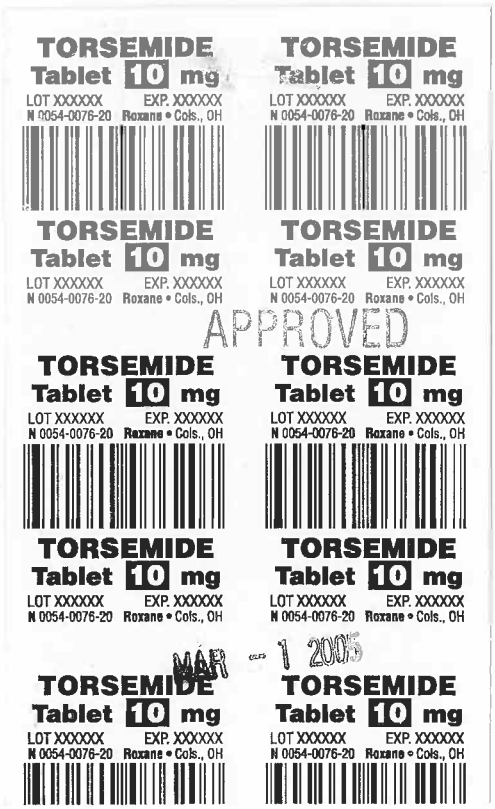
Boehringer Ingelheim
Roxane Laboratories


USUAL DOSAGE: See package insert.
Dispense in tight containers as defined in USP/NF.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
NDC 0054-0075-25 100 Tablets
TORSEMIDE
Tablets
5 mg
Each tablet contains 5 mg torsemide.
Rx only
APPROVED
MAR - 1 2005
Roxane Laboratories, Inc.
Columbus, Ohio 43216
Boehringer Ingelheim
Roxane Laboratories
EXP. LOT
0054-0075-25
10002980/01
© RLI, 2004


USUAL DOSAGE: See package insert.
Dispense in tight containers as defined in USP/NF.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
NDC 0054-0076-25 100 Tablets
TORSEMIDE
Tablets
10 mg
Each tablet contains 10 mg torsemide.
Rx only
APPROVED
MAR - 1 2005
Roxane Laboratories, Inc.
Columbus, Ohio 43216
Boehringer Ingelheim
Roxane Laboratories
EXP. LOT
0054-0076-25
10002979/01
© RLI, 2004


USUAL DOSAGE: See package insert.
Dispense in tight containers as defined in USP/NF.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
NDC 0054-0077-25 100 Tablets
TORSEMIDE
Tablets
20 mg
Each tablet contains 20 mg torsemide.
Rx only
APPROVED
MAR - 1 2005
Roxane Laboratories, Inc.
Columbus, Ohio 43216
Boehringer Ingelheim
Roxane Laboratories
EXP. LOT
0054-0077-25
10002982/01
© RLI, 2004


NDC 0054-0077-29 500 Tablets
TORSEMIDE
Tablets
20 mg
Each tablet contains 20 mg torsemide.
USUAL DOSAGE: See package insert.
Rx only
APPROVED
MAR - 1 2005
Dispense in tight containers as defined in USP/NF.
Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature.]
Boehringer Ingelheim
Roxane Laboratories
10002981/01
© RLI, 2004
Roxane Laboratories, Inc.
Columbus, Ohio 43216
EXP. LOT
0054-0077-29


TORSEMIDE
Tablet 10 mg
LOT XXXXXX EXP. XXXXXX
N 0054-0076-20 Roxane • Cols., OH
APPROVED
MAR - 1 2005


TORSEMIDE
Tablet 20 mg
LOT XXXXXX EXP. XXXXXX
N 0054-0077-20 Roxane • Cols., OH
APPROVED
MAR - 1 2005

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-943

LABELING REVIEWS

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

ANDA Number:	76-943
Date of Submission:	December 12, 2003
Applicant's Name:	Roxane Laboratories, Inc.
Established Name:	Torsemide Tablets, 5 mg, 10 mg and 20 mg

Labeling Deficiencies

1. CONTAINER [5 mg and 10 mg: Bottles of 100s; 20 mg: Bottles of 100s and 500s]
   a. Please revise the storage statement to read: " Store at 20°-25°C (68°-77°F) [see USP Controlled Room Temperature]."
   b. Delete —— from the established name

2. UNIT DOSE BLISTER [10 mg and 20 mg: 10s]
   a. It is difficult to read the strengths of the product. Please revise.
   b. Revise to read "TORSEMIDE" [delete the extra space between "R" and "S"]

3. BLISTER CARTON [10 mg and 20 mg: 10 x 10]
   Refer to comments for CONTAINER

4. INSERT
   a. Please note that USAN names are common nouns and should be treated as such in a text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone on labels or in the title of the package insert.
   b. CLINICAL PHARMACOLOGY, Clinical Effects, first paragraph: Delete the first sentence.
   c. HOW SUPPLIED: refer to comment 1.a.

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:

Are the caps for the Bottles of 100s CRC?

"Packaging Configurations and Sizes" on pg. 1630 of Vol. A1.5 states that the

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 [Vol. A1.1, pg. 6]

   Patent Data

[redacted]					
020136	001	RE34672	AUG 11,2006	IV	None

   Exclusivity Data

   There is no unexpired exclusivity for this product.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
Roxane Laboratories, Inc.
1809 Wilson Rd
Columbus, Ohio 43228
[Vol. A1.4, pg. 1127]

4. CONTAINER/CLOSURE
Bottle: HDPE
Caps: For bottles of 100s-appear to be CRC **but need to verify with Chemist**; Screw Caps for bottles of 500s
Blister: film-Heat sealable film with high moisture barrier properties; cover backing-peelable heat sealable foil
[Vol. A1.5, pg. 1538-1540 &1630]

5. INACTIVE INGREDIENTS
The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.4, pg. 1061] Torsemide, microcrystalline cellulose, lactose, povidone, crospovidone, magnesium stearate,

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, and 20mg in [ ]
tablets. Chemist will be notified.
[Vol. A1.5, pg. 1630]

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: Will ask firm to revise to read: 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: same as RLD

9. TABLET IMPRINT & SCORING

RLD-tablets are <u>scored</u>

ANDA: [vol. A1.5]

- 5 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 015" on the other side. [pg. 1671]
- 10 mg: White to off white, round, standard bioconvex, beveled edged tablet, scored on one side and debossed with product identification "54 016" on the other side. [pg. 1685]
- 20 mg: White to off white, round, standard bioconvex, beveled edged tablet, scored on one side and debossed with product identification "54 017" on the other side. [pg. 1699]

10. BIOAVAILABILITY/BIOEQUIVALENCE:
Pending as of 02/19/04

Date of Review: February 26, 2004 Date of Submission: December 12, 2003

Primary Reviewer: Ruby Wu RWu Date: 2/26/04

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

cc:
ANDA: 76-943
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSNZ\ROXANE\LTRS&REV\76943.na1.L.doc
Review

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

ANDA Number: 76-943
Date of Submission: March 22, 2004 (Amendment-FPL)
Applicant's Name: Roxane Laboratories, Inc.
Established Name: Torsemide Tablets, 5 mg, 10 mg and 20 mg

APPROVAL SUMMARY

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

2. CONTAINER [5 mg and 10 mg: Bottles of 100s; 20 mg: Bottles of 100s and 500s]
Satisfactory in final print as of the March 22, 2004 submission. [Vol. A3.1]

3. UNIT DOSE BLISTER [10 mg and 20 mg: 10s]
Satisfactory in final print as of the March 22, 2004 submission. [Vol. A3.1]

4. BLISTER CARTON [10 mg and 20 mg: 10 x 10]
Satisfactory in final print as of the March 22, 2004 submission. [Vol. A3.1]

5. INSERT
Satisfactory in final print as of the March 22, 2004 submission. [Vol. A3.1, 2004]

6. Revisions needed post-approval: yes. The following are requested labeling revisions from my review of your amendment March 22, 2004 dated for ANDA 76-943 for Torsemide Tablets, 5 mg, 10 mg, and 20 mg. The revisions are "**POST-APPROVAL**" revisions and may be submitted in an annual report, provided the changes are described in full.
UNIT DOSE BLISTER [10 mg and 20 mg: 10s]- We encourage the use of boxing, contrasting colors, or other means to differentiate the 10 mg and 20 mg strengths of this drug.
INSERT
   - PRECAUTIONS, Laboratory Values, Blood Urea Nitrogen, first paragraph, second sentence: "...(70 mmol/L)."
   - HOW SUPPLIED: We encourage you to add "NDC Code" above the first column and "Description" above the second column.

PATENT AND EXCLUSIVITY

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:

From Labeling Review #1-
Chemist responded via email on 2/27/04
Are the caps for the Bottles of 100s CRC? The 100 cc bottles have CRC.

"Packaging Configurations and Sizes" on pg. 1630 of Vol. A1.5 states that the

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 [Vol. A1.1, pg. 6]

Patent Data

[redacted]					
020136	001	RE34672	AUG 11,2006	IV	None

Exclusivity Data

There is no unexpired exclusivity for this product.

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
Roxane Laboratories, Inc.
1809 Wilson Rd
Columbus, Ohio 43228
[Vol. A1.4, pg. 1127]

4. CONTAINER/CLOSURE
Bottle: HDPE
Caps: For bottles of 100s- CRC (see note to the chemist); Screw Caps for bottles of 500s
Blister: film-Heat sealable film with high moisture barrier properties; cover backing-peelable heat sealable foil
[Vol. A1.5, pg. 1538-1540 &1630]

5. INACTIVE INGREDIENTS
The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Vol. A1.4, pg. 1061] Torsemide, microcrystalline cellulose, lactose, povidone, crospovidone, magnesium stearate,

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 in bottles of 100s ONLY; 10mg, and 20mg in unit dose blister film and bottles of 100s. The 20 mg will also be packaged in bottles of 500s. (see note to the chemist)
[Vol. A1.5, pg. 1630]

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: same as RLD

9. TABLET IMPRINT & SCORING

RLD-tablets are <u>scored</u>

ANDA: [vol. A1.5]

- 5 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 015" on the other side. [pg. 1671]
- 10 mg: White to off white, round, standard bioconvex, beveled edged tablet, scored on one side and debossed with product identification "54 016" on the other side. [pg. 1685]
- 20 mg: White to off white, round, standard bioconvex, beveled edged tablet, scored on one side and debossed with product identification "54 017" on the other side. [pg. 1699]

10. BIOAVAILABILITY/BIOEQUIVALENCE:
Pending as of 02/19/04

Date of Review: March 31, 2004 Date of Submission: March 22, 2004

Primary Reviewer: Ruby Wu RWu Date: 3/31/04

Team Leader: John Grace John Grace Date: 4/16/04

cc:
ANDA: 76-943
DUP/DIVISION FILE
HFD-613/RWu/JGrace (no cc)
V:\FIRMSNZ\ROXANE\LTRS&REV\76943.ap.L.doc
Review

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-943

CHEMISTRY REVIEWS

#1

ANDA 76-943

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

Roxane Laboratories, Inc.

Benjamin Lim, Ph.D.
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-943

2. REVIEW #: 1

3. REVIEW DATE: 3/02/04
   4/22/04 (Revised)

4. REVIEWER: Benjamin Lim, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
N/A	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Original ANDA Submission	December 12, 2003
Telephone Amendment	February 5, 2004
Patent Amendment	February 9, 2004
Labeling Amendment	March 22, 2004
FDA Acknowledgement Letter (Acceptable for filing: December 15, 2003)	February 9, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories, Inc.
Address:	1809 Wilson Road Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	(614) 272-4785
Fax:	(614) 276-2470

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Torsemide Tablets

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Roxane Laboratories Inc.'s proposed ANDA for Torsemide Tablets, 5, 10 and, 20 mg is the approved, reference listed drug, Demadex (torsemide) Tablets, 5, 10 and 20 mg, the subject of NDA #020136, held by Roche Laboratories.

b. Roxane Laboratories, Inc. certifies that U.S. Patent No: RE34672 which expires on August 11, 2006, will not be infringed by the manufacture, use or sale of Torsemide 5 mg, 10 mg and 20 mg Tablets for which this application is submitted. Roxane Laboratories also certifies that Applicant will comply with the notice requirements under § 314.95(a) by providing a notice to the owner of the RE34672 patent or its representative and to the holder of the approved application for the listed drug product, and with the requirement under § 314.95(c) with respect to the content of the notice.

c. Roxane Laboratories, Inc., in its opinion, and to the best of its knowledge, in accordance with the list published in the Approved Drug Product with Therapeutic Equivalence (Orange Book, 21st Edition and supplements) there are no unexpired exclusivity for the listed drug, Demadex (torsemide) Tablets.

10. PHARMACOL. CATEGORY:

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

11. DOSAGE FORM: Tablets

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

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

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

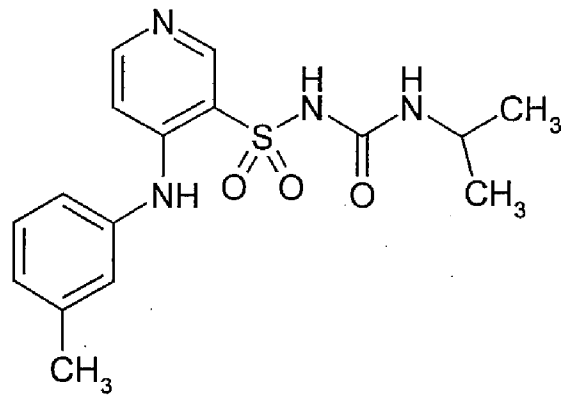
_____SPOTS product – Form Completed

___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[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Inadequate	2/24/04	Reviewed by K. Woodland
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			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
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Acceptable	4-16-04	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:

The Chemistry Review for ANDA 76-943

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 diuretic of the pyridine-sulfonylurea class. Its chemical name is 1-isopropyl-3-[4-m-toludino-3-pyridyl)sulfonyl]urea. Its molecular formula is $C_{16}H_{20}N_4O_3S$, pKa is 7.1, and its molecular weight is 384.43. It is a white to off-white crystalline powder.

Drug Product:
The Torsemide Tablets are manufactured for oral administration and contains torsemide, crospovidone, lactose, magnesium stearate, microcrystalline cellulose, and povidone. The tablets have the following descriptions:

5 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 015" on the other side.

10 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 016" on the other side.

20 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 017" on the other side.

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

Oral tablets

C. Basis for Approvability or Not-Approval Recommendation

There are CMC deficiencies related to the drug substance specifications, in-process control, container/closure system testing and stability specifications.
- Bio Pending
- EER Pending

III. Administrative

A. Reviewer's Signature

B. Endorsement Block

Benjamin Lim, Ph.D./4/12/04 4/30/04
Shing Liu, Ph.D./4/14/04 S.H. Liu 4/30/04
Wanda Pamphile, Pharm. D./ 4/30/04

C. CC Block

APPEARS THIS WAY
ON ORIGINAL

Redacted 20 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #1

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

1. The bioequivalence portion of your submission is under review. Deficiencies, if any, will be communicated to you under separate cover. Please be advised that the acceptance of the dissolution method and specifications are contingent upon the acceptance by DBE. You may be required to submit additional accelerated stability data using the method and specifications recommended by DBE.

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. Please provide any available drug product room temperature stability data.

4. The USP methods for the drug substance are the regulatory methods. In the event of a dispute, the USP method will prevail.

5. Please be advised that submission of an amendment to add a new strength will automatically convert the MINOR deficiencies to MAJOR deficiencies.

Sincerely yours,

Ahigh Hon Lee for 4/30/04

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

cc: ANDA 76-943
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/B. Lim, Ph.D./4/12/04/4/26/04 4/30/04
HFD-620/S. Liu, Ph.D./4/14/04/4/26/04 S. H. Liu 4/30/04
HFD-617/W. Pamphile, Pharm. D./ 4-30-04

F/T by:ard/4/23/04/4/29/04
V:\FIRMSNZ\ROXANE\LTRS&REV\76943.CR01.doc

TYPE OF LETTER: NOT APPROVABLE - MINOR

#2

SEP 10 2004

ANDA 76-943

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

Roxane Laboratories, Inc.

Benjamin Lim, Ph.D.
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-943

2. REVIEW #: 2

3. REVIEW DATE: 8/2/04

4. REVIEWER: Benjamin Lim, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Firm	
Original ANDA Submission	December 12, 2003
Telephone Amendment	February 5, 2004
Patent Amendment	February 9, 2004
Labeling Amendment	March 22, 2004
Controlled Correspondence	June 10, 2004
Agency	
FDA Acknowledgement Letter (Acceptable for filing: December 15, 2003)	February 9, 2004
Deficiency Letter (CMC)	May 3, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (CMC)	July 8, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories, Inc.
Address:	1809 Wilson Road Columbus, OH 43228
Representative:	Elizabeth Ernst
Telephone:	(614) 272-4785
Fax:	(614) 276-2470

Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Torsemide Tablets

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Roxane Laboratories Inc.'s proposed ANDA for Torsemide Tablets, 5, 10 and, 20 mg is the approved, reference listed drug, Demadex (torsemide) Tablets, 5, 10 and 20 mg, the subject of NDA #020136, held by Roche Laboratories.

b. Roxane Laboratories, Inc. certifies that U.S. Patent No: RE34672 which expires on August 11, 2006, will not be infringed by the manufacture, use or sale of Torsemide 5 mg, 10 mg and 20 mg Tablets for which this application is submitted. Roxane Laboratories also certifies that Applicant will comply with the notice requirements under § 314.95(a) by providing a notice to the owner of the RE34672 patent or its representative and to the holder of the approved application for the listed drug product, and with the requirement under § 314.95(c) with respect to the content of the notice.

c. Roxane Laboratories, Inc., in its opinion, and to the best of its knowledge, in accordance with the list published in the Approved Drug Product with Therapeutic Equivalence (Orange Book, 21st Edition and supplements) there are no unexpired exclusivity for the listed drug, Demadex (torsemide) Tablets.

10. PHARMACOL. CATEGORY:

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

11. DOSAGE FORM: Tablets

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

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

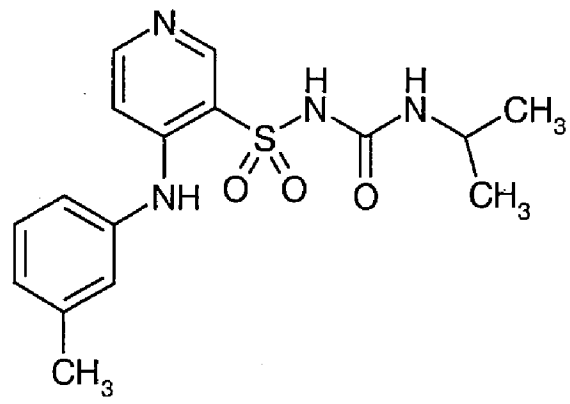
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

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[1]	STATUS[2]	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			
	III			4			
	III			4			
	III			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
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Acceptable	4-16-04	Ruby Wu
Bioequivalence	Deficient	8-30-04	Z. Wahba
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:

The Chemistry Review for ANDA 76-943

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 diuretic of the pyridine-sulfonylurea class. Its chemical name is 1-isopropyl-3-[4-m-toludino-3-pyridyl)sulfonyl]urea. Its molecular formula is $C_{16}H_{20}N_4O_3S$, pKa is 7.1, and its molecular weight is 384.43. It is a white to off-white crystalline powder.

Drug Product:
The Torsemide Tablets are manufactured for oral administration and contains torsemide, crospovidone, lactose, magnesium stearate, microcrystalline cellulose, and povidone. The tablets have the following descriptions:

5 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 015" on the other side.

10 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 016" on the other side.

20 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 017" 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 -25^0C (68^0-77^0F). Dispense in a tight, light-resistant container. The expiration of the product is 2 years.

C. Basis for Approvability or Not-Approval Recommendation

- The validation for the ——— method is not acceptable. The drug product stability limits for ———.
- Bioequivalence deficiencies
- Pending EER

III. Administrative

A. Reviewer's Signature

9/10/04

B. Endorsement Block

Benjamin Lim, Ph.D./8/3/04 9/10/04
Shing Liu, Ph.D./ 9/10/04
Wanda Pamphile, Pharm. D./ 9/9/04

C. CC Block

Redacted 12 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #2

cc: ANDA 76-943
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/B. Lim, Ph.D./ 9/10/04
HFD-620/S. Liu, Ph.D./ S.H. Liu 9/10/04
HFD-617/W. Pamphile, Pharm. D./ WP 9/9/04

F/T by:

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TYPE OF LETTER: NOT APPROVABLE - MINOR

#3

ANDA 76-943

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

Roxane Laboratories, Inc.

Benjamin Lim, Ph.D.
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-943

2. REVIEW #: 3

3. REVIEW DATE: 11/23/04, revised 12/28/04

4. REVIEWER: Benjamin Lim, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Firm	
Original ANDA Submission	December 12, 2003
Telephone Amendment	February 5, 2004
Patent Amendment	February 9, 2004
Labeling Amendment	March 22, 2004
Controlled Correspondence	June 10, 2004
Amendment (CMC)	July 8, 2004
Agency	
FDA Acknowledgement Letter	February 9, 2004
(Acceptable for filing: December 15, 2003)	
Deficiency Letter (CMC)	May 3, 2004
Deficiency Letter (Bio)	September 3, 2004
Deficiency Letter (CMC)	September 10, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (CMC)	October 15, 2004

7. NAME & ADDRESS OF APPLICANT:

Name:	Roxane Laboratories, Inc.
Address:	1809 Wilson Road
	Columbus, OH 43228
Representative:	Elizabeth Ernst

Chemistry Review Data Sheet

Telephone: (614) 272-4785
Fax: (614) 276-2470

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Torsemide Tablets

1. LEGAL BASIS FOR SUBMISSION:

a. The basis for Roxane Laboratories Inc.'s proposed ANDA for Torsemide Tablets, 5, 10 and, 20 mg is the approved, reference listed drug, Demadex (Torsemide) Tablets, 5, 10 and 20 mg, the subject of NDA #020136, held by Roche Laboratories.

b. Roxane Laboratories, Inc. certifies that U.S. Patent No: RE34672 which expires on August 11, 2006, will not be infringed by the manufacture, use or sale of Torsemide 5 mg, 10 mg and 20 mg Tablets for which this application is submitted. Roxane Laboratories also certifies that Applicant will comply with the notice requirements under § 314.95(a) by providing a notice to the owner of the RE34672 patent or its representative and to the holder of the approved application for the listed drug product, and with the requirement under § 314.95(c) with respect to the content of the notice.

c. Roxane Laboratories, Inc., in its opinion, and to the best of its knowledge, in accordance with the list published in the Approved Drug Product with Therapeutic Equivalence (Orange Book, 21st Edition and supplements) there are no unexpired exclusivity for the listed drug, Demadex (Torsemide) Tablets.

2. PHARMACOL. CATEGORY:

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

11. DOSAGE FORM: Tablets

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

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

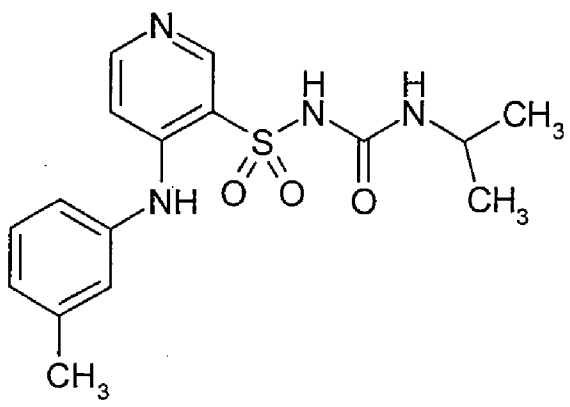
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X___Not a SPOTS product

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

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[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
	II			1	Inadequate	11/23/04	Reviewed by B. Lim
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			
	III			4			

Chemistry Review Data Sheet

—	III	—	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
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	10/6/04	
Methods Validation	N/A		
Labeling	Acceptable	4/16/04	Ruby Wu
Bioequivalence	Acceptable	11/4/04	Z. Wahba
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 76-943

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 diuretic of the pyridine-sulfonylurea class. Its chemical name is 1-isopropyl-3-[4-m-toludino-3-pyridyl)sulfonyl]urea. Its molecular formula is $C_{16}H_{20}N_4O_3S$, pKa is 7.1, and its molecular weight is 384.43. It is a white to off-white crystalline powder.

Drug Product:
The Torsemide Tablets are manufactured for oral administration and contains torsemide, crospovidone, lactose, magnesium stearate, microcrystalline cellulose, and povidone. The tablets have the following descriptions:

5 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 015" on the other side.

10 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 016" on the other side.

20 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 017" 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 20 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 -25^0C (68^0-77^0F). Dispense in a tight, light-resistant container. The expiration of the product is 2 years.

C. Basis for Approvability or Not-Approval Recommendation

- The DMF is inadequate.

III. Administrative

A. Reviewer's Signature

Benjamin Lim 12/28/04

B. Endorsement Block

Benjamin Lim, Ph.D./11/23/04 Ben Lim 12/28/04
Shing Liu, Ph.D./12/9/04 S.H Liu 12/28/04
Ben Danso, Pharm. D./

C. CC Block

Redacted 9 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #3

cc: ANDA 76-943
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/B. Lim, Ph.D./12/28/04 B. Lim 12/28/04
HFD-620/S. Liu, Ph.D./12/28/04 S.H. Liu 12/28/04
HFD-617/B. Danso, Pharm. D./ BD 12/29/04

F/T by:

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TYPE OF LETTER: NOT APPROVABLE - MINOR

#4

ANDA 76-943

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

Roxane Laboratories, Inc.

Benjamin Lim, Ph.D.
Chemistry Division III

Table of Contents

Chemistry Review Data Sheet

1. ANDA 76-943

2. REVIEW #: 4

3. REVIEW DATE: February 16, 2005

4. REVIEWER: Benjamin Lim, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
Firm	
Original ANDA Submission	December 12, 2003
Telephone Amendment	February 5, 2004
Patent Amendment	February 9, 2004
Labeling Amendment	March 22, 2004
Controlled Correspondence	June 10, 2004
Amendment (CMC)	July 8, 2004
Amendment (CMC)	October 15, 2004
Agency	
FDA Acknowledgement Letter (Acceptable for filing: December 15, 2003)	February 9, 2004
Deficiency Letter (CMC)	May 3, 2004
Deficiency Letter (Bio)	September 3, 2004
Deficiency Letter (CMC)	September 10, 2004
Deficiency Letter (CMC)	December 30, 2004

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (CMC)	January 19, 2005

7. NAME & ADDRESS OF APPLICANT:

Name: Roxane Laboratories, Inc.
Address: 1809 Wilson Road

Columbus, OH 43228
Representative: Elizabeth Ernst
Telephone: (614) 272-4785
Fax: (614) 276-2470

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Torsemide Tablets

1. LEGAL BASIS FOR SUBMISSION:

a. The basis for Roxane Laboratories Inc.'s proposed ANDA for Torsemide Tablets, 5, 10 and, 20 mg is the approved, reference listed drug, Demadex (Torsemide) Tablets, 5, 10 and 20 mg, the subject of NDA #020136, held by Roche Laboratories.

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c. Roxane Laboratories, Inc., in its opinion, and to the best of its knowledge, in accordance with the list published in the Approved Drug Product with Therapeutic Equivalence (Orange Book, 21st Edition and supplements) there are no unexpired exclusivity for the listed drug, Demadex (Torsemide) Tablets.

2. PHARMACOL. CATEGORY:

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

11. DOSAGE FORM: Tablets

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

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X_Rx ___OTC

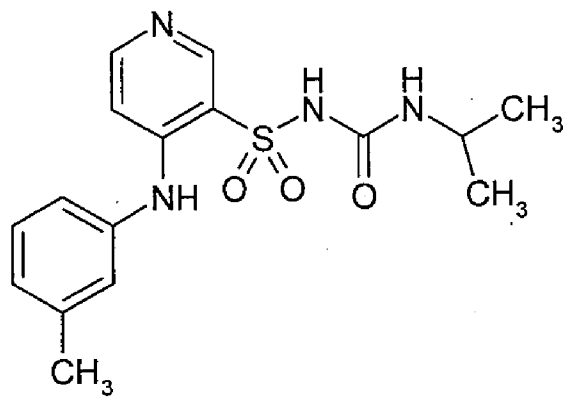
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

___X__Not a SPOTS product

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

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[1]	STATUS[2]	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			

Chemistry Review Data Sheet

	III		4			
	III		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
N/A		

18. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Microbiology	N/A		
EES	Acceptable	10/6/04	
Methods Validation	N/A		
Labeling	Acceptable	4/16/04	Ruby Wu
Bioequivalence	Acceptable	11/4/04	Z. Wahba
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 76-943

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 diuretic of the pyridine-sulfonylurea class. Its chemical name is 1-isopropyl-3-[4-m-toludino-3-pyridyl)sulfonyl]urea. Its molecular formula is $C_{16}H_{20}N_4O_3S$, pKa is 7.1, and its molecular weight is 384.43. It is a white to off-white crystalline powder.

Drug Product:
The Torsemide Tablets are manufactured for oral administration and contains torsemide, crospovidone, lactose, magnesium stearate, microcrystalline cellulose, and povidone. The tablets have the following descriptions:

5 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 015" on the other side.

10 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 016" on the other side.

20 mg: White to off-white, round, standard biconvex, beveled edged tablet, scored on one side and debossed with product identification "54 017" 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 20 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 -25^0C (68^0-77^0F). Dispense in a tight, light-resistant container. The expiration of the product is 2 years.

C. Basis for Approvability or Not-Approval Recommendation

III. Administrative

A. Reviewer's Signature

2/22/05

B. Endorsement Block

Benjamin Lim, Ph.D./2/18/05/ 2/22/05
Shing Liu, Ph.D./2/18/05/ S. H. Liu 2/22/05
Ryan Nguyen, Pharm. D./2/18/05/ 2/22/05

C. CC Block

Redacted 7 page(s)

of trade secret and/or

confidential commercial

information from

CHEMISTRY REVIEW #4

32. LABELING

Acceptable on 4/16/04 by R. Wu

33. ESTABLISHMENT INSPECTION

Acceptable on October 6, 2004.

34. BIOEQUIVALENCE

Acceptable on November 4, 2004 by Z. Wahba

35. ENVIRONMENTAL IMPACT CONSIDERATIONS/CATEGORICAL EXCLUSION:

Satisfactory in review #1

cc: ANDA 76-943
ANDA DUP
DIV FILE
Field Copy

Endorsements (Draft and Final with Dates):

HFD-620/B. Lim, Ph.D./2/18/05/ 2/22/05
HFD-620/S. Liu, Ph.D./2/18/05/ S.H. Liu 2/22/05
HFD-617/R. Nguyen, Pharm. D./2/18/05/ 2/22/05

F/T by: RTN/2/22/05

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TYPE OF LETTER: APPROVABLE

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-943

BIOEQUIVALENCE REVIEWS

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-943
Drug Product Name	Torsemide Tablets
Strength	5 mg, 10, and 20 mg
Applicant Name	Roxane Laboratories
Address	Columbus, OH
Submission Date(s)	12/12/03
Amendment Date(s)	-
Reviewer	Z.Z. Wahba
First Generic	No
File Location	V:\firmsnz\Roxane\ltrs&rev\76943n1203.doc

I. Executive Summary

This submission consisted of two (fasting and non-fasting) bioequivalence (BE) studies on the 20 mg strength and dissolution data on the 5 mg, 10 mg, and 20 mg strengths. Both BE studies are single dose two-way crossover studies in normal males and females (fasting, n=23; non-fasting, n=26). The reference listed drug is Roche's Demadex® Tablets, 20 mg.

Statistical analyses of the plasma concentration data for torsemide for both studies demonstrate bioequivalence. For the fasting BE study, torsemide results are (point estimate, 90% CI): $LAUC_t$ of 1.01, 97.42-104.71%; $LAUC_i$ of 1.00, 96.71-103.77% and LCmax of 1.10, 102.95-118.40%. For the non-fasting BE study, torsemide results are (point estimate, 90% CI): $LAUC_t$ of 1.02, 99.41-104.48%; $LAUC_i$ of 1.02, 99.11-104.07% and LCmax of 1.06, 98.89-114.62%.

The firm has also requested a waiver for the strengths, 5 mg, and 10 mg of the test product, based on formulation proportionality and dissolution profile comparability between the 20 mg strength and the 5 mg, and 10 mg strengths, using the FDA recommended method for this drug. The waiver request is not granted at this time due the deficiency cited in the deficiency section.

The application has been found incomplete due to several deficiencies. The firm didn't provide information on adverse events for both studies, some case reports forms for the study under fasting conditions, the approved Institutional Review Board (IRB) forms for both studies, and the standard operating procedure (SOP) describing the bioanalytical method (details see the deficiency section of this review).

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Torsemide Tablets, 5 mg, 10 mg, and 20 mg
Reference Product	Demadex®Tablets, 5 mg, 10 mg, and 20 mg (The drug is also available in 100 mg tablets)
RLD Manufacturer	Roche
NDA No.	20-136
RLD Approval Date	08/23/93
Indication	Indicated for the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease.

B. PK/PD Information

Bioavailability	approximately 80%
Food Effect	Simultaneous food intake delays the time to C_{max} by about 30 minutes, but overall bioavailability (AUC) and diuretic activity are unchanged
Tmax	peak (C_{max}) within 1 hour
Metabolism	Hepatic metabolism. 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.
Excretion	Excretion into the urine.
Half-life	approximately 3.5 hours
Relevant OGD or DBE History	• The electronic Orange Book states the following strengths for Torsemide Tablets, 5, 10, 20 and 100 mg. Only the 20 mg strength is designated as the RLD (with the sign "+"). • The DBE has reviewed several control documents and ANDA submissions on Torsemide Tablets, 5, 10, 20 and 100 mg. The DBE requests the following: (a) Fasting and fed studies on the 20-mg strength of this product and measurement of only the parent compound in the BE study samples, (b) Granting waivers to the 5, 10 and 100 mg strengths, are based on formulation proportionality and comparative dissolution profiles based on the FDA recommended dissolution method.
Agency Guidance	BA/BE guidance
Drug Specific Issues (if any)	-

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	3
Waiver requests	Yes	2
BCS Waivers	No	
Vasoconstrictor Studies	No	
Clinical Endpoints	No	
Failed Studies	No	
Amendments	No	

D. Pre-Study Bioanalytical Method Validation

Information on p 208, vol. C1.2	**Parent (Torsemide)**
Analyte name	Torsemide
Internal Standard	[redacted]
Method description	LC/MS/MS
QC range (ng/mL)	25.0 to 2500.0 (p 221)
Standard curve range (ng/mL)	10.0 to 4000.0 (p 220)
Limit of quantitation	10 ng/mL
Average recovery of Drug (%)	50.3% (p 224)
Average Recovery of Int. Std (%)	42.6% (p 225)
QC Intraday precision range (%CV)	3.5 % to 12.4%
QC Intraday accuracy range (%)	94.0% to 109%
QC Interday precision range (%CV)	7.3% to 10.7%
QC Interday accuracy range (%)	97.6% to 102%
Bench-top stability (hrs)	24 hrs
Stock stability (days)	36 days
Processed stability (hrs)	48 hrs
Freeze-thaw stability (cycles)	3 cycles
Long-term storage stability (days)	151 days (p 200, vol. C1.2)
Dilution integrity	112% @1:4 for dilution of 5000 ng/mL (p 227, vol. C1.2)
Specificity	Yes
SOPs submitted	See the deficiency section
Bioanalytical method is acceptable	See the deficiency section
20% Validation Chromatograms included (Y/N)	Yes
Random or Serial Selection of Chrom	Serial Selection

E. In Vivo Studies

1. Single-dose Fasting Bioequivalence Study

Study Summary, Fasting Bioequivalence Study	
Study No.	Protocol #TORE-01
Study Design	Randomized, 2-way crossover study under fasting conditions
No. of subjects enrolled	28 (subject #101-128)
No. of subjects completing	23 (except subjects 115, 118, 122, 127, and 128)
No. of subjects analyzed	23
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male: 12 Female: 11
Test product	Torsemide Tablets
Reference product	Demadex® Tablets
Strength tested	20 mg
Dose	1 X 20 mg

Summary of Statistical Analysis, Fasting Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.01	97.42-104.71
AUC_{∞}	1.00	96.71-103.77
C_{max}	1.10	102.95-118.40

Reanalysis of Study Samples, Fasting Bioequivalence Study Additional information in Appendix, Table 6								
Reason why assay was repeated (information on p 280, vol. C1.2)	**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**
Low or high internal standard	0	2	0	0.26	0	2	0	0.26
Unacceptable chromatogram	3	2	0.38	0.26	3	2	0.38	0.26
Retention time shift	2	2	0.26	0.26	2	2	0.26	0.26
Peak in pre-dose sample with internal standard	1	1	0.13	0.13	1	1	0.13	0.13
Total (total # of samples 782)	6	7	0.77	0.91	6	7	0.77	0.91

Did use of recalculated plasma concentration data change study outcome? No
There were no reassayed samples analyzed due to PK reasons. The above flaws in the bioassay did not provide any values for those samples. Therefore, the firm left out the original values for those samples blank.

2. Single-dose Fed Bioequivalence Study

Study Summary, Fed Bioequivalence Study	
Study No.	Protocol #TORE-02
Study Design	Randomized, 2-way crossover study under fed conditions
No. of subjects enrolled	28 (subject #201-228)
No. of subjects completing	26 (except subjects 218, and 228)
No. of subjects analyzed	26
Subjects (Healthy or Patients?)	Healthy
Sex(es) included (how many?)	Male 21 Female 5
Test product	Torsemide Tablets
Reference product	Demadex® Tablets
Strength tested	20 mg
Dose	1 X 20 mg

Summary of Statistical Analysis, Fed Bioequivalence Study		
Parameter	**Point Estimate**	**90% Confidence Interval**
AUC_{0-t}	1.02	99.41-104.48
AUC_{∞}	1.02	99.11-104.07
C_{max}	1.06	98.89-114.62

Reanalysis of Study Samples, Fed Bioequivalence Study Additional information in Appendix, Table 17								
Reason why assay was repeated (information p 752, vol.C1.3)	**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**
Retention time shift (no original values obtained)	1	2	0.11	0.22	1	2	0.11	0.22
Peak in pre-dose sample with internal standard	1	0	0.11	0	1	0	0.11	0
Possible labeling error during extraction or loading error	6	6	0.68	0.69	6	6	0.68	0.69
Total (total # of samples 884)	8	8	0.90	0.91	8	8	0.90	0.91

Did use of recalculated plasma concentration data change study outcome? No
There were no reassayed samples analyzed due to PK reasons. The 12 samples that were reanalyzed for valid analytical reasons because of possible labeling error during extraction or loading error, the mean of 3 obtained values were reported.
The data were reanalyzed by the reviewer using the original values of these reassay samples. The results of the reanalysis showed that the reassay of these samples had no

significant impact on the study outcome, as seen in the 90% confidence intervals calculated by the reviewer.

F. Formulation

Location in appendix	SectionIV.B, Page 25
Are inactive ingredients within IIG limits?	Yes
If not, list ingredients outside of limits	-
If a tablet, is the product scored?	Yes
If yes, which strengths are scored?	5 mg, 10 mg, and 20 mg
Is scoring of RLD the same as test?	Yes (5 mg, 10 mg, and 20 mg)
Is the formulation acceptable?	Yes
If not acceptable, why?	-

G. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA (per DBE Dissolution Database)
Medium	0.1 N HCL
Volume (mL)	900 mL
USP Apparatus type	Type II (Paddles)
Rotation (rpm)	50 rpm
Firm's proposed specifications	-
FDA-recommended specifications	NLT—% (Q) in 15 min. (based on DBE Database)
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolving
Is method acceptable?	Yes
If not then why?	-

F2 metric, lower strengths compared to highest strength			
Low strength	Highest strength	F2 metric for test	F2 metric for RLD
N/A			

F2 metric, test compared to reference	
Strength	F2 metric
N/A	

H. Waiver Request(s)

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

I. Deficiency Comments

1. The information on adverse events in both fasting and fed studies was not provided in the submission.

2. The case report forms, from the fasting study, for subjects #101 to 110 were not provided in the submission.

3. The approved Institutional Review Board (IRB) forms for the fasting and fed studies were not in provided in the submission.

4. The standard operating procedures (SOP) describing the bioanalytical method and data (sample acceptance and rejection criteria) for the studies under fasting and fed conditions were not provided in the submission.

J. Recommendations

1. The two bioequivalence studies under fasting (protocol #TORE-01) and fed (protocol #TORE-02) conditions, conducted by Roxane Laboratories, Inc. on its drug product, Torsemide Tablets, 20 mg, Lot #039020A, comparing it to Roche's Demadex® Tablets, 20 mg, Lot #E1863, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Roxane's Torsemide Tablets, 20 mg, is bioequivalent to the reference product, Roche's Demadex® Tablets, 20 mg, under fasting, and fed conditions. The application is incomplete due to deficiency comments #1-4.

2. The dissolution testing conducted by the firm on its drug product, Torsemide Tablets, 5 mg, 10 mg, and 20 mg, is acceptable.

3. The waivers of bioequivalence requirements for the 5 mg, and 10 mg strengths were not granted at this time due to deficiencies stated above.

The firm should be informed of the deficiency comments and recommendations.

Zakaria Z. Wahba

Zakaria Z. Wahba, Ph.D. Date: 8/30/04
Review Branch III

RD INITIALED YCHuang
FT INITIALED YCHuang Date: 8/30/2004

Concur: Dale P. Conner Date: 8/30/04
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence

IV. Appendix

A. Individual Study Reviews

1. Single-dose Fasting Bioequivalence Study

a) Study Design

Study Information (p 542, vol. C1.3)	
Study Number	Protocol #TORE-01
Study Title	Randomized, 2-way crossover study under fasting conditions
Clinical Site	[redacted]
Principal Investigator	[redacted], D.O. (p 544, vol. C1.3)
Study/Dosing Dates	Period 1: 09/06/03; Period 2: 09/13/03 (p 605, vol. C1.3)
Analytical Site	[redacted] (p 545)
Analytical Director	[redacted] (p 166, vol. C1.2)
Analysis Dates	09/19/03 to 10/04/03 (p 270, vol. C1.2)
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	28 days

Treatment ID	Test	Reference
Test or Reference	T	R
Product Name	Torsemide Tablets	Demadex® Tablets
Manufacturer	Roxane Laboratories	Roche Laboratories
Batch/Lot No.	039020A (p 134, vol. C1.2)	E1863 (p 134, vol. C1.2)
Manufacture Date	07/15/2003 (p 95, vol. C1.1)	N/A
Expiration Date	N/A	03/2005
Strength	20 mg	20 mg
Dosage Form	Tablet	Tablet
Batch Size	[redacted] tablets (p 1063, vol. C1.4)	N/A
Production Batch Size	[redacted]tablets (p 1063, vol. C1.4)	N/A
Potency	99.6% (p 95)	97.6% (p 107)
Content Uniformity (mean, %CV)	98.7% (%CV=0.8%)	98.5% (%CV=1.3)
Formulation	See Appendix Section B	
Dose Administered	1 X 20 mg	1 X 20 mg
Route of Administration	Orally with 240 mL of water	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	None
Washout Period	7 days
Randomization Scheme	Yes, p 551, vol. C1.3
Blood Sampling Times	Predose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	Plasma separated after centrifuging, and stored at -20°C
IRB Approval	Not provided (See the deficiency section)
Informed Consent	Yes
Subjects Demographics	See Table 1
Length of Fasting	10 hours predose until 4 hours postdose
Length of Confinement	10 hours predose until 24 hours postdose
Safety Monitoring	Vital signs (sitting blood pressure and heart rate) measured prior to dosing and at completion of the study.

Comments on Study Design: The study design is acceptable. However, due the deficiency comments cited in the deficiency section, the application is incomplete.

b) Clinical Results

Table 1 Demographics of Study Subjects

(information on enrolled subjects, reported on pages 131, vol. C1.2)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	81
Mean	24.67	Mean	68	18-40	93	Male	52	Afr. Amer.	19
SD	7.23	SD	3	41-64	7	Female	48	Hispanic	0
Range	20-33	Range	65-71	65-75	0			Asian	0
				>75	0			Others	0

Table 2 Dropout Information

(information on p 552, vol.C1.3)

Subject No	Reason	Period	Replaced?
15, 18, 27	The subjects were never dosed	Before Period-1	None
22	Withdrew between Period-1 and Period-2 due to an adverse event	Before Period-2	None
27	Subject did not return for Period-2 dosing	Before Period-2	None

Table 3 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
No adverse events summary/information was provided in the submission (see deficiency section).		

Table 4 Protocol Deviations

(information on page 142, vol. C1.2)

Type	Subject #s (Test)	Subject #s (Ref.)
Few minutes change (+) in some blood sampling times, except one blood sample the delay was 24 minutes (at the 4-hrs sampling time, for subject 119, R-Trt, P-1). Note: Tmax for this drug is 0.75 hr. Total number of samples= 782	3	2

Comments on Dropouts/Adverse Events/Protocol Deviations: The adverse events information was not provided in the submission. The reported protocol deviations are not likely to compromise the integrity of study. However, due the deficiency comments cited in the deficiency section, the application is incomplete.

c) Bioanalytical Results

Table 5 Assay Quality Control – Within Study

(Info on pp 277, 279, vol. C1.2)	Parent (Torsemide)
QC Conc. (ng /mL)	25.0, 250.0, 2500.0, and 6000.0
Inter day Precision (%CV)	8.8 to 12.7
Inter day Accuracy (%)	97.9 to 105.0
Cal. Standards Conc. (ng /mL)	10.0 to 8000.0
Inter day Precision (%CV)	3.7 to 7.4
Inter day Accuracy (%)	96.3 to 104.0
Linearity Range (range of R^2 values)	0.9964185 to 0.9995584

Comments on Study Assay Quality Control: The QC data are acceptable. However, due to the deficiency cited in the deficiency section, the application is incomplete.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially selected

Comments on Chromatograms: Acceptable

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

SOP No.	Date of SOP	SOP Title
Not provided (see the deficiency section)		

Table 7 Additional Comments on Repeat Assays

Were all SOPs followed?	See deficiency section
Did recalculation of plasma concentrations change the study outcome?	See deficiency section
Does the reviewer agree with the outcome of the repeat assays?	See deficiency section
If no, reason for disagreement	See deficiency section

Summary/Conclusions, Study Assays: Incomplete due to the deficiency cited in the deficiency section.

d) Pharmacokinetic Results

Table 8 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 11 and Figure 1

(N=23)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCI	12066.56	36.06	11767.40	33.68	1.03
AUCT	11763.65	34.68	11570.89	33.04	1.02
CMAX	4980.00	26.00	4572.17	29.65	1.09
KE	0.17	18.34	0.16	18.54	1.01
THALF	4.32	17.80	4.38	20.15	0.99
TMAX	0.75	36.24	0.89	46.19	0.84

Treatment T = Test, Treatment R = Reference

UNIT: AUC=ng hr/mL, CMAX=ng/mL, KE=hrs^{-1} , THALF=hrs, TMAX=hrs

Table 9 Least Squares Geometric Means and 90% Confidence Intervals

(N=23)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	11208.64	11188.69	1.00	96.71	103.77
LAUCT	11129.30	11019.36	1.01	97.42	104.71
LCMAX	4821.99	4367.60	1.10	102.95	118.40

Table 10 Additional Study Information

Root mean square error, AUC_{0-t}	0.071034
Root mean square error, AUC_{∞}	0.068947
Root mean square error, C_{max}	0.137636
K_{el} and AUC_{∞} determined for how many subjects?	All 23 subjects except subjects #8 and #12
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	-
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as C_{max}	None
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis: Acceptable, however, due to the deficiency comments cited in the deficiency section, the application is incomplete.

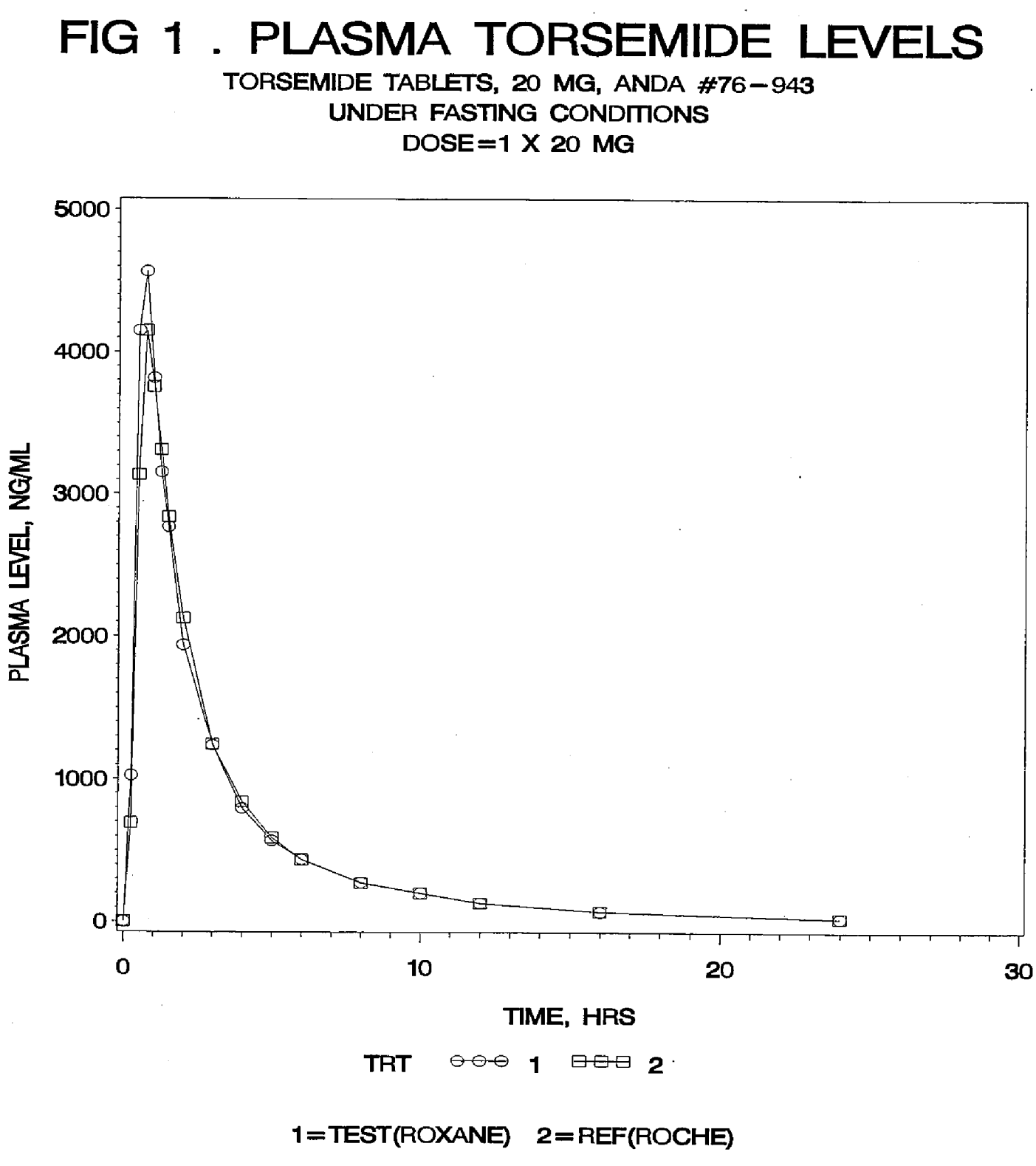
Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The 90% confidence intervals for AUCt, AUCi, and Cmax were within the acceptable range limits of 80-125%. However, the BE study is incomplete due to the deficiencies cited in the deficiency section.

Table 11 Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

(n=23)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
0.25	1024.80	97.03	690.57	132.32	1.48
0.5	4149.96	43.94	3134.30	57.23	1.32
0.75	4565.22	35.42	4148.22	36.54	1.10
1	3815.65	32.29	3752.61	36.61	1.02
1.25	3153.04	29.78	3309.57	31.22	0.95
1.5	2766.96	30.16	2836.96	27.68	0.98
2	1938.87	35.10	2126.43	35.81	0.91
3	1236.39	40.36	1243.17	38.75	0.99
4	795.91	43.58	842.00	45.77	0.95
5	570.04	48.43	589.52	48.46	0.97
6	437.43	50.32	436.83	51.58	1.00
8	275.83	57.18	270.80	57.59	1.02
10	200.87	68.78	199.06	63.10	1.01
12	129.91	75.59	129.11	68.34	1.01
16	69.37	83.33	68.89	81.03	1.01
24	24.70	111.67	24.09	113.02	1.03

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



2. Single-dose Fed Bioequivalence Study

a) Study Design

Study Information	
Study Number	Protocol #TORE-02
Study Title	Randomized, 2-way crossover study under fed conditions
Clinical Site	[redacted]
Principal Investigator	[redacted], D.O.
Study/Dosing Dates	Period 1: 09/06/03; Period 2: 09/13/03 (p 605, vol. C1.3)
Analytical Site	[redacted] (p 545)
Analytical Director	[redacted]
Analysis Dates	09/27/03 to 10/14/03 (p 742, vol. C1.3)
Storage Period (no. of days from the first day of sample collection to the last day of sample analysis)	38 days

Treatment ID	**Test Product**	**Reference Product**
Test or Reference	T	R
Product Name	Torsemide Tablets	Demadex® Tablets
Manufacturer	Roxane Laboratories	Roche Laboratories
Batch/Lot No.	039020A (p 604, vol. C1.3)	E1863 (p 604, vol. C1.3)
Manufacture Date	07/15/2003	N/A
Expiration Date	N/A	03/2005
Strength	20 mg	20 mg
Dosage Form	Tablet	Tablet
Batch Size	[redacted] tablets	N/A
Production Batch Size	[redacted] tablets	N/A
Potency	99.6% (p 95)	97.6% (p 107)
Content Uniformity	98.7% (%CV=0.8%)	98.5% (%CV=1.3)
Formulation	See Appendix Section B	
Dose Administered	1 X 20 mg	1 X 20 mg
Route of Administration	Orally with 240 mL of water	

No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	None
Washout Period	7 days
Randomization Scheme	Yes (p 1030, vol. C1.4)
Blood Sampling Times	Predose, 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 16, and 24 hours
Blood Volume Collected/Sample	7 mL
Blood Sample Processing/Storage	Plasma separated after centrifuging, and stored at -20°C
IRB Approval	Not provided (see deficiency section)
Informed Consent	Yes
Subjects Demographics	See **Table 12**
Length of Fasting before Meal	10 hours predose until 30 minutes before dosing
Length of Confinement	10 hours predose until 24 hours postdose
Safety Monitoring	Vital signs (sitting blood pressure and heart rate) measured prior to dosing and at completion of the study.
Standard FDA Meal Used?	Yes (p 51025, vol. C1.4)
If no, then meal is listed in table below	N/A

Composition of Meal Used in Fed Bioequivalence Study		
Composition	**Percent**	**Kcal**
Fat	N/A (FDA standard meal)	
Carbohydrate		
Protein		
Total		

Comments on Study Design: The study design is acceptable; however, due the deficiency comments cited in the deficiency section, the application is incomplete.

b) Clinical Results

Table 12 Demographics of Study Subjects

(information on enrolled subjects, reported on pages 603, vol. C1.3)

Age		Weight (kg)		Age Groups		Gender		Race	
				Range	%	Sex	%	Category	%
				<18	0			Caucasian	96
Mean	25.43	Mean	78.43	18-40	93	Male	82	Afr. Amer.	4
SD	6.67	SD	16.49	41-64	7	Female	18	Hispanic	0
Range	18-45	Range	50-105	65-75	0			Asian	0
				>75	0			Others	0

Table 13 Dropout Information

(information on p 1031, vol. C1.4)

Subject No	Reason	Period	Replaced?
218	The subject did not chick in for Period-2.	Before Period-2	None
228	The subject left during Period-1 due to an adverse effect.	Period-1	None

Table 14 Study Adverse Events

Adverse Event Description	# in Test Group	# in Ref. Group
No adverse events summary/information was provided in the submission (see deficiency section).		

Table 15 Protocol Deviations

Type	Subject #s (Test)	Subject #s (Ref.)
No deviations were reported		

Comments on Adverse Events/Protocol Deviations: The adverse events information was not provided in the submission. There were no protocol deviations in this study. The application is incomplete due to the deficiency comments cited in the deficiency section,

c) Bioanalytical Results

Table 16 Assay Quality Control – Within Study

(Info on pp 749, 751, vol. C1.3)	Parent (Torsemide)
QC Conc. (ng /mL)	25.0, 250.0, 2500.0, and 6000.0
Inter day Precision (%CV)	11.4 to 12.3
Inter day Accuracy (%)	99.4 to 104
Cal. Standards Conc. (ng /mL)	10.0 to 8000.0
Inter day Precision (%CV)	3.8 to 9.2
Inter day Accuracy (%)	95.7 to 103
Linearity Range (range of R^2 values)	0.9970494 to 0.9972135

Comments on Study Assay Quality Control: The QC data are acceptable, however, the application is incomplete due to the deficiency cited in the deficiency section.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially selected

Comments on Chromatograms: Acceptable

Table 17 SOP's dealing with analytical repeats

SOP No.	Date of SOP	SOP Title
Not provided (see the deficiency section)		

Table 18 Additional Comments on Repeat Assays

Were all SOPs followed?	See deficiency section
Did recalculation of plasma concentrations change the study outcome?	See deficiency section
Does the reviewer agree with the outcome of the repeat assays?	See deficiency section
If no, reason for disagreement	See deficiency section

Summary/Conclusions, Study Assays: Incomplete due to the deficiency cited in the deficiency section.

d) Pharmacokinetic Results

Table 19 Arithmetic Mean Pharmacokinetic Parameters

Mean plasma concentrations are presented in Table 22 and Figure 2

(n=26)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
PARAMETER					
AUCI	12142.78	39.16	11900.78	37.91	1.02
AUCT	11912.58	37.42	11710.20	37.28	1.02
CMAX	3215.38	28.33	3045.38	28.80	1.06
KE	0.18	21.38	0.19	19.40	0.91
THALF	4.06	17.46	3.72	19.49	1.09
TMAX	1.59	35.92	1.70	45.33	0.93

Treatment T = Test, Treatment R = Reference

UNIT: AUC=ng hr/mL, CMAX=ng/mL, KE=hrs^{-1} , THALF=hrs, TMAX=hrs

Table 20 Least Squares Geometric Means and 90% Confidence Intervals

(n=26)

	LSM1	LSM2	RLSM12	LOWCI12	UPPCI12
LAUCI	11405.95	11230.90	1.02	99.11	104.07
LAUCT	11276.86	11064.79	1.02	99.41	104.48
LCMAX	3116.74	2927.48	1.06	98.89	114.62

Table 21 Additional Study Information

Root mean square error, AUC_{0-t}	0.052409
Root mean square error, AUC_{∞}	0.051449
Root mean square error, C_{max}	0.155523
K_{el} and AUC_{∞} determined for how many subjects?	All 26 subjects except subject #24
Do you agree or disagree with firm's decision?	Yes
Indicate the number of subjects with the following:	-
-measurable drug concentrations at 0 hr	None
-first measurable drug concentration as C_{max}	None
Were the subjects dosed as more than one group?	No

Comments on Pharmacokinetic and Statistical Analysis: Acceptable, however, due to the deficiency comments cited in the deficiency section, the application is incomplete.

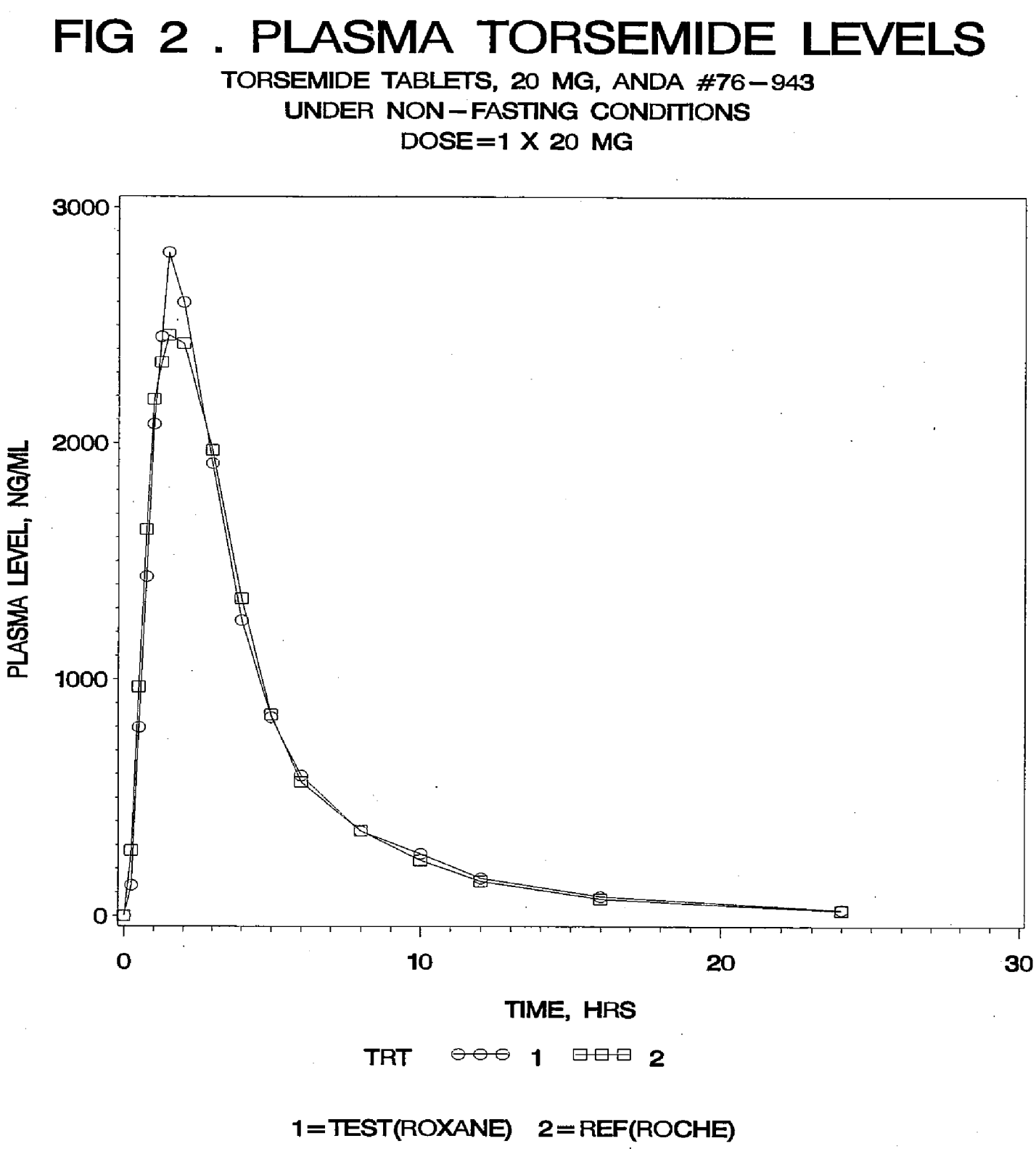
Summary and Conclusions, Single-Dose Fed Bioequivalence Study: The 90% confidence intervals for AUCt, AUCi, and Cmax were within the acceptable range limits of 80-125%. However, the BE study is incomplete due to the deficiencies cited in the deficiency section.

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

(n=26)

	MEAN1	CV1	MEAN2	CV2	RMEAN12
TIME HR					
0	0.00	.	0.00	.	.
0.25	130.06	134.94	276.47	191.04	0.47
0.5	797.66	101.07	968.16	110.87	0.82
0.75	1434.19	61.20	1633.31	73.26	0.88
1	2080.15	42.55	2185.31	51.78	0.95
1.25	2450.92	34.85	2341.69	43.90	1.05
1.5	2808.85	37.39	2456.50	38.14	1.14
2	2597.31	25.98	2422.69	31.16	1.07
3	1914.31	36.68	1969.15	39.24	0.97
4	1249.65	53.85	1341.58	43.71	0.93
5	839.92	56.85	850.62	50.32	0.99
6	594.65	60.43	567.27	53.89	1.05
8	358.77	78.31	360.04	67.47	1.00
10	263.22	87.33	235.66	69.82	1.12
12	159.09	94.73	146.55	75.42	1.09
16	81.52	103.49	71.92	92.37	1.13
24	27.16	126.83	22.26	130.17	1.22

Figure 2 Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study



B. Formulation Data

(Quantitative compositions of Torsemide Tablets 5 mg, 10mg, and 20mg are provided in volume C1.1 on page 80).

Components	5 mg tablet Amount per tablet (mg)	10 mg tablet Amount per tablet (mg)	20 mg tablet Amount per tablet (mg)
Torsemide, USP	5.0	10.0	20.0
Lactose, NF	[redacted]	[redacted]	[redacted]
Microcrystalline Cellulose NF			
Povidone, USP			
Crospovidone, NF			
Magnesium stearate NF			
Total Tablet Weight	100.0 mg	200.0 mg	400.0 mg

Comments

- The amounts of ingredients in the 5 mg, 10 mg, and 20 mg tablets are dose proportional.
- All inactive ingredients are within the acceptable range in the Inactive Ingredients Guide (IIG).

C. Dissolution Data

(information on pages 90-109, vol. C1.1)

Source of Method (USP, FDA or Firm)	FDA (per DBE Dissolution Database)
Medium	0.1 N HCL
Volume (mL)	900 mL
USP Apparatus type	Type II (Paddles)
Rotation (rpm)	50 rpm
Firm's proposed specifications	-
FDA-recommended specifications	NLT—% (Q) in 15 min.

(based on DBE Database)

Sampling Time (minutes)	Test Product, Torsemide Tablets Strength 5 mg Lot No. 039018			Reference Product, Demadex® Tablets Strength 5 mg Lot No. E0009-01		
	Mean	%CV	Range	Mean	%CV	Range
10	101	2.6		101	2.2	
20	101	2.7		102	1.9	
30	101	2.6		102	1.9	

Sampling Time (minutes)	Test Product, Torsemide Tablets Strength 10 mg Lot No. 039019			Reference Product, Demadex® Tablets Strength 10 mg Lot No. E0029-01		
	Mean	%CV	Range	Mean	%CV	Range
10	98	1.4		98	3.6	
20	99	1.3		100	2.1	
30	99	1.2		100	1.8	

Sampling Time (minutes)	Test Product, Torsemide Tablets Strength 20 mg Lot No. 039020			Reference Product, Demadex® Tablets Strength 20 mg Lot No. E1863		
	Mean	%CV	Range	Mean	%CV	Range
10	99	1.5		95	2.7	
20	100	1.5		99	1.8	
30	100	1.4		99	1.8	

Figure 3 Dissolution Profiles

N/A

D. Consult Reviews

None

E. SAS Output

Type of study	Plasma Data	PK Data	SAS Code	SAS Output
Fasting study	76943_Fast_Plasma.txt	76943_Fast_PK.txt	76943_Fast_sas.txt	76943_Fast_output.txt
Fed Study	76943_Fed_Plasma.txt	76943_Fed_PK.txt	76943_Fed_sas.txt	76943_Fed_output.txt

F. Additional Attachments

None

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA:76-943 APPLICANT: Roxane Laboratories , Inc.

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

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

1. The information on adverse events in both fasting and fed studies was not provided in the submission. Please provide information on adverse events observed in the studies. The information (tabulated) should include the following items: subject number, period number, study drug (test or reference), type of adverse events, onset (date & time), resolution (date & time), event duration (hours), degree of severity (mild, moderate, severe), Action taken to resolve the problem, relationship to study drug (possible, probable, definite, remote), and comment by the clinician. Please also provide an overall tabulated summary for all adverse events. This tabulated summary should include each type of adverse event, number of events observed with test product and number of events observed with the reference product and a brief comment on the outcome with regard to the integrity of study.

2. The case report forms from the fasting study for subjects #101 to 110 were not provided in the submission. Please provide the missing information.

3. The approved Institutional Review Board (IRB) forms for the studies were not provided in the submission.

4. The standard operating procedures (SOP) describing the acceptance or rejection criteria of assay values for the studies under fasting and fed conditions were not provided in the submission. Please provide these SOPs. The SOP number, date of SOP approved, and SOP title should be included.

For future applications:

- The study summary should include a brief summary of the chronological history of the bioequivalence study [e.g., study start and end, dosing dates, washout period, analytical dates (start and end), product lot number, lot size (production and planned), manufacture date of the test drug, expiration date of the reference drug, name and address of the medical and analytical facilities, name of the medical and analytical principle investigators, adverse events (see the provided comment, above), demographic (see the provided comment, below), subjects enrolled, subject dropped-out, reasons for drop-out, deviation from protocols (e.g. blood collection deviation, subjects taken medication, etc), sample reassay, and summary of statistical analysis, etc.].

- The submitted tabulated demographic data should include the type of treatment (test or reference product) and period, in addition to the following items: subject number, age, body weight, gender and race. The mean value of each item, standard deviation (SD), range (minimum and maximum), % of each gender, and % of each race category, for all subject enrolled, as well as for those subjects who completed the study, should be provided.

Sincerely yours,

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

ANDA #76-943 (Roxane's Torsemide Tablets, 5 mg, 10 mg, and 20 mg)

CC: ANDA #76-943
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer
HFD-658/ Team Leader

Endorsements:
HFD-658/ Z. Wahba ZW 8/30/04
HFD-658/ YC Huang YH 8/30/2004
HFD-650/ D. Conner DM 8/30/04

V:\firmsnz\Roxane\ltrs&rev\76943n1203.doc

BIOEQUIVALENCE – Incomplete Submission date: 12/12/03

1. FASTING STUDY (STF) OIC
   Strength: 20 mg
   Outcome: IC
   Clinical Study Site: _____
   Analytical Site: _____

2. FOOD STUDY (STP) OIC
   Strength: 20 mg
   Outcome: IC
   Clinical Study Site: _____
   Analytical Site: _____

3. DISSOLUTION WAIVER (DIW) OIC
   Strength: 10 mg
   Outcome: IC

4. DISSOLUTION WAIVER (DIW) OIC
   Strength: 5 mg
   Outcome: IC

NOTE:
AC - Acceptable UN - Unacceptable
NC - No Action IC - Incomplete

Outcome Decision: **Incomplete**
WINBIO COMMENTS: **Incomplete**

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-943
Drug Product Name	Torsemide Tablets
Strength	5 mg, 10, and 20 mg
Applicant Name	Roxane Laboratories
Address	Columbus, OH
Submission Date(s)	(Original submission on 12/12/03)
Amendment Date(s)	09/17/04
Reviewer	Z.Z. Wahba
First Generic	No
File Location	V:\firmsnz\Roxane\ltrs&rev\76943a0904.doc

I. Executive Summary

This submission is an amendment containing the firm's responses to deficiencies in the original application (Submission date: 12/12/03; DBE review date: 08/30/04). All responses are acceptable.

The submission consisted of two (fasting and non-fasting) bioequivalence (BE) studies on the 20 mg strength and dissolution data on the 5 mg, 10 mg, and 20 mg strengths. Both BE studies are single dose two-way crossover studies in normal males and females (fasting, n=23; non-fasting, n=26). The reference listed drug is Roche's Demadex® Tablets, 20 mg.

Statistical analyses of the plasma concentration data for torsemide for both studies demonstrate bioequivalence. For the fasting BE study, torsemide results are (point estimate, 90% CI): $LAUC_t$ of 1.01, 97.42-104.71%; $LAUC_i$ of 1.00, 96.71-103.77% and LCmax of 1.10, 102.95-118.40%. For the non-fasting BE study, torsemide results are (point estimate, 90% CI): $LAUC_t$ of 1.02, 99.41-104.48%; $LAUC_i$ of 1.02, 99.11-104.07% and LCmax of 1.06, 98.89-114.62%.

The formulations of the 5 mg, and 10 mg strengths are proportionally similar to that of the 20 mg strength, which underwent acceptable in vivo testing. The dissolution testing and data on all strengths met the FDA dissolution specifications (paddle 50 rpm in 900 mL 0.1 N HCl – NLT —% (Q) in 15 minutes) for torsemide tablets. The waiver requests of in vivo BE study requirements for the 5 mg, and 10 mg tablets are granted.

However, the application is incomplete. The firm should be advised to acknowledge acceptance of FDA's recommended dissolution method and specifications.

II. Table of Contents

III. Submission Summary

A. Drug Product Information

Test Product	Torsemide Tablets, 5 mg, 10 mg, and 20 mg
Reference Product	Demadex®Tablets, 5 mg, 10 mg, and 20 mg (The drug is also available in 100 mg tablets)
RLD Manufacturer	Roche
NDA No.	20-136
RLD Approval Date	08/23/93
Indication	Indicated for the treatment of edema associated with congestive heart failure, renal disease, or hepatic disease.

B. Contents of Submission

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

C. Formulation

The formulation was previously submitted and reviewed (DBE review date: 08/30/04, submission date: 12/12/03, V:\firmsnz\Roxane\ltrs&rev\76943n1203.doc)

D. In Vitro Dissolution

Source of Method (USP, FDA or Firm)	FDA (per DBE Dissolution Database)
Medium	0.1 N HCL
Volume (mL)	900 mL
USP Apparatus type	Type II (Paddles)
Rotation (rpm)	50 rpm
Firm's proposed specifications	-
FDA-recommended specifications	NLT—% (Q) in 15 min. (based on DBE Database)
F2 metric calculated?	No
If no, reason why F2 not calculated	Rapidly dissolving
Is method acceptable?	Yes
If not then why?	-

E. Waiver Request(s):

Strengths for which waivers are requested	5 mg and 10 mg
Regulation cited	21 CFR 320.22(d)(2)
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	Yes
Waivers granted?	Yes
If not then why?	-

F. Responses to Deficiency Comments

The deficiency comments are as stated in the DBE Review dated 08/30/04 (submission date 12/12/03):

FDA Deficiency Comment #1

The information on adverse events in both fasting and fed studies was not provided in the submission. Please provide information on adverse events observed in the studies. The information (tabulated) should include the following items: subject number, period number, study drug (test or reference), type of adverse events, onset (date & time), resolution (date & time), event duration (hours), degree of severity (mild, moderate, severe), Action taken to resolve the problem, relationship to study drug (possible, probable, definite, remote), and comment by the clinician. Please also provide an overall tabulated summary for all adverse events. This tabulated summary should include each type of adverse event, number of events observed with test product and number of events observed with the reference product and a brief comment on the outcome with regard to the integrity of study.

Firm's Response to Deficiency Comment #1

The adverse events are included in the submission ((Attachment A, in the September 17, 2004 Amendment). The following is a summary of the adverse events for the fasting and fed studies.

Fasting Study (Tore-01)		
Adverse Event Description	# in Test Group	# in Ref. Group
Headache	3	6
Blurred vision	0	1
Dizziness	0	1
Fainting	0	1
Feverish	0	1
Kidney stone	0	1
Lightheaded	3	5
Nausea	2	3
Nervousness	0	1
Sweating	0	1
Urinary frequency	1	0
Vomiting	1	1
Total	10	22

Fed Study (Tore-02)		
Adverse Event Description	# in Test Group	# in Ref. Group
Aching joints	1	0
Blurred vision	0	1
Deyhydration	0	1
Dizziness	0	1
Dizzy	1	0
Headache	3	7
Lightheaded	0	3
Nausea	0	1
Neck strain	0	1
Nose bleeds	0	1
Pale	1	0
Polyuria	1	0
Right foot cramping	0	1
Syncope	1	0
Urinary frequency	2	1
Urinary urgency	1	0
Vomiting	1	0
Total	12	18

Comments: All adverse events were judged as mild to moderate in severity and were resolved with no treatment. All vomited subjects (#104, 121, and 212) were included in statistical analysis. Under fasting conditions, subjects #104 (Trt-R, Per-2) and # 121 (Trt-T, Per-1) experienced vomiting beyond twice the median Tmax for that dosing period. Under fed conditions, subject #212 (Trt-T, Per-1) vomited within twice the median Tmax for that dosing

period. Inclusion or exclusion of subject #212 in the statistical analysis had no significant impact on the study outcome, as seen in the 90% confidence intervals calculated by the reviewer.

DBE's Comment on Deficiency #1:
The firm's response is acceptable

FDA Deficiency Comment #2

The case report forms from the fasting study for subjects #101 to 110 were not provided in the submission. Please provide the missing information.

Firm's Response to Deficiency Comment #2

The case report forms are included in the current submission (Attachment B, in the September 17, 2004 Amendment).

DBE's Comment on Deficiency #2:
The firm's response is acceptable

FDA Deficiency Comment #3
The approved Institutional Review Board (IRB) forms for the studies were not provided in the submission.

Firm's Response to Deficiency Comment #3

The Institutional Review Board (IRB) approval forms for the study protocol are included in the submission (Attachment C, in the September 17, 2004 Amendment).
The IRB approval date was on 08/04/03.

DBE's Comment on Deficiency #3:
The firm's response is acceptable

FDA Deficiency Comment #4
The standard operating procedures (SOP) describing the acceptance or rejection criteria of assay values for the studies under fasting and fed conditions were not provided in the submission. Please provide these SOPs. The SOP number, date of SOP approved, and SOP title should be included.

Firm's Response to Deficiency Comment #4

The relevant SOP was provided in the current amendment (Attachments D, in the September 17, 2004 Amendment):

SOP No.	Date of SOP approved	SOP Title
SOPL200.108	06/10/03	Procedures - Sample Analysis (Chromatographic)

DBE's Comment on Deficiency #4:

The firm's response is acceptable.

Overall comment: The firm did not propose the dissolution specification. From the CMC review, it appears that the firm's in-house specification is NLT —% in 30 minutes. The firm should be advised to acknowledge acceptance of FDA's recommended specification.

G. Recommendations

1. The two bioequivalence studies under fasting (protocol #TORE-01) and fed (protocol #TORE-02) conditions, conducted by Roxane Laboratories, Inc. on its drug product, Torsemide Tablets, 20 mg, Lot #039020A, comparing it to Roche's Demadex® Tablets, 20 mg, Lot #E1863, have been found acceptable by the Division of Bioequivalence. The studies demonstrate that the test product, Roxane's Torsemide Tablets, 20 mg, is bioequivalent to the reference product, Roche's Demadex® Tablets, 20 mg, under fasting, and fed conditions.

2. The dissolution testing conducted by the firm on its drug product, Torsemide Tablets, 5 mg, 10 mg, and 20 mg, is acceptable.

3. The formulations of the test Torsemide Tablets, 5 mg, and 10 mg, are proportionally similar to that of the 20 mg strength that underwent acceptable in vivo bioequivalence testing. The waivers of bioequivalence requirements for the 5 mg, and 10 mg strengths are granted.

4. The dissolution testing should be conducted in 900 mL of 0.1 N HCl at 37°C using USP Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specification:

   Not less than —% (Q) of the labeled amount of Torsemide is dissolved in 15 minutes

5. The firm should be advised to acknowledge acceptance of DBE's recommended dissolution method and specifications.

Zakaria Z. Wahba 10/13/04

Zakaria Z. Wahba, Ph.D. Date:_____
Review Branch III

RD INITIALED YCHuang
FT INITIALED YCHuang _____ Date: 10/13/2004

Concur: Barbara M. Davit Date: 10/14/04
Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs

BIOEQUIVALENCE DEFICIENCIES

ANDA:76-943 APPLICANT: Roxane Laboratories

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

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

Please acknowledge your acceptance of the following dissolution method and specification:

> The dissolution testing should be conducted in 900 ml of 0.1 N HCl using USP Apparatus 2 (paddle) at 50 rpm. The test product should meet the following specification:
>
> > Not less than ___% (Q) of the labeled amount of torsemide in the dosage form is dissolved in 15 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,

for Barbara M. Saunit

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

CC: ANDA 76-943
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
HFD-651/ Bio Drug File
HFD-658/ Reviewer
HFD-658/ Team Leader

Endorsements:
HFD-658/ Z. Wahba ZW 10/13/04
HFD-658/ YC Huang YH 10/13/2004
HFD-650/ D. Conner BD 10/14/04

V:\firmsnz\Roxane\ltrs&rev\76943a0904.doc

BIOEQUIVALENCE - INCOMPLETE submission date: 09/17/04

NOTE: The firm needs to acknowledge acceptance of FDA's recommended dissolution method and specification.

1. Study Amendment (STA) 6/C

Strength: all
Outcome: IC

Outcome Decisions: IC - Incomplete

WinBio Comments: Incomplete

NOV 4 2004

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # : 76-943 SPONSOR : Roxane Laboratories
DRUG AND DOSAGE FORM : Torsemidee Tablets
STRENGTH(S) : 5 mg, 10 mg, and 20 mg
TYPES OF STUDIES: Fasting and Fed studies
CLINICAL STUDY SITE(S) : ~~~~~
ANALYTICAL SITE(S) : ~~~~~
STUDY SUMMARY: The fasting and fed studies are acceptable
DISSOLUTION : The dissolution testing and data are acceptable
WAIVER: The waiver request for the 5 mg, and 10 mg, strength is granted.

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic _No__ New facility _____ For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

Proposed Dissolution Method and Spec from Original Submission Acceptable Yes_____
No___X___
(If No, Project Manager (PM) should verify and sign below when acknowledgement amendment is received)

DBE Dissolution Method and Spec acknowledged by firm; Yes ___X___

PROJECT MANAGER: _____ Date: 04NOV04

PRIMARY REVIEWER : Zakaria Z. Wahba, Ph.D. BRANCH: III

INITIAL : ZZW DATE : 11/4/04

TEAM LEADER : Yih-Chain Huang, Ph.D. BRANCH: III

INITIAL : _____ DATE : 11/4/2004

DIRECTOR, DIVISION OF BIOEQUIVALENCE : DALE P. CONNER, Pharm.D.

INITIAL : DPC DATE : 11/4/04

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-943

ADMINISTRATIVE DOCUMENTS

TELEPHONE MEMO

TO: Rebecca Braatz

Firm: Roxane Labs

REF# ANDA 76-200

FROM: Leo Zadecky

DATE: January 27, 2004

SUBJECT: Torsemide Tablets, 5 mg, 10 mg, and 20 mg

CONTENT:

Ms. Braatz was phoned to resolve deficiencies with Roxane Lab's ANDA 76-943.

1) **The Categorical exclusion for Environmental testing referenced was incorrect 21 cfr 25.24 © . Ms Braatz will amend the reference to 21 cfr 25.31 (a)**

2) **The Spectra and Chromatograms (of the active ingredient) for reference and test samples are missing from the Raw materials section of the application. Ms Braatz will research and send the missing data.**

OGD APPROVAL ROUTING SUMMARY

ANDA # 76-943 Applicant Roxane Laboratories, Inc.
Drug Torsemide Tablets Strength(s) 5 mg, 10 mg, and 20 mg

APPROVAL ☒ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ OTHER ☐

REVIEWER: **DRAFT Package** **FINAL Package**

1. Martin Shimer
Chief, Reg. Support Branch
Date 23 Feb 2005 Date 3/1/05 Rw for
Initials MS Initials

Contains GDEA certification: Yes ☑ No ☐ Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)
Pediatric Exclusivity System
RLD = NDA# 20-136
Patent/Exclusivity Certification: Yes ☑ No ☐ Date Checked 3/1/05
If Para. IV Certification- did applicant Nothing Submitted ☒
Notify patent holder/NDA holder Yes ☑ No ☐ Written request issued ☐
Was applicant sued w/in 45 days: Yes ☐ No ☑ Study Submitted ☐
Has case been settled: Yes ☐ No ☐ Date settled:
Is applicant eligible for 180 day
Generic Drugs Exclusivity for each strength: Yes ☐ No ☑
Type of Letter: PIV to RE34672, not sued w/in 45 days
Comments: Teva TBD for RE672 expired ∴ eligible for Full Approval

2. Project Manager, RYAN NGUYEN Team 11 Date 2/22/05 Date 2/24/05
Review Support Branch Initials RN Initials RN

Original Rec'd date 12/15/03 ✓ EER Status Pending ☐ Acceptable ☒ OAI ☐
Date Acceptable for Filing 12/15/03 Date of EER Status 10/6/04
Patent Certification (type) IV Date of Office Bio Review 11/4/04
Date Patent/Exclus.expires 8/11/06 Date of Labeling Approv. Sum 4/16/04
Citizens' Petition/Legal Case Yes ☐ No ☒ Date of Sterility Assur. App. N/A
(If YES, attach email from PM to CP coord) Methods Val. Samples Pending Yes ☐ No ☒
First Generic Yes ☐ No ☒ MV Commitment Rcd. from Firm Yes ☐ No ☒
Acceptable Bio reviews tabbed Yes ☒ No ☐ Modified-release dosage form: Yes ☐ No ☒
Suitability Petition/Pediatric Waiver Interim Dissol. Specs in AP Ltr: Yes ☐
Pediatric Waiver Request Accepted ☐ Rejected ☐ Pending ☐

Previously reviewed and tentatively approved ☐ Date _____
Previously reviewed and CGMP def. /NA Minor issued ☐ Date _____
Comments:

3. David Read **(PP IVs Only)** Pre-MMA Language included ☐ Date _____
OGD Regulatory Counsel, Post-MMA Language Included ☐ Initials _____
Comments:

4. Div. Dir./Deputy Dir.
Chemistry Div. I II OR III
Comments:
2/25/05 Date 2/28/05
Initials

one satisfactory.

REVIEWER: FINAL ACTION

5. Frank Holcombe **First Generics Only** Date_____
Assoc. Dir. For Chemistry Initials_____
Comments: (First generic drug review)
N/A. Multiple ANDAs have been approved for this drug product.
Note: TEVA's ANDA 76-110 was approved on 5/14/02 and was eligible for 180-day generic drug exclusivity. TEVA's exclusivity has expired.

6. Vacant RLD = Demadex Tablets 5mg, 10mg, 20mg Date_____
Deputy Dir., DLPS Hoffmann La Roche, Inc. NDA 20-136 (001,002,003) Initials_____

7. Peter Rickman Date 3/1/05
Director, DLPS Initials
Para.IV Patent Cert: Yes ☐ No ☐; Pending Legal Action: Yes ☐ No ☐; Petition: Yes☐ No☐
Comments: Acceptable EES dated 10/6/04 (Verified 3/1/05). No O.I. alerts noted. Bioequivalence studies (fasting + non-fasting) on 20mg strength found acceptable 11/4/04. Dissolution testing on all 3 strengths also found acceptable, waivers granted to the 5mg and 10mg strengths under 21 CFR 320.22(d)(2). Biostudy test sites have acceptable GCP inspection histories. Office Level bioendorsed 11/4/04. FPL found acceptable for approval 4/16/04. CMC found acceptable for approval 2/22/05. Methods validation was not requested.

8. Robert L. West Date 3/1/2005
Deputy Director, OGD Initials
Para.IV Patent Cert: Yes☒ No☐; Pending Legal Action: Yes☐ No☒; Petition: Yes☐ No☐
Comments: Roxane made a paragraph IV certification to the '672 patent, and was not sued within the 45-day period. There is no unexpired exclusivity listed in the current "Orange Book" for this drug product. In addition, TEVA's 180-day generic exclusivity for this drug product has expired.
This ANDA is recommended for approval.

9. Gary Buehler Date 3/1/05
Director, OGD Initials GB
Comments:

First Generic Approval ☐ PD or Clinical for BE ☐ Special Scientific or Reg.Issue ☐

10. Project Manager, Team 6 Ryan Nguyen Date 3/1/05
Review Support Branch Initials RN
N/A Date PETS checked for first generic drug (just prior to notification to firm)
Applicant notification:
10:40 Time notified of approval by phone 10:45 Time approval letter faxed
FDA Notification:
3/1/05 Date e-mail message sent to "CDER-OGDAPPROVALS" distribution list.
3/1/05 Date Approval letter copied to \\CDS014\DRUGAPP\ directory.

File V:/division/dlps/approvrou8.doc

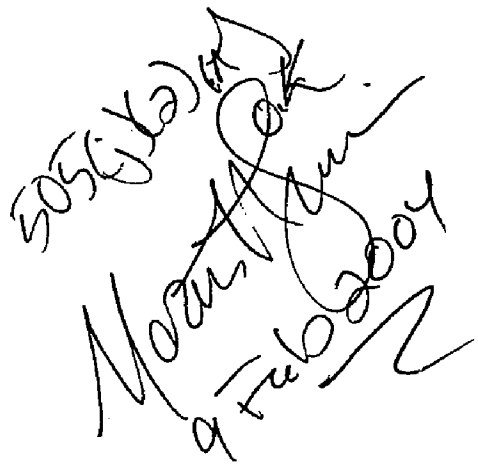
CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 76-943

CORRESPONDENCE

Boehringer Ingelheim
Roxane Laboratories



December 12, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Abbreviated New Drug Application
Torsemide Tablets, 5, 10, and 20 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

Dear Madam/Sir:

In accordance with 21 CFR 314.94, Roxane Laboratories, Inc. is submitting an Abbreviated New Drug Application (ANDA) for Torsemide Tablets, 5, 10, and 20 mg. This ANDA consists of eight (8) volumes. The ANDA was formatted in accordance with the *Guidance for Industry, Organization of an ANDA, February 1999*.

The reference listed drug is DEMADEX® (torsemide) Tablets, 20 mg, manufactured by Roche. The active ingredient is torsemide.

Four complete copies of the draft labeling are contained in the Archival and CMC Review copies of this application. The drug product will be manufactured, tested, labeled, packaged and released by Roxane Laboratories, Inc. No contract manufacturers or packagers are used for the proposed drug product. *In vivo* bioequivalence study reports are also included in this application. Furthermore, two copies of the ANDA Section XV, Analytical Methods, are enclosed separately along with this application.

Please note that electronic versions of the bioequivalency data (in SAS Transport format) and the FDA Form 356H, the Table of Contents, and this cover letter (in pdf format) are provided as per the *Guidance for Industry, Providing Regulatory Submissions in Electronic Format – ANDAs, June 2002*. These electronic documents are provided on a CD in a separate Archival (blue) binder. These documents are the only portion of this ANDA provided in electronic format.

Samples and the methods validation package will be submitted upon the request and direction of the Office of Generic Drugs. Roxane Laboratories, Inc. commits to provide full cooperation to resolve any problems that may arise during the methods validation testing as part of the "Post-Approval" for the above listed drug product.

We have also submitted a copy of the technical sections contained in the archival and review copies of this application to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Rebecca Braatz, Regulatory Affairs Associate, at (614) 272-4709.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

2.1

Boehringer Ingelheim
Roxane Laboratories

NAE MAB 2-12-04

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Leo Zadecky

February 5, 2003 4

NEW CORRESP

NC

TELEPHONE Amendment
ANDA 76-943
Torsemide Tablets, 5, 10, and 20 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Telefax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Mr. Zadecky:

This correspondence is the hard copy follow-up to the fax response we sent to your attention on February 5, 2003. In response to your telephone call of January 27, 2004, we wish to amend ANDA 76-943 for Torsemide Tablets, 5, 10, and 20 mg. Enclosed please find the following materials you requested for acceptance for filing.

- Revised Categorical Exclusion with updated CFR reference for Section XIX
- Roxane chromatograms and spectra for API used in ANDA lot manufacture
- API Manufacturer ——— chromatograms and spectra for API used in ANDA lot manufacture

We have also submitted a copy of this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at (614) 272-4785 and by fax at (614) 276-2470. In my absence, please contact Rebecca Braatz, Regulatory Affairs Associate, at (614) 272-4709.

Respectfully,

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

RECEIVED
FEB 06 2004
OGD/CDER

76. 2.1

ANDA 76-943

FEB 09 2004

Roxane Laboratories, Inc.
Attention: Elizabeth Ernst
1809 Wilson Rd.
Columbus, OH 43228

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 also made to the telephone conversation dated January 27, 2003 and your correspondence dated February 5, 2004.

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

DATE (RECEIVED) December 12, 2003

ACCEPTABLE FOR FILING: December 15, 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 copy of a court order or judgement 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

ANDA 76-943

cc: DUP/Jackets
HFD-600/Division File
Field Copy
HFD-610/G. Davis
HFD-92

Endorsement:
HFD-615/M.Shimer, Chief, RSB _____ date 9 Feb 2004
HFD-615/L.Zadecky, CSO _____ date 09FEB2004

Word File\\CDS013\OGDS11\FIRMSAM\ROXANE\LTRS&REV\76943.doc

F/T 2-5-03

ANDA Acknowledgment Letter!

2.1

Boehringer Ingelheim
Roxane Laboratories

NAI RR. for 1672 NOT Sued in 45 days
2/13/04

Roxane Laboratories, Inc.

February 9, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Leo Zadecky

XP

PATENT AMENDMENT

ANDA 76-943
Torsemide Tablets, 5, 10, and 20 mg

Elizabeth Ernst
Associate Director,
DRA-Multisource Products
Telephone: 614.272.4785
Telefax: 614.276.2470
E-Mail: eernst@
col.boehringer-ingelheim.com

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Mr. Zadecky:

We wish to amend ANDA 76-943. In accordance with 21 CFR 314.95(b), this letter certifies that on December 17, 2003, a notice of certification of non-infringement of a patent was sent to F. Hoffman-La Roche Ltd., owner of U.S. Reissue Patent No. Re 34,672 (see attached copy). Roche is also the holder of the approved application, NDA No. 020136. A separate copy of the notice was also sent to Roche's Legal Department Head, and to Roche's Chief Executive Officer for the U.S. The notice met the content requirements in accordance with 21CFR 314.95(c). Copies of the signed return receipt of the notice letters are provided in accordance with 21 CFR 314.05(e). The Paragraph IV Certification was filed in the ANDA submitted to the Office of Generic Drugs on December 12, 2003. The ANDA is being evaluated for acceptance of filing as of February 9, 2004.

In accordance with 21 CFR 312.95(f), this letter certifies that no legal action was taken by Roche 45 days after receipt of the notice.

We have also submitted a copy of this amendment to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by fax at (614) 276-2470. In my absence, please contact Rebecca Braatz, Regulatory Affairs Associate, at (614) 272-4709.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

Boehringer Ingelheim
Roxane Laboratories

Roxane Laboratories, Inc.

March 22, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

ORIG AMENDMENT
N/AF

Elizabeth Ernst
Associate Director,
DRA-Multisource Products
Telephone: 614.272.4785
Telefax: 614.276.2470
E-Mail eernst@ col.boehringer-ingelheim.com

Attention: Ruby Wu

Abbreviated New Drug Application 76-943
Torsemide Tablets, 5, 10, and 20 mg

Labeling Amendment

P. O. Box 16532
Columbus, Ohio 43216-6532
Telephone (614) 276-4000
Telefax (614) 274-0974

Dear Ms. Wu:

We wish to amend ANDA 76-943, Torsemide Tablets, 5, 10, and 20 mg. Enclosed please find revised labels/labeling and side-by-side comparisons in response to the deficiency letter received from the Labeling Review Branch by facsimile dated March 10, 2004 (copy attached).

We have also submitted a copy of this amendment to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at (614) 272-4785 and by telefax at (614) 276-2470. In my absence, please contact Rebecca Braatz, Regulatory Affairs Associate, at (614) 272-4709.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

RECEIVED
MAR 2 3 2004
OGD/CDER

Boehringer Ingelheim
Roxane Laboratories

Firm will submit Amdt on 7/10/04

June 10, 2004

NEW CORRESP
MC

KMH 6/28/04

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Wanda Pamphile

Controlled Correspondence
ANDA 76-943
Torsemide Tablets 5 and 10 mg

Dear Ms. Pamphile:

We are contacting you in regard to our ANDA 76-943 for Torsemide Tablets, 5 and 10 mg. We would like to receive comments from FDA regarding a recent amendment to Drug Master File No. [redacted] the drug substance manufacturer.

Roxane has been notified by [redacted] informs us that there are no outstanding deficiencies for Drug Master File No. [redacted]

Roxane would like to request verification from FDA that all necessary information regarding this change has been submitted by [redacted] Roxane will provide to FDA an updated drug substance specification including testing and limits for [redacted]. This specification will be included in our response to the Minor Amendment for ANDA 76-943 dated May 3, 2004.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at 614-272-4785 and by fax at 614-276-2470. In my absence, please contact Rebecca Braatz, Regulatory Associate, at 614-272-4709.

Respectfully,

Elizabeth A. Ernst
~~Associate~~ Director,
DRA-Multisource Products

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone 614-272-4785
Fax 614-276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

ORIGINAL

3.1

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT
N/AM

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Wanda Pamphile

July 8, 2004

Minor Amendment
ANDA 76-943
Torsemide Tablets, 5, 10, and 20 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone (614) 272-4785
Fax (614) 276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Ms. Pamphile:

We wish to amend ANDA 76-943 for Torsemide Tablets, 5, 10, and 20 mg. In response to your May 3, 2004 minor deficiency letter (copy attached), please find a point-by-point response to your questions and comments.

We have also submitted a copy of this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at 614-272-4785 and by fax at 614-276-2470. In my absence, please contact Rebecca Braatz, Regulatory Associate, at 614-272-4709.

Respectfully,

Rebecca Braatz

(Rebecca Braatz, Regulatory Associate) for
Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

RECEIVED
JUL 0 9 2004
OGD / CDER

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT

N 1AP3

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Beth Fabian-Fritsch

September 17, 2004

BIOEQUIVALENCY Amendment
ANDA 76-943
Torsemide Tablets, 5, 10, and 20 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone 614-272-4785
Fax 614-276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Ms. Fabian-Fritsch:

We wish to amend ANDA 76-943 for Torsemide Tablets, 5, 10, and 20 mg. In response to your September 3, 2004 bioequivalency deficiency letter (copy attached), please find enclosed a point-by-point response to your questions and comments.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at 614-272-4785 and by fax at 614-276-2470. In my absence, please contact Dr. Gregory M. Hicks, Clinical Research Manager, at 614-241-4106.

Respectfully,

(Gregory M. Hicks, Clinical Research Manager) for
Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

RECEIVED
SEP 2 0 2004
OGD/DMER

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT

NDA

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

Attention: Wanda Pamphile

October 15, 2004

Minor Amendment
ANDA 76-943
Torsemide Tablets, 5, 10, and 20 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone 614-272-4785
Fax 614-276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Ms. Pamphile:

We wish to amend ANDA 76-943 for Torsemide Tablets, 5, 10, and 20 mg. In response to your September 10, 2004 minor deficiency letter (copy attached), please find a point-by-point response to your questions and comments.

We have also submitted a copy of this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at 614-272-4785 and by fax at 614-276-2470. In my absence, please contact Rebecca Braatz, Regulatory Associate, at 614-272-4709.

Respectfully,

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

RECEIVED
OCT 18 2004
OGD / CDER

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT

NDA

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

October 27, 2004

Attention: Steven Mazzella

BIOEQUIVALENCY Amendment
ANDA 76-943
Torsemide Tablets, 5, 10, and 20 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone 614-272-4785
Fax 614-276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Mr. Mazzella:

We wish to amend ANDA 76-943 for Torsemide Tablets, 5, 10, and 20 mg. In response to your October 18, 2004 bioequivalency deficiency letter (copy attached), please find enclosed Roxane Laboratories' drug product specifications, revised in accordance with your request.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at 614-272-4785 and by fax at 614-276-2470. In my absence, please contact Dr. Gregory M. Hicks, Clinical Research Manager, at 614-241-4106.

Respectfully,

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

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OCT 28 2004
OGD / CDER

Boehringer Ingelheim
Roxane Laboratories

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

XP

December 17, 2004

Attention: Wanda Pamphile

ANDA 76-943
Torsemide Tablets, 5, 10, and 20 mg

PATENT AMENDMENT

Elizabeth Ernst
Associate Director,
DRA-Multisource Products
Telephone: 614.272.4785
Fax: 614.276.2470
E-Mail: eernst@
col.boehringer-ingelheim.com

Dear Ms. Pamphile:

We wish to amend ANDA 76-943. In accordance with 21 CFR 314.95(b), this letter certifies that on November 17, 2004, a notice of certification of non-infringement of a patent has been sent to Roche Laboratories, owner of U.S. Patent No. RE34672 (see attached copy). Roche is also the holder of the approved application, NDA No. 020136. A separate copy of the notice was also sent to Roche's General Counsel. The notice met the content requirements in accordance with 21CFR 314.95(c). Copies of the signed return receipt of the notice letters are provided in accordance with 21 CFR 314.05(e). The Paragraph IV Certification was filed in the ANDA submitted to the Office of Generic Drugs on December 12, 2003. The ANDA was accepted for filing on December 15, 2003.

In accordance with 21 CFR 312.95(f), this certifies that no legal action was taken by Roche 45 days after receipt of the notice.

We have also submitted a copy of this amendment to Ms. Kathleen Culver, Pre-Approval Manager, FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097

Correspondence concerning this application should be directed to Elizabeth Ernst, Associate Director, DRA-Multisource Products, Roxane Laboratories, Inc. I can be reached at 614-272-4785 and by fax at 614-276-2470. In my absence, please contact Rebecca Braatz, Regulatory Associate, at 614-272-4709.

Respectfully,

Elizabeth Ernst
Associate Director, DRA-Multisource Products

Boehringer Ingelheim
Roxane Laboratories

ORIG AMENDMENT
N/BAM

Office of Generic Drugs
Center for Drug Evaluation and Research/FDA
Metro Park North II
Standish Place, Room 150
Rockville, MD 20855-2773

January 19, 2005

Attention: Benjamin Danso

Minor Amendment
ANDA 76-943
Torsemide Tablets, 5, 10, and 20 mg

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

Telephone 614-272-4785
Fax 614-276-2470
E-Mail eernst@col.boehringer-ingelheim.com

1809 Wilson Road
Columbus, Ohio 43228

P.O. Box 16532
Columbus, Ohio 43216-6532

Dear Mr. Danso:

We wish to amend ANDA 76-943 for Torsemide Tablets, 5, 10, and 20 mg. In response to your December 30, 2004 minor deficiency letter (copy attached), please find a point-by-point response to your questions and comments.

We have also submitted a copy of this amendment to Ms. Kathleen Culver (Pre-Approval Manager), FDA District Office, 6751 Steger Drive, Cincinnati, Ohio 45237-3097.

Correspondence concerning this application should be directed to my attention. I can be reached by telephone at 614-272-4785 and by fax at 614-276-2470. In my absence, please contact Rebecca Braatz, Regulatory Associate, at 614-272-4709.

Respectfully,

Elizabeth A. Ernst
Associate Director,
DRA-Multisource Products

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